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ORIGINAL ARTICLE

The prevalence of systemic sclerosis is increased among patients with alopecia areata: a population-based study

Khalaf Kridin[1] · Dana Tzur Bitan[2] · Doron Comaneshter[3] · Arnon D. Cohen[3,4]

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Abstract

Although the coexistence of alopecia areata (AA) and systemic sclerosis (SSc) has been anecdotally reported, the association between these conditions has been poorly investigated. We aimed to assess the association between AA and SSc using a large-scale real-life computerized database. A cross-sectional study was conducted comparing the prevalence of SSc among patients with AA and among age-, sex-, and ethnicity-matched control subjects. Chi-square and *t* tests were used for univariate analysis, and logistic regression model was used for multivariate analysis. The study was performed utilizing the computerized database of Clalit Health Services ensuring 4.4 million subjects. A total of 51,561 patients with AA and 51,410 controls were included in the study. The prevalence of SSc was increased in patients with AA as compared with the control group (0.1% vs. 0.0%, respectively; OR, 2.30; 95% CI, 1.2–4.4; $P = 0.010$). The association was stronger among older and Jewish patients. In a multivariate analysis adjusting for sex, age, ethnicity, and other comorbidities, AA was still independently associated with SSc (OR, 2.3; 95% CI, 1.2–4.4; $P = 0.012$). In conclusion, a significant positive association was revealed between AA and SSc. Further studies are necessary to establish these findings in other study populations and to elucidate the mechanism underlying this association. Awareness of SSc may be of importance for physicians treating patients with AA, and screening for SSc in patients with relevant symptoms may be considered.

Keywords Alopecia areata · Systemic sclerosis · Patients

Introduction

Alopecia areata (AA) is a common autoimmune disorder which targets the hair follicles and presents as sharply demarcated circular areas of non-scarring hair loss. The worldwide lifetime incidence of AA is estimated at approximately 2% and appears to increase at an almost linear rate with age [1]. AA is thought to be an organ-specific T cell-driven autoimmune disease characterized by a collapse of the immune privilege zone from an unknown autoantigen [2]. While most patients achieve complete remission, some can experience a chronic and relapsing course of the disease, and might progress to total scalp hair loss (alopecia totalis) or complete scalp and body hair loss (alopecia universalis) [3]. Being of autoimmune and inflammatory nature, AA was observed to coexist with several autoimmune and atopic conditions [4].

Systemic sclerosis (SSc) is a chronic, multisystem, autoimmune, collagen-tissue disease characterized by fibroproliferative alterations of the microvasculature leading to fibrosis and loss of function of the skin and internal organs. It is thought that disruption in humoral and cellular immunity induces a whole cascade that terminates in excessive deposition of collagen fibers [5]. SSc is a potentially devastating condition typified by the highest case-specific mortality and serious non-lethal complications among all rheumatologic diseases [6]. Clinically, SSc is a heterogeneous disease with a wide spectrum of manifestations, including Raynaud's phenomenon, as well as cutaneous, renal, cardiovascular, gastrointestinal, and pulmonary involvement [7]. Skin evaluation in SSc is of pivotal importance since its thickening is a robust predictor of internal organ involvement and poor outcome [8].

✉ Khalaf Kridin
dr_kridin@hotmail.com

[1] Department of Dermatology, Rambam Health Care Campus, POB 9602, 31096 Haifa, Israel

[2] Department of Behavioral Sciences, Ariel University, Ariel, Israel

[3] Siaal Research Center for Family Medicine and Primary Care, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

[4] Department of Quality Measurements and Research, Chief Physician's Office, Clalit Health Services, Tel Aviv, Israel

Despite the facts that patients with AA are predisposed to comorbid autoimmune diseases [4], and that skin involvement is common in SSc [8], the link between AA and SSc has been poorly investigated. The evaluation of potential comorbid conditions and providing the required screening and care are crucial to improve outcome of patient with autoimmune diseases. The aim of the current study is to evaluate the association between AA and SSc in a population-based settings utilizing one of the largest cohorts of patients with AA reported so far.

Methods

Study design and setting

We conducted a retrospective, population-based, cross-sectional study utilizing information from the Clalit Health Services (CHS) database. CHS is the largest health maintenance organization in Israel, serving a population of approximately 4,400,000 as for 2017. CHS exploits a comprehensive computerized database with continuous real-time input from medical, pharmaceutical, and administrative operating systems that enables data collection for observational studies. The validity of diagnoses in this dataset, which are based on reports from both hospital and primary care physicians and specialists, was proven to be of high reliability [9]. A chronic disease register is gathered from these data sources and continuously updated and validated through algorithmic checks [9]. The current study was approved by the institutional ethical board of Ben-Gurion University and CHS.

Study population and covariates

All medical files of CHS members were screened for the diagnosis of AA, and data on all prevalent cases of AA was retrieved. The diagnosis of AA was based on the documentation of an AA-specific diagnostic code registered by a board-certified dermatologist. A comparison group of individuals without AA was selected through 1:1 matching based on age, sex, ethnicity, and primary care practice. The control group was randomly selected from the list of CHS members frequency-matched to cases excluding patients with AA. The age matching was grounded on the exact year of birth (1-year strata). Controls had to be alive and contributing data to CHS on the date of the diagnosis of the matched case.

Other covariates in the analysis included comorbid conditions as determined using Charlson comorbidity index [10], a weighted index used to categorize the degree of comorbidity of a patient by taking into account the number and severity of comorbid conditions. It is a validated method of measuring comorbidity which has been shown to be a reliable predictor of mortality. The higher the score, the more likely the predicted outcome will result in mortality [10]. Socioeconomic status (SES) was defined according to the poverty index of the member's residence area as defined during the 2008 National Census. The population was divided into 3 categories according to their poverty index (low, intermediate, and high) [11]. Data on ethnicity is based on the address of the patient's primary care clinic.

Statistical analysis

The distribution of sociodemographic and clinical features was compared between case and control subjects using chi-square test for sex and socioeconomic status, and *t* test for age. Conditional logistic regression was then used to calculate adjusted ORs, and 95% CIs, to compare cases and controls with respect to the presence of SSc. All statistical analysis was performed using SPSS software, version 23 (SPSS, Chicago, IL, USA).

Results

Our study population comprised 51,561 patients with AA and 51,410 age-, sex-, and ethnicity-matched control subjects. The mean (± standard deviation) age of patients with AA was 34.1 ± 17.1, which is identical to the age of control subjects at their enrollment date. In all, 20,476 (39.7%) of AA patients were female and similar proportion was documented among controls. No significant differences in ethnic background and SES were noted between the two groups. Comorbidity rates, measured by the Charlson comorbidity index, were comparable between the two groups, with 1352 (2.6%) AA patients and 1354 (2.6%) control subjects having severe comorbidities (Table 1).

The prevalence of SSc was greater in patients with AA than in control subjects (0.1% vs. 0.0%, respectively; OR, 2.3; 95% CI, 1.2–4.4; $P = 0.010$; Table 2). When stratified by age, the association between AA and SSc was statistically significant among individuals older than 34 years (OR, 2.2; 95% CI, 1.1–4.4; $P = 0.029$), whereas it was of only marginal statistical significance in those younger than 34 years (OR, 3.0; 95% CI, 0.6–14.8; $P = 0.158$). Although significant in both sexes, the association was greater among female patients (OR, 2.0; 95% CI, 1.0–3.9; $P = 0.038$). Interestingly, the association was stronger among patients of Jewish ancestry as compared with Arabs, and also among those with intermediate and high SES as compared with those with low SES (Table 2).

After controlling for putative confounding factors such as sex, age, ethnic background, and comorbidities, AA demonstrated an independent association with SSc in multivariable logistic regression analysis (OR, 2.3; 95% CI, 1.2–4.4; $P = 0.012$). Increasing age and female sex were also found to be independently associated with SSc (Table 3).

Table 1 Descriptive characteristics of the study population

Characteristic	Patients with alopecia areata ($N = 51,561$)	Controls ($N = 51,410$)	P value
Age, years			
Mean ± SD	34.1 ± 17.1	34.1 ± 17.0	1.000
Median (range)	34.0 (0–99.0)	34.0 (0–99.0)	
Male sex, *N* (%)	31,085 (60.3%)	31,001 (60.3%)	1.000
Ethnicity, *N* (%)			
Jews	34,800 (67.5%)	34,656 (67.4%)	0.732
Arabs	16,761 (32.5%)	16,754 (32.6%)	
SES, *N* (%)			
Low	25,218 (48.9%)	25,179 (48.9%)	1.000
Intermediate	17,396 (33.7%)	17,328 (33.7%)	
High	8758 (17.0%)	8720 (17.0%)	
Unknown	189 (0.4%)	183 (0.4%)	
Charlson comorbidity score, *n* (%)			
None (0)	42,076 (81.6%)	42,383 (82.4%)	<0.001
Moderate (1–2)	8133 (15.8%)	7673 (14.9%)	<0.001
Severe (≥ 3)	1352 (2.6%)	1354 (2.6%)	1.000
Body mass index (Kg/m2), Mean ± SD	25.5 ± 6.3	25.9 ± 5.6	<0.001

N, number; *SD*, standard deviation; *BMI*, body mass index; *SES*, socioeconomic status

Discussion

The current large-scale study of 102,971 participants is the first population-based study aiming to investigate the associations between AA and SSc. Our findings revealed a significant association between the two conditions, with SSc being 2.3 times more frequent among patients with AA relative to matched control subjects. The association was more prominent among older patients and those of Jewish ancestry.

Individuals affected by an autoimmune condition, as well as their family members, are more likely to develop additional autoimmune comorbidities [12–14]. This concept is known as

Table 2 The association between alopecia areata and systemic sclerosis stratified by age, gender, and ethnicity

Subgroup	Number	Systemic sclerosis in patients with alopecia areata ($N = 51,561$) *n* (%)	Systemic sclerosis in controls ($N = 51,410$) *n* (%)	OR (95%CI)	P value
All	102,971	30 (0.1%)	13 (0.0%)	*2.30 (1.20–4.41)*	*0.010*
Age, years					
< 34	50,410	6 (0.0%)	2 (0.0%)	3.00 (0.60–14.84)	0.158
≥ 34	52,561	24 (0.1%)	11 (0.0%)	*2.18 (1.07–4.44)*	*0.029*
Gender					
Male	62,086	4 (0.0%)	0 (0.0%)	*NA*	*0.046*
Female	40,885	26 (0.1%)	13 (0.1%)	*2.00 (1.03–3.88)*	*0.038*
Ethnicity					
Jews	69,456	25 (0.1%)	10 (0.0%)	*2.49 (1.20–5.19)*	*0.012*
Arabs	33,515	5 (0.0%)	3 (0.0%)	1.67 (0.40–6.97)	0.480
SES					
Low	33,515	7 (0.0%)	7 (0.0%)	0.99 (0.35–2.85)	0.998
Intermediate	34,724	15 (0.1%)	4 (0.0%)	*3.74 (1.24–11.26)*	*0.012*
High	17,478	8 (0.1%)	2 (0.0%)	3.96 (0.85–18.77)	0.059

OR, odds ratio; *N*, number; *CI*, confidence interval; *NA*, not applicable

Significant values are italicized

Table 3 The association between alopecia areata and systemic sclerosis: multivariate logistic regression analysis*

Variable	Multivariate OR*	95% CI	*P* value
Alopecia areata	*2.29*	*1.20–4.41*	*0.012*
Female sex	*12.91*	*4.59–36.33*	*< 0.001*
Age (per year)	*1.03*	*1.01–1.04*	*0.004*
Jewish ancestry	1.04	0.42–2.56	0.935
Intermediate and high vs low SES	1.44	0.69–3.00	0.330
Charlson comorbidity index (per score)	1.24	0.99–1.55	0.062

*Adjusting for sex, age, ancestry, SES, and Charlson comorbidity index

OR, odds ratio; *CI*, confidence interval; *SES*, socioeconomic status

Significant values are italicized

"the autoimmune diathesis" and has been solidified by a multitude of observational studies demonstrating the coexistence and clustering of several autoimmune diseases [15]. Based upon the findings of well-designed controlled observational studies, a firm association between AA and autoimmune thyroid diseases had emerged [16]. Scattered case reports and case series unveiled the coexistence of AA with the several autoimmune conditions like diabetes mellitus type 1, vitiligo, Addison's disease, myasthenia gravis, and pernicious anemia [17, 18]. Congruently, patients with SSc were found to be at increased risk of developing inflammatory bowel disease and multiple sclerosis [19]. More recently, a significant association was revealed between SSc and psoriasis with an OR of 2.2 (95% CI, 1.4–3.4) [20].

The coexistence of AA and SSc was reported anecdotally in the past, but the real association between the conditions is yet to be elucidated. Thompson et al. [21] described one patient presenting concomitantly with SSc (termed scleroderma), AA, ulcerative colitis, and vitiligo, with AA manifesting as subtotal alopecia and preceding SSc by 5 years. In a questionnaire analysis of 800 patients with AA, the prevalence of SSc was estimated at 0.25% [22].

Although the molecular mechanism underlying this association has yet to be fully established, several hypotheses might be postulated to explain the putative link between AA and SSc. Multiple experimental studies had demonstrated that both $CD4^+$ (including Th1 and Th2) and $CD8^+$ T cells exert a pathogenic role in AA [23–25]. Correspondingly, T cells appear to play a prominent role in the pathogenesis of SSc, with a predominant Th1 immune response in the early phase of the disease and a Th2 polarity in the later stages [26–28]. $CD4^+$ T cells, including follicular helper T cells, may drive autoantibody production, while interactions between $CD4^+$Th2 T cells and fibroblasts, that release profibrotic mediators (IL-4, IL-6, IL-13), may contribute to the skin phenotype of SSc. The shared role of T cells may explain, at least in part, the association between the two conditions. Additionally, a genome-wide association study revealed that several genomic regions, such as genes controlling cytotoxic T lymphocyte associated antigen 4, IL-21/IL-2, IL-2 receptor A, and HLA antigen region, are significantly associated with AA as well as with other autoimmune conditions including SSc [29–31].

Patients with AA oftentimes show autoantibodies to several autoantigens [18], whereas serum autoantibodies directed to multiple intracellular antigens are present in more than 95% of patients and are considered a serological hallmark of SSc [7]. This implies that epitope spreading phenomenon might account for the observed association. In this concept, an inflammatory event exposes new target antigens to the immune system, thus inducing a subsequent autoimmune response to new antigens [32]. Further research is necessary to clarify the pathomechanism underlying this association.

Alongside the seminal findings it provides, our study utilizes a standardized and large cohort size that gives sufficient power to exclude chance as the source of the findings and reduces the probability of selection and ascertainment biases which embody a crucial concern in observational studies. This study is a large population-based study of a relatively uncommon disease that enables a precise estimation of prevalence rates which have otherwise been unavailable in hospital-based and small-scale studies.

Our study, however, has some limitation to be aware of. First, the cross-sectional design interferes with addressing the temporal relationship between AA and SSc and, therefore, intercept drawing meaningful conclusions concerning causal relationship between the two conditions [33]. Second, the CHS registry was originally designed for clinical purposes and not for fulfilling formal disease criteria. Nevertheless, specialists are required to confirm the diagnoses of these two diagnoses, which are then registered by primary care physicians into the database. Previous studies based on the CHS database have shown that the data is of high reliability and external validity [34]. Further studies are needed to confirm our results using more strict diagnostic criteria for SSc. Third, data concerning the clinical characteristics and the severity of the two diseases could not be retrieved for the current study.

In conclusion, the present population-based study demonstrates that the burden of SSc is increased among patients with AA. Further observational studies are necessary to establish this association in longitudinal cohorts of patients originating

from different ethnic backgrounds. Physicians treating patients with AA might be aware of this possible association. Screening for SSc may be of benefit in AA patients with relevant symptoms, and systemic therapies that were proven effective for both conditions may be administered.

Compliance with ethical standards

Conflict of interest ADC served as an advisor, investigator, or speaker for Abbvie, BI, Dexcel Pharma, Janssen, Novartis, Perrigo, Pfizer, and Rafa. None of the other authors have any conflicts of interest to declare.

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