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Incident alopecia areata and vitiligo in adult women with atopic dermatitis: Nurses' Health Study 2:

Atopic dermatitis and risk of alopecia areata and vitiligo

Aaron M Drucker, MD^{1,2}, Jordan M Thompson, BS¹, Wen-Qing Li, PhD^{1,3}, Eunyoung Cho, ScD^{1,3,4}, Tricia Li, MS⁴, Emma Guttman-Yassky, MD, PhD⁵, and Abrar A Qureshi, MD, MPH^{1,2,3,4}

¹Department of Dermatology, Warren Alpert Medical School, Providence, RI

²Department of Dermatology, Rhode Island Hospital, Providence, RI, United States

³Department of Epidemiology, School of Public Health, Brown University, Providence, RI

⁴Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

⁵Laboratory for Investigative Dermatology, Rockefeller University and Department of Dermatology and the Laboratory for Inflammatory Skin Diseases, Icahn School of Medicine at Mount Sinai, New York, NY

Abstract

We aimed to determine the risk of AA and vitiligo associated with AD in a large cohort of US women, the Nurses' Health Study 2. We used logistic regression to calculate age- and multivariate-adjusted odds ratios to determine the risk of incident AA and vitiligo associated with AD diagnosed in or before 2009. A total of 87,406 and 87,447 participants were included in the AA

Corresponding author: Abrar A Qureshi, 593 Eddy Street, APC-10, Providence, RI 02903, Phone: (401) 444-2595, Fax: (401) 444-7105, abrar_qureshi@brown.edu.

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and vitiligo analyses, respectively. A history of AD in 2009 was reported in 11% of participants. There were 147 incident cases of AA and 98 incident cases of vitiligo over 2 years of follow-up. AD was associated with increased risk of developing AA (OR 1.80, 95% CI 1.18–2.76) and vitiligo (OR 2.14, 95% CI 1.29–3.54) in multivariate models. In this study of US women, AD was associated with increased risk of incident vitiligo and AA in adulthood.

Keywords

Atopic dermatitis; alopecia areata; vitiligo; epidemiology; comorbidities

Introduction

Atopic dermatitis (AD) is a chronically relapsing skin disease characterized by skin barrier defects and Th2 and Th22 inflammation.(1) Alopecia areata (AA) is a non-scarring form of hair loss characterized by autoimmune attack on the bulb of the hair follicle. Inflammation in AA is also characterized by Th2 cytokine production, in addition to Th1, IL-23 and IL-9/TH9.(2) Vitiligo is characterized by depigmentation of the skin, with predominantly Th1-mediated inflammation.(3)

A systematic review and meta-analysis found that a history of AD increased the odds of having AA and vitiligo by over 2.5 and 7.5 times, respectively.(4) However, because most included studies lacked control groups, the meta-analysis for AA was based on only 3 studies with 6,460 cases and fewer than 10,000 participants combined, and the meta-analysis for vitiligo was based on only 2 studies with 85 cases and fewer than 4,000 participants combined. Further, the included studies for AA comprised 1 case-control study(5) and 2 cross-sectional studies(6, 7) and the 2 vitiligo studies were both cross-sectional.(8, 9) A more recent large cross-sectional study based on healthcare claims data from Denmark found even stronger associations between adult AD and AA (Odds Ratio (OR) 26.31, 95% confidence interval (CI) 14.48–47.80) and vitiligo (OR 17.98, 95% CI 7.70–42.01).(10) We aimed to conduct the first prospective study examining the association of incident AA and vitiligo with AD in the Nurses' Health Study 2 (NHS2).

Methods

Population

NHS2 is an ongoing prospective cohort study of female US registered nurses established in 1989 when 116,430 participants completed a baseline questionnaire with questions about demographic and lifestyle factors, anthropometric variables, and disease history. Follow-up questionnaires are sent biennially to participants, updating information on diseases, anthropometric factors and other risk factors. This study was approved by the institutional review board of Brigham and Women's Hospital.

Assessment of exposure, outcome and covariates

AD was first assessed in 2009, when participants were asked whether they "ever had clinician-diagnosed eczema (atopic dermatitis)." In 2013, participants were again asked

about a history of clinician-diagnosed AD, in addition to the year they were diagnosed in intervals (before 1995, 1995–2002, 2003–2008, 2009–2010, 2011+). For our primary analyses, AD cases were defined by self-report in 2009 or by self-report in 2013 of diagnosis prior to 2009. In *a priori* sensitivity analyses to address concerns of reverse-causation, AD cases were restricted to those who reported AD onset prior to 2002 on the 2013 questionnaire.

AA and vitiligo were assessed by self-report in 2011 with the question, “Since June 2009, have you had any of these clinician-diagnosed illnesses?” “Alopecia areata (Dr. dx – ever),” “Vitiligo (Dr. dx – ever),” along with intervals of year of diagnosis (<June 2009, June 2009–June 2011, > June 2011). Cases of incident AA and vitiligo were defined by self-report of diagnosis June 2009–June 2011 or >June 2011. In a sensitivity analysis, cases of AA and vitiligo were defined by self-report of diagnosis occurring at any time.

Race/ethnicity, height and sunburn susceptibility were assessed at cohort baseline. Information on body weight, physical activity, smoking status, alcohol intake, menopausal status and hormone replacement use have been collected and updated during cohort follow-up.

Statistical analysis

A total of 94,030 participants returned the 2011 biennial questionnaire. We excluded participants missing data on AD and AA or vitiligo for their respective analyses. This left 87,406 and 87,447 participants in the AA and vitiligo analyses, respectively.

We used logistic regression models to calculate age- and multivariate-adjusted OR and 95% CI for the association between lifetime history of AD up to 2009 and incident AA and vitiligo. A multivariate analysis was conducted adjusting for age (per 1 year, as a continuous variable), race/ethnicity (White, Hispanic, Asian, or Black), BMI (<19, 19–21.9, 22–24.9, 25–29.9, 30–34.9, or ≥ 35 kg/m²), alcohol intake (0, 0.1–4.9, 5–9.9, >10 g/day), physical activity (by quintile in metabolic equivalent hours/week), cigarette smoking status (never, past or current in cigarettes/day [≤ 15, >15]) and history of postmenopausal hormone replacement use (premenopausal, post-menopausal and never used, post-menopausal and current use and post-menopausal and past use). Age, race, BMI, alcohol intake, physical activity and cigarette smoking have all been associated with AD in previous studies and have therefore been included in the models. Post-menopausal hormone use was included as it is a common exposure in this cohort (see Table 1) and has been associated with various immune alterations.⁽¹¹⁾ An indicator variable was created for the missing data of each covariate. We used covariate information from 2009 (with the exception of height and race) for this analysis.

Sensitivity analyses were conducted additionally adjusting for susceptibility to sunburn and limiting to White participants only. Andersen et al. found that a history of smoking significantly increased the association between AD and various autoimmune comorbidities, so we conducted analyses stratified by smoking status (never vs. ever smokers). Interaction tests were used to determine statistical significance.

All statistical analysis was performed with SAS, version 9.2 (SAS Institute, Inc., Cary, NC). A two-tailed $P < 0.05$ was considered statistically significant.

Results

Characteristics of the study population in the AA analysis by history of AD in 2009 are presented in Table 1. AD cases and non-cases were similar with respect to major characteristics. There were no material differences between the populations included in the AA and vitiligo analyses (data not shown).

Between 2009 and 2011 there were 147 incident cases of AA and 98 incident cases of vitiligo. AD was associated with increased risk of developing AA (OR 1.80, 95% CI 1.18–2.76) and vitiligo (OR 2.14, 95% CI 1.29–3.54) in multivariate models over the 2-year study follow-up (Table 2). In the stratified analyses by smoking status, we did not find statistically significant effect modification by ever smoking status on the association of AD with AA (OR (95% CI) 1.60 (0.92–2.80) vs. 2.14 (1.10–4.18), P for interaction 0.64) or vitiligo (2.46 (1.39–4.38) vs. 1.40 (0.48–4.09), P for interaction 0.43).

In sensitivity analyses using only AD cases diagnosed before 2002, the multivariate-adjusted risk of AA (OR 1.85, 95% CI 1.08–3.17) and vitiligo (OR 2.55, 95% CI 1.42–4.58) did not change materially. In sensitivity analyses examining the association of AD with a history of ever being diagnosed with AA or vitiligo, the association with AA was similar (OR 1.89, 95% CI 1.57–2.29) and the association with vitiligo was somewhat attenuated (OR 1.44, 95% CI 1.15–1.79). Sensitivity analyses further adjusting for susceptibility to sunburn did not materially change the results. In analyses limited to White participants, the odds ratio for AA was attenuated (OR 1.60, 95% CI 1.00–2.56) with no significant change in the vitiligo results.

Discussion

In the present analysis, AD is a risk factor for developing AA and vitiligo in adulthood. This provides further evidence that these conditions are frequently comorbid, and ours is the first large study to prospectively determine the risk of AA and vitiligo in AD. Our sensitivity analysis including only those cases of AD diagnosed before 2002 strengthens our conclusions that AD is a risk factor for the development of AA and vitiligo later in life.

While these 3 immune-mediated diseases are etiologically distinct, their association does have therapeutic implications. AD, AA and vitiligo have been reported to respond to inhibition of the JAK-STAT pathway, and so patients with more than one of these diseases may specifically benefit from that therapeutic approach.(12–14) Furthermore, patients with AD and AA may respond to ustekinumab, an anti-p40 IL-12/23 monoclonal antibody.(15, 16)

Our study is strengthened by the well-established cohort with high-quality data on participant characteristics and outcomes, but is limited by its reliance on self-report of AD, AA and vitiligo. Additionally, hypopigmentation may occur as a result of atopic dermatitis or topical corticosteroid use, which may result in misclassification of vitiligo cases. While

this is a prospective study, elements of it are retrospective, including participants' recall of their date of cutaneous disease diagnosis. While our sensitivity analysis is reassuring with regards to reverse-causation bias, the short follow-up time limited our ability to do a lag analysis and limited the number of incident cases of AA and vitiligo. Detection bias is another concern whenever two dermatologic diseases are associated. The inclusion of women only and the racial/ethnic homogeneity of NHS2 limit the generalizability of our results.

In conclusion, in this study of US women, history of AD increased the risk of developing AA and vitiligo in adulthood.

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Table 1

Characteristics of Nurses' Health Study 2 participants in 2009 included in the analysis of alopecia areata by history of atopic dermatitis

	No atopic dermatitis (n=78,172)	Atopic dermatitis (n=9,234)
Age *	54.5 (4.7)	54.4 (4.6)
Race		
White, %	96	95
Hispanic, %	0.1	0.1
Black, %	1	2
Asian, %	1	2
BMI, kg/m ²	27.6 (6.4)	28.1 (6.7)
Alcohol intake, g/d	6.4 (10.2)	6.5 (10.5)
Physical activity MET/wk	23.8 (29.8)	23.1 (28.6)
Past smokers, %	28	30
Current smokers, %	6	5
Postmenopausal, %	64	65
Postmenopausal hormone use, %	23	25

Values are means (SD) or percentages and are standardized to the age distribution of the study population.

* Value is not age adjusted

BMI: Body Mass Index; MET: Metabolic equivalent hours

Table 2

a) Odds ratios of incident alopecia areata and vitiligo (2009–2011) according to history of atopic dermatitis (up to 2009) in the Nurses' Health Study 2

<u>Alopecia areata</u>				
	AA cases	Non-cases	Age-adjusted OR (95% CI)	MV-adjusted OR *
No AD	121	78,051	Ref	Ref
AD	26	9,208	1.82 (1.19–2.78)	1.80 (1.18–2.76)
<u>Vitiligo</u>				
	Vitiligo cases	Non-cases	Age-adjusted OR (95% CI)	MV-adjusted OR *
No AD	79	78,096	Ref	Ref
AD	19	9,253	2.04 (1.23–3.36)	2.14 (1.29–3.54)

AA, alopecia areata; OR, odds ratio; MV, multivariate

* Adjusted for age (per 1 year, as a continuous variable), race/ethnicity (White, Hispanic, Asian, or Black), BMI (<19, 19–21.9, 22–24.9, 25–29.9, 30–34.9, or ≥35 kg/m²), alcohol intake (0, 0.1–4.9, 5–9.9, >10 g/day), physical activity (by quintile in metabolic equivalent hours/week), cigarette smoking status (never, past or current in cigarettes/day [≤15, 15+]) and history of postmenopausal hormone replacement use (premenopausal, postmenopausal but never used, postmenopausal and currently use and postmenopausal and past use)