Clinical Trial

Hemochromatosis and Iron Overload Screening Study (HEIRS)

First received on May 25, 2000. Last updated on April 13, 2016.

Purpose

To determine the prevalence, genetic and environmental determinants, and potential clinical, personal, and societal impact of iron overload and hereditary hemochromatosis, in a multi-center, multiethnic, primary care-based sample of 100,000 adults. The study is conducted by the Division of Epidemiology and Clinical Applications of the NHLBI, the Division of Blood Diseases and Resources of the NHLBI, and the Ethical, Legal, and Social Implications (ELSI) Research Program of the NHGRI.

Status Completed
Condition Blood Disease
Phase N/A
Study Type Observational
Study Design N/A

Further study details (as provided by National Institutes of Health Clinical Center (CC))

Detailed Description

BACKGROUND: Hereditary iron overload, or hemochromatosis, is a common inherited disorder among Caucasians, with an estimated prevalence of 0.25-0.50 percent, though it is mistakenly believed by many to be quite rare. The disease is insidious in onset, and many or even most individuals diagnosed with this disorder are not identified until advanced organ damage is present. However, in the absence of anemia, which can be caused by tissue damage from iron in late stages of the disease, it is relatively easy to treat the disorder by removing the excess iron through repeated phlebotomy. Evidence suggests that early diagnosis and treatment can prevent disease manifestations and enable normal life expectancy The discovery of the HFE C282Y and H63D variants in the HLA gene region on chromosome 6 provides an opportunity for early and rapid genetic identification of individuals at risk for development of hereditary hemochromatosis. Much remains to be learned about the penetrance and expression of these alleles, including their relevance to the full spectrum of clinical disease. To date, the HFE alleles appear predominantly associated with disease mainly in populations of Caucasian descent. While 80-90 percent of Caucasian hemochromatosis patients have HFE abnormalities, there are hetero- and homozygotes that do not manifest any evidence of disease, or manifest disease at different ages and with different outcomes, implying the existence of other genetic or environmental factors. Similarly, not all hemochromatosis patients have HFE abnormalities. Other genes yet to be discovered are also likely to be involved in pathogenesis of iron overload and familial hemochromatosis in non-Caucasian populations as well. This project is intended to examine the genetic and environmental determinants and correlates of iron overload and hereditary hemochromatosis in diverse populations. Increases in body iron may be due to increased absorption (hemochromatosis), increased oral intake of non-therapeutic iron, unneeded iron therapy, or multiple blood transfusions in the absence of bleeding. The excess iron is deposited in body tissues, and can reach toxic levels leading to organ damage. The toxicity can affect most tissues and organs, but particularly the liver, causing cirrhosis; the endocrine system, causing diabetes, hypogonadism, and sometimes hypoparathyroidism; and the heart, causing arrhythmias and cardiomyopathy. Iron overload and hereditary hemochromatosis have not been as extensively studied in non-Caucasian racial/ethnic groups as they have in Caucasians. The toxicity of excess iron in non-Caucasians appears to be similar to that in Caucasians, but the prevalence of iron overload is unknown and while a genetic contribution to that overload is suspected it has not been proven in all groups. It has long been assumed that iron storage disease in populations of sub-Saharan Africa is due to increased iron absorption from beer brewed in iron pots, but more recent information suggests there is also a hereditary component to that accumulation of iron. However, iron overload among Africans does not appear to be due to HFE abnormalities, nor to other genes in the HLA region at all. Primary iron overload has been reported in African Americans but it remains to be determined

whether or not this is linked to HFE or other genetic factors. Iron overload has been reported in Asian populations, but the frequency and genetic contributions (if any) are not known. In some studies where HFE variants have been found in non-Caucasians, additional genetic testing has suggested that Caucasian admixture may have been involved. Hispanic-Americans appear to have a frequency of iron overload similar to non-Hispanic Caucasians, although further study of the genetic and environmental correlates is warranted. There has been almost no study of iron overload and hereditary hemochromatosis in Native American populations. Hemochromatosis may be suitable for detection and intervention through primary care or population-based screening strategies because: 1) it is relatively common; 2) it is asymptomatic in its early stages; 3) screening methods are reliable; 4) standard diagnostic methods are widely available in developed countries and relatively inexpensive; 5) it is easily treatable; and 6) if untreated, the subsequent burden of morbidity and mortality is substantial. The feasibility and benefits of such programs remain to be assessed, however, since the prevalence of the disorder and the factors related to its phenotypic expression (such as the optimal age for reliable detection and effective intervention) are unknown. Other questions needing to be addressed include public acceptability of screening and testing; sensitivity and specificity of the screening methods, particularly in non-Caucasians; optimal timing and setting of screening and testing; as well as the benefits and costs and/or other burdens associated with screening and testing. A major objective of the project is to gather information needed to develop recommendations regarding possible primary care- or population-based screening for hemochromatosis. Estimating the burden of preventable illness from unrecognized hemochromatosis is one of the most important of these needs. Comparing the relative value and acceptability of diagnosis and screening by genotype vs phenotype is also important. In particular, differences by racial/ethnic group, age and other characteristics will need to be examined. Some of these issues, such as appropriate thresholds for transferrin saturation screening, may be resolved during the proposed study's planning phase, while others will constitute key research questions to be addressed by the study itself.

DESIGN NARRATIVE: The Hemochromatosis and Iron Overload Screening Study is a multi-center epidemiological study of the prevalence and genetic and environmental determinants of iron overload and hereditary hemochromatosis in a diverse and representative primary care-based sample of men and women aged 25 and older. Over 101,000 patients undergoing routine screening or testing involving a blood draw were recruited from five Field Centers and screened for transferrin saturation levels. Cost-effective population-based strategies for recruitment was also considered. A repeat fasting transferrin saturation screen in conjunction with a serum ferritin assay was used to identify potential 'case' participants with confirmed elevated transferrin saturation levels and matched random 'control' participants with confirmed non-elevated transferrin saturation levels. In order to obtain data on the prevalence of genetic factors in a routine care population, a random subgroup of approximately 20-40 percent of the 101,000 screenees will be genotyped for known variants, such as HFE C282Y and H63D, related to iron metabolism and overload. The panel of genotypes to be assayed will reflect the state of knowledge at the time this phase of the study is conducted. In particular, any newly discovered variants related to iron overload and hemochromatosis in non-Caucasian populations, such as for iron overload among Africans, will be included. The results of the genotyping will not directly impact the selection of case and control participants; case/control selection will be based only on the transferrin saturation/serum ferritin screen results. It is likely that many HFE genotype positive persons will have confirmed elevations of transferrin saturation and thus may get selected as confirmed elevated transferrin saturation case participants. Genotype positive persons with non-elevated transferrin saturation levels, who are not randomly selected as controls, will constitute a third group and undergo the same intensive studies as cases and controls. A random sample of the individuals being recruited to participate in the genotyping subgroup will be surveyed to determine their knowledge and attitudes about, interest in, and support for such screening programs. Both qualitative and quantitative measures will be employed. Efforts will be made to ascertain reasons for refusal and related information from those who decline participation. In addition, 2,000 primary care patients will be selected to participate in a substudy comparing phenotype- versus

genotype-based screening and testing methods. Following these transferrin and random subgroup genotyping screens, a comprehensive clinical examination will be conducted in the confirmed elevated transferrin saturation potential case participants, the genotype-positive participants, and the confirmed non-elevated control participants to assess iron stores, distinguish between primary and secondary causes of iron overload and to examine the associated hepatic, endocrinologic, hematologic and cardiovascular disease correlates and sequelae of hemochromatosis. A detailed family and medical history will be obtained. Examination participants not previously genotyped will undergo genotyping, with a panel of genotypes as described above, for use in association analyses. The genotype-positive participants will receive counseling on their results. The examination will also include an extended ELSI assessment of issues related to genetic screening and testing and diagnosis of disease. Data will be collected on the participants' acceptability of genetic testing, their experience with screening, their understanding and interpretation of their results, and on the impact this information is having on their own lives as well as those of their family members. Specific components of the comprehensive clinical examination will be determined during protocol development. Follow-up ELSI assessments will examine issues such as impact of the screening program on relationships with family members, and any experiences with stigmatization and discrimination. A family study, using comprehensive clinical examinees as probands, will seek to identify modifier genetic variants related to the expression of iron overload and hereditary hemochromatosis disorders via genome scanning and assessment of linkage. Identification of new genetic variants, particularly in minorities, is also of great interest, but it is possible this study will not achieve sufficient power to do so. Proposed efforts to improve the power, such as combining data from other studies, will be considered. The family study ELSI assessment will examine family members' experiences with the screening program, the impact of this information on their lives and relationships, and any experiences with stigmatization and discrimination. A repository of blood specimens will be established to permit additional studies of genetic and environmental factors relating to iron overload. This will require careful attention to the details of informed consent. For some later studies, the specimens may be anonymized. The study has five Field Centers, a Coordinating Center (which will subcontract for any necessary Reading Centers such as an ECG Reading Center), and a Central Laboratory (which may subcontract for novel assays and/or the genome-wide scan).

Eligibility

Criteria

No eligibility criteria

Contacts and Locations

Please refer to this study by its ClinicalTrials.gov identifier: NCT00005541

Locations

Sponsors and Collaborators
National Heart, Lung, and Blood Institute (NHLBI)

More Information

Other Publications