

A Threefold Association Between Vitiligo and Alopecia Areata: Results from a Nationwide Case-control Observational Study

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To the Editor,

Alopecia areata (AA) is a complex dermatological autoimmune condition affecting both children and adults, resulting in varying degrees of chronic, nonscarring hair loss that significantly impacts quality of life. AA shares pathogenic mechanisms with vitiligo, as both conditions involve interactions between genetic, environmental, and immune factors, including interferon- α and activated interferon- γ signalling pathways (1, 2). Additionally, potential markers of oxidative stress-related genes, such as KLB (Klotho beta) and EIF3C (eukaryotic translation initiation factor 3 subunit C), have been identified in both AA and vitiligo, suggesting co-regulatory mechanisms (3).

Beyond their shared pathogenesis, the potential epidemiological association between AA and vitiligo has been raised and partially investigated. However, obtaining new, large-scale data from diverse populations worldwide is essential to address this question comprehensively.

The present study aimed to investigate the association between AA and vitiligo through a population-based case-control approach.

We conducted a retrospective case-control cohort study using data from Maccabi Healthcare Services (MHS), Israel's second-largest state-mandated health fund, which covers approximately 26% of the nation's population (nearly 2,354,000 individuals). The study included all patients diagnosed with AA between 2005 and 2019, with diagnoses made by board-certified dermatologists and identified using standardized diagnostic codes. Cases of AA were matched in a 1:2 ratio with healthy controls based on sex. Statistical analyses, including regression models, were conducted using SPSS version 28.0 (IBM Corp, Armonk, NY, USA). The study protocol was approved by the MHS Institutional Review Board.

The analysis included 33,401 patients with AA and 66,802 controls. Both groups had similar sex distributions, with 56.5% males and 43.5% females. The mean age at onset of AA was 29.9 ± 16.9 years. Among patients with AA, 87.0% were born in Israel, while 13.0% were immigrants from other countries. In the healthy group, 80.6% were born in Israel, and 19.4% were immigrants. Overall, vitiligo was diagnosed in 1.9% ($n=635$) of patients with AA and in 0.6% ($n=401$) of controls, cor-

responding to a significant threefold association (odds ratio [OR]=3.32, 95% CI [2.92–3.77], $p<0.01$).

These results demonstrate a strong association between AA and vitiligo, aligning with the existing literature and contributing valuable additional data to the field. The strengths of this study include the large and representative population involved and the precise diagnoses provided by MHS. However, it is limited by the lack of subgroup analyses, particularly regarding age and other potential comorbidities. Indeed, a meta-analysis of comorbidities associated with AA, encompassing 102 studies, identified several risk factors, with vitamin D deficiency showing the strongest association. Other associated conditions included systemic lupus erythematosus, metabolic syndrome, Hashimoto's thyroiditis, and vitiligo (OR=5.30, 95% CI [1.86–15.10]), though with substantial heterogeneity (4). Additionally, a retrospective case-control analysis from a Finnish dermatology department involving 176 patients with AA revealed that over 60% had at least 1 comorbid condition, with atopic dermatitis being the most common. In this cohort, vitiligo affected 0.6% of AA patients, ranking below atopic dermatitis and thyroid diseases as a comorbidity (5). The association between AA and vitiligo is reciprocal, as for vitiligo a meta-analysis also demonstrated higher risks of associated autoimmune and connective tissue diseases, including AA (OR=2.63, 95% CI [2.50–2.78]) (6).

Both AA and vitiligo are increasingly being treated with Janus kinase (JAK) inhibitors (7, 8). This recent drug class targets and blocks cytokine signalling mediated by the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway, thus regulating immune response and cell growth. The main dermatological indications of these drugs are inflammatory and autoimmune diseases such as psoriasis, vitiligo, atopic dermatitis, and alopecia areata, showing evidence of efficacy.

The progression and duration of AA are unpredictable and may be influenced by the presence of comorbidities. Investigating whether co-occurrence of AA and vitiligo presents a unique indication for JAK inhibitors or other emerging treatments could provide valuable insights for clinical management and therapeutic strategies.

The authors have no conflicts of interest to declare.

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