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Celiac Disease and Alopecia Areata: Report of a New Association

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Celiac disease is frequently associated with other autoimmune disorders but has never been reported in association with alopecia areata. In a routine clinical practice, 3 patients with such an association were observed. In one of the patients, celiac disease was diagnosed after the occurrence of malabsorption symptoms. In the youngest patient, a 14-year-old boy, gluten-free diet resulted in complete regrowth of scalp and body hair. A prospective screening program for celiac disease using antigliadin and antiendomysial antibodies was therefore set up in 256 consecutive outpatients with alopecia areata. Three patients, all completely asymptomatic for intestinal diseases, were found to be positive and underwent biopsy. Histological analysis showed a flat intestinal mucosa consistent with the diagnosis of celiac disease. The results show that alopecia areata may constitute the only clinical manifestation of celiac disease and that the association between these two conditions is a real one because the observed frequency of association is much greater than can be expected by chance. It is suggested that antigliadin and antiendomysial antibodies should be included in the work-up of patients with alopecia areata.

Celiac disease has been reported in association with many other conditions, particularly those of autoimmune origin.[1,2] From a clinical standpoint, the importance of recognizing such associations is twofold: on one hand, celiac disease may present only with the symptoms of the second disease, which thus become particularly important for the diagnosis; on the other hand, gluten-free diet may lead to a significant clinical improvement also in the associated disease.

Alopecia areata (AA) is an autoimmune disease characterized by areas of hair loss that show a smooth nonscarred scalp with no obvious inflammation. Both celiac disease and AA are characterized by the presence of organ-specific autoantibodies,[3,4] T-lymphocyte infiltration at the site of the lesion,[5,6] association with HLA genes,[7,8] and possible etiologic importance of viral cofactors.[9,10] However, celiac disease and AA have never been reported in association.

In this case report, we describe 3 patients in whom celiac disease was associated with AA, leading to the recognition of this novel association. We report the results of a prospective study in which celiac disease was searched for using highly reliable, noninvasive screening tests, such as antigliadin and antiendomysial antibodies, in 256 consecutive patients with AA.

Case Reports

Patient 1

A 27-year-old woman presented in July 1987, 2 months after giving birth to her first child, with watery diarrhea, nausea, vomiting, weight loss of 8 kg, muscular cramps, and great weakness. Her previous history showed a late menarche at the age of 15, with subsequent menstrual irregularities, iron-deficiency anemia, and AA appearing in 1983. Clinical examination showed malnutrition (actual weight, 79% of ideal body weight), marked abdominal distention, koilonychia, dry and pigmented skin, and three vast areas of patchy AA on her scalp. Hematochemical evaluation showed low values of serum hemoglobin (4.9 mmol/L [normal, 8.1–9.9 mmol/L]), iron (6.98 μmol/L [normal, 9.0–26.9 μmol/L]), potassium (3.3 mmol/L [normal, 3.5–5.0 mmol/L]), and calcium (1.8 mmol/L [normal, 2.1–2.6 mmol/L]) but normal values of albumin (40 g/L [normal, 40–50 g/L]). Her HLA phenotype was DR3/DQw2, and antigliadin antibodies were positive. She underwent a jejunal biopsy, and mucosal specimens showed subtotal villous atrophy. After 6 months of gluten-free diet, a second biopsy showed the regrowth of villi, the symptoms had disappeared, and the hematochemical parameters returned to normal values. The patient is still under observation, and, after years of strict gluten-free diet, two of the three patches of alopecia have almost completely disappeared. In 1992, Graves's disease developed in the patient.

Patient 2

A 38-year-old man, a physician, presented in March 1989. Since the age of 18 months, he had had universalis AA

Abbreviations used in this paper: AA, alopecia areata.

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and allergic asthma. He never complained of diarrhea or weight loss, but the search for serum anti-gliadin antibodies, performed a year earlier at another hospital for recurrent aphthous stomatitis, was positive. When he came to our outpatient clinic, the only complaint was a mild weakness with nail clubbing. The nutritional status was completely normal (actual weight, 102% of ideal body weight; midarm circumference, 28 cm [normal, 23 cm]; triceps skinfold, 14.4 mm [normal, 11.3 mm]) as were all hematochemical parameters except for positive antigliadin and antiendomysial antibodies. He underwent multiple endoscopic biopsies of the distal duodenum; the specimens showed all the classical features of subtotal villous atrophy. Although the absolute need to comply with a gluten-free diet was explained very clearly to him, after 3 months of poor compliance, the patient refused to continue the diet and undergo any further examinations.

Patient 3

A 14-year-old adolescent boy presented in July 1991. His only complaint was AA, which appeared at the age of 10 years and for which his parents had consulted various specialists in addition to dermatologists. His hair loss was universal. Previous treatments included systemic steroids and psoralen plus UVA without hair regrowth. His personal and family history was negative for gastrointestinal diseases. Clinical examination showed no signs of malnutrition (actual weight, 98% of ideal body weight) or stunted growth. Hematochemical evaluation showed values within the normal range (hemoglobin, 8.3 mmol/L; serum iron, 17.5 μmol/L; potassium, 4.4 mmol/L; calcium, 2.2 mmol/L; and albumin, 42 g/L). Our previous experience with the first 2 patients led us to perform a search for antigliadin and antiendomysial antibodies, which was highly positive for both. HLA phenotype was DR3/DQw2. Multiple endoscopic biopsy specimens were therefore taken at the distal duodenum, showing subtotal villous atrophy with areas of severe partial villous atrophy. After a year of gluten-free diet, a second biopsy specimen showed a significant improvement in mucosal architecture and, from a clinical standpoint, the patient had gained 6 kg in weight. There was complete regrowth of hair, eyebrows, and eyelashes (Figure 1). Three years later, with continuation of gluten-free diet, the situation is unchanged.

Prospective Study

After observing the 3 patients, we decided to set up a prospective screening program to ascertain whether the association between celiac disease and AA was real or coincidental. Two-hundred fifty-six patients with AA (128 male and 128 female; mean age, 27.9 years; age range, 1–74 years) underwent the search for serum antigliadin and antiendomysial antibodies.

Immunoglobulin (Ig) A and IgG serum antigliadin antibodies were measured by a micro–enzyme-linked immunosorbent assay (ELISA) test as previously described.[11] IgA and IgG were expressed in arbitrary ELISA units. The lower limit of positive antigliadin antibodies was 1 ELISA unit based on the mean + 2SD of the results obtained in a large series of healthy subjects.

IgA antiendomysial antibodies were detected using an indirect immunofluorescent technique and commercial sections of monkey esophagus as antigen (BioSystems, Milano, Italy).[12] Sera containing antibody at a titer of 1:5 or more were considered to be positive.

In our laboratory, the antigliadin and antiendomysial antibody sensitivity and specificity values, previously verified in a large panel of patients, are 92% and 90% for antigliadin antibodies and 99% and 100% for antiendomysial antibodies.[13] All patients with AA who had antigliadin antibody positivity underwent the search for antiendomysial antibodies according to a two-step procedure recently proposed.[14] All patients with AA who had either positivity underwent intestinal biopsy.

Informed consent was obtained from each patient after full explanation, and the investigation was approved by the local ethical committee.

Results

Circulating antigliadin and antiendomysial antibodies were found in 3 of 256 patients with AA; the patients' clinical, laboratory, and histological features are shown in Table 1. Another antigliadin antibody–positive patient, who also had Down's syndrome, was antiendomysial antibody negative; however, in view of the already shown association between celiac disease and Down's syndrome,[15] the patient underwent intestinal biopsy. The specimen showed a slight and zonal partial villous atrophy with an increase in intraepithelial lymphocytes. The patient has not yet been considered as being affected by celiac disease but could be the carrier of a latent form of this condition and will therefore undergo follow up. Patients 4 and 5, who had alopecia universalis, and patient 6, who had patchy alopecia, were both anti-gliadin and antiendomysial antibody positive; in all 3, the intestinal biopsy specimen showed a subtotal villous atrophy. Patient 4 has already undergone the second biopsy, which showed the regrowth of the intestinal villi. It is important to note that the search for celiac disease using antigliadin and antiendomysial antibodies in the relatives of this patient has led to a positive diagnosis of the patient's brother and of the brother's daughter.

As can be seen in Table 1, none of the 3 new patients with celiac disease had clinical or laboratory results indicative of celiac disease.

We explained very clearly to all 3 patients the need to follow a gluten-free diet to cure the celiac disease and to possibly improve the AA. Patient 6 refused to comply with the gluten-free diet, but patient 4 had complete regrowth of the eyelashes and eyebrows and initial regrowth of pubic and underarm hair after 1 year of the diet. No effect has been observed so far in patient 5.

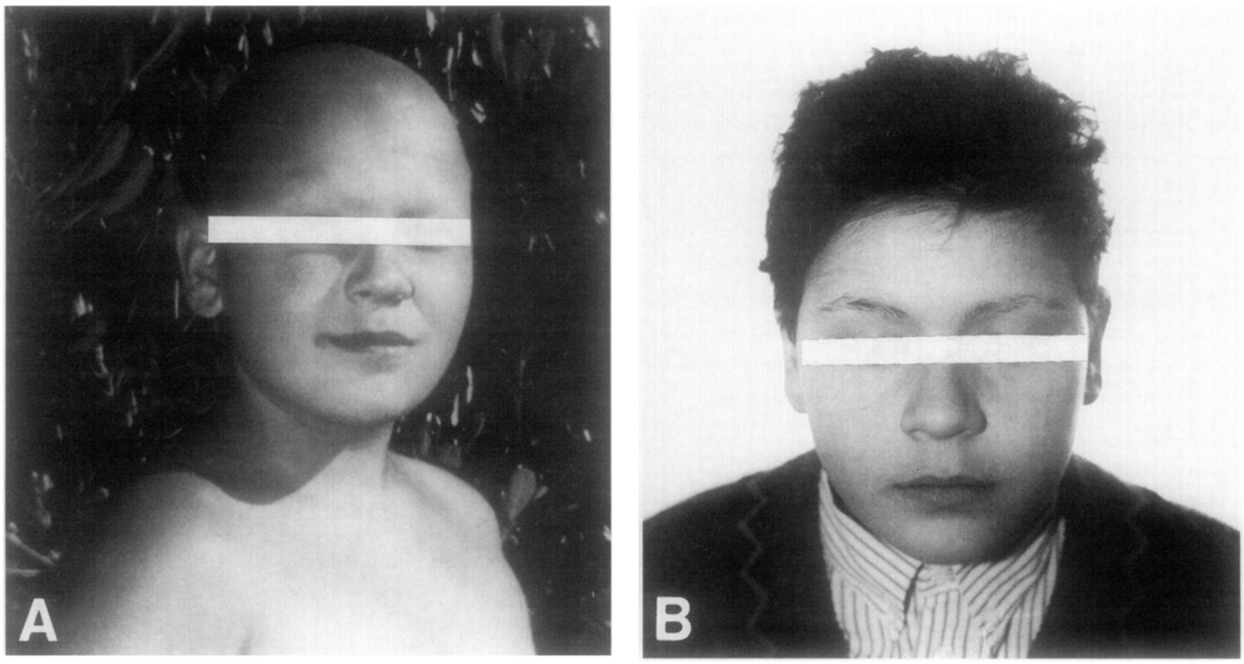

Figure 1. Patient 3. (*A*) Complete loss of scalp and facial hair before treatment. (*B*) Scalp and facial hair regrowth 1 year after gluten-free diet.

In conclusion, the prevalence of celiac disease in the patients with AA who participated in our prospective study was 1 of 85 (3 of 256).

Discussion

AA tends to cluster in the same individuals with other autoimmune disorders, such as Addison's disease, autoimmune thyroiditis, atrophic gastritis, systemic lupus erythematosus, rheumatoid arthritis, myasthenia gravis, and vitiligo.[16] Among the autoimmune diseases affecting the intestinal wall, AA has been reported in association with ulcerative colitis.[17,18] This association was recently described in a mother and her son.[19] In contrast, AA has never been described in association with celiac disease, although the coexistence of AA and subtotal villous atrophy indistinguishable from human celiac disease has been reported in a rhesus monkey.[20]

Table 1. Clinical, Laboratory, and Histological Features of 3 Patients With AA and Celiac Disease

	Patient 4	Patient 5	Patient 6
Sex	F	M	F
Age (*yr*)	29	15	19
Pattern of AA	Universalis	Universalis	Patchy
Diarrhea	No	No	No
% of ideal body wt	92	93	90
Hemoglobin	7.7	8.2	6.7
Mean cell volume	78.0	79.8	79.0
Iron	6.8	9.1	4.6
Potassium	4.1	3.9	4.0
Calcium	2.2	2.3	2.4
Albumin	42	38	41
HLA status	DR7/DQw2	DR3/DQw2	DR3/DQw2
IgA	Positive	Negative	Positive
Anti-GA IgG	Positve	Positive	Negative
Anti-EMA	Positive	Positive	Positive
Small intestinal histology	SVA	SVA	SVA

Anti-GA, antigliadin antibodies; anti-EMA, antiendomysial antibodies; SVA, subtotal villous atrophy.

In this study, we report 6 patients in whom celiac disease was associated with AA. These cases show that AA associated with celiac disease is more frequently the universalis type (4 of 6 cases). In 3 of these patients, celiac disease was diagnosed during our routine clinical practice and in the other 3 in the course of a prospective screening study on patients with AA. Of the first 3, only in patient 1 was the diagnosis made as a result of the presence of the classic symptoms of intestinal malabsorption. In patient 2, the occurrence of an extraintestinal complaint such as recurrent aphthous stomatitis led to the anti-gliadin antibody search and intestinal biopsy; in patient 3, the AA itself prompted us to perform intestinal biopsy. Also, in the 3 patients identified during the prospective screening study, no clinical symptoms or hematochemical abnormalities classically indicative of celiac disease were found. It is therefore possible to conclude that, in at least 4 of our 6 patients, the diagnosis of celiac disease was made because of the presence of AA. Nor should it be forgotten that the diagnosis of patient 4 also made it possible to identify this patient's brother and his small niece, who, as all families of new patients,[21]

underwent studies for antigliadin and antiendomysial antibodies.

In all 6 patients with celiac disease and AA, the diagnosis of AA preceded the diagnosis of celiac disease even by several years; however, this does not mean that the hair bulb involvement in these patients preceded the jejunal mucosa lesions. We know that adult celiac disease can start in the majority of cases in a subclinical or completely silent form[22]; it is therefore possible that the intestinal lesions preceded the skin lesions in our patients. It is known that some fluctuations with the possibility of spontaneous remission and recurrence may be observed during the clinical course of AA.[23] This could have occurred in patients 1 and 4 but not likely in patient 3, a 14-year-old boy with alopecia universalis, because spontaneous regrowths are considered extremely rare in patients of this age and with this type of alopecia.[24] In this patient, the withdrawal of gluten from the diet strictly coincided with the complete regrowth of scalp and other body hair, and no further recurrence of AA was observed in the 3 years after the start of gluten-free diet. The positive effects of gluten-free diet on the pattern of the autoimmune conditions associated with celiac disease have been attributed to a normalization of the immune response.[25] It is therefore possible that gluten-free diet can in the same way determine a beneficial effect on AA in patients affected by both conditions. There are no controlled studies specifically addressed to this subject except for dermatitis herpetiformis.[26] However, a beneficial effect of gluten-free diet on other immunologic conditions associated with celiac disease has already been reported in recurrent aphthous stomatitis,[27] cutaneous vasculitis,[28] recurrent pericarditis,[29] insulin-dependent diabetes mellitus,[30] thrombocytopenic purpura,[31] primary IgA nephropathy,[32] arthritis,[33] systemic lupus erythematosus,[34] and primary sclerosing cholangitis.[35]

A crucial question this study must therefore answer is whether the association between these two conditions is real or not. The likelihood of a chance association can now be calculated because reliable prevalence data have been derived for both conditions from population studies. The prevalence of celiac disease and AA in the general population is 1 of 305[36] and 1 of 819,[37] respectively. These figures indicate a coincidental association of the two conditions in 1 of ≈250,000 individuals, whereas, in our prospective study, the prevalence of celiac disease in patients with AA was 1 of 85, i.e., almost 3000 times higher. Although these calculations may be affected to a small extent by the diversity of the study conditions, there is no doubt that celiac disease and AA are associated.

In conclusion, this study shows for the first time that AA may be the only clinical manifestation of celiac disease and, therefore, that patients with this condition constitute a novel risk group of celiac disease. We suggest that an active search of celiac disease using serological screening tests should be performed, particularly in patients with alopecia universalis.

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