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A comparison between whites and blacks with severe, multi-organ iron overload identified in 16,152 autopsies

James C. Barton, Ronald T. Acton, Laura E. Anderson, and C. Bruce Alexander

Southern Iron Disorders Center, Birmingham, Alabama, Departments of Medicine, Microbiology, and Pathology, University of Alabama at Birmingham, Birmingham, Alabama

Abstract

Background & Aims—Little is known about differences in the prevalence of severe iron overload at death in whites and blacks. We evaluated data and samples from 16,152 autopsies (8,484 whites, 7,668 blacks) performed at a single university hospital.

Methods—Cases of severe, multi-organ iron overload were identified by review of autopsy protocols and Perls-stained tissue specimens, analysis of hepatocyte and Kupffer cell iron levels, and measurement of liver tissue iron concentrations.

Results—We analyzed autopsy data from 10,345 adults (age ≥ 21 y), 1,337 children (1–20 y), and 4,470 infants (<1 y). Iron overload without reports of excessive exogenous iron was observed in 18 adults; the prevalence in whites and blacks was 0.0019 and 0.0015, respectively ($p = 0.6494$). Twenty-nine adults and 2 children had iron overload with reports of excessive exogenous iron. In adults, the prevalences of iron overload with reports of excessive exogenous iron in whites and blacks were 0.0040 and 0.0013, respectively ($p = 0.0107$). Among adults, the prevalence of cirrhosis was 6-fold greater in those with iron overload. In adults with severe iron overload, 67% without reports of excessive exogenous iron and 14% with reports of excessive exogenous iron died of hepatic failure or cardiomyopathy due to siderosis. The overall prevalence of deaths due to severe iron overload in whites and blacks was 0.0021 and 0.0009, respectively ($p = 0.0842$).

Conclusions—The prevalence of severe iron overload without reports of excessive exogenous iron did not differ significantly between whites and blacks. The prevalence of iron overload with reports of excessive exogenous iron was greater in whites. Hepatic failure and cardiomyopathy were common causes of death in severe iron overload cases.

Correspondence: Dr. James C. Barton, G105, 2022 Brookwood Medical Center Drive, Birmingham, AL 35243, Telephone 205.877.2888; FAX 205.877.2039, ironmd@dnaimail.com.

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Keywords

African Americans; hemochromatosis; cirrhosis

Introduction

Iron overload (IO) in U.S. adults is usually due to heritable disorders such as hemochromatosis or to chronic erythrocyte transfusion. More than 80% of U.S. whites with hemochromatosis are homozygous for the *HFE* missense mutation C282Y.^{1,2} The prevalence of mild or moderate non-transfusion IO in persons without C282Y homozygosity is similar in whites and blacks.³ Acquired anemia may occur in either whites or blacks.

There are few prevalence estimates of severe, multi-organ IO in U.S. whites and blacks examined at autopsy at a single institution. A Baltimore study of 47,961 subjects described coronary atherosclerosis in 41 adults (24 whites, 17 blacks) with multi-organ IO phenotypes not due to chronic transfusion.⁴ Another study reported hepatic iron concentrations in 157 white and 99 black adults in a St. Louis hospital.⁵ Some reports of IO in U.S. autopsy case series of adult blacks are based solely on examination of livers.^{6,7} Other reports do not specify the race/ethnicity of study subjects.⁸

We reviewed 16,152 evaluable autopsy protocols of a Birmingham, Alabama university hospital for the interval 1945–2001. We tabulated the types of severe, multi-organ IO phenotypes without and with reports of excessive exogenous iron, compared the prevalence of IO cases in whites and blacks, and estimated the prevalence of deaths due to IO. We discuss the relationships of the present observations to clinical case series of hemochromatosis and IO, to prevalence estimates of IO in other U.S. autopsy series, and to rates of hemochromatosis- and IO-associated mortality in U.S. whites and blacks.

Materials and Methods

Overall selection and characterization of cases

This project was approved by the Institutional Review Board of the University of Alabama at Birmingham. We performed a manual and computerized review of all autopsy protocols of the Department of Pathology for the interval February 1, 1945–March 26, 2001. We used the autopsy protocols as the sole source of clinical information. We defined infants as subjects aged <1 year, children as subjects aged 1–20 years, and adults as subjects aged ≥21 years. We defined “whites” as subjects designated as “white” or “Caucasian.” We defined “blacks” as subjects designated as “black,” “colored,” “Negro,” or “African American.”

Identification of subjects with severe iron overload

We first identified potential severe multi-organ IO cases by evaluating autopsy protocols for diagnoses that suggested IO or related conditions. Sections of tissues obtained at respective autopsies had been prepared with Perls technique at the discretion of the autopsy pathologist. We performed microscopic review of all tissues in all cases selected by initial review of autopsy protocols in which excessive iron was reported in two or more tissues by the autopsy pathologist (n = 204). We confirmed the presence of severe, multi-organ IO in 49 (24.0%) of these cases using grading of hepatocyte and Kupffer cell iron and by reviewing all other tissues stained for iron. We also measured liver iron concentrations in cases in which paraffin-embedded liver was available. We did not review cases for tissue iron content if excessive stainable tissue iron were not reported by the autopsy pathologist. Details of these methods are displayed in a Supplemental File.

Causes of death due to severe iron overload

We defined two causes of death as consequences of IO: 1) hepatic failure (including primary liver cancer) associated with severe iron deposition in hepatocytes, Kupffer cells, or both; and 2) cardiomyopathy due to myocardial siderosis.

Statistical Considerations

There were 21,262 autopsy cases; 16,152 were evaluable. Exclusions and analyses are described in a Supplemental File. Values of $p < 0.05$ were defined as significant.

Results

Characteristics of 16,152 subjects

Protocols of 16,152 subjects ages 0–105 years comprised 8,484 whites and 7,668 blacks. There were 10,345 adults (3,728 white men, 2,044 white women, 2,668 black men, and 1,905 black women), 1,337 children, and 4,470 infants (Fig. 1).

Severe iron overload phenotypes without reports of excessive exogenous iron

There were 18 adult cases (11 whites, 7 blacks) (Table 1). Nine whites had phenotypes consistent with hemochromatosis; more than three-quarters had cirrhosis. Six blacks had phenotypes consistent with African American IO; one-half had cirrhosis. Three young adults (two white, one black) had clinical and pathologic phenotypes of juvenile hemochromatosis. 9 Each had cirrhosis; two died of cardiomyopathy due to myocardial siderosis (Table 1). The mean age of the juvenile hemochromatosis subjects was lower than that of subjects with either hemochromatosis or African American IO phenotypes ($p < 0.0001$, respectively).

Severe iron overload phenotypes with reports of excessive exogenous iron

There were 31 cases, including two children (Table 2). Thirty subjects (96.7%) had IO attributed predominantly to chronic erythrocyte transfusion; the other subject had IO due to chronic ingestion of iron supplements. Seven subjects (22.6%) had cirrhosis; one had cardiomyopathy due to myocardial siderosis (Table 2).

Hepatocyte and Kupffer cell iron grades in severe iron overload cases

In cases without reports of excessive exogenous iron, the mean hepatocyte and Kupffer cell iron grades were 3.4 ± 0.7 and 2.1 ± 1.1 , respectively. Mean hepatocyte iron grades did not differ significantly between whites and blacks; likewise, mean Kupffer cell iron grades did not differ between these groups. In cases with reports of excessive exogenous iron, the mean hepatocyte iron grade was 3.7 ± 0.8 and the mean Kupffer cell iron grade was 2.7 ± 0.6 . Previous reports indicate that iron appears in the Kupffer cells of persons with hemochromatosis and severe IO, perhaps as a consequence of hepatocyte necrosis. Iron deposition in hepatocytes occurs in severe transfusion IO.¹⁰

Liver iron concentrations in severe iron overload cases

Paraffin blocks containing liver were available for one case without report of excessive exogenous iron; the hepatic iron concentration was 5,945 $\mu\text{g/g}$ dry weight (hepatic iron index 1.8 $\mu\text{mol/g}$ dry weight/y). Liver was available in fourteen cases with reports of excessive exogenous iron; the mean hepatic iron concentration ($\pm$ S.D.) in these cases was $20,134 \pm 14,381$ $\mu\text{g/g}$ dry weight (range 5,594–56,695 $\mu\text{g/g}$ dry weight; mean hepatic iron index 10.3 ± 8.7 , range 1.7–31.5 $\mu\text{mol/g}$ dry weight/y).

Prevalence of severe iron overload in adults

The overall prevalence of cases without reports of excessive exogenous iron was 0.0017 (18/10,345) and that of cases with reports of excessive exogenous iron was 0.0028 (29/10,345). These prevalence estimates did not differ significantly. The overall prevalence in whites was 0.0059 (34/5,772) and in blacks was 0.0028 (13/4,573) ($p = 0.0221$). The prevalence of cases without reports of excessive exogenous iron in whites was 0.0019 (11/5,772) and in blacks was 0.0015 (7/4,573) ($p = 0.6494$). The prevalence of cases with reports of excessive exogenous iron in whites was 0.0040 (23/5,772) and in blacks was 0.0013 (6/4,573) ($p = 0.0107$). The prevalence of cases without reports of excessive exogenous iron in men was 0.0016 (10/6,396) and in women was 0.0020 (8/3,949) ($p = 0.5836$). The prevalence of cases with reports of excessive exogenous iron was 0.0023 in men (15/6,396) and was 0.0041 (16/3,949) in women ($p = 0.1229$).

Prevalence of cirrhosis

The prevalence of cirrhosis in adults with severe IO was 0.4286 (21/49), and the prevalence of cirrhosis in all adults was 0.0640 (662/10,345) ($p < 0.0001$). Cirrhosis was not present in the two children with severe IO.

Prevalence of death due to severe iron overload in adults

Death due to IO occurred in 12 of 18 adults (66.7%) with severe IO without reports of excessive exogenous iron (Table 1). Death due to IO was reported in 4 of 29 adults (13.8%) with severe IO with reports of excessive exogenous iron (Table 2). The prevalence of deaths due to IO was greater in cases with severe IO without reports of excessive exogenous iron ($p < 0.0001$). Deaths due to severe IO were reported in 12 whites (10 men, 2 women) and 4 blacks (1 man, 3 women). The prevalence of IO-related deaths in whites (0.0021; 12/5,772) and blacks (0.0009; 4/4,573) did not differ significantly.

Severe iron overload in children and infants

Two of 1,337 children had IO associated with chronic transfusion (Table 2). Neither of them had cirrhosis or cardiomyopathy. The prevalence of IO associated with reports of excessive exogenous iron in children did not differ significantly from that in adults (0.0015 vs. 0.0028). We identified no cases of severe IO, cirrhosis, primary liver cancer, or myocardial siderosis in 4,470 infants.

Discussion

Severe, multi-organ IO causes death in some central Alabama whites and blacks, consistent with clinical case series from this geographic area.^{2,11–13} The prevalence of severe IO without reports of excessive exogenous iron in whites was 0.0019 and in blacks was 0.0015. Using data from a Baltimore study,⁴ we deduced that the prevalence estimates of non-transfusion IO were also similar in whites (0.0008) and blacks (0.0009). We cannot exclude the possibility that some of the present cases without reports of excessive exogenous iron arose due to primary cirrhosis (e.g., due to viral hepatitis or alcoholism) complicated by secondary accumulation of iron. For example, Ludwig and colleagues reported that iron content was elevated in 20.3% of 447 cirrhotic livers, and that the hepatic iron index was 1.9 in 8.5% of the 447 subjects.¹⁴ Nonetheless, in that and other studies of cirrhotic livers, information about the iron content of organs other than the liver was not reported.^{14–17} We observed that only 21 of 662 subjects with cirrhosis (3.2%) had multi-organ IO. This is consistent with previous reports that the combination of elevated serum iron measures and genetic markers typical of *HFE* hemochromatosis is very uncommon in persons with cirrhosis.^{14–17} We observed that 13 of 18 subjects (72.2%) who had severe, multi-organ IO

without reports of excessive exogenous iron also had cirrhosis. Except the subject with compound heterozygosity for *HJV* G320V/I222N, determining which of these 13 subjects had a primary IO genotype was beyond the scope of the present study.

The overall prevalence of severe, multi-organ IO at autopsy was greater in whites than blacks. This difference was due largely to the two-fold greater prevalence of cases with reports of excessive exogenous iron in whites than in blacks. This is consistent with the report of Brown *et al.*, in which 27 adults examined at autopsy in St. Louis had hepatic iron concentration greater than twice the upper limit of normal; 23 (85.1%) had received transfusion.⁵ Some present subjects who received chronic transfusion may have also had increased absorption of dietary iron, especially those with refractory sideroblastic anemia¹⁸ or sickle cell disease.¹⁹ We observed severe IO attributed to chronic ingestion of iron supplements was observed in one adult with beta-thalassemia minor, consistent with a previous report.²⁰

Severe IO in infants or children was uncommon. Only two children had severe IO; both received multiple erythrocyte transfusions. We observed no cases of neonatal hemochromatosis or acute iron poisoning, the most common form of accidental intoxication of children. We did not identify subjects with juvenile hemochromatosis phenotypes who died in childhood or early adolescence.¹³

The prevalence of cirrhosis in adults with severe IO was more than six-fold greater than that in all adults. Corresponding observations have been reported previously.²¹ Hepatic failure due to cirrhosis was the predominant cause of death in subjects we identified without reports of excessive exogenous iron, but was an uncommon cause of death among cases with reports of excessive exogenous iron. In many reports, the relative risk of primary liver cancer is increased in persons with severe IO, especially those with cirrhosis.^{21–24} We did not discover cases of severe, multi-organ IO associated with primary liver cancer, but the number of severe IO cases with cirrhosis herein is small.

The present study substantiates that deaths associated with severe, non-transfusion IO do not occur only in whites. In a large North American screening study, 0.0003 of blacks and 0.006 of whites had both elevated transferrin and ferritin measures and abnormal *HFE* genotypes. ²⁵ *HFE* C282Y homozygosity is uncommon in African Americans.^{1,25} There is a paucity of genotypes in African Americans that would explain non-transfusion IO.^{19,26–29} Altogether, this suggests that a relatively high proportion of severe IO cases in African Americans is due to non-genetic factors. In contrast, hepatic IO measured at hospital or coroner autopsy is relatively common in non-transfused African American adults.^{5–7,30} There are significant positive correlations of heavy liver iron staining with hepatic steatosis, inflammation, and fibrosis/cirrhosis, and of elevated serum iron measures with hepatitis C RNA positivity in African Americans.^{7,31} African Americans have higher mean levels of serum ferritin than whites,^{1,25,31} due in part to a greater prevalence of common liver disorders in African Americans.^{25,31} These observations suggest that hepatic IO in non-transfused African Americans is more often related to common liver disorders than to primary, multi-organ IO.

Multiple-cause mortality data from U.S. death certificates indicate that mortality rates for hemochromatosis and IO increased progressively during the interval 1979–1992.³² Nonetheless, the proportion of persons with hemochromatosis who develop serious or life-threatening complications of IO is small;³³ most have normal life expectancy.³⁴ In contrast, life expectancy is decreased in persons with severe secondary IO.^{35,36} U.S. mortality rates for hemochromatosis and IO were approximately three-fold greater for whites than for non-whites of all ages.³² We did not observe significant differences in the prevalence of severe

IO in white and black adults. In a previous report, listings of “liver disease” and “cardiomyopathy” on death certificates were more prevalent in cases with hemochromatosis or IO than in control decedents,³² consistent with the present observations.

The prevalence estimates of IO in this autopsy series are conservative. The autopsies were performed to ascertain causes of death and not to detect or quantify IO, and thus some IO cases may have been overlooked by clinicians or autopsy pathologists. The proportion of persons with *HFE* hemochromatosis and severe IO in the general population cannot be estimated accurately from the present autopsy data due to selection biases. Large hospital autopsy series include only persons with fatal outcomes in academic medical centers who had attending physicians and family members motivated to learn more about their medical conditions. Some patients may have had little or no IO at death because they had been treated with phlebotomy. Nonetheless, our prevalence estimates of severe IO in adults are similar to those in another autopsy study of adults that used similar autopsy protocol review criteria.⁴

The prevalence of severe, multi-organ IO phenotypes in African Americans in the present study was relatively low (0.15% without and 0.13% with reports of excessive exogenous iron). The prevalence of hepatic IO in three previous autopsy studies of African Americans was relatively high (1.2–9.1%), with or without adjustment for previous transfusion.^{5–7} In one report, more than half of African American subjects who had heavy hepatic iron staining also had hepatic inflammation, and more than one-quarter had hepatic steatosis.⁷ A greater proportion of African Americans than persons of other races respond to chronic hepatitis C infection with an increase in iron stores, after adjustment for age, alcohol intake, gender, menopausal status, education, body mass index, and poverty index.³¹ Thus, we postulate that three previous studies included many African Americans who had inflammatory liver disorders associated with hepatic but not systemic IO.^{7,37,38}

The present autopsy series does not comprise all hospital patients who died at our institution during the study interval, and therefore our results may not include all subjects who had severe IO at death. Over the 56-year interval of the autopsy series, the respective protocols of 5,109 persons examined by autopsy were unavailable or inevaluable; the autopsy on a single Asian subject (without IO) was excluded. We presume that the prevalence of severe IO and related conditions in the excluded cases would have been similar to that in the present cohort. It is possible that we excluded some cases of hemochromatosis or IO in subjects who had severe liver injury, especially if extrahepatic organ or tissue samples stained using Perls technique were not examined by the autopsy pathologist. Nonetheless, there was good correspondence of the descriptions of hepatic iron deposition described in the autopsy protocols and our independent histologic grades of iron positivity in liver sections.

In summary, we identified 49 cases of severe multi-organ IO in 16,152 hospital autopsies. Severe IO without reports of excessive exogenous iron was observed in 18 adults; the prevalence in whites and blacks did not differ significantly. Twenty-nine adults and two children had severe IO due to excessive exogenous iron attributed predominantly to erythrocyte transfusion. In the latter 29 adults, the prevalence of severe IO was greater in whites than in blacks. Among all 10,345 adults, there was a six-fold increase in the prevalence of cirrhosis in those with severe IO. In the 49 severe IO cases, hepatic failure and cardiomyopathy were common causes of death. The overall prevalence of deaths due to severe IO in whites was numerically greater than that in blacks, but these estimates did not differ significantly.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

IO iron overload

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Figure 1.
Ages at death of 16,152 subjects at hospital autopsy

Table 1

Characteristics of 18 subjects with severe iron overload without reports of excessive exogenous iron¹

Iron overload phenotype (n)	Mean age, y (range)	Men; women	Hepatic cirrhosis, % (n)	Death due to iron overload, % (n) ²
Hemochromatosis (9)	57 ± 11 (45–75)	7; 2	77.8 (7)	66.7 (6)
African American iron overload (6) ³	59 ± 18 (24–73)	2; 4	50.0 (3)	50.0 (3)
Juvenile hemochromatosis (3) ⁴	27 ± 9 (21–37)	1; 2	100.0 (3)	100.0 (3)

¹ There were 11 white and 7 black adults. Phenotypes are defined in the Supplemental File and elsewhere.^{9,11,13,26,39}

² Twelve subjects died of complications of iron overload. Ten died of hepatic failure. Two subjects with juvenile hemochromatosis phenotypes died of cardiomyopathy caused by myocardial siderosis.

³ A 24 year-old black female with iron overload had sickle cell disease but was never transfused, consistent with previous reports.¹⁹

⁴ A 23 year-old white female had hemojuvelin (*HJV*) G230V/I222N compound heterozygosity.³⁹

Table 2

Characteristics of 31 subjects with severe iron overload with reports of excessive exogenous iron ¹

Cause of iron overload ²	Mean age, y	Men; women	Hepatic cirrhosis, % (n)	Death due to iron overload, % (n) ³
Chronic erythrocyte transfusion (30)	46 ± 17 (12–74)	14; 16	23.3 (7)	13.3 (4)
Oral iron supplements (1)	49	1; 0	100.0 (1)	100.0 (1)

¹There were 24 whites and 7 blacks; 29 subjects were adults and two were children (12 year-old black female with severe aplastic anemia; 20 year-old white male with Fanconi anemia).

²Underlying disorders in 30 subjects who received chronic transfusion were hematologic malignancies (n = 17; 14 whites, 3 blacks), renal failure (n = 5; 4 whites, 1 black), severe heritable forms of anemia (3 sickle cell disease (all blacks); 1 Fanconi anemia (white)), severe aplastic anemia (n = 3; 2 whites, 1 black), and anemia of unstated cause (n = 1; white). A white man with beta-thalassemia minor ingested oral iron supplements daily for decades.

³Three subjects died of hepatic failure; one died of cardiomyopathy.