Hyperferritinemia in the Chinese and Asian community: A retrospective review of the University of British Columbia experience

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BACKGROUND AND METHODS: Elevated serum ferritin is a common clinical finding. The etiology of hyperferritinemia in the Asia-Pacific population is less clear due to a low prevalence of known HFE mutations such as C282Y and H63D, as well as an increased prevalence of viral hepatitis and hereditary anemia. A retrospective case review of 80 patients of Asian ethnicity referred to three subspecialists in tertiary care teaching hospitals between January 1997 and March 2005 for assessment of hyperferritinemia was performed.

RESULTS: Only four patients (5%) had iron overload on liver biopsy or quantitative phlebotomy. Forty-nine patients (61%) had secondary causes for their hyperferritinemia, of which 26 had liver disease; 16 of those patients also had viral hepatitis. Thirteen patients fulfilled criteria for the insulin resistance syndrome. Other causes included hematological disorders (n=10), malignancy (n=2) and inflammatory arthritis (n=2). Twenty-seven cases (34%) of unexplained hyperferritinemia were found. Of a total of 22 patients who underwent liver biopsy, significant iron deposition was found in one patient. Fifteen patients underwent C282Y and H63D genotyping, with two cases of H63D heterozygosity. Fourteen patients had first-degree relatives with hyperferritinemia. Three families were identified with more than two members affected, which is suggestive of a possible hereditary hyperferritinemia syndrome.

CONCLUSION: Secondary causes of elevated ferritin in the Asian population, particularly liver disease, are common, but primary iron overload syndromes appear to be rare. In a significant proportion of patients, the etiology remains unexplained. The genetic basis for hyperferritinemia in Asians is poorly defined and requires further study.

Key Words: Asian; Chinese; Ferritin; Hyperferritinemia; Iron

Classical hereditary hemochromatosis is currently the most well-described iron overload syndrome following the discoveries of the pathogenic gene on the short arm of chromosome 6 by Simon et al (1) and the coveries of the pathogenic gene on the short arm of chromosome 16 by Simon et al (1) and the.

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achieve a serum ferritin level less than 50 μg/L) were hepatic iron concentration and quantitative phlebotomy (to liver iron graded by the Tirmann-Schmelzer technique (10), in liver enzymes were found. Results of liver biopsy, stainableatitis C virus (HCV) serology was performed if abnormalities women and 0.50% in men. Hepatitis B virus (HBV) and hep-
transferrin saturation was defined as greater than 0.45% in
ed elevated transferrin saturation. Two patients underwent liver biopsies, alcohol intake, iron supplementation and liver
der intermediate and per cent saturation were determined. Elevated transferrin saturation was defined as greater than 0.45% in
settings of alcohol consumption, insulin resistance and inflammatory states.
With this in mind, we report our review of a series of patients of Asian ethnicity referred to three subspecialists in
tertiary care teaching hospitals for assessment of hyperferritinemia. A significant proportion of these patients had iso-
het offense syndrome. Seven patients underwent phlebotomy, with a
amount of 8.4 treatments to achieve a serum ferritin level of less

### RESULTS
A total of 80 consecutive patients (53 men and 27 women) were reviewed. Demographics are displayed in Table 1. The majority of patients were of Chinese ethnicity (n=66, 82.5%). Japanese (n=5, 6.25%), Vietnamese (n=5, 6.25%), Filipino (n=3, 3.75%) and Thai patients (n=1, 1.25%) accounted for the remainder. Forty-nine patients (61%) had alternate explanations for their hyperferritinemia. Twenty-seven patients (34%) had isolated and unexplained elevations in serum ferritin. Only four patients (5%) had primary iron overload that was demonstrated on liver biopsy or quantitative phlebotomy. Twenty-two patients underwent liver biopsy, with significant iron deposition in one patient. An analysis for HFE mutations (C282Y, H63D) in 15 patients revealed only two cases of H63D heterozygosity.

In the four patients with primary iron overload, the mean serum ferritin level was 2444 μg/L (range 690 μg/L to 6000 μg/L). Three patients required 21, 27 and 30 phlebotomies to achieve a serum ferritin level of less than 50 μg/L. One patient had qualitative iron overload on liver biopsy with grade III iron deposition in hepatocytes and Kupffer cells. She was H63D heterozygous but could not tolerate therapeutic phlebotomy due to anemia. Three of these patients had a concomitant diagnosis of viral hepatitis (HCV, n=2; HBV, n=1). One patient was H63D heterozygous.

Of the 49 patients with secondary causes, 26 had liver disease; the most predominant diagnosis was viral hepatitis in 16 patients (HBV, n=7; HCV, n=8; HBV and HCV coinfection, n=1). Causes of nonviral liver disease included nonalcoholic steatohepatitis (n=4), excessive alcohol intake (n=3), Wilson’s disease (n=1), autoimmune hepatitis (n=1) and undefined liver disease (n=1). Hematological disorders were identified in 10 patients (thalassemia variants, n=8; myelodysplastic syndrome, n=2). Two patients had malignancies, and two had inflammatory arthritis (Figure 1). Thirteen patients had one or more features of the insulin resistance syndrome: body mass index greater than 25 kg/m², diabetes or hyperlipidemia. Ten patients had more than one identifiable cause. The mean serum ferritin level was 1135 μg/L (range 394 μg/L to 5277 μg/L) but was higher in the viral hepatitis group (mean 1780 μg/L, range 667 μg/L to 5277 μg/L). Eighteen patients underwent liver biopsy, with eight showing no increase in stainable iron, and 10 showing grade I or II iron deposition. Quantitative iron assessment was performed in two patients, both with normal hepatic iron concentration (less than 25 μmol/g). Eight patients were tested for HFE mutations (C282Y, H63D), with the lone finding of H63D heterozygosity in a patient with insulin resistance syndrome. Seven patients underwent phlebotomy, with a mean of 8.4 treatments to achieve a serum ferritin level of less than 50 μg/L. Twenty-one patients had elevated transferrin saturation.

A cause for hyperferritinemia was indeterminate in 27 patients. The majority of patients (26 of 27) had normal liver biochemistry. The mean ferritin level in this group was 811 μg/L (range 351 μg/L to 1747 μg/L). One patient with abnormal liver biochemistry demonstrated on two occasions had normal transferrin saturation, and negative HBV and HCV serology. In five patients tested, no HFE mutations were found. Seven patients had elevated transferrin saturation – two patients underwent liver biopsy, which showed mild stainable iron, while the remaining patients underwent

<table>
<thead>
<tr>
<th>TABLE 1Clinical and biochemical characteristics of Asian patients referred to subspecialists for hyperferritinemia (n=80)</th>
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<tbody>
<tr>
<td><strong>Age (at referral), years, mean (range)</strong></td>
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<tr>
<td><strong>Male, n (%)</strong></td>
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<td><strong>Female, n (%)</strong></td>
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<td><strong>Ethnicity, n (%)</strong></td>
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<td>Chinese</td>
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<td>Thai</td>
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<td><strong>Serum ferritin level, μg/L, mean (range)</strong></td>
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<td><strong>Transferrin saturation, %, mean (range)</strong></td>
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<td><strong>HFE genotyping, n</strong></td>
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<tr>
<td>C282Y homozygote/heterozygote</td>
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<tr>
<td>H63D homozygote</td>
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<tr>
<td>H63D heterozygote</td>
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<td>C282Y/H63D compound heterozygote</td>
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The present study received approval from the Clinical Research Ethics Board at the University of British Columbia, Vancouver, British Columbia. A retrospective office chart review was performed on all patients of Asia-Pacific ethnicity (ie, Southeast Asian) who were referred to three tertiary care hospital-based subspecialists (one gastroenterologist and two hematologists) for assessment of hyperferritinemia between January 1997 and March 2005. For inclusion into the study, an elevated ferritin level was defined as a level greater than 200 μg/L in women and 300 μg/L in men.

### PATIENTS AND METHODS

**Patients**
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**Methods**
Demographic data were collected on all patients. Patients underwent a clinical assessment by a subspecialist at the time of referral, including documentation of family history of liver disease or known hyperferritinemia; history of red blood cell transfusions, alcohol intake, iron supplementation and liver disease; as well as a physical examination. Baseline blood count, liver enzymes, serum iron level, total iron binding capacity and per cent saturation were determined. Elevated transferrin saturation was defined as greater than 0.45% in women and 0.50% in men. Hepatitis B virus (HBV) and hepatitis C virus (HCV) serology was performed if abnormalities in liver enzymes were found. Results of liver biopsy, stainable liver iron graded by the Tirmann-Schmelzer technique (10), hepatic iron concentration and quantitative phlebotomy (to achieve a serum ferritin level less than 50 μg/L) were recorded, if performed.
quantitative phlebotomy, all requiring fewer than eight phlebotomies (less than 2 g of elemental iron removed). A total of eight patients underwent a phlebotomy, with an average number of 6.6 treatments. In the entire cohort, 14 patients had first-degree relatives with hyperferritinemia, representing eight families. The genealogy of two of the three families that had more than two members affected is shown in Figure 2.

**DISCUSSION**

**Secondary causes**

In the present study, we described a series of patients of Asian descent who were referred to three tertiary care subspecialists for assessment of hyperferritinemia. Elevated serum ferritin is a common clinical finding. In the HEIRS study (3), 101,168 primary care adults were screened for clinical, laboratory and genetic features of iron overload. Of 98,529 patients without a previous diagnosis of hereditary hemochromatosis or iron overload, 8652 (8.8%) had elevated serum ferritin levels (greater than 400 µg/L in men and 300 µg/L in women). The prevalence of hyperferritinemia in participants of Asian background (mean ± SD 19.00%±0.35%) was higher than in the majority of other ethnic groups (3,9).

A significant proportion of our patients had alternate explanations for elevated ferritin levels. Liver disease was found in a majority of these patients (26 of 49), with the most common diagnosis being viral hepatitis (16 of 49). This finding is consistent with both epidemiological data demonstrating the high prevalence of chronic HBV infection in Asian populations (11), as well as a documented association between chronic viral hepatitis and elevated serum markers of iron stores (12,13). A similar study in a multiracial population found that the majority of patients referred for elevated ferritin levels did not have HFE-linked hemochromatosis (14). Diagnoses of HBV and HCV were equally common in our study, likely reflecting the partial gastroenterology referral base in our study.

The mean ferritin level in our patients with viral hepatitis was 1780 µg/L (range 667 µg/L to 5277 µg/L), which is higher than the mean ferritin levels reported in other studies (12,15). None of our 12 patients with viral hepatitis who underwent liver biopsy had significantly elevated hepatic iron content by qualitative analysis, corroborating previous reports that elevated ferritin in the setting of chronic viral hepatitis does not correlate with hepatic iron stores (12).

Hyperferritinemia, in association with features of the metabolic syndrome, has been reported, although a causal link remains to be established (16,17). This syndrome, dysmetabolic hyperferritinemia, is characterized by an elevated ferritin level, the insulin resistance syndrome (one or more of body mass index greater than 25 kg/m², diabetes or hyperlipidemia) and mild hepatic iron excess (18). Thirteen patients (16%) fulfilled criteria for the insulin resistance syndrome.

**Primary iron overload**

In our series, true iron overload was suggested in four patients (5%) by liver biopsy or quantitative phlebotomy. Three patients had a concomitant diagnosis of viral hepatitis (HCV, n=2; HBV, n=1), and the fourth patient had no other identifiable cause for iron overload. Her serum ferritin level was greater than 6000 µg/L, and 30 phlebotomies (7.5 g iron) were required to achieve a serum ferritin level of less than 50 µg/L. Only 5% of the total liver biopsies (one of 22) demonstrated significant iron overload (Timmann-Schmelzer method grade III or IV), compared with 36% of liver biopsies (52 of 146) in a similar multicentric study (14). The present data appear to substantiate current evidence showing that primary iron overload syndromes are rare in Asians (19-21).

**Isolated hyperferritinemia**

In 27 patients, a secondary etiology was not found, despite an extensive assessment. In the small number of cases in which liver biopsy or quantitative phlebotomy was performed, the results were not consistent with significant hepatic iron excess (less than 2 g of iron removed to achieve a serum ferritin level of less than 50 µg/L). HFE mutation analysis in this group revealed no C282Y or H63D alleles and two cases of H63D

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**Figure 1** Etiology of hyperferritinemia in 80 Asian patients. Fe Iron; IRS Insulin resistance syndrome; Misc Miscellaneous; MDS Myelodyplastic syndrome

**Figure 2** Pedigree of the elevated ferritin phenotype in two families (per cent saturation [% sat] = transferrin saturation). Shaded squares (men) and circles (women) represent individuals who express elevated ferritin. Question marks indicate an unknown phenotype.
REFERENCES

9. Conclusions

Our data suggest that, in referral populations, alternative explanations for hyperferritinemia are common in Asians, but primary iron overload syndromes are rare. The evaluation of these patients should include assessments for occult viral hepatitis and features of the metabolic syndrome. Hyperferritinemia is rare in this population, and testing for these alleles is seldom useful. Regardless, in a significant proportion of Asian patients with hyperferritinemia, the etiology remains unexplained, with a suggestion of a familial basis in some cases. This may represent a hereditary hyperferritinemia syndrome specific to the Asian population. Ferroportin mutation analysis, which is not commercially available in British Columbia, may be helpful in the future, but the genetic causes of isolated hyperferritinemia, as well as underlying iron overload disorders in Asians, remain poorly defined and require further study.

CONCLUSIONS

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