

# Diabetic Ketoacidosis as a Presentation of Hemochromatosis

Sondra Vazirani, MD, MPH and Mehran J. Kashefi, DO

When this patient presented with symptoms of diabetic ketoacidosis, blood tests revealed elevated iron levels associated with a common genetic mutation.

**H**ereditary hemochromatosis (HH) is a genetic disorder of iron metabolism associated with mutation of the hemochromatosis gene, *HFE*.<sup>1</sup> The disorder is common among populations of northern European origin and can cause excess iron deposits throughout the body.<sup>2</sup> It often presents in patients as diabetes mellitus (DM) or diabetic ketoacidosis (DKA). To heighten awareness of this fact, here, we report a case of HH involving an older, male veteran who presented to the emergency department (ED) with symptoms of DKA.

### INITIAL EXAM

The patient, a 60-year-old, white man, presented to the ED reporting weight loss, weakness, confusion, and polydipsia during the preceding 2 weeks. He also reported fatigue and hyperpigmentation of his bilateral lower extremities during the past month. His medical history was remarkable for arthritis and protein C deficiency. He had a history of 2 right lower extremity deep venous thromboses, leading to placement of an

inferior vena cava filter. He was not taking warfarin, however, because he refused this medication after the diagnosis of his deep venous thromboses due to concerns of adverse effects and the need for monitoring.

Upon presentation, the patient had a blood serum pH level of 7.3, a serum glucose level of 369 mg/dL, a bicarbonate level of 13 mEq/L, a creatinine level of 1.9 mg/dL, an anion gap of 26 mEq/L, and “large” serum ketones. He had no family history of diabetes and no clear precipitant to DKA.

### TREATMENT COURSE

The patient was admitted to the intensive care unit for initial treatment. He was noted to have thrombocytopenia and elevated liver function test results. He was transferred to the General Medicine Department for further evaluation and to begin an insulin regimen. Results of hepatitis serologic tests were negative. Blood tests revealed an elevated ferritin level of 7,030 ng/mL (reference range, 22 ng/mL to 322 ng/mL), with an iron level of 124 µg/dL (reference range, 60 µg/dL to 170 µg/dL), a total iron-binding capacity of 111 µg/dL (reference range, 240 µg/dL to 400 µg/dL), and a transferrin level of 83 mg/dL (reference range, 180 mg/dL to 329 mg/dL). Abdominal ultrasonography revealed cirrhosis

and splenomegaly. Genetic testing for the hemochromatosis gene mutation was ordered and insulin therapy was initiated.

The patient was discharged with instructions to undergo phlebotomy every 2 weeks and to follow up with the Gastroenterology Department. After discharge, results of the genetic testing revealed the patient was homozygous for the mutation *HFE* C282Y.

Since being discharged, the patient has required subspecialty follow-up to manage his condition. While his hemoglobin levels are managed with phlebotomy treatments, his HH has led to hypogonadism and osteoporosis. The patient has had numerous fractures, and most recently underwent a right total hip arthroplasty to manage avascular necrosis. He requires follow-up with the Gastroenterology, Cardiology, and Endocrinology Departments, and has required consultation with the Rheumatology Department for inflammatory arthropathy. The patient consented to resume anticoagulation therapy with warfarin.

### ABOUT THE CONDITION

The most commonly identified genetic disorder in the white population, HH is concentrated in individuals of northern European descent, particularly of Nordic or

**Dr. Vazirani** is a hospitalist and **Dr. Kashefi** is an internist, both at the VA Greater Los Angeles Healthcare System, Los Angeles, California. In addition, Dr. Vazirani is an associate clinical professor of medicine and Dr. Kashefi is a clinical instructor, both at the David Geffen School of Medicine, University of California, Los Angeles.

Celtic ancestry, in whom the prevalence is close to 1 per 200 of the population.<sup>1,2</sup> The gene defect associated with HH, first described in 1996, is a G to A missense mutation leading to the substitution of tyrosine for cysteine at the 282 amino acid position of the protein product of the hemochromatosis gene located on the short arm of chromosome 6 (6p).<sup>3</sup> In most studies to date, C282Y/C282Y homozygosity has been found in more than 90% of HH cases.<sup>4</sup>

Homozygous HH is characterized by the increased absorption of both heme and nonheme iron.<sup>5,6</sup> In contrast to iron absorption in patients without HH, the absorption of heme iron in patients with HH is not regulated by iron stores, thus leading to progressive iron accumulation. The clinical condition of HH evolves in a series of stages, beginning with clinically insignificant iron accumulation (up to 5 g) in the parenchymal cells. This build up can take place over the course of the first 20 years of a person's life. Iron overload (without disease) may continue, with 10 g to 20 g parenchymal iron storage, at approximately 20 to 40 years of age. If left untreated, organ damage may occur (usually with more than 20 g parenchymal iron storage and at age greater than 40 years).<sup>7,8</sup>

The iron storage has a predilection for the liver, heart, pancreas, and pituitary gland, which can result in the life-threatening complications of cirrhosis, hepatocellular cancer, diabetes, and heart disease.<sup>4</sup> Cardiac dysrhythmias and cardiomyopathy are the most common causes of sudden death in patients with iron overload. These conditions stem from iron deposition in the myocardium and conduction system.<sup>4</sup>

Patients with HH present with skin hyperpigmentation (70%), DM (48%), weakness and lethargy, and

arthralgias. Almost half (45%) of male patients with HH present with impotence. In addition, HH causes abnormal liver function test results in 75% of patients. The classic triad of cirrhosis, DM, and skin pigmentation ("bronze diabetes") occurs late in the disease when the total body iron content has reached greater than 20 g—more than 5 times the normal limit.<sup>9,10</sup> When HH presents in patients who are older than age 40 years, hepatic iron concentration is likely to exceed 10,000 µg/g dry weight, and liver biopsy results are more likely to show fibrosis and cirrhosis.<sup>11,12</sup>

DM, and other signs of HH (such as liver disease or skin hyperpigmentation), develop in about half of HH cases.<sup>13,14</sup> It has been suggested that the degree of glucose intolerance and DM in HH is closely associated with the stage of iron overload and the stage of the accompanying liver disease. Early disease is associated with insulin resistance, which might be improved partially with phlebotomy treatment. When advanced iron overload occurs, iron accumulation in pancreatic beta-cells deteriorates pancreatic insulin secretion and leads to insulin-dependent DM, which cannot be reversed with iron removal. Interestingly, patients with heterozygous HH also are at increased risk for developing DM.<sup>15</sup>

The initial approach to diagnosing HH is by indirect serologic markers of iron stores. Transferrin saturation (TS) is derived by dividing the serum iron by the total iron-binding capacity. When the fasting value exceeds 50% for women and 60% for men, TS has a sensitivity of 92%, a specificity of 93%, and a positive predictive value of 86% for HH.<sup>16-18</sup> Overnight fasting avoids circadian or postprandial variations and eliminates 80% of false-positive TS results.<sup>16</sup> Fur-

ther evidence for an HH diagnosis is the demonstration of increased iron stores, which usually are discovered after biopsy of the liver. HH also can be defined genotypically by a family history of iron overload associated with C282Y homozygosity or C282Y/H63D compound heterozygosity.<sup>19</sup>

Patients who should be screened for HH include those with: (1) unexplained liver disease or a presumably known cause of liver disease with 1 or more abnormal serum iron markers; (2) DM associated with hepatomegaly, elevated liver enzyme levels, atypical cardiac disease, or early onset sexual dysfunction; (3) early onset atypical arthropathy, cardiac disease, or male sexual dysfunction; (4) abnormal serum iron markers discovered during routine testing; or (5) a first-degree relative with confirmed HH.

Phlebotomy has proven to be a highly effective therapy for HH. When instituted early, it prevents morbidity and promotes normal longevity.<sup>20</sup> As described above, patients with HH and DM who require insulin therapy may note a decrease in insulin requirements following therapeutic iron removal—if the removal is performed in the early stages of HH. Unfortunately, phlebotomy treatment does not affect the glucose intolerance that results from insulin resistance in patients with cirrhosis and DM, demonstrating how critical early diagnosis is.<sup>21</sup>

## IN SUMMARY

HH is associated with a hemochromatosis gene mutation that causes increased intestinal iron absorption, leading to excessive iron deposition in tissues. It can present with multisystem organ damage, with DM present in about half of patients. Mechanisms for DM associated with HH include insulin resistance from

iron deposition in the liver and hypoinsulinemia from pancreatic beta-cell infiltration. HH should be included in the differential diagnosis for patients presenting with DM or DKA in the setting of liver, heart, pancreas, or pituitary abnormalities. ●

### Author disclosures

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