SHORT COMMUNICATION

Large-scale Retrospective Cohort Study of Psychological Stress in Patients with Alopecia Areata According to the Frequency of Intralosomal Steroid Injection

Shinwon HWANG1, Jaeyong SHIN2, Tae-Gyun KIM3, Do-Young KIM4 and Sang Ho OH1*

1Department of Dermatology, Severance Hospital, Cutaneous Biology Research Institute, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 03722, and 2Institute of Health Services Research, Department of Preventive Medicine, Graduate School of Public Health, Yonsei University, Seoul, Korea. E-mail: oddung93@yuhs.ac

#These authors contributed equally to this study.

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Alopecia areata (AA) is a non-scarring alopecia resulting from an immune response against hair follicles. It occurs equally in both sexes and can affect every age group. AA is a chronic disease that can negatively affect a patient’s mental health due to its relapsing nature and effect on appearance. Previous cross-sectional, case-control studies have demonstrated a relationship between AA and psychological stress (1–5). Among multiple therapeutic approaches, intralosomal injection (ILI) of corticosteroids is most widely used for treating alopecic patches of AA, but this invasive procedure usually reflects disease severity and chronicity and is accompanied by painful discomfort.

There is currently a lack of evidence from a large-scale population-based cohort study to directly examine the presence of psychological stress in patients with AA according to the invasive therapeutic modalities used. In this study, psychiatric appointments and the burden of AA were analysed in patients with AA using Korea National Health Insurance Cohort Data (NHICD) from 2002 to 2013. In addition, the study evaluated the association between psychiatric appointments and other factors, such as type of AA and treatment modalities.

MATERIAL AND METHODS

From a cohort of subjects younger than 20 years, participants who had been newly diagnosed with AA during the study period were included as the AA group, and those who had never been diagnosed with AA during the same period were included as the control group. Since the study aimed to explore only those patients with new onset of AA, subjects with a history of AA and psychiatric appointments were excluded. The adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for visits to psychiatrists by type of disease and treatment modality were calculated using Cox proportional-hazard regression (see Appendix S1 for details).

RESULTS

This study included 370,019 subjects, including 4,707 patients with AA (1.3%) and 23,943 patients who had visited the psychiatric clinic at least once during the follow-up period (Table S1). The ratio of patients visiting a psychiatric clinic was approximately 1.6 times higher in patients with AA than in the non-AA group. Patients with AA had higher rate of psychiatric visits compared with controls (2,862.5 vs. 853.7 cases/100,000 person-years). The demographic findings of enrolled participants were investigated based on psychiatric visits (Table S1). The multivariate analyses of all patients were analysed with basic demographic data, including age, sex, income, type of disease and treatment modality. The tendency for visits to psychiatrists was significantly higher in patients with AA compared with the control group (HR 1.64, 95% CI 1.45–1.86) (Table S1). Moreover, compared with non-AA controls, the adjusted HRs for psychiatric visits were significantly increased according to the number of ILI treatments (Table I, ILI=1 vs. ILI=2 vs. ILI≥3; HR 1.54, 95% CI 1.09–2.03 vs. HR=2.09, 95% CI 1.31–2.02 vs. HR 1.57, 95% CI 1.22–2.03, respectively). Patients with alopecia totalis or universalis showed an increased adjusted HR for psychiatric clinic visits compared with patients with localized AA; however, this was not statistically significant (HR 1.41, 95% CI 0.90–2.20). The psychiatric visit risk for patients who used oral steroids did not differ from that of control groups (HR 1.08, 95% CI 0.76–1.53).

DISCUSSION

Hair is an important part of our appearance, and hair loss can drastically affect self-esteem and social relationships. A positive correlation between AA and psychiatric appointments has been confirmed through Minnesota Multiphasic Personality Inventory, surveys and questionnaires (6–8). However, most of these studies

Table I. Adjusted hazard ratios (HR) for outpatient visits to psychiatrists by type of disease and treatment modality

<table>
<thead>
<tr>
<th>Disease/Treatment</th>
<th>HR (95% CI)</th>
<th>p-value</th>
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<tr>
<td>Alopecia areata</td>
<td></td>
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<tr>
<td>Localized</td>
<td>1.00</td>
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<tr>
<td>Totalis or universalis</td>
<td>1.41 (0.90–2.20)</td>
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<td>Oral steroids</td>
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<td>No</td>
<td>1.00</td>
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<td>Yes</td>
<td>1.08</td>
<td>0.76–1.53</td>
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<tr>
<td>Intralosomal steroid injection</td>
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<td>No alopecia areata</td>
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<tr>
<td>0</td>
<td>1.663</td>
<td>1.372–2.016</td>
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<tr>
<td>1</td>
<td>1.540</td>
<td>1.131–2.098</td>
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<tr>
<td>2</td>
<td>2.089</td>
<td>1.464–2.979</td>
</tr>
<tr>
<td>3 or more</td>
<td>1.573</td>
<td>1.221–2.028</td>
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</tbody>
</table>

CI: confidence interval.

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were case series with a small sample size. To the best of our knowledge, this study was the first longitudinal cohort study, using a large sample size examining the relationship between AA and psychiatric appointments. Our study showed that patients with AA had significantly higher risk for visits to psychiatric clinics compared with the control group, and even higher hazards for visits to psychiatric clinics were observed as the number of ILI increased. The selection of ILI as a treatment option for AA and the frequencies of ILI could reflect the disease severity of AA because the use of topical steroid alone or observational follow-up is more common in mild cases of AA. On the other hand, there could be some personality or psychopathological factors that influence patients’ decisions to accept doctors’ proposal to undergo invasive and potentially painful ILI procedure in AA. Thus, a medical history of ILI might be a “red flag” for risk of mental health problems in patients with AA. However, it is possible that pain during ILI might exacerbate psychological stress in patients with AA, considering that mental health appointments in patients with AA increased with increased number of ILI. However, further research is needed into the relationship between psychological stress and the response and pain to therapy.

The present study has several limitations. Firstly, psychiatric appointments do not strictly imply that the cause of psychological stress is AA. Secondly, initial cohort population only included subjects younger than 20 years, because we wanted to check the psychological stress due to AA at ages when social stress is relatively lacking, which may have led to age selection bias. Nevertheless, these data might represent the status of psychological stress among adolescent patients with AA and further study is needed to directly compare psychological stress between adolescent and adult patients with AA.

In conclusion, this study suggests that AA is closely associated with psychological stress and ILI, a treatment option for AA can be associated with increase in psychological stress because ILI can mirror the disease severity of AA and may result in psychological stress caused by painful procedures. Therefore, dermatologists should pay close attention to psychological stress in patients with AA who receive multiple ILI treatments and consider them for early referral to psychiatrists.

ACKNOWLEDGEMENTS
IRB approval status: reviewed and approved by the Graduate School of Public Health at Yonsei University (IRB approval number: 2-1040939-AB-N-01-2014-239).

The authors have no conflicts of interest to declare.

REFERENCES
Appendix S1.

SUPPLEMENTARY MATERIALS AND METHODS

Data
We analysed the Korea National Health Insurance Cohort Data (NHICD), which includes information about approximately 1 million patients. This information was obtained from a random sample stratified according to age, sex, region, health insurance type, income level, and individual total medical costs in 2002. The participants were reassessed and followed until 2013. NHICD includes age, sex, type of insurance, diagnoses according to the International Classification of Disease (ICD-10), medical costs claimed, prescription drugs, and medical history. The Institutional Review Board (IRB) of the Graduate School of Public Health at Yonsei University approved the use of this data and the study design (IRB approval number: 2-1040939-AB-N-01-2014-239).

Participants
On 31 December 2002, a total of 1,025,340 NHICD participants were selected for the present study. From this initial population, a cohort of subjects younger than 20 years who had been newly diagnosed with AA (ICD-10 code: L63) was chosen for the present analysis, based on the natural history of AA. To improve diagnostic accuracy and reduce the study bias, AA, which was only the main diagnosis of each patient, not any comorbidities observed during outpatient visits to medical specialists, including dermatologists and paediatricians, was included. Because the present study aimed to assess only new cases of AA, subjects with a history of AA from 2002 to 2004 were not included. Furthermore, participants who had been diagnosed with a psychiatric disorder prior to diagnosis of AA or prior to 2004 were also excluded. Then we defined patients with AA, who had been newly diagnosed with AA (ICD-10 code: L63). The control group was defined as participants who had never been diagnosed as AA during the follow-up.

A total of 370,019 participants were enrolled in this study, including 4,707 patients with AA.

Covariates
Multiple demographic characteristics were assessed, including age, sex, and area of residence. Socioeconomic characteristics, such as income level and type of medical insurance, were also assessed, and the NHI premium was used as a proxy for measuring exact income, including earnings and capital gains. The income deciles of the NHI members were categorized into the following 4 groups: low (first and second deciles), low–middle (third to fifth deciles), high–middle (sixth to eighth deciles), and high (ninth and tenth deciles).

Severity of AA
The severity of AA was measured by the affected area of AA or the number of intralesional injection (ILI). For patients with more areas, physicians usually enter a diagnosis code with alopecia totalis (L63.0) or alopecia universalis (L63.1). Thus, we consider that the main illness code for alopecia totalis or alopecia universalis is a proxy for AA severity.

We also consider that the number of invasive treatments is a proxy for AA severity. ILI is one of the standard treatments for AA. If topical steroid does not lead to any improvement, consecutive ILI is strongly suggested. This may also make patients with AA uncomfortable due to substantial pain. When we consider that the participants are all aged under 20 years, this invasive treatment should be used only when AA is not controlled well if ILIs are performed repetitively.

Outcome measures
The primary outcome measurement was defined as an outpatient visit to a psychiatrist. The evaluated psychiatric disorders included mood disorder (F30–39), neurotic, stress-related and somatization disorder (F40–49), personality disorder and behaviour and emotional disorder (F–60–69, F90–98) occurring in childhood and adolescence.

Statistical analysis
The demographic characteristics of patients with AA were assessed at baseline. Continuous variables were expressed as means, standard deviations (SDs), or medians and were compared using Student’s t-tests or Kruskal–Wallis tests. Baseline categorical variables were expressed as numbers and percentages and were compared using a χ² test. In addition, the adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) for visits to a psychiatrist were estimated by applying a Cox proportional-hazard regression model. Model fitting was performed using the PHREG command in SAS version 9.3 (SAS Institute Inc.; Cary, NC, USA).
### Table SII. Demographic findings of participants in this study according to psychiatric visits

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>Controls n (%)</th>
<th>Patients with AA n (%)</th>
<th>Total n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>190,429 (52.1)</td>
<td>2,498 (53.1)</td>
<td>192,927</td>
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<tr>
<td>Female</td>
<td>174,883 (47.9)</td>
<td>2,209 (46.9)</td>
<td>177,092</td>
</tr>
<tr>
<td>Enrolled age*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 years</td>
<td>108,015 (29.6)</td>
<td>495 (10.5)</td>
<td>108,510</td>
</tr>
<tr>
<td>1–5 years</td>
<td>50,370 (13.8)</td>
<td>592 (12.6)</td>
<td>50,962</td>
</tr>
<tr>
<td>6–10 years</td>
<td>71,813 (19.7)</td>
<td>829 (17.6)</td>
<td>72,642</td>
</tr>
<tr>
<td>10–14 years</td>
<td>68,367 (18.7)</td>
<td>1,148 (24.4)</td>
<td>69,515</td>
</tr>
<tr>
<td>15–20 years</td>
<td>66,747 (18.3)</td>
<td>1,643 (34.9)</td>
<td>68,390</td>
</tr>
<tr>
<td>Residential area</td>
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<tr>
<td>Rural</td>
<td>112,433 (30.8)</td>
<td>1,474 (31.3)</td>
<td>113,907</td>
</tr>
<tr>
<td>Urban</td>
<td>252,879 (69.2)</td>
<td>3,233 (68.7)</td>
<td>256,112</td>
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<td>Type of insurance**</td>
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<tr>
<td>Employee</td>
<td>159,439 (43.6)</td>
<td>2,314 (49.2)</td>
<td>161,753</td>
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<tr>
<td>Self-employed</td>
<td>196,539 (53.8)</td>
<td>2,256 (48.1)</td>
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</tr>
<tr>
<td>Medical aid</td>
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<td>127 (2.7)</td>
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<td>Income level</td>
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<tr>
<td>Low</td>
<td>37,295 (10.2)</td>
<td>513 (10.9)</td>
<td>37,808</td>
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<tr>
<td>Low–middle</td>
<td>83,211 (22.8)</td>
<td>1,064 (22.6)</td>
<td>84,275</td>
</tr>
<tr>
<td>Middle–high</td>
<td>148,602 (40.7)</td>
<td>1,685 (35.8)</td>
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<tr>
<td>High</td>
<td>96,204 (26.3)</td>
<td>1,445 (30.7)</td>
<td>97,649</td>
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<tr>
<td>Psychiatric disorder</td>
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<tr>
<td>No</td>
<td>341,852 (93.6)</td>
<td>4,224 (89.7)</td>
<td>346,076</td>
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<tr>
<td>Yes</td>
<td>23,460 (6.4)</td>
<td>483 (10.3)</td>
<td>23,943</td>
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<table>
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<tr>
<th>Rate 95% CI</th>
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<tr>
<td>Psychiatric disorder rate</td>
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<tr>
<td>(cases/100,000 person-years)</td>
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<td>853.7 (842.8–864.7)</td>
<td>2,862.5 (2,641.7–866.0)</td>
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<tr>
<td>Total</td>
<td>365,312</td>
<td>4,707</td>
</tr>
<tr>
<td>100.0</td>
<td>370,019</td>
<td></td>
</tr>
</tbody>
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*Age when enrolled in this cohort study. **In Korea, national health insurance service is being applied and type of insurance of participants was decided by insurance of participants’ parents until participants get their jobs.

CI: confidence interval.

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### Table SIII. Adjusted hazard ratios (HR) for outpatient visits to psychiatrists according to baseline characteristics

<table>
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<th>Demographic characteristics</th>
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<td>Sex</td>
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<tr>
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<td>15–20 years</td>
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<td>1.64</td>
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CI: confidence interval.

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### Table SI. Demographic findings of participants in this cohort

<table>
<thead>
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<tbody>
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CI: confidence interval.

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Rate 95% CI: number of psychiatric disorder cases per 100,000 person-years.