Prevalence of Iron Overload in African-Americans: A Primary Care Experience

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Article Summary: Iron overload has historically been thought of as an inherited disease in Caucasian patients and associated with increased iron intake in African patients. African-American patients have been less well studied. We present data from a primary care practice in Westchester County, New York, where we have used serum ferritin to screen for iron overload in African American patients. We present information on disease prevalence and response to treatment among this population, and we note the first reported C282Y mutation among African-American patients.

Key Words: Hemochromatosis, Genetic Iron Overload, Serum Ferritin, Total Iron Binding Capacity,

3,517 Words.

Background

Introduction:

Hemochromatosis remains an underdiagnosed and underreported disease entity.[1] In the United States, as many as one million persons may be affected by iron overload, genetic hemochromatosis being the primary cause. Iron overload has been described as a cause of liver disease, diabetes, osteoporosis, arthritis, and hepatocellular carcinoma in both HLA linked hereditary hemochromatosis and dietary African iron overload.[2,3] While there are subtle differences in the pathology of iron overload, the clinical symptomatology and treatment are similar. HLA-linked hemochromatosis has been shown to occur in patients of predominantly Northern European heritage; studies to date have shown a much smaller prevalence among African Americans. We would like to report a case series of hemochromatosis in the latter population group that is unrelated to dietary iron overload and we also note the first documented case of a C282Y mutation found in a patient of African-American descent.

Iron Overload in Africans

Iron overload has been reported in both Africans and African-Americans. In African populations, the disease has been described since 1929. Krainin published the first case of hemochromatosis in African Americans in 1950.[4] In some populations of Africa, the prevalence can reach 10%.[5] Iron overload in Africa was originally thought to be an environmental effect; it has been ascribed to drinking beer home-brewed in steel drums, where iron is available in ionized form.[6] In fact, with a decline in the consumption of the home brewed beer, the iron intake of this population declined. The importance of dietary intake was demonstrated by one study observing that over a 16-year period, the hepatic iron content did not rise in this population.[7] Radioactive iron uptake studies have demonstrated that hemochromatosis patients absorb a higher percentage of iron than do normal individuals.[8]

More recently, however, the role of a genetic linkage has come into question. In a segregation analysis of 36 African families containing index cases of iron overload, there was evidence of both a genetic component and an effect of dietary iron. The authors argued for an autosomal dominant role in patients with excess dietary intake, but an autosomal recessive role for those without excess dietary intake.[9]

A study of 45 additional pedigrees conducted later by the same group modified their approach by obtaining morning blood draws to limit the effect of diurnal variation of iron. The authors defined affected patients as those with a transferrin saturation greater than 80% and a 'high' serum ferritin; UIBC and ferritin:AST ratio were also observed. Segregation analysis was then applied 21 patients with iron overload on biopsy and indirect measurement. The study confirmed that in some Africans exposure to increased dietary intake of iron, a dominant genetic defect allows an elevation in serum ferritin and in transferrin saturation. [10]

Iron Overload in African Americans

Iron overload has also been documented in African-Americans not exposed to the same environment or iron-laden beer as their African colleagues.

One reported case was that of an African-American man who presented with arthritis of the 2nd and 3rd Metacarpal-phalangeal joints of both hands in the setting of hypouricemia. Serum iron, Total Iron Binding Capacity (TIBC), and transferrin saturation were all normal; serum ferritin levels were 242-251. A liver biopsy, however, revealed extensive iron deposition in the parenchymal hepatocytes and minimal iron in kupffer cells.[11] This patient subsequently had 12 grams of iron removed by phlebotomy.[12] Muir later published a case series that contrasted this patient's presentation of elevated total body stores and normal biochemical findings with other possible presentations: that of cardiac, arthritic, or hepatic abnormalities accompanied by elevated biochemical tests, or patients with severe overload and fulminant disease. Rosner's patient is the only (described) African-American among them.

Barton et al[13] described seven cases of iron overload in African Americans, most of them male, from a single primary care practice in Alabama. They report that while iron saturation levels were sometimes normal, in most patients an elevated ferritin and transferrin saturation greater than 60% were

observed at least once. None of those patients had consumed excess iron. None had received blood transfusions. Four had arthropathy, four had alpha-thalassemia, 5 had hepatomegaly and five had elevated concentrations of hepatic enzymes. The four patients treated had 4.6 to 6.8 grams of iron removed by phlebotomy.

An additional four cases were described by Wurapa et al[14], all men, 27-50 years of age, with Ferritin >600 ng/ml and transferrin saturation of 95% or greater. Each of these patients had documented alcohol use but hepatic iron indices >1.9. Patients with alcoholic liver disease alone do not have iron indices exceeding 1.7.[15,16].

Disease Prevalence

The documentation of cases of iron overload among African-American patients begets the question of its prevalence in that population. An autopsy series conducted by Wurapa (ibid) revealed that 2.6% of men and 5.7% of women had markedly elevated hepatic iron concentrations. Twelve of the 220 had a hepatic iron concentration greater than or equal to 1.9; however, after adjusting for blood transfusions, only four remained in that group. These patients demonstrated iron in hepatic macrophages and hepatic fibrosis. Of these four patients, one had CLL, DM, and alcohol use, and had been receiving chemotherapy and blood transfusions. The other three patients each had a solid tumor (lung, pancreas, and esophagus), had received varying amounts of blood transfusions, and the latter two had received radiation or chemotherapy.

Larger studies of the prevalence of hemochromatosis in multiracial populations have been undertaken. Edwards et al[17] describe a large-scale prospective screening study of blood donors in Utah. Fasting transferrin saturation of 62% was used to identify probands, who were then asked to undergo percutaneous needle biopsy and HLA typing. Of 11,065 donors, 668 had transferrin saturation greater than 50%, and 221 had transferrin saturation greater than 61%. Of the 668, 42 had saturation greater than 61% when re-tested while fasting. Of these, 35 had liver biopsies, and seven of these had liver biopsies considered diagnostic of hemochromatosis. Seven siblings with identical HLA types had saturation >61%.

Nine additional patients with increased (but not diagnostic) hepatocellular iron concentrations were identified.

In total, when fasting transferrin saturation was used as a screening tool, 0.45% of men tested had an elevation of serum transferrin, demonstrating a gene frequency of 6.7% among the population. This was a study conducted among a mostly white population, however, and women had notably lower saturation than did men. Iron loss through menstruation or childbirth may not play a role, as transferrin saturation drops only when iron-deficient erythropoiesis becomes imminent. Notably, the serum ferritin was a relatively poor indicator of iron status: of 25 homozygotes, only 10 had elevated ferritin values.

Another study compared ferritin, transferrin saturation, and C282Y mutation among blood donors in England. This study noted that a transferrin saturation of 46% had 100% sensitivity and 95%specificity for iron overload among men, and became less sensitive and more specific with higher threshold values. However, homozygosity for C282Y mutations was not necessarily associated with high transferrin or ferritin levels; four patients homozygous for the mutation had transferrin saturation less than 46% and ferritin level of 109 ug/L or less. However, the odds of a C282Y homozygote having a saturation >46% was 56 times that of a heterozygote or normal.[18]

In a separate study, Edwards evaluated the variation of transferrin saturation over a 24-hour period in treated and untreated hemochromatosis patients. He noted an average transferrin saturation of 70% (range 32-107) among previously phlebotomized males (n=19) with ferritin values ranging from 2 ng/ml to 291 ng/ml. Untreated men (n=11) demonstrated an average of 81% saturation with an average serum ferritin of 489 ng/ml. Untreated women had an average saturation of 69%, with an average ferritin of 957 ng/ml. Normal volunteers had an average saturation of 52% in men and 46% in women. (Edwards, 1989). There was very little variation during the day for most patients thought to be homozygotes.

Other prevalence studies have been undertaken. Phatak et al[19] studied 16,031 patients from primary care clinics in Rochester, NY, where patients over age 18 underwent transferrin saturation testing. Patients who had elevated ferritin levels and elevated iron saturation were offered liver biopsy. This procedure was used to make the diagnosis when possible; patients who did not have this procedure were diagnosed with hemochromatosis if their transferrin saturation was greater than 55% and serum ferritin greater than 200 with no identifiable cause of secondary iron overload were considered to have the disease.

In all, 25 patients had hemochromatosis proven by biopsy, and another 22 had clinically proven hemochromatosis. Only one patent, from the latter group, was African-American. Based on the African-American population of 2268 patients screened, the authors calculated a prevalence of 0.9 per thousand patents screened, compared to 5.4 per thousand for the white group.

Other studies have estimated the prevalence to lie between 3 and 8 per thousand among Caucasian populations.[20]

Genetic Studies in African Americans

Since the discovery of the HFE gene in 1996, the incidence of the mutation has been evaluated in a number of population groups. In the first group of patients studied after identification of the gene, the C282Y mutation was shown to be present on 85% of 178 patients tested (148 homozygotes and 9 heterozygotes), with a near absence of H63D.[21] A study done in Oxford by Merryweather[22] of 2978 people of different ethnic backgrounds found that while C282Y allele frequencies were relatively high in some populations, they were absent in others. Irish and Danish people tested had a 10% and 9.5% allele frequency, respectively. The gene was absent from African, Asian, and Australasian (n=1085) subjects, though there was a zero to three percent incidence of H63D among those populations. In a follow-up to Moyo's 1998 study, 25 individual Africans with a high likelihood of having a genetic predisposition to iron overload were tested for both C282Y and H63D; none carried either of the two mutations. [23]

Most patients with hereditary hemochromatosis are homozygous for C282Y, while smaller numbers are compound heterozygotes for C282Y and H63D.[24] To our knowledge, the C282Y mutation has not yet been described in African-American patients.

Methods

Patient Selection

We retrospectively reviewed the records of African American patients presenting to a general internal medicine practice in White Plains, NY. During the period from 1992 to 2000, these patients were screened for elevated ferritin levels. (Smith-Kline Beecham laboratories). Patients who did not originally have an elevated ferritin had been sporadically retested as clinically warranted. Cases of interest were defined as those patients with a ferritin level greater than 300 in men and 250 in women. Identified cases were screened for hemoglobinopathies, assessed for the presence of diseases that might cause a secondary elevation of ferritin, and, after the tests became available, underwent genetic testing for the C282Y and H63D mutations.

Laboratory Testing

Genetic testing was carried out by Smith-Kline Beachem. Serum Ferritin was tested by Quest Diagnostics as well as by a local hospital laboratory. In all cases, blood ferritin levels, blood glucose, liver function indices, and hematocrit were measured. A hemoglobin electrophoresis was also done. In many patients, but not all, percent transferrin saturation was measured. One patient underwent abdominal MRI to evaluate iron deposition in the liver.

Intervention:

Patients identified as having possible iron overload by elevated ferritin levels were asked to adhere to a low iron diet (free of red meat, iron-containing vitamins, vitamin C supplements, corn, and certain vegetables such as spinach and collard greens). Male patients who had a hematocrit of >.35 and women with a hematocrit of >.33 underwent phlebotomy. A total of 450 cc of blood was removed at each session, each containing approximately 250 mg of iron. One patient who was anemic (AgB) was treated with Procrit rather than phlebotomy.

Results

1,315 Black patients of non-African birth (but of African or Caribbean descent) underwent screening during the 8 years of screening. This group consisted of 866 women and 446 men. Patients ranged in age from 27 to 70. Sixty-two cases were identified as having an elevated serum ferritin. Twenty-five of these were ultimately excluded because of various hemoglobinopathies [8 SS, 1 SC, 4 AS, 1 AC, 5 Alpha Thalassemia trait, and Six Beta thalassemia trait]. Two patients were excluded for inflammatory diseases. The remaining thirty-five patients had normal hemoglobin electrophoresis. Table 1 shows the peak ferritin levels for the patients, as well as their response to phlebotomy. All but nine of these thirty-five patients underwent phlebotomy. Phlebotomized blood was discarded by the blood bank.

Altogether, there were 15 diabetics, 16 patients with arthritis, 11 hypertensive patients, 13 with high cholesterol, 5 with Coronary Artery Disease (CAD), and five with erectile dysfunction.

Of note, two patients tested positive for the presence of mutations. One patient, a 69-year-old diabetic woman (#11), was found to be heterozygous for C282Y after we noted a serum ferritin of 1187. She refused phlebotomy (her hematocrit has been .36-.39), and has been treated with a low iron diet, with a decline in her ferritin to 763.

A second patient (#33) is a gentleman who was found to be a heterozygote for the H63D mutation. He presented with a ferritin of 583. After 5 phlebotomies over the course of 9 months, his ferritin dropped to 178. This began to rise after phlebotomy was discontinued, and reached 246 six months after the cessation of phlebotomy.

A third patient (#17) was treated with Procrit, rather than phlebotomy, because of a low baseline hematocrit. Her hematocrit rose from 31% to 41.6% over a period of approximately one year, with a drop in her serum ferritin from 534 to 156.

We have noted that the average peak ferritin at presentation among the diabetic patients tended to be higher than that of the non-diabetic patients (651 vs. 454, p=.066). Four of the fifteen diabetic patients had peak ferritin levels that exceeded those of all non-diabetics. Two diabetic individuals had ferritin levels that exceeded 1000, something not found in African-Americans.

Transferrin saturation levels among these patients were less likely to be elevated. Only two patients (numbers 7 and 8) had elevated transferrin saturations. Notably, a transferrin saturation of 42% is about 2 standard deviations above the mean for African-Americans in the second National Health and Nutrition Examination Survey. (Moyo, 1998).

Discussion

We would like to point out that this case series of African-Americans with iron overload is notable because it contains the first documented African-American patient to carry the C282Y mutation for hemochromatosis. This was one of two mutations of the population tested; the other, an H63D mutation, has already been reported in the literature (Merryweather et al). A review of the patient's pedigree revealed no Caucasian relatives in the two generations of family history available. While the allele has not been described in studies of African patients, there is a prevalence of admixture between Caucasian and African genes in the African-American population, though we could detect no such admixture in this patient or her ancestors. One study of African-Americans in Pittsburgh suggested that the prevalence of Caucasian genes among this population might be as high as 25.2%.[25] Another possibility is that of a de novo mutation in this patient. Our C282Y heterozygote has refused phlebotomy, and we have recently measured her ferritin at 1071 with an iron saturation of 17% at a time when her erythrocyte sedimentation rate was only 29. We believe that this is a strong argument for the use of ferritin as a screening tool in Black patients.

We have demonstrated a prevalence of hemochromatosis in African-American patients to a degree not previously seen in other studies of patients of this background. The prevalence of 2.6% far exceeds that previously reported in both African-Americans and Caucasians, and may be an overestimation of the true prevalence among African-Americans. We believe this has resulted from using serum ferritin as a screening tool and an expanded case definition to include those with serum ferritin above 300 in the absence of secondary causes.

Patients suspected of having inflammatory diseases were eliminated from the study, as these are causes of elevated ferritin. The 8 patients whose erythrocyte sedimentation rates were checked had rates of

four to 30 mm/hour. Additionally, patients found to have abnormal hemoglobin electrophoresis were also excluded, because of dyserythropoiesis that could be associated with an elevated serum ferritin, because of decreased RBC half-life leading to greater iron turnover.

In the American Society of Hematology 2000 Education Manual, Brissot et al argue that liver biopsy may be avoided in patients who have a serum ferritin of less than 1000, normal transaminases, and who have no hepatomegaly.[26] Previous studies demonstrate good correlation of MRI findings and hepatic iron as measured by biopsy[27,28]. Therefore, an alternative method such as an abdominal MRI may be used to look for iron in the liver. In our patient who presented with a ferritin of 1906 (#15), an abdominal MRI did demonstrate iron in the liver (see figures 1 and 2).

We have also noted a relatively rapid response to phlebotomy and diet among our patients. Only three required more three phlebotomies to treat their iron overload, and ten patients were able to lower their ferritin through iron-depleted diets alone. One patient was successfully treated with Procrit. Here, we believe the Procrit caused the patient to use her own storage iron for the production of red blood cells. No patient required desferrioxamine.

We have observed that the mean peak ferritin among the diabetic group exceeded that of the non-diabetics (651 vs. 454, p=.066). Given iron's role in the 'bronze diabetes' of genetic hemochromatosis, we believe that this data suggests a greater severity of iron overload among the diabetic portion of the population. We have not, however, formally studied the role of phlebotomy on the effect of diabetes in these patients.

Conclusion:

Our suggestion of using serum ferritin to screen for hemochromatosis in African-Americans is contrary to the reports of transferrin saturation as the more sensitive and specific test for the disease in Caucasians. One study by Dadone[29] found serum ferritin to be an inferior test to the percent saturation, but this study was carried out largely among Caucasians. We believe that ferritin, rather than transferrin saturation, should be used for screening the African-American population. We have demonstrated that the

percent saturation is relatively low in most of the patients we tested and suggest that this should not be used to screen for the disease in African-American patients.

Iron overload has a similar phenotypic presentation in both African-Americans and Caucasians. We have documented that 15 of our 35 patients are diabetics, and have noted patients with cardiomyopathy, erectile dysfunction, decreased libido, and arthritis. We suggest screening patients who present with any of these as they may be manifestations of iron overload.

Because our patients responded well to phlebotomy, an inexpensive measure, we would advocate for a screening program among African Americans using the serum ferritin in addition to the transferrin saturation as screening parameters. We believe that this will result in a greater identification of cases than is currently observed using transferrin saturation alone. Ferritin is a relatively inexpensive test, costing $56 at one of our laboratories.

Finally, while we recognize the low prevalence of C282Y mutations among this population, we suggest continued genotypic testing of those patients with elevated ferritin. Ten to fifteen percent of patients with iron overload in the United States do not have any of the recognized genetic mutations (C282Y, H63D, or S65C)[28]. We believe that this speaks to the heterogeneity of this disease and hypothesize that other mutations have not yet been found. We therefore recommend further study of the genetic origin of this disease in African-Americans.

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Figure 1: Axial T1 weighted image through the liver with normal T1 signal.

Figure 2: Axial T2 weighted image through the liver with loss of signal of the liver secondary to iron deposition disease.

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