

# Iron Screening in Alopecia Areata Patients May Catch Hereditary Hemochromatosis Early

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## PRACTICE POINTS

- Hereditary hemochromatosis (HHC) is a disorder of iron overload that presents with clinical phenotypic heterogeneity. Complications can be mitigated with early intervention.
- Alopecia areata (AA) may be a rare early cutaneous manifestation of HHC in individuals with a predisposition for autoimmunity; therefore, it is important to evaluate iron status as part of the AA workup.

Hereditary hemochromatosis (HHC), a disorder of iron overload, presents with clinical phenotypic heterogeneity. Complications can be mitigated with early intervention. The association between HHC and alopecia areata (AA) is unknown. We report 4 patients with HHC concurrent with AA. In 2 patients, the HHC diagnosis was revealed from the results of laboratory iron studies as part of an alopecia consultation workup. Alopecia areata may be a rare early cutaneous manifestation of HHC in individuals with a predisposition for autoimmunity; however, the genetic relationship between the 2 disorders is currently unknown. Patients at high risk for HHC such as those with a family history and/or those who fit the demographic profile may benefit from laboratory iron screening if they present to the clinic with AA.

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**T**he role of micronutrients in the hair follicle cycle is not fully understood; thus deficiency and/or excess of certain micronutrients may be a modifiable risk factor associated with the development and/or treatment

of some types of hair loss and therefore may be included in the workup during an alopecia consultation.

Hereditary hemochromatosis (HHC) is the most common genetic disorder identified in White individuals, with a worldwide prevalence of 1 in 220 to 1 in 250 individuals for a homozygous mutation. It most commonly affects individuals of Northern European descent.<sup>1</sup> Men usually present in the fourth to sixth decades of life, while women usually develop symptoms after menopause, as pregnancy and menstruation delay the onset of the disease.<sup>2</sup> Early symptoms of HHC include fatigue, joint pain, abdominal pain, and weight loss. Men are more likely to develop complications; in fact, 1 in 10 men with HHC will develop severe liver disease.<sup>3</sup> As the disease progresses, affected individuals can present with cardiomyopathy (restrictive and dilated), cirrhosis, hypogonadism (usually hypogonadotrophic), arthropathy, diabetes mellitus, hepatomegaly, hepatic cirrhosis, and primary liver cancer (eg, hepatocellular carcinoma, cholangiocarcinoma).<sup>2</sup> Approximately 90% of patients with HHC present with hyperpigmentation at the time of diagnosis.<sup>4</sup> Thinning or loss of hair is another finding in HHC, primarily reported in the axillae and pubic regions, and is ascribed to hepatotesticular insufficiency.<sup>5</sup>

Alopecia areata (AA) is the most common cause of autoimmune, inflammation-induced hair loss, with a calculated lifetime risk of 2%.<sup>6</sup> This disease manifests as loss of hair in well-circumscribed patches of skin, most commonly on the scalp; AA also may affect other hair-bearing sites on the body. It is associated with an increased risk for other autoimmune disorders, such as psoriasis, thyroid

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disease, rheumatoid arthritis, systemic lupus erythematosus, and vitiligo.<sup>7</sup>

Alopecia areata is induced by an inflammatory infiltrate of CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocytes around hair follicles in the anagen stage, the active growth phase.<sup>8</sup> Although the diagnosis is clinical, some clinicians order laboratory thyroid studies to investigate conditions that may be associated with AA. Common treatments include topical, intralesional, and/or systemic corticosteroids; contact immunotherapy; topical and more recently oral minoxidil; phototherapy; and topical and systemic JAK inhibitors, including tofacitinib.<sup>4,9</sup>

We reviewed the medical records of 533 patients who were seen in The University of Texas Southwestern (Dallas, Texas) dermatology clinic from January 2015 through January 2020 and were diagnosed with AA. We examined their demographic data and medical history. We sought to determine any relationship between various types of alopecia and certain micronutrient levels through laboratory test results. Ferritin and iron saturation studies were evaluated. We report 4 cases of HHC concurrent with AA, of which 2 HHC diagnoses were uncovered through iron studies as part of the alopecia evaluation.

## Case Reports

*Patient 1*—A 55-year-old White woman presented to the clinic for an alopecia consultation. She had a medical history of hypothyroidism and AA that was treated unsuccessfully with triamcinolone acetonide steroid injections; topical minoxidil; topical steroids; and systemic steroids, specifically oral prednisone. Following evaluation, she successfully transitioned to treatment with oral tofacitinib and continued to do well on tofacitinib.

The patient's alopecia workup revealed a ferritin level of 245 ng/mL (reference range, 13–150 ng/mL) and iron saturation of 60% (reference range, 20%–50%). She was referred to the hematology department for further evaluation and was diagnosed with HHC. Genetic testing revealed a heterozygous H63D mutation; therapeutic phlebotomy was recommended. Her sister also was recently diagnosed with HHC.

*Patient 2*—A 55-year-old White man was referred for evaluation and treatment of alopecia universalis. He had a medical history of skin cancer and vitiligo. He attempted contact immunotherapy with diphenylcyclopropenone scalp treatment but stopped due to intolerable inflammation. Intervention with a topical steroid and topical minoxidil was unsuccessful, but use of triamcinolone acetonide steroid injection on the scalp and topical bimatoprost 0.03% on the eyebrows produced satisfactory results.

The patient's alopecia workup revealed a ferritin level of 422 ng/mL (reference range, 30–400 ng/mL), which prompted a hematology consultation for further evaluation. Notably, the patient ate red meat several times a week, used iron skillet, and denied receiving blood transfusions. His social habits included 3 alcoholic

beverages a night, 5 days a week. Ultrasonography of the liver was recommended to assess potential damage from iron overload and alcohol consumption; the results suggested chronic liver disease, not definitive for cirrhosis, and no evidence of hepatocellular carcinoma. Genetic analysis later revealed the heterozygous H63D variant; therapeutic phlebotomy was recommended.

*Patient 3*—A 22-year-old White man presented with AA involving his facial beard. He had a medical history of vitiligo and psoriasis and a family history of AA as well as other autoimmune diseases including Hashimoto thyroiditis, psoriasis, eczema, and autoimmune hepatitis. Diphenylcyclopropenone treatment was not successful.

Laboratory studies revealed mildly elevated transaminase and ferritin levels. The patient also presented to the gastroenterologist for evaluation of abdominal pain. Subsequent hematology evaluation confirmed the presence of compound heterozygous C282Y and H63D mutations in the *HFE* gene, and the patient's mother was later determined to be homozygous for the C282Y mutation with no elevated ferritin level. The patient's ferritin level at diagnosis was approximately 500 ng/mL (reference range, 22–322 ng/mL); he required a modest number of therapeutic phlebotomies to normalize his ferritin level.

*Patient 4*—A 62-year-old White woman presented for evaluation and treatment of patchy hair loss on the scalp of 7 months' duration. She was subsequently diagnosed with AA. After unsuccessful treatment with a triamcinolone acetonide steroid injection, topical immunotherapy with diphenylcyclopropenone was recommended. The patient achieved full hair regrowth after 35 treatments administered at 3-week intervals.

The patient had a medical history of HHC, including homozygosity for the C282Y mutation, and a family history of HHC in 1 sister. Treatment was therapeutic phlebotomy.

## Comment

*HHC in the Setting of AA*—We presented 4 White patients with both HHC and AA. A PubMed search of articles indexed for MEDLINE using the terms *HHC* and *AA* yielded only 1 other reported case of newly identified HHC in a 56-year-old man who presented with pigmented purpuric dermatitis and AA that affected the beard.<sup>10</sup> Because HHC is the most common genetic disorder identified in White individuals and has a varied clinical presentation, the documentation of AA may be an important cutaneous clue to help clinicians diagnose HHC early.

*Iron Overload in Patients With HHC*—The genetic association between HHC and AA, if any, is unknown. What is known is that iron overload can catalyze reactive oxygen species, which can overwhelm cellular antioxidant capacities at particular levels and cause injury to its constituents.<sup>11</sup> Data show that the levels of oxidative stress are elevated in the scalp of patients with AA compared

to controls and increased 2-fold during the early phase of disease vs late-phase disease.<sup>12</sup> Thus, it is possible that increased iron levels in HHC may contribute to AA in genetically susceptible individuals by direct toxicity that ultimately results in the AA hair disorder that is CD8<sup>+</sup> T-cell mediated.

Data show that 78% (31/40) of men and 36% (14/39) of women identified with homozygous C282Y mutations determined from family genetic analyses exhibited iron overload.<sup>13</sup> In general, a normal life expectancy is possible for patients promptly treated with appropriate therapeutic phlebotomies.<sup>14</sup> Thus, early diagnosis and appropriate therapy can prevent consequences of iron overload, which include cirrhosis, diabetes mellitus, and cardiomyopathy.<sup>13</sup>

*Iron Screening in the Alopecia Workup*—Our cases illustrate how iron screening tests as part of the alopecia workup identified a cohort of White patients with iron overload and subsequently led to an early diagnosis of HHC. The calculated 2% lifetime risk for developing AA highlights the importance of evaluating iron status as part of the AA workup, particularly for White men, and the potential health benefit from early diagnosis of HHC. Limitations of this case series included its retrospective nature and small patient number.

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