Bidirectional association between alopecia areata and major depressive disorder among probands and unaffected siblings: A nationwide population-based study

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Background: Alopecia areata (AA) has long been associated with major depressive disorder (MDD). However, most evidence to date has derived from cross-sectional or case-control studies.

Objective: To investigate the bidirectional association between AA and MDD among probands and unaffected siblings.

Methods: Study participants were recruited from the National Health Insurance Research Database in Taiwan. We included 2123 probands with AA, 2298 unaffected siblings, and 9192 matched controls to assess the risk of MDD. We included 16,543 probands with MDD, 17,352 unaffected siblings, and 69,408 matched controls to assess the risk of AA. The Breslow-Cox model was used to calculate the adjusted relative risk.

Results: Compared with controls, AA probands and unaffected siblings had adjusted relative risks of 8.22 (95% confidence interval [CI], 6.41-10.54) and 2.55 (95% CI, 1.91-3.40), respectively, for MDD. MDD probands and unaffected siblings had adjusted relative risks for AA of 1.66 (95% CI, 1.24-2.22) and 1.64 (95% CI, 1.27-2.12), respectively.

Limitation: The National Health Insurance Research Database lacked information on disease severity, body mass index, smoking habit, alcohol consumption, and stressful life events.

Conclusion: Our study demonstrated a bidirectional association between AA and MDD among probands and unaffected siblings, thus suggesting shared familial mechanisms underlying AA and MDD. (J Am Acad Dermatol 2020;82:1131-7.)

Key words: alopecia areata; cohort study; epidemiology; major depressive disorder; siblings; Taiwan's National Health Insurance Research Database.

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Alopecia areata (AA) is a common cause of noncicatricial alopecia, with an estimated lifetime risk of 1.7%.[1-3] It is typically characterized by well-circumscribed patches of hair loss on the scalp. AA may progress to a complete loss of hair on the scalp (alopecia totalis) or even on the entire body (alopecia universalis).[4] Although AA is not painful or life threatening, its cosmetic effects impose a significant psychosocial burden on those affected. Many therapeutic modalities have been used to treat AA; however, successful management of extensive AA remains challenging.[5,6]

While the exact pathogenesis of AA is still poorly understood, current evidence suggests that the collapse of immune privilege in hair follicles leads to the development of AA.[7] Psychological stress has long been suspected to be involved in the pathogenesis of AA.[8] Previous studies have shown a significant association between AA and major depressive disorder (MDD), but the interpretation of these findings is hampered by several limitations, including small sample size, cross-sectional or case-control design, and self-report of depressive symptoms rather than systematic diagnostic assessments by psychiatrists.[9,10] Therefore, whether MDD leads to AA, or vice versa, remains unclear.

A recent population-based cohort study observed a bidirectional association between AA and MDD, suggesting a shared pathogenesis underlying both diseases.[11] Previous studies have demonstrated familial aggregation of AA and MDD, suggesting familial mechanisms underlying the 2 conditions.[12,13] Siblings of AA probands may share some risk factors with the probands, making them more susceptible to MDD. Likewise, siblings of MDD probands may have an increased risk for AA. However, the association between AA and MDD has never been examined among unaffected siblings of probands with either of the 2 diseases. Investigating these associations will provide important information for clinical assessment, prevention, treatment, and etiologic research of these diseases. This current nationwide population-based study examined the bidirectional association between AA and MDD among probands with either of the 2 diseases and their unaffected siblings.

CAPSULE SUMMARY

- Alopecia areata has been associated with major depressive disorder, while the temporal relationship remains uncertain.
- Compared with controls, alopecia areata probands and unaffected siblings have an increased risk of major depressive disorder, and vice versa. This bidirectional association suggests that alopecia areata and major depressive disorder share familial risk factors.

METHODS

Data source

The Taiwan National Health Insurance (NHI) program was established in 1995 and covered approximately 99.6% of all Taiwanese residents at the end of 2010. The NHI Research Database (NHIRD) contains comprehensive information about the insured individuals, including demographic details (date of birth, sex, and residential location) and claims data (outpatient and inpatient care, medical diagnoses, prescriptions, and operations). The NHIRD has been widely used in epidemiologic studies in Taiwan.[14-18] To protect individual privacy, a unique identification number is assigned to each beneficiary and enciphered before the data are released for scientific purposes. Our study used the unique identification number to link all of the health care records of each beneficiary.

Family relationships were established by analyzing the birth certificate and the dependent, insurance, and employment status. The methods of genealogy reconstruction using recorded family relationships in the NHIRD have been described previously.[15,19-21] The diagnostic codes used were based on the *International Classification of Diseases, 9th Revision, Clinical Modification*. This study was approved by the Taipei Veterans General Hospital Institutional Review Board (2018-07-016AC).

Study population, exposure, and outcome

Risk of MDD. A bidirectional cohort study design was used to investigate the longitudinal association between AA and MDD. The study cohort included individuals born before 1990 from the NHIRD. In study 1, we included individuals with AA and their unaffected siblings in the cohort. The primary outcome assessed was new-onset MDD. AA was identified by *International Classification of Diseases, 9th Revision, Clinical Modification* code 704.01, and MDD was identified by codes 296.2 and 296.3. The diagnoses of AA and MDD were made at least 3 times by board-certified dermatologists and psychiatrists, respectively. To identify the incidence of MDD, we excluded individuals with a previous MDD diagnosis, invalid insurance status, unknown

Abbreviations used:

CI: confidence interval
MDD: Major Depressive Disorder
NHIRD: National Health Insurance Research Database

sex status, or unknown covariates. Participants and controls were monitored from January 1, 1996, until a diagnosis of MDD, death, or December 31, 2011.

Risk of AA. The cohort in study 2 included individuals with MDD and their unaffected siblings. The primary outcome assessed was new-onset AA. Likewise, to identify incident AA, we excluded those with a previous AA diagnosis, invalid insurance status, unknown sex status, or unknown covariates. Participants and controls were monitored from January 1, 1996, until a diagnosis of AA, death, or December 31, 2011.

Matched controls

For each unaffected sibling of probands with AA/MDD, 4 matched controls were randomly selected from the NHIRD Longitudinal Health Insurance Database. These individuals were matched for age, sex, monthly income, and residence. Monthly income was classified into \$0-\$500, \$501-\$800, and ≥\$801 (United States dollars). Residence was classified into 5 levels of urbanization, with level 1 indicating the most urbanized area and level 5 the least urbanized area. Monthly income and urbanization levels were used to represent socioeconomic status. The Charlson Comorbidity Index was used for clinical prognosis and comorbidity adjustment.

Statistical analysis

For between-group comparisons, the *t* test or Wilcoxon rank sum test was used for continuous variables, and the Pearson test was used for categorical variables. The standardized mean difference was used to compare baseline characteristics between study groups. Given an equal follow-up time for all participants in each matched set, the Breslow-Cox proportional hazards model was used to calculate the relative risks of AA and MDD between study participants and controls.[22-24] Adjusted relative risks were computed after controlling for potential confounders, including age, sex, monthly income, and urbanization. A 2-sided *P* value of <.05 was considered as statistically significant. Data analyses were

Table I. Demographic data of probands with alopecia areata (*AA*), unaffected siblings, and controls

Variable*	AA probands (n = 2123)	Unaffected siblings (n = 2298)	Controls (n = 9192)	SMD†	SMD‡	SMD§
Age, median (range), y	31.3 (7.5-69.5)	31.4 (21.0-75.0)	31.3 (20.1-75.6)	−0.0434	−0.0432	0.0000
Sex				0.0502	0.0501	0.0000
Male	951 (44.8)	1086 (47.3)	4344 (47.3)			
Female	1172 (55.2)	1212 (52.7)	4848 (52.7)			
Monthly income in USD				−0.0468	−0.0468	0.0000
0-500	649 (30.6)	667 (29.0)	2668 (29.0)			
501-800	713 (33.6)	756 (32.9)	3024 (32.9)			
≥801	761 (35.9)	875 (38.1)	3500 (38.1)			
Residence				0.0237	0.0239	0.0000
1 (urbanized)	599 (28.2)	650 (28.3)	2600 (28.3)			
2	766 (36.1)	822 (35.8)	3288 (35.8)			
3	261 (12.3)	329 (14.3)	1316 (14.3)			
4	188 (8.9)	197 (8.6)	788 (8.6)			
5 (rural)	309 (14.6)	300 (13.1)	1200 (13.1)			
Charlson Comorbidity Index				−0.2129	−0.1043	0.1149
0	1475 (69.5)	1253 (54.5)	5542 (60.3)			
1	376 (17.7)	671 (29.2)	2451 (26.7)			
2	180 (8.5)	259 (11.3)	827 (9.0)			
3	53 (2.5)	72 (3.1)	228 (2.5)			
≥4	39 (1.8)	43 (1.9)	144 (1.6)			

SMD, Standardized mean difference; *USD*, United States dollars.
*Data are presented as the number (%), unless indicate otherwise.
†Probands vs unaffected siblings.
‡Probands vs controls.
§Unaffected siblings vs controls.

Table II. Multivariable analysis for risk of major depressive disorder (*MDD*) and alopecia areata (*AA*) among probands and unaffected siblings

	Risk of MDD		Risk of AA	
Variable	**Adjusted RR* (95% CI)**	***P***	**Adjusted RR* (95% CI)**	***P***
AA proband or trait		<.0001		<.0001
AA probands vs control	8.22 (6.41-10.54)	<.0001	1.66 (1.24-2.22)	.0006
Unaffected siblings vs control	2.55 (1.91-3.40)	<.0001	1.64 (1.27-2.12)	.0002
Age	0.98 (0.93-1.03)	.3516	1.02 (0.96-1.08)	.5126
Sex, male vs female	0.75 (0.57-0.99)	.0394	0.63 (0.44-0.89)	.0088
Residence†		.0626		.9917
2 vs 1	0.83 (0.55-1.26)	.3882	1.02 (0.62-1.67)	.9452
3 vs 1	1.19 (0.63-2.24)	.5965	0.89 (0.51-1.56)	.6860
4 vs 1	0.75 (0.40-1.41)	.3769	0.95 (0.42-2.16)	.9061
5 vs 1	0.48 (0.28-0.81)	.0064	0.92 (0.49-1.72)	.7857
Monthly income in USD		<.0001		.0648
501-800 vs 0-500	0.60 (0.41-0.88)	.0095	1.79 (1.09-2.94)	.0218
≥801 vs 0-500	0.39 (0.25-0.59)	<.0001	1.32 (0.75-2.31)	.3367
Charlson Comorbidity Index		<.0001		.0333
1 vs 0	2.45 (1.83-3.28)	<.0001	1.12 (0.86-1.45)	.3943
2 vs 0	3.96 (2.75-5.69)	<.0001	1.21 (0.80-1.82)	.3667
3 vs 0	3.91 (2.11-7.28)	<.0001	2.32 (1.29-4.19)	.0051
≥ 4 vs 0	7.32 (4.07-13.17)	<.0001	0.42 (0.13-1.32)	.1367

CI, Confidence interval; *RR*, relative risk; *USD*, United States dollars.
*Adjusted for age, sex, monthly income, urbanization, and Charlson Comorbidity Index score.
†Residence: 1 indicates urbanized; 5 indicates rural.

performed using SAS 9.4 software (SAS Institute Inc, Cary, NC).

RESULTS

Risk of MDD

The study included 2123 probands with AA, 2,298 unaffected siblings, and 9192 controls. Age, sex, monthly income, and residence were matched and did not have between-group differences among unaffected siblings and controls (Table I). Overall, MDD developed in 7.87% of the AA probands (n = 167) and in 2.79% of the unaffected siblings (n = 64) compared with 1.02% of the controls (n = 94). After adjustment for potential confounders (age, sex, monthly income, urbanization, and Charlson Comorbidity Index score), AA probands and unaffected siblings had 8.22-fold and 2.55-fold increased risk for MDD, respectively (Table II). The association between AA and MDD risk remained significant when we stratified the participants by sex. Other independent risk factors for MDD were female sex, urban residence (urbanization level 1 vs 5), low monthly income, and high Charlson Comorbidity Index score.

Risk of AA

The study included 16,543 probands with MDD, 17,352 unaffected siblings, and 69,408 controls (Table III). During the study period, AA developed in 0.45% of the MDD probands (n = 75) and in 0.37% of the unaffected siblings (n = 65) compared with 0.23% of the controls (n = 160). After adjusting for potential confounders (age, sex, monthly income, urbanization, and Charlson Comorbidity Index score), MDD probands and unaffected siblings had 1.66-fold and 1.64-fold increased risk for AA, respectively. After the stratification of participants by sex, the association between MDD and AA risk remained significant for both sexes.

DISCUSSION

This nationwide population-based cohort study observed a bidirectional association between AA and MDD. Evidence of a correlation between AA and MDD has been reported; however, because of limited evidence from prospective studies, the temporality in these associations remains uncertain. One cohort study showed that MDD increased the risk of developing AA (hazard ratio, 1.90; 95% confidence, 1.67-2.15; $P < .001$), and AA increased the risk of developing MDD (hazard ratio, 1.34; 95% confidence interval, 1.23-1.46; $P < .001$).[11] In agreement with the study by Vallerand et al,[11] our study confirmed the bidirectional association between AA and MDD among probands with either of the 2 diseases.

In addition, our study strengthens and extends existing evidence by demonstrating that unaffected siblings of probands with AA/MDD are at increased

Table III. Demographic data of probands with major depressive disorder (*MDD*), unaffected siblings, and controls

Variable*	MDD probands (n = 16,543)	Unaffected siblings (n = 17,352)	Controls (n = 69,408)	SMD†	SMD‡	SMD§
Age, median (range), y	31.4 (11.1-85.3)	31.1 (21.0-82.2)	31.1 (20.0-82.8)	0.0494	0.0492	0.0000
Sex				0.2916	0.2895	0.0000
Male	6377 (38.6)	9184 (52.9)	36,736 (52.9)			
Female	10,166 (61.5)	8168 (47.1)	32,672 (47.1)			
Monthly income (USD)				−0.2323	−0.2309	0.0000
0-500	6204 (37.5)	5070 (29.2)	20,280 (29.2)			
501-800	5878 (35.5)	5798 (33.4)	23,192 (33.4)			
≥801	4461 (27.0)	6484 (37.4)	25,936 (37.4)			
Residence				0.0229	0.0230	0.0000
1 (urbanized)	4613 (27.9)	4956 (28.6)	19,824 (28.6)			
2	5703 (34.5)	6080 (35.0)	24,320 (35.0)			
3	2314 (14.0)	2354 (13.6)	9416 (13.6)			
4	1620 (9.8)	1622 (9.4)	6488 (9.4)			
5 (rural)	2293 (13.9)	2340 (13.5)	9360 (13.5)			
Charlson Comorbidity Index				0.3699	0.5073	0.0984
0	7129 (43.1)	10,322 (59.5)	44,637 (64.3)			
1	5499 (33.2)	4920 (28.4)	17,750 (25.6)			
2	2490 (15.1)	1471 (8.5)	4980 (7.2)			
3	808 (4.9)	406 (2.3)	1328 (1.9)			
≥4	617 (3.7)	233 (1.3)	713 (1.0)			

SMD, Standardized mean difference; USD, United States dollars.
*Data are presented as the number (%), unless indicated otherwise.
†Probands vs unaffected siblings.
‡Probands vs controls.
§Unaffected siblings vs controls.

risks for MDD/AA, which, to our knowledge, has not been previously reported. Further, the increased risks of AA/MDD were consistent with individuals' association with the disease, with the highest adjusted relative risks of AA/MDD among probands, followed by unaffected siblings and controls. Our analyses showed that the magnitude of the association between AA and MDD appeared to be stronger in the direction from AA to MDD than from MDD to AA among probands with AA/MDD. These results are in contrast with those reported by Vallerand et al.[11]

Further research is needed to elucidate the mechanisms underlying these findings. The current study found the risk for developing AA/MDD was increased in female probands and unaffected siblings compared with their male counterparts. Our findings are in agreement with those reported in previous studies, which suggested that women were at greater risk of psychiatric comorbidities compared with men.[25] Prior studies showed that women experience greater feelings of loss and report more negative thoughts and emotions than men.[26] However, the exact cause of this sex-based difference in the bidirectional association between AA and MDD is unclear. Further studies are needed to elucidate the underlying mechanism.

Although the shared pathogenesis underlying AA and MDD remains elusive, some hypotheses may account for this bidirectional association: (1) AA induces MDD, (2) AA is the consequence of MDD, or (3) AA and MDD have shared pathogenesis. First, hair loss has a negative impact on body image, self-esteem, and self-confidence, which could induce enormous emotional suffering and social isolation, putting an individual at a high risk of developing depression and anxiety.[27,28]

Second, psychological stress accompanied by MDD has been suggested to play an important role in the pathogenesis of AA. In fact, AA was regarded as a well-known example of psychosomatic diseases in the past.[25] Current evidence indicates that AA is an autoimmune disease caused by collapse of the immune privilege of the hair follicle. Acute stress triggers the hair follicle equivalent of the hypothalamic-pituitary-adrenal (HPA) axis and results in the increased secretion of corticotropin-releasing hormone (CRH), which stimulates mast cell production and degranulation in the skin. Activation of mast cells leads to release of a broad

array of mediators, including tumor necrosis factor-α, interleukin (IL) 6, and IL-1. The resulting neurogenic inflammation collapses the immune privilege of hair follicles and induces premature destruction of the follicle.[29]

Third, the association between AA and MDD may be explained by shared pathophysiologic mechanisms, including genetic background and common immunologic pathways. A genetic predisposition for AA has been suggested by studies reporting familial aggregation, twin studies, and genome-wide association studies.[12,30,31] There is evidence that AA and MDD share some common genetic risk factors. For example, macrophage migration inhibitory factor, which codes for a cytokine involved in cell-mediated immunity, immunoregulation, and inflammation,[32] has been associated with both AA and MDD. Macrophage migration inhibitory factor shows polymorphisms at its promoter level, which are associated with extensive forms of AA, especially with an early onset of the disease.[33] In addition, macrophage migration inhibitory factor levels have been found to be elevated in patients who are depressed patients and are strong predictors of treatment response to antidepressants.[34,35]

The possibility of sharing vulnerability genes in probands with AA/MDD and unaffected siblings may explain the observed association of the 2 conditions. The bidirectional association between AA and MDD can also be partially explained by immune dysregulation, which has been reportedly involved in the pathogenesis of both diseases. Serum levels of IL-6, tumor necrosis factor-α, IL-17A, IL-21, IL-22, and IL-23 have been found to be elevated in patients with AA, which is suggestive of the functional role of these cytokines in the pathogenesis of AA.[36-38]

In recent years, depression has been shown to include an inflammatory component that may share some of the same mediators seen in AA, such as IL-6 and tumor necrosis factor-α.[39] Proinflammatory cytokines have been shown to induce stress-reactive neuroendocrine and central neurotransmitter changes reminiscent of those in depression, and can contribute directly to the development of depressive symptoms.[40] A recent study showed that patients with AA have increased serum levels of the type 2 cytokines IL-33, IL-31 and IL-17E, in addition to the type 17 cytokines.[41] Among these cytokines, levels of IL17E/25 and IL-22 positively predict the depression score. These findings suggested the role of peripheral inflammation in the pathogenesis of AA and MDD and may explain the possible link between the 2 conditions.

To our knowledge, this is the first study to investigate the bidirectional association between AA and MDD among unaffected siblings of probands with AA and MDD. The present study adds to the existing body of knowledge on the direction and strength of the association between AA and MDD. The strengths of this study include a cohort study design with a large sample size and reliable diagnosis made by corresponding specialists.

The study has some limitations, however. First, the incidence of AA and MDD might be underestimated because only those who sought consultation and treatment were included in the study.

Second, the NHIRD lacks some important confounding factors, including disease severity, body mass index, smoking habit, alcohol consumption, and stressful life events.

Third, the possibility of misclassification of diagnoses may exist. However, AA and MDD were diagnosed by board-certified dermatologists and psychiatrists, respectively, thus yielding a better diagnostic validity relative to the self-reported questionnaire.

Finally, because almost all our participants were Taiwanese, the external validity of our findings remains uncertain. The lifetime prevalence of MDD varies widely across different cultures, ranging from 1.1% in Taiwan to 19% in Beirut.[42,43] Taiwan has the lowest prevalence of MDD, and only one-third of Taiwanese individuals with MDD sought help despite having twice the number of lost workdays compared with the United States population.[44] These epidemiologic differences may potentially limit the generalizability of our results.

CONCLUSION

A bidirectional association between AA and MDD was observed among probands and unaffected siblings in this nationwide population-based study. Further studies are needed to elucidate the common familial risk factors for AA and MDD.

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