ORIGINAL ARTICLE

Alopecia Areata as a Proximal Risk Factor for the Development of Comorbid Depression: A Population-based Study

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Alopecia areata and depression tend to co-occur; however, their temporal association has not been comprehensively investigated. The aim of this study was to examine the temporal association between alopecia areata and depression. The study included only cases with a comorbid presentation of alopecia areata and depression ($n = 1,936$), extracted from the databases of the Clalit Health Services, Israel. Survival analyses were used to assess the cumulative probability of receiving alopecia areata as comorbid diagnosis in the years following depression, and vice versa, compared with the opposite trajectory. The results indicate that patients with alopecia areata had greater odds of subsequent depression within 2 years from alopecia areata diagnosis, and showed a steeper increase in cumulative probability of depression as time progressed (log-rank =336.38, $p < 0.001$), compared with the opposite trajectory. All patients with alopecia areata had comorbid depression within 10 years of alopecia areata, compared with 70% of depression patients receiving diagnoses of comorbid alopecia areata within the same time-frame.

Key words: alopecia areata; depression; comorbidity: temporal precedence.

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SIGNIFICANCE

This study found that, although depression tends to precede alopecia areata, its presentation among patients with alopecia areata occurs more rapidly than the presentation of alopecia areata following depression. Thus, alopecia areata may serve as a proximal risk factor for the development of depression, whereas depression is a more distal risk factor for future development of alopecia areata. These time-frames can point clinicians and researchers to the specific time-periods that may lead to increased risk of comorbid depression, so as to screen for potential distress during this time-period.

Alopecia areata (AA) is an autoimmune hair-loss disorder, which affects approximately 2% of the population, and is characterized by non-scarring, typically remitting, hair loss of varying degrees from the scalp and body (1). Many studies have demonstrated the psychological correlates of AA, which include anxiety (2), stress (3), and social and functional deficits (4). The disease has also been found to be highly correlated with depression (5), a psychiatric disorder characterized by lower mood, reduced energy, and functional and social withdrawal (6, 7). According to the WHO, depression is a leading cause of morbidity and mortality worldwide, and can be minimized by effective treatment (8). Studies assessing the effect of comorbid depression among patients with AA found that their co-occurrence was associated with impaired social and career-related functioning, sleep disruption, and even suicidal ideation (9, 10). Thus, the study of the mechanisms leading to this co-occurrence is of great empirical and clinical significance.

Studies attempting to delineate the trajectories leading from either AA to depression, or vice versa, have suggested bidirectional effects to account for this concurrence. It has been suggested that relapsing episodes of hair loss can provoke psychological distress through effects on self-image, subjective loss of control, and even loss of sense of self (11). On the other hand, both clinical and biological studies have demonstrated that stress, a well-recognized potentiator of depression, can independently trigger or exacerbate hair loss, largely through pro-inflammatory or neuroendocrine effects (12–15). Although these findings point to several potential causal trajectories, only a few studies have attempted to assess the temporal relation of AA and depression. In a study utilizing the National Health Insurance (NHI) database of Taiwan, Chu et al. (16) analysed 146 patients with both AA and depression, and reported that the onset of comorbid AA in patients first diagnosed with depression appeared in 54.1% of cases. However, the authors did not perform further analyses focusing on the temporal progression of the development of the second diagnosis. In a different, large-scale, retrospective population-based study in the UK, cohorts with either depression ($n = 405,339$) or AA ($n = 6,861$) were compared with respective reference cohorts to determine the risk of developing the second disorder (17). The authors reported that depression increased the risk of developing subsequent AA by 90%, whereas AA increased the risk of subsequent

depression by 34%. Nonetheless, the time between the onset of the first condition and the co-occurrence of the second condition was not evaluated.

The aim of this population-based study was to provide a detailed temporal characterization of the relationship between AA and depression. Cases of patients with comorbid AA and depression were extracted, and the time gap was calculated by extracting dates of both diagnoses. Cases were divided to belong either to AA followed by depression, or depression followed by AA. The odds of receiving the comorbid diagnosis of either AA or depression within the consecutive years following the onset of the first condition were then estimated. The study utilized the databases of the Clalit Health Services (CHS), a comprehensive data registry of the largest healthcare organization in Israel, which contains a highly validated registry of diagnoses.

MATERIALS AND METHODS

Study design

Data were extracted from the CHS database. The CHS is the largest healthcare service in Israel, covering medical care costs for the majority of the country's population: 5 million citizens in Health Ministry reports of 2018 (18). The database harbours detailed administrative, as well as medical, data from a wide range of medical settings, including clinics, hospitals, specialists and pharmacies. Automated and manual validation is routinely performed to ensure updated and authentic data. The CHS database received external validation in a previous evaluation study (19) and was previously validated for both dermatological and psychiatric diagnoses (20–22). This study was approved by the institutional review board of CHS. Informed consent was waived, as strictly non-identifiable data were used.

Study population

Data regarding diagnoses and their time of registry were extracted in April 2020, employing the International Classification of Diseases (ICD-9) for identification of medical records (23). All AA diagnoses utilized were registered by board-certified dermatologists (code 704). Depression diagnoses were included only if registered by a board-certified psychiatrist or following hospital discharge. Diagnoses included Major Depressive Disorder (code 2962, 2963, 311), Major Depressive Affective Disorder (codes 29620-29626, 29630-29626), Adjustment Reaction with Depressive Reaction (3090-3091), Depressive Type Psychosis (2980), and Neurotic Depression (3004). Socioeconomic status (SES) was obtained using the CHS index, calculated as an index score combining information from social services, and demographic variables, such as district and current address. Data extraction was performed from a database containing a total of 41,184 patients diagnosed with AA. From this database, 1,936 (4.7%) cases were identified as AA with comorbid depression diagnoses. These cases served as the sample for all reported analyses.

Statistical analysis

Demographic and clinical information was assessed with a χ^2 test for categorical variables and a Student's *t*-test for age. Cases were aggregated prior to statistical analyses to belong to either AA followed by depression, or depression followed by AA, through the dates and years of diagnoses. Cases of simultaneous presentation (within the same year) were excluded from the temporal analyses. Univariate logistic regressions were employed to assess the odds of receiving a comorbid diagnosis of either AA or depression in the years following the onset of the first condition. Estimated projections of the cumulative probability of receiving a diagnosis of either comorbid AA, or comorbid depression, were obtained using Kaplan–Meier analysis. The log-rank test was used to determine whether survival curves differed statistically between patients with AA who presented with later co-occurring depression, or individuals with depression who presented with later co-occurring AA. Statistical analysis was performed with SPSS software, version 25 (SPSS, Chicago, IL, USA).

RESULTS

A visual illustration of the distribution of comorbid cases (AA followed by depression, depression followed by AA, and simultaneous diagnosis) is shown in **Fig. 1**.

As can be seen, of the 1,936 patients with comorbid AA and depression, 1,211 (62.6%) were first diagnosed with depression and later developed AA; 591 patients (30.5%) were first diagnosed with AA and later developed depression; and 134 patients (6.9%) received the 2 diagnoses within the same year. Demographic characteristics of the 2 groups (depression with subsequent AA, AA with subsequent depression) are shown in **Table I**.

As can be seen, patients with depression and subsequent AA were older (mean ± standard deviation (SD) (52.26 ± 14.93 years) in comparison with patients with AA and subsequent depression (46.95 ± 15.53 years), $p<0.001$. Higher proportions of males were found among patients with depression and subsequent AA compared with patients with AA and subsequent depression (41.0% vs 45.9%, respectively, $p=0.05$). In addition, patients with depression and subsequent AA had a higher SES (medium-high), in comparison with patients with AA and subsequent depression (61.4% vs 56.0, $p<0.05$). Married cases accounted for 45.2% of patients with depression

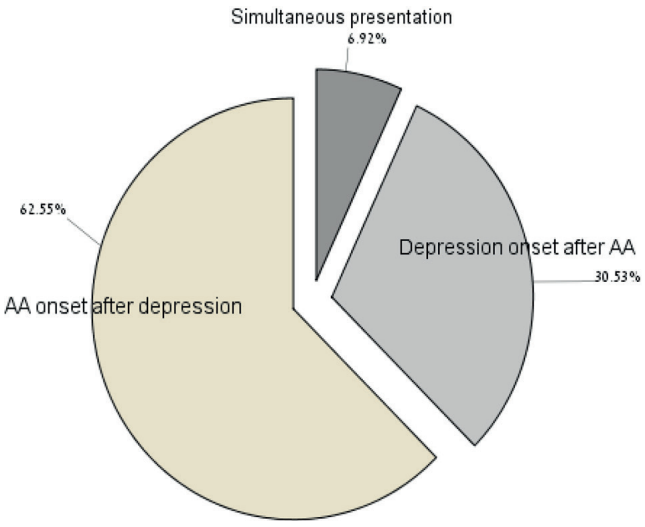

Fig. 1. Graphical illustration of prevalence of time precedence ($n=1,936$). AA: alopecia areata.

Table I. Demographic characteristics of the study population

	AA onset after depression ($n=1,211$)	Depression onset after AA ($n=591$)	Total sample	p-value
Age, years, mean (SD)	52.26 (14.93)	46.95 (15.53)	50.22 (15.40)	<0.001
Sex, male, *n* (%)	497 (41.0)	271 (45.9)	832 (43.0)	0.05
SES, *n* (%)				
Medium-high	743 (61.4)	331 (56.0)	1153 (59.6)	<0.05
Low	465 (38.4)	260 (44.0)	779 (40.2)	
Marital status (married), *n* (%)	547 (45.2)	255 (43.1)	865 (44.7)	0.42
Smoking, *n* (%)	670 (55.3)	319 (54.0)	1,064 (55.0)	0.61
Obesity, *n* (%)	333 (27.5)	144 (24.4)	506 (26.1)	0.17
BMI, kg/m^2, mean (SD)	27.04 (5.38)	26.55 (5.92)	26.82 (5.59)	0.09
Diabetes, *n* (%)	182 (15.0)	76 (12.9)	276 (14.3)	0.22
Years to comorbid diagnosis, mean (SD)	8.37 (10.9)	4.02 (2.44)	6.95 (9.34)	<0.001

AA: alopecia areata; SD: standard deviation; SES: socioeconomic status; BMI: body mass index.

and subsequent AA ($n=547$), and 44.0% of patients with AA and subsequent depression ($n=260$), with no significant differences between the groups. Smoking rates were also similar, with 670 (55.3%) and 319 (54.0%), respectively. Rates of obesity, diabetes, and mean body mass index (BMI) values were similar across groups. Finally, the time from first diagnosis was different between groups, with time for depression followed by AA being longer (8.37 ± 10.9 years) compared with time for AA followed by depression (4.02 ± 2.44 years), $p<0.001$.

The estimated cumulative probabilities of AA onset subsequent to depression or depression onset subsequent to AA are shown in **Fig. 2**.

As can be seen, survival analysis indicates that patients with AA had greater odds of developing depression within the first 2 years after the onset of AA compared with the odds of patients with depression developing AA. Moreover, patients with initial AA presented a more rapid increase in the cumulative probability of being diagnosed with depression over time (log-rank test=336.38, $p<0.001$), with all cases of comorbid depression developing within 10 years of initial AA. In contrast, the cumulative probability of being diagnosed with AA subsequent to depression manifested as a more moderate incline, with only 70% of patients with depression developing comorbid AA by the end of the first decade.

Table II presents the odds of receiving a comorbid diagnosis after initial AA or depression, at different time points since initial diagnosis. As can be seen, the odds of developing AA subsequent to depression were higher in the time-period 2–4 years after depression diagnosis, odds ratio (OR) 1.33, 95% confidence interval (95% CI) (1.00–1.77), $p<0.05$, compared with the odds of after 0–2 years. After 2–4 years, the odds of AA onset subsequent to depression increased progressively until reaching a maximum of 8 years or more since diagnosis of depression (OR 15.89, 95% CI 10.39–24.31), $p<0.05$. In contrast, the odds of depression onset after AA diagnosis were lower in the 2–4-year period following the AA diagnosis, OR 0.74 95% CI (0.56–0.99), $p<0.05$, with the odds gradually decreasing over time.

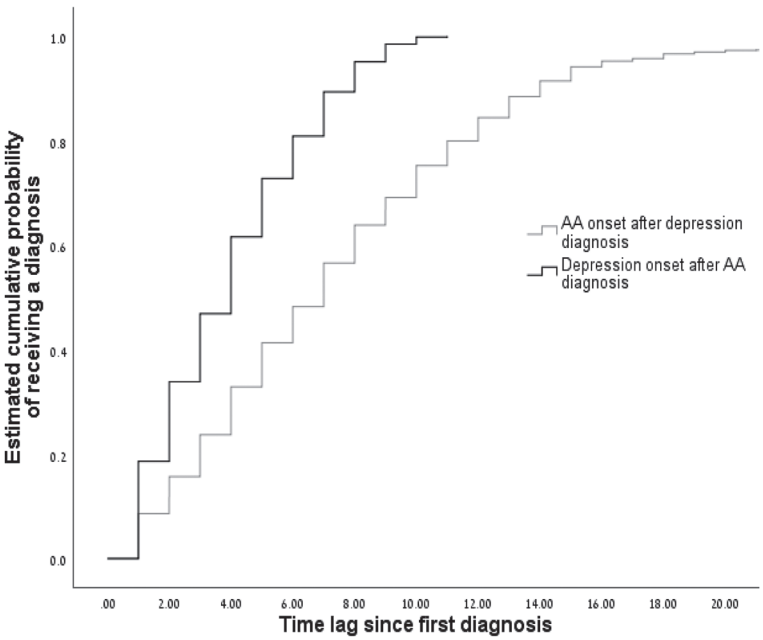

Fig. 2. Cumulative probability of receiving a diagnosis of alopecia areata (AA) after the diagnosis of depression and vice versa.

DISCUSSION

The initial examination of patients with dual diagnoses demonstrated that the majority of patients (62.55%) were first diagnosed with depression and only later with AA. However, a closer analysis of progression to second diagnosis, revealed differences in temporal patterns between the groups. Survival and regression analyses indicated that onset of depression after AA occurred at a faster rate than the onset of AA after depression, with the highest odds of depression onset manifesting within the first few years following the initial AA diagnosis. Overall, all cases of AA received a comorbid diagnosis of depression within the 10-year period after diagnosis of AA. On the other hand, the onset of comorbid AA after initial depression was far slower, and occurred more than 20 years after the initial diagnosis. Only 70% of those with initial depression showed a comorbid presentation of AA within the first decade, with odds increasing over time. These findings indicate a highly intricate temporal relationship between depression and AA. Although a bidirectional relationship between AA and depression exists, AA may manifest as a more proximal risk factor for the development of subsequent depression, whereas depression may serve as a more distal risk factor.

Previous studies assessing the nature of directional patterns of depression and AA

Table II. Multivariate logistic regression analysis of the probabilities of alopecia areata (AA) onset subsequent to depression and depression onset subsequent to AA, stratified by time since first diagnosis

Time since first diagnosis	Depression followed by AA			AA followed by depression		
	n (%)	OR (95% CI)	*p*-value	*n* (%)	OR (95% CI)	*p*-value
0–2 years	190 (15.7)	1	1	200 (33.8)	1	1
2–4 years	208 (17.2)	1.33 (1.00–1.77)	< 0.05	164 (27.7)	0.74 (0.56–0.99)	< 0.05
4–6 years	186 (15.4)	1.71 (1.26–2.33)	< 0.01	114 (19.3)	0.58 (0.42–0.79)	< 0.01
6–8 years	189 (15.6)	2.36 (1.71–3.27)	< 0.001	84 (14.2)	0.42 (0.30–0.58)	< 0.001
≥ 8 years	438 (36.2)	15.89 (10.39–24.31)	< 0.001	29 (4.9)	0.06 (0.04–0.09)	< 0.001

OR: odds ratio; 95% CI: 95% confidence interval.
Period 0–2 years served as the reference group for the multivariate analyses.

have reported similar patterns to those reported in the current study. Chu et al. (16) similarly found that, in the case of comorbidity, depression occurred earlier than AA in the majority of cases (54%). In another large-scale cohort study, Vallerand et al. (17) found that 662 individuals in the depression cohort subsequently developed AA, whereas only 513 patients in the AA cohort were subsequently diagnosed with depression. These results correspond to the earlier findings reported in this study, which indicate that 62% of the current sample was first diagnosed with depression and later developed AA. Nonetheless, as these studies did not include an analysis of the time intervals between the first and second diagnoses, they typically portray a partial picture of the pattern of temporal association.

Although Chu et al. (16) did not perform a temporal analysis in the form of a continuous follow-up from the time of the first disorder until the development of the second, the authors reported the median time interval between the first and second diagnoses within each group. Their report indicated that, although 54.1% of patients had pre-existing depression before AA, the onset of depression after having AA occurred faster in approximately 30% of cases. In a study conducted in Taiwan (24), the authors assessed the bidirectional association between AA and depression among probands and unaffected siblings compared with controls. The authors found that the risk of developing depression among patients with AA was 8.22-fold greater than controls, approximately 5 times higher than depressed patients developing AA (1.66-fold higher risk compared with controls). Although the findings of the current study suggest that comorbid cases are more frequently diagnosed with depression followed by AA, this comparison is restricted only to the cohort of comorbid cases. Thus, it is possible that issues related to the overall prevalence of the 2 conditions, the age of onset, and other aetiological factors, are responsible for this differential pattern of presentation. Interestingly, the authors found that unaffected siblings of patients with AA had a 2.55-fold risk of developing depression compared with controls, vs unaffected siblings of patients with depression with only a 1.64-fold increased risk of developing AA. These findings strengthen the idea that, while a bidirectional genetic predisposition exists, it appears to be more profound in the direction of AA predisposing to subsequent depression. These reports provide additional support for our later findings, indicating that patients may be at more immediate risk of developing depression after AA than vice versa.

The first 2 years after diagnosis of AA were found to be the most likely time-period for developing depression. Given the extensive impairment AA patients report in self-image, relationships, and career, it is plausible that depression develops as a result of the negative psychosocial effects of AA, which might manifest within the first few years after its onset. In a study of 162 patients with AA, patients stressed the loss of self-confidence, fear of socializing, poor work performance, and feeling of helplessness (25). Other studies have reported a high correlation with psychiatric diseases and even suicidal ideation (10, 26). A meta-analysis of 21 studies worldwide, representing 2,530 adult patients, showed that patients with AA experience significantly impaired health-related quality of life, especially in mental health domains, as well as concurring depression and anxiety, which further reduced quality of life (27). An alternative explanation can be found in immunological findings, which indicate high levels of type 17 and type 2 immune response cytokines, including IL-17A, IL-21, IL-23 and IL-17F and IL-33, IL-3, IL17E(IL-25), in patients with AA. This study also reported a correlation of IL-22 and IL-17E with depression, suggesting an immunological mechanism for the development of depression (28). Finally, depression has been shown to often be a chronic, recurrent condition, with many patients not fully recovering for years after onset (29). This could suggest an ongoing immune dysregulation may contribute to the late occurring AA comorbidity. Thus, the current study may support the idea of molecular pathways that are potentially involved in the pathogenesis of depression subsequent to AA. Such explanatory hypotheses require further evaluation.

This study has several strengths and limitations. The study presents a novel analysis of the temporal relationship between AA and depression, demonstrating the intricate and complex nature of the bidirectional relationship on a relatively large sample of patients with the co-occurring conditions. Clinicians should be mindful of the specific time-periods that may lead to increased risk of comorbid depression, and screen for potential distress during this time-period. Furthermore, studies indicate that patients with AA with comorbid depression tend to have exacerbations of dermatological disease, poor disease management, and increased suicidal ideation (30). The knowledge of the time interval in which probability is high for such co-occurrence may allow dermatologists to provide early intervention and prevent

further dermatological and psychological complications. Empirically, the results of the current study could serve as an infrastructure for future studies assessing the aetiology and phenomenology of depression and AA comorbidity. The analyses of differences in demographic characteristics indicated that there are some differences between individuals who develop depression followed by subsequent AA, and individuals who develop AA followed by subsequent depression. Future studies should explore potential pathways leading to these differences. Several limitations should also be acknowledged. Specific parameters such as subtype, severity, or treatment of AA and depression were not assessed in this study. Further studies should comprehensively elucidate the pathogenesis underlying the disorders while testing the association within the different subtypes. As cultural factors might be associated with the results reported in this study, future studies should further assess the cross-cultural validity of the reported findings. Taken together, the results prompt improved clinical interventions and provide further grounds for additional investigative research.

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