Changing the Clinical Management of Hereditary Hemochromatosis

Translating Screening and Early Case Detection Strategies Into Clinical Practice

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Background: This article describes the effect of an extensive physician educational program on detection and management of hereditary hemochromatosis (HH) before and after a hemochromatosis population screening study.

Methods: We measured the changes in clinical management by medical chart review for newly diagnosed cases before and after the educational program. The effect on detection of HH cases was determined by mail survey to primary care physicians in our health system.

Results: The median age at diagnosis of HH was 54 years before the study and 45 years after the study (P=.12). In the same period, among those with diagnosed hemochromatosis, the mean prestudy ferritin level changed from 1848 ng/mL to 606 ng/mL after the study (P=.03). The mean number of units removed by phlebotomy to complete “de-ironing” in diagnosed patients was 40 U before the study and 18 U after the study (P=.06); the number of months required for de-ironing was 15 months before the study and 6 months after the study (P=.02). Before the study, no primary care physician was screening for HH. Two years after completion of the study, 11% (6/54) of primary care physicians indicated they had continued to screen all patients for hemochromatosis.

Conclusions: Early detection and treatment of iron overload may be facilitated by educating health care providers and insurers about an “iron-avid” state, occurring in healthy patients who would benefit from periodic surveillance of their iron status. Continued education of physicians concerning diagnosis and treatment of HH aids progress toward increased early case detection.

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January 1999, the Primary Care Department Executive Committee reviewed the study data and endorsed hemochromatosis screening as a preventive health measure using a 1-time serum iron and total iron-binding capacity assessment. This article describes changes in patient comorbidities, iron burden, and outcomes of hemochromatosis care in the St John’s Health System before and after the educational intervention. We also report on the results of surveys and interviews of physicians regarding their screening practices for hemochromatosis. The study received institutional review board approval.

METHODS

MEDICAL CHART REVIEW

A medical chart review of the clinical characteristics and care of patients identified and treated for hemochromatosis was conducted at the largest multispecialty clinic (90 physicians) within the St John’s Health System. Clinical symptoms, laboratory data, and comorbidities associated with HH were collected, including arthritis, cardiac disease, abnormal liver functions, fatigue, abdominal pain, glucose intolerance, and hepatomegaly. The clinic had data tapes of 10 years of claims data. Before 1997, the clinic included 15 internists or family practitioners. From 1997 to 1999, 6 new internists or family practitioners joined and 2 internists retired. Data tapes for all claims data from 1990 through 1999 were reviewed, and all patients who had a claim submitted using International Classification of Diseases, Ninth Revision code 275.0 (disorder of iron metabolism) were identified. Medical records for these patients were reviewed.

Clinical information was included if the diagnosis of hemochromatosis was established by a physician at the clinic between 1990 and 1999, based on at least 1 of the following criteria: (1) homozygosity for C282Y mutation and serum ferritin level greater than the 95th percentile for sex, (2) hepatic iron index of 1.9 or greater, (3) hepatic iron concentration greater than 2000 μg/g with no other clinical reason for iron overload, or (4) more than 4 g of iron removed by quantitative phlebotomy, defined by 1 to 2 U weekly until hemoglobin equaled 10 g/dL or serum ferritin was less than 20 ng/mL. Iron depletion (“de-ironing”) was considered complete if at the end of phlebotomy serum ferritin was 20 ng/mL or less or the postphlebotomy hemoglobin persisted below 11 g/dL without further phlebotomies.

PHYSICIAN SURVEYS AND INTERVIEWS

At the outset of the screening study, we recognized that physician educational materials and tools available to guide evaluation of patients with suspected hemochromatosis were inadequate to support a population screening study, especially in a setting of multiple practice sites. The content of standard texts on hemochromatosis was primarily directed toward the evaluation of advanced, symptomatic cases. Therefore, we developed and field tested educational materials to ensure the appropriate management of patients identified in the study with early HHs and defined the appropriate interpretation of the newly identified HFE genetic test.

Educational materials developed to support the study included the following: (1) a short primer on the natural history of hemochromatosis, advancing from excess iron uptake to asymptomatic iron overload to symptomatic disease and significant morbidity; in addition, the rationale for screening and the tests to be used, including iron measures and HFE genotype tests, were discussed in the primer; (2) a “decision matrix,” which was an algorithm to stage patients based on the results of the serum iron, total iron-binding capacity, ferritin, and HFE genotype data; (3) clinical management guidelines presented as a flow diagram to direct the physicians in the initial diagnosis of hemochromatosis, de-ironing, and subsequent management; (4) a set of form letters that could be used to notify physicians and patients of results; and (5) an educational booklet for patients and their families to explain hemochromatosis and the HFE genotype results. To ensure acceptance of the proposed physician clinical management tools and physician educational materials, all were reviewed and approved by the 7 gastroenterologists and 2 hematologists employed by the St John’s Health System. These specialists were chosen because they would most likely be the referral physicians for patients identified by the screening study. The physician educational packet was distributed to all health system primary care and medical specialty physicians at the start of the screening study.

All internists and family practitioners in St John’s Health System were surveyed early in the study to determine whether the patient care plan packet of educational materials prepared for the study was helpful; the return rate was 96% (67/70). The survey was in a brief yes or no answer format with a request for written comment on the usefulness and clarity of the physician educational tools. The educational tools were further refined based on this input. The exceptional response rate was presumed to be because of the educational activities and involvement of local specialists and collaboration with the Centers for Disease Control and Prevention Public Health Preparedness Program.

A second survey in 2000 sought to determine how many physicians were routinely screening for hemochromatosis. The survey was mailed to all 98 internists and family practitioners, with a 55% (54/98) return. This survey was sent 2 years after completion of the population screening study and associated educational activities. The second survey was considerably longer and more complex; we attribute the lower return rate to these factors. The clinicians are located among 80 clinics across much of southwest Missouri and northwestern Arkansas, varying from urban to rural settings. Equal proportions of surveys were returned from internists and family practitioners and from clinics inside Springfield vs those in rural areas. The surveys included structured questions and allowed additional space for comments. Except for 3 physicians hired since the time of the screening study, most of the responding physicians had received the original patient care plan educational packet (12 did not remember receiving the packet) and the follow-up materials, including the results of the screening study and the document from the Primary Care Department Executive Committee in February 1999 that included the educational brief on hemochromatosis and recommendations endorsing screening for hemochromatosis as a preventive health measure.

RESULTS

MEDICAL CHART REVIEW

Preceding the educational intervention for the screening study, 2 persons per year were diagnosed as having HH. Subsequent to the screening study education, 8 persons per year were diagnosed during the 2 years of follow-up. Several clinical variables were different in patients diagnosed as having hemochromatosis before the study compared with those diagnosed afterward (Table), although not all changes were statistically significant. The median age at diagnosis changed from 54 years to 45 years...
(P = .12), the mean ferritin level at presentation decreased from 1848 ng/mL to 606 ng/mL after the study (P = .03), and the mean number of units removed for phlebotomy to complete de-ironing changed from 40 U to 18 U (P = .06). The number of months required for de-ironing changed from 15 months to 6 months (P = .02). De-ironing was completed in 10 of 13 patients before the study and in 14 of 15 patients after the study (P = .09).

The mean iron saturation test result for the group as a whole was 74% (range, 48%-95%). Twelve patients underwent liver biopsy with hepatic iron concentrations that ranged from 2056 µg/g to 30477 µg/g. Genetic test results were recorded for 3 (20%) of 15 of the presstudy patients and 14 (93%) of 15 of the poststudy patients. Among the presstudy patients, 2 men were C282Y homozygotes and 1 woman was a C282Y heterozygote with a 20-year history of supplemental iron use; she presented with a serum ferritin level of 4228 ng/mL before de-ironing. Among poststudy patients, 12 were homozygous for the C282Y mutation, 1 was a compound heterozygote, and 1 was homozygous for the H63D mutation; the latter patient also had hereditary spherocytosis and had developed iron loading after splenectomy.

Medical record review suggested that patients presented with a greater number of comorbidities in the presstudy than in the poststudy era, but asymptomatic patients were rare in both periods. Given the small series, it is not possible to conclude that there was a significant difference in comorbidities associated with HH. The major observed difference was that 100% of patients (13) in the presstudy period had at least 1 chronic medical diagnosis. In the poststudy period, however, 40% of patients (6/15) had no other chronic medical diagnosis except HH. Recommendations for family screening were documented in the medical chart for all but 1 patient in both periods.

PHYSICIAN SURVEYS AND INTERVIEWS

Of the respondents to the first physician survey, 86% (48 of 57 who responded to the question) indicated that they had used the educational materials to evaluate patients during the screening study, and 91% (51 of 56 who responded to the question) indicated that the educational materials “were helpful in evaluating patients.” In the second survey done 2 years after the study closed, we attempted to determine whether physicians were still screening for HH. Of the 54 respondents to the second survey, only 6 (11%) indicated they were currently screening for hemochromatosis (Figure). Four of the 6 who were routinely screening had diagnosed hemochromatosis in the past 2 years.

In an open-ended question, 4 reasons were commonly given for not screening. Twenty-three (48%) of 48 responses cited the lack of a screening recommendation by a major health advisory body such as the Centers for Disease Control and Prevention, National Institutes of Health, or United States Preventive Health Services Task Force. In 18 responses (38%), physicians indicated that they considered screening appropriate but had not yet incorporated it into their usual preventive health practice. Ten responses (21%) indicated lack of knowledge of the correct screening test and appropriate follow-up. Eight physicians (17%) had stopped screening be-
cause of insurance reimbursement denials. One physician had ceased screening as a result of “not having found a case.”

By interviewing primary care providers about the survey results, we also found resistance to the application of a diagnosis of hemochromatosis in the absence of more traditional criteria for iron overload as found in medical textbooks. The primary care physicians did, however, accept the recommendation to follow-up such “iron-avid” but not iron-loaded patients without a clinical diagnosis of hemochromatosis with an annual or a biannual serum ferritin test, with reinvestigation if an abnormal serum ferritin finding occurred.

Our data suggest that hemochromatosis was detected more frequently and at an earlier age at an earlier stage of iron overload during and after our screening study, compared with the period before. This effect may be an artifact due to changes in practice among a small number of providers. Given the lack of a control group and changes in the physician pool, we cannot conclude that the physician educational program was responsible for earlier detection of cases. It seems likely, however, that the various activities related to the screening study, including physician education, heightened awareness of hemochromatosis as a clinical diagnosis among at least some physicians in the community.

Despite data from the screening study demonstrating undiagnosed cases in the employee population, only a small percentage of internists and family practitioners continued to screen for HH after the study closed. Our data suggest that primary care physicians were reluctant to screen in the absence of recommendations from major advisory organizations such as the Centers for Disease Control and Prevention. They were also reluctant to apply the diagnosis of HH to asymptomatic patients with elevated serum iron measures, as advised by the College of American Pathologists and a Centers for Disease Control and Prevention expert panel. The fact that physicians were reluctant to diagnose HH solely based on College of American Pathologists criteria is consistent with another expert panel recommendation on the appropriate nomenclature in iron-overload disease.

It may be an important educational objective to increase primary care physician familiarity with the concept of the iron-avid state as a detectable stage in the natural history of HH and its potential to progress to clinically important iron overload. In our experience, delaying the formal diagnosis of hemochromatosis until the patient developed serum ferritin levels just above the upper limits of normal has not yet resulted in identifying a patient with more than 4 g of mobilizable iron. These results are consistent with findings recently published showing that cirrhosis is rare in association with serum ferritin levels less than 1000 ng/mL. As long as the patient returns for subsequent examinations, the risk of clinical disease seems to be minimal with this strategy, and it avoids diagnoses of hemochromatosis in those whose risk for this condition is unknown. Therefore, a heightened awareness of hemochromatosis and a preceding iron-avid state may help physicians to consider the diagnosis appropriately in the differential diagnosis of patients with nonspecific symptoms seen early in the course of the disease.

Whether clinicians should screen for HH as opposed to considering the diagnosis only in certain clinical settings is controversial. Early detection provides an opportunity to initiate de-ironing treatment, preventing late-stage complications such as cirrhosis, and some experts advocate universal screening to accomplish this goal. Such screening has already been endorsed and is practiced in other health systems (eg, Kaiser Permanente). Others favor a case-finding approach within clinical care settings, mainly because of the concern that a large number of persons who screen positive by serum iron measures might never require treatment and thus might be exposed unnecessarily to the social and medical consequences of the diagnosis of hemochromatosis without health benefit. This distinction is important because emerging data suggest that many people with a genetic susceptibility to iron overload remain healthy without treatment. For example, screening investigations in southern California estimated that only half of people with the C282Y/C282Y HFE genotype—the genotype conferring the highest risk for iron overload—develop elevated transferrin saturation, and as few as 1% develop clinical symptoms.

At St John’s Health System, we addressed many of the barriers to screening before advising screening as a preventive health strategy. Screening by iron saturation testing for hemochromatosis in our community was endorsed by the county medical society, county public health department, and a county- and city-sponsored community action committee to promote public health. As a measure to support screening within our region, we were able to persuade the medical director for Medicare Part B services for Missouri to approve reimbursement of serum mean iron saturation testing (local medical review policy 64) if supported by diagnosis codes for diabetes mellitus, cardiomyopathy, cardiac dysrhythmia, abnormal elevation of transaminases, or an elevated serum iron level, thus addressing an important concern of our physicians. In addition, our local blood bank received a Food and Drug Administration variance to use therapeutic phlebotomy blood from otherwise eligible hemochromatosis donors for transfusion. Missouri state legislation has protection, albeit incomplete, against insurance carriers using genetic test results as preexisting conditions. With these protections in place, our health system concluded that recommendations for screening were appropriate in our community. However, even with intense local education and removal of barriers to screening, this study shows that screening is unlikely to be sustained without additional interventions.

We recommend that physicians be educated about an iron-avid state as a risk factor for HH. It will be helpful to physicians and patients to recognize that such individuals are not ill and require monitoring rather than medical treatment. Whether this concept will be endorsed by clinicians or will protect patients from insur-
formance discrimination or other adverse effects of labeling will need to be assessed in future studies. This approach is important, however, because the diagnosis of hemochromatosis before the onset of clinical disease requires a high degree of suspicion or universal screening. Yet, this practice will identify many persons with abnormal iron saturation who do not have an abnormal ferritin level or evidence of clinical iron overload; their likelihood of progressing to clinical disease will be low but substantially above that of the general population. Conversely, in the absence of screening, community-based investigations suggest that most patients will still be iron overloaded when diagnosed. Whether screening produces a net benefit, given the attendant labeling and follow-up concerns for healthy people with evidence of “iron avidity,” is an important public health issue.

Before screening or increased efforts at early case detection are undertaken, work will need to be done in collaboration with insurance carriers to ensure that serum iron and total iron-binding capacity testing is reimbursed when used for screening or case finding for HH or secondary iron overload. Because most carriers follow the lead of the Health Care Financing Administration, we recommend that clinicians advocate for a change in adjudication rules to reimburse the use of mean iron saturation tests for the indication of case finding to evaluate some chronic symptoms. We suggest that it is clinically valid to use the iron saturation test to evaluate depression, fatigue, weakness, arthralgias, arthritis, glucose intolerance, early gonadal failure, impotence, abnormal liver functions, chronic abdominal pain, cardiomyopathy, cardiac dysrhythmia, or congestive heart failure in patients in whom another specific cause is not found by history, physical examination, or other evaluation.

Finally, to be able to diagnose and manage the iron-avid state and early stages of hemochromatosis, physicians will need to have ready access to a graphical, easy-to-understand algorithm similar to tools developed to help manage hyperlipidemia to prevent atherosclerosis. Easily assimilated educational tools with decision-support algorithms as we created for our population study must be disseminated to guide management of (1) iron avidity measured by the serum mean iron saturation test, (2) iron burden measured by serum ferritin level, liver biopsy, or quantitative phlebotomy, (3) genetic risk as determined by detection of the known mutations if present, and (4) clinical manifestations of iron overload. These tools will need to be updated as research provides additional information about the factors that affect the transition from the iron-avid state to clinically significant iron overload. These are not insurmountable barriers, and development of and implementation of such tools may help to avert the significant health burden associated with hemochromatosis.

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REFERENCES