Clinical Characteristics and HLA Alleles of a Family With Simultaneously Occurring Alopecia Areata

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Alopecia areata (AA) is a T-cell-mediated autoimmune disease resulting in partial or total noncicatricial hair loss. HLA class II antigens are the most important markers that constitute genetic predisposition to AA. Various life events and intense psychological stress may play an important role in triggering AA attacks. We report an unusual case series of 4 family members who had simultaneously occurring active AA lesions. Our aim was to evaluate the clinical and psychiatric features of 4 cases of active AA lesions occurring simultaneously in a family and determine HLA alleles. The clinical and psychological features of all patients were examined. HLA antigen DNA typing was performed by polymerase chain reaction with sequence-specific primers. All patients had typical AA lesions over the scalp and/or beard area. Psychological examinations revealed obsessive-compulsive personality disorder in the proband's parents as well as anxiety and lack of self-confidence in both the proband and his sister. HLA antigen types were not commonly shared with family members. These findings suggest that AA presenting concurrently in members of the same family was not associated with genetic predisposition. Shared psychological disorders and stressful life events might be the major key points in the concurrent presentation of these familial AA cases and development of resistance against treatment.


PRACTICE POINTS
• The etiopathogenesis of alopecia areata (AA) is not clearly understood, but its occurrence and progression can involve immune dysfunction, genetic predisposition, infections, and physical and psychological trauma.
• Alopecia areata is observed to occur sporadically in most patients. Simultaneous presence of AA in more than 3 members of the same family is rare, and these cases have been observed in different generations and time periods.
• HLA antigen alleles, which provide predisposition to AA, have been investigated, and associations with many different HLA antigens have been described for AA. In previous studies, HLA-DQB1*03 allele was reported as the most common HLA allele in patients with AA.
• Psychological disorders and shared stressful life events may play an important role in the occurrence of AA and lead to the development of resistance against treatment in familial and resistant AA cases.
body, the most commonly affected sites are the scalp, beard area, eyebrows, and eyelashes. The incidence of AA is 1% to 2% in the general population and it is more common in males than females younger than 40 years. Although the majority of patients present with self-limited and well-circumscribed hairless patches that resolve within 2 years, 7% to 10% display a chronic and severe prognosis.

The etiopathogenesis of AA is not clearly understood, but its occurrence and progression can involve immune dysfunction, genetic predisposition, infections, and physical and psychological trauma. Alopecia areata is observed to occur sporadically in most patients. Family history has been found in 3% to 42% of cases, but simultaneous occurrence of AA in family members is rare. In this case series, we present 4 cases of active AA lesions occurring simultaneously in a family who also had associated psychologic disorders.

**Case Series**

**Patient 1 (Proband)**—An 11-year-old boy presented with a 6-year history of ongoing AA with recurrent improvement and relapses on the scalp, eyebrows, and eyelashes. Various topical and oral medications had been prescribed by several outside dermatologists; however, these treatments provided minimal benefit and resulted in the recurrence of AA. Dermatologic examination revealed hair loss on the entire frontal, parietal, and temporal regions of the scalp, as well as half of the occipital region and one-third of the lateral side of the eyebrows (Figure 1). Psychological evaluation revealed introvert personality characteristics, lack of self-confidence, and signs of depression and anxiety.

**Patient 2 (Proband’s Father)**—A 38-year-old man presented with a 16-year history of recurrent loss and regrowth of hair on the scalp and beard area and white spots on the penis and arms. He previously had

![Figure 1. Alopecia areata of the scalp (A and B)(patient 1).](image1)

![Figure 2. Hairless patches on the scalp and beard (A) as well as hypopigmented macular lesions on both forearms (B)(patient 2).](image2)
not undergone any treatments. Dermatologic examination revealed well-circumscribed, 1- to 4-cm, hairless patches on the occipital region of the scalp and in the beard area (Figure 2A) and multiple, 2- to 10-mm, vitiliginous lesions on both forearms (Figure 2B) and the penis. The patient had been unemployed for 6 months. Psychological evaluation revealed obsessive-compulsive disorder and obsessive-compulsive personality disorder.

Patient 3 (Proband’s Mother)—A 32-year-old woman presented with a 3-year history of chronic AA. She previously had not undergone any treatments. Dermatologic examination revealed 2 well-circumscribed, 3- to 4-cm patches of hair loss on the occipital and left temporal regions of the scalp (Figure 3). Psychological evaluation revealed obsessive-compulsive personality disorder and depression. The patient did not have any autoimmune diseases.

Patient 4 (Proband’s Sister)—A 10-year-old girl presented with a 6-year history of recurrent, self-limited AA on various areas of scalp. She previously had not undergone any treatments. Dermatologic examination revealed a 3-cm hairless patch on the occipital region of the scalp (Figure 4). Psychiatric evaluation revealed narcissistic personality disorder, anxiety, and lack of self-confidence.

Laboratory Evaluation and HLA Antigen DNA Typing—Laboratory testing including complete blood cell count; liver, kidney, and thyroid function; and vitamin B12, zinc, folic acid, and fasting blood sugar levels were performed in all patients.

HLA antigen DNA typing was performed by polymerase chain reaction with sequence-specific primers in all patients after informed consent was obtained. Clinical and laboratory examinations revealed no symptoms or findings of Epstein-Barr virus and cytomegalovirus infections, cicatricial alopecia, or connective tissue diseases in any of the patients. HLA antigen DNA typing revealed the following HLA alleles: B*35/40, C’04/15, DRB1’08/10, and DQB1’03/05 in patient 1; B’04/13, C’06/15, DRB1’07/10, and DQB1’02/05 in patient 2; B’33/37, C’04/06, DRB1’08/15, and DQ’06/06 in patient 3; B’13/37, C’06/06, DRB1’07/15, and DQB1’02/06 in patient 4.

Laboratory testing revealed vitamin B12 deficiency in patient 2 and iron deficiency anemia in patient 3; all other laboratory tests were within reference range. Antithyroglobulin and antithyroid peroxidase autoantibodies were all negative. Clinical features and laboratory analyses for all patients are summarized in the Table.

Treatment—All patients were recommended psychiatric therapy and started on dermatologic treatments. Topical corticosteroids, intralesional triamcinolone acetonide (8 mg/mL) injections into areas of hair loss, 8 total sessions of cryotherapy administered at 3-week intervals, and minoxidil solution 2% were administered respectively to all 4 patients. Alopecia areata in patients 3 and
## Clinical Features of Patients and Results of Laboratory Analyses

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient 1 (Proband)</th>
<th>Patient 2 (Proband’s Father)</th>
<th>Patient 3 (Proband’s Mother)</th>
<th>Patient 4 (Proband’s Sister)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>11</td>
<td>38</td>
<td>32</td>
<td>10</td>
</tr>
<tr>
<td>Sex</td>
<td>M</td>
<td>M</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>Duration of lesions, y</td>
<td>6</td>
<td>16</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Location of lesions</td>
<td>Scalp, eyebrows, eyelashes</td>
<td>Occipital region of the scalp, beard area</td>
<td>Occipital and temporal regions of the scalp</td>
<td>Occipital region of the scalp</td>
</tr>
<tr>
<td>Lesion size</td>
<td>Almost all of the scalp</td>
<td>Diameter of 1–4 cm, well-circumscribed, oval/round</td>
<td>Diameter of 3–4 cm, oval</td>
<td>Diameter of 3 cm, oval</td>
</tr>
<tr>
<td>Number of lesions</td>
<td>Multiple</td>
<td>Single on scalp, multiple on beard</td>
<td>2</td>
<td>Single</td>
</tr>
<tr>
<td>Accompanying autoimmune diseases</td>
<td>None</td>
<td>Vitiligo</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Accompanying psychiatric disorders</td>
<td>Introvert personality characteristics, lack of self-confidence, signs of depression and anxiety</td>
<td>Obsessive-compulsive disorder, obsessive-compulsive personality disorder</td>
<td>Obsessive-compulsive personality disorder, depression</td>
<td>Narcissistic personality disorder, anxiety, lack of self-confidence</td>
</tr>
<tr>
<td>Laboratory abnormalities</td>
<td>None</td>
<td>Vitamin B12 deficiency</td>
<td>Iron deficiency anemia</td>
<td>None</td>
</tr>
<tr>
<td>HLA alleles</td>
<td>B<em>35/40, C</em>04/15, DRB1<em>08/10, DQB1</em>03/05</td>
<td>B<em>04/13, C</em>06/15, DRB1<em>07/10, DQB1</em>02/05</td>
<td>B<em>33/37, C</em>04/06, DRB1<em>08/15, DQ</em>06/06</td>
<td>B<em>13/37, C</em>06/06, DRB1<em>07/15, DQB1</em>02/06</td>
</tr>
<tr>
<td>Treatment</td>
<td>Topical corticosteroids, IL triamcinolone acetonide injections (8 mg/mL)(3 × at 3-wk intervals), cryotherapy (8 sessions at 3-wk intervals), minoxidil solution 2%, narrowband UVB phototherapy (3 × weekly for 7 mo [total of 57 sessions])</td>
<td>Topical corticosteroids, IL triamcinolone acetonide injections (8 mg/mL)(3 × at 3-wk intervals), cryotherapy (8 sessions at 3-wk intervals), minoxidil solution 2%</td>
<td>Topical corticosteroids, IL triamcinolone acetonide injections (8 mg/mL)(1 session), cryotherapy (8 sessions at 3-wk intervals), minoxidil solution 2%</td>
<td>Topical corticosteroids, IL triamcinolone acetonide injections (8 mg/mL)(1 session), cryotherapy (8 sessions at 3-wk intervals), minoxidil solution 2%</td>
</tr>
<tr>
<td>Treatment response</td>
<td>Partial response and recurrence</td>
<td>Partial response and recurrence</td>
<td>Good response</td>
<td>Good response</td>
</tr>
</tbody>
</table>

**Abbreviations:** M, male; F, female; IL, intrallesional.
4 completely regressed; however, no benefit was observed in patients 1 and 2 after 1 year of treatment. Because there was no response to the prior interventions, patient 1 was started on treatment with cyclosporine 2.5 mg/kg twice daily. However, therapy was discontinued after 1 month and treatment with narrowband UVB (3 times per week for 7 months [total of 57 sessions]) and topical corticosteroids were initiated (Table). The patient partially benefited from these regimens and recurrence was observed during the course of the treatment.

Although it was recommended that all 4 patients undergo psychiatric treatment and follow-up regularly with a psychiatrist, the patients declined. After approximately 1 year of dermatologic treatment, all 4 patients were lost to follow-up.

**Comment**

The etiopathogenesis of AA is unclear, but there is strong evidence suggesting that it is a T-cell–mediated autoimmune disease targeting the hair follicles. Common association of AA with autoimmune diseases such as vitiligo and thyroiditis support the immunological origin of the disease.1 In our case, patient 2 had AA along with vitiligo, but no associated autoimmune diseases (eg, vitiligo, diabetes mellitus, pernicious anemia, thyroid diseases) were noted in the other patients. Genetic and environmental factors are known to be influential as much as immune dysfunction in the etiology of AA.

The presence of family history in 20% of patients supports the genetic predisposition of AA.4 In a genetic study by Martinez-Mir et al,5 susceptibility loci for AA were demonstrated on chromosomes 6, 10, 16, and 18. HLA antigen alleles, which provide predisposition to AA, have been investigated and associations with many different HLA antigens have been described for AA. In these studies, a relationship between AA and HLA class I antigens was not determined. Notable results mainly focused on HLA class II antigens.6-8 Colombe et al7 and Marques Da Costa et al8 demonstrated that long-lasting alopecia areata or alopecia universalis (AT/AU) patients had a strong relationship with HLA-DQB1*03/05 in patient 1 who had the earliest onset and most severe presentation of AA. In some studies, HLA-DRB1*03 was found to be less frequent in patients with AA, and this allele was suggested to be a protective factor.6,12 However, this allele was not detected in any of our patients.

The association of HLA alleles and AA has been investigated in Turkish patients with AA.13-15 Akar et al13 and Kavak et al14 detected that the frequency of HLA-DQB1*03 allele was remarkably higher in patients with AA than in healthy controls. These results were consistent with Colombe et al.10 On the other hand, Kavak et al14 reported that the frequency of HLA-DR16 was decreased in the patient group with AA. In another study, the frequency of HLA-B62 was increased in patients with AA compared to healthy controls.15 The HLA-DQB1*03 allele was found to be associated with AA in only patient 1 in our case series, and HLA alleles were not commonly shared among the 4 patients. Additionally, lack of consanguinity between patients 2 and 3 (the parents) also suggested that genetic factors were not involved in our familial cases.

Blaumeiser et al16 reported a lifetime risk of 7.4% in parents and 7.1% in siblings of 206 AA patients; however, because these studies investigated the presence of AA in any given life period of the family members, their results do not reflect frequency of simultaneous AA presence within one family. In a literature search using PubMed, Google Scholar, and other national databases for the terms alopecia areata as well as family, sibling, concurrently, concomitant, co-existent, and simultaneously, only 2 cases involving a husband and wife and 1 case of 2 siblings who concurrently had AA have been previously reported.17,18 Simultaneous presence of AA in more than 3 members of the same family is rare, and these cases have been observed in different generations and time periods.19 Among our patients, despite different age of onset and duration, AA was simultaneously present in the entire family.

Moreover, Rodriguez et al20 reported that the concordance rate of AA in identical twins was 42% and dizygotic twins was 10%. Environmental factors and infections also have been implicated in the etiology of AA. Infections caused by viruses such as cytomegalovirus and Epstein-Barr virus have been thought to be potential triggering factors; however, no evidence has been found.21,22 The clinical and laboratory examinations in our study did not reveal any presence and/or history of any known infectious disease, and there was no history of contact with water infected by acrylamide or a similar chemical.
Various life events and intense psychological stress may play an important role in triggering AA. Depression, hysteria, psychopathic deviance, psychasthenia, schizophrenia, anxiety, health concerns, bizarre thoughts, and family problems were found to be more frequent in patients with AA than healthy controls. The most common psychological disorders associated with AA are generalized anxiety disorder, major depressive disorder, adjustment disorders, and phobias.

Ruiz-Doblado et al determined the presence of psychiatric comorbidities in 66% (21/32) of AA cases. Chu et al reported that the differences in ages of onset of AA revealed differences in psychiatric comorbidities. The risk for depression was higher in patients with AA younger than 20 years. An increased rate of anxiety was detected with patients with an onset of AA between the ages of 20 and 39 years. Obsessive-compulsive disorder and anxiety were more common in patients aged 40 to 59 years. Interestingly, the investigators also observed that approximately 50% of psychiatric disorders occurred prior to onset of AA. One study showed higher rates of stressful life events in children than in controls. Ghanizadeh reported at least 1 psychiatric disorder in 78% (11/14) of children and adolescents with AA. In the same study, obsessive-compulsive disorder was found to be the second common condition following major depression in AA.

In our patients, psychiatric evaluations revealed obsessive-compulsive personality disorder in patients 2 and 3, depression in patient 3, and symptoms of anxiety with a lack of self-confidence in patients 1 and 4. Psychiatric disorders affecting the entire family may stem from unemployment of the father. Similar to the results noted in prior studies, depression, the most commonly associated psychiatric disorder of AA, was present in 2 of 4 patients. Obsessive-compulsive disorder, the second most common psychiatric disorder among AA patients, was present in patients 2 and 3. These results indicate that AA may be associated with shared stressful events and psychiatric disorders. Therefore, in addition to dermatologic treatment, it was recommended that all patients undergo psychiatric treatment and follow-up regularly with a psychiatrist; however, the patients declined. At the end of a 1-year treatment period and follow-up, resistance to therapy with minimal recovery followed by a rapid recurrence was determined in patients 1 and 2.

**Conclusion**

This report demonstrated that familial AA was strongly associated with psychological disorders that were detected in all patients. In our patients, HLA alleles did not seem to have a role in the development of familial AA. These results suggest that HLA was not associated with AA triggered by psychological stress. We believe that psychological disorders and stressful life events may play an important role in the occurrence of AA and lead to the development of resistance against treatment in familial and resistant AA cases.

**REFERENCES**