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## Hereditary hemochromatosis of tongue

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Hereditary hemochromatosis (HH) refers to several inherited disorders of iron metabolism leading to tissue iron overload. Classical HH is associated with mutations in HFE (C282Y homozygotes or C282Y/H63D compound heterozygotes) and is almost exclusively found in populations of northern European descent. Non-HFE-associated HH is caused by mutations in other recently identified genes involved in iron metabolism. Hepcidin is an iron regulatory hormone that inhibits ferroportin-mediated iron export from enterocytes and macrophages. Defective hepcidin gene expression or function may underlie most forms of HH. Target organs and tissues affected by HH include the liver, heart, pancreas, joints, and skin, with cirrhosis and diabetes mellitus representing late signs of disease in patients with markedly elevated liver iron concentration. Recently, we have encountered the rare representation of this disease of the oral cavity associated with generalized burning sensation of the tongue. The diagnosis was established accidentally, from the lab investigations, otherwise the patient was healthy and free from classical signs and symptoms of the disease. The patient was adequately treated by phlebotomy. To conclude, all patients with a chief complaint of burning sensation of the oral cavity and tongue should be adequately screened for hereditary hemochromatosis to prevent the associated mortality and morbidity with the hemochromatosis. (**Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;111:e1-e5**)

Hemochromatosis is the abnormal accumulation of iron in parenchymal organs, leading to organ toxicity.<sup>1</sup> It is the most common inherited liver disease in whites and the most common autosomal recessive genetic disorder. The classic tetrad of manifestations resulting from hemochromatosis consists of (1) cirrhosis, (2) diabetes mellitus, (3) hyperpigmentation of the skin, and (4) cardiac failure. Clinical consequences also include hepatocellular carcinoma, impotence, and arthritis.

### PATHOPHYSIOLOGY

Hereditary hemochromatosis is an adult-onset disorder characterized by inappropriately high iron absorption resulting in progressive iron overload. The organs involved are the liver, heart, pancreas, pituitary, joints, and skin.<sup>2</sup>

Adults preserve a constant level of body iron by efficient conservation, maintaining rigorous control over absorption to balance losses. An adult man loses

approximately 1 mg of iron daily, mostly in desquamated epithelium and secretions from the gut and skin. During the childbearing years, healthy women lose an average of an additional milligram of iron daily from menstrual bleeding (40-mL blood loss) and approximately 500 mg with each pregnancy. In addition, normal daily fecal loss of approximately 0.7 mL of blood (0.3 mg of iron) occurs. Only a small quantity of iron is excreted in urine (<0.1 mg/d).

In healthy adults, losses are balanced by absorption of sufficient dietary iron (1 to 2 mg) to maintain a relatively constant amount of body iron throughout life. Although excretion is quantitatively as important as absorption in the maintenance of iron balance, absorption usually plays the more active regulatory role. In hereditary hemochromatosis, dysregulation of intestinal iron absorption occurs, wherein iron continues to be efficiently absorbed even in the face of substantial elevation of body iron stores.<sup>3</sup>

The gene responsible for the disease is called *HFE* and is located on chromosome 6. It is mutated in most individuals with hereditary hemochromatosis. *HFE* interacts with the transferrin receptor and causes a clear decrease in the affinity with which the receptor binds transferrin. This interaction also may modulate cellular iron uptake and decrease ferritin levels. When a mutant or nonfunctional variant of the *HFE* gene is present, ferritin levels are not under the influence of a normal and functional *HFE* gene, which leads to enhanced accumulation of iron in peripheral tissues.

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Fig. 1. Normal fissured tongue.

Findings suggestive of increased iron transport at the basolateral membrane of enterocytes in hemochromatosis have emerged from numerous studies of *HFE*-related hemochromatosis in humans<sup>4</sup> and in mice.

Hepcidin, a human antimicrobial peptide synthesized in the liver,<sup>5</sup> plays a key role in the downregulation of iron release by enterocytes and macrophages. The absence of this new peptide is associated with a severe early-onset iron-loading phenotype. It is also inappropriately low in adult-onset *HFE*-related disease.<sup>6</sup>

Excess iron is hazardous because it produces free radical formation. The presence of free iron in biological systems can lead to the rapid formation of damaging reactive oxygen metabolites, such as the hydroxyl radical and the superoxide radical. These can produce DNA cleavage, impaired protein synthesis, and impairment of cell integrity and cell proliferation, leading to cell injury and fibrosis.<sup>7</sup>

We have encountered 2 similar cases of hemochromatosis associated with burning sensation in the tongue with no further abnormality in the metabolic system of the body.

#### CASE REPORT 1

A 55-year-old female patient was referred to our outpatient dental hospital at Al-Yamamah Hospital, Riyadh, Saudi Arabia, with a chief complaint of generalized burning sensation of tongue for the past 1 year. History reveals that none of the family members were affected with similar symptoms. On examination, nothing abnormal was detected (Fig. 1). Other causes of burning mouth syndrome had been ruled out. Blood investigations showed persistently elevated transferrin saturation and serum ferritin higher than 200  $\mu\text{g/L}$ . Serum iron concentration was higher than 150  $\mu\text{g/dL}$ . Other investigations were within normal limits and the patient had no medical history. The complete blood count (CBC) of the patient was normal. Based on these findings, a diagnosis of hemochromatosis was established after consulting with her primary



Fig. 2. Smooth and blanched tongue.

care physician. The patient was referred to the hematology department for phlebotomy for the same and the symptoms were completely resolved. Adequate follow-up was done for 2 years and there was no recurrence of the disease.

#### CASE REPORT 2

A 40-year-old female patient was referred to our outpatient dental hospital at Al-Yamamah Hospital, Riyadh, Saudi Arabia, with the same complaint as mentioned in Case Report 1 (Fig. 2). The patient did not give any familial history with similar symptoms. The blood investigations showed elevated levels of transferrin and serum ferritin higher than 200  $\mu\text{g/L}$ . Serum iron concentration was 165  $\mu\text{g/dL}$ . The patient had no medical history and the CBC within normal limits. The hemoglobin report of the patient was also within normal limits. The histologic appearance of the labial salivary gland, with heavy deposition of iron in acinar and duct epithelial cells and absence of focal lymphoid cell infiltration, did not support a diagnosis of Sjögren syndrome. Based on the clinical and laboratory findings, a diagnosis of hemochromatosis was established. Adequate follow-up was done for 1 year and the patient remained symptom free; after that, the patient did not return for follow-up.

#### DISCUSSION

Hereditary hemochromatosis is an adult-onset disorder characterized by inappropriately high iron absorption resulting in progressive iron overload. The organs involved are the liver, heart, pancreas, pituitary, joints, and skin.<sup>8</sup>

#### Frequency

In the United States, the prevalence is approximately 1 case in 300 persons. Most are of northern European origin.<sup>9</sup> The carrier state is estimated to be approximately 10%.

Hemochromatosis has the same prevalence in Europe, Australia, and other Western countries, with the highest prevalence being noted in people of Celtic origin. Hemochromatosis is less common among Africans.<sup>10</sup>

**Mortality/morbidity**

Hemochromatosis results in liver cirrhosis, heart failure, diabetes mellitus, impotence, and arthritis. If untreated, hemochromatosis may lead to death from cirrhosis, diabetes, malignant hepatoma, or cardiac disease. Mortality is estimated to be 1.7 cases per 10,000 deaths. This number increases to 3.2 cases per 10,000 deaths in autopsy series. The death rate associated with hemochromatosis increased from 0.5 persons per million population in 1968 to 0.9 persons per million population in 1992 because of improved recognition of the disease.

**Race**

Prevalence in whites is 6 times higher than in African Americans. C282Y homozygotes account for 82% to 90% of clinical diagnoses of hereditary hemochromatosis among persons of northern European descent.<sup>11</sup> One in 227 white people were homozygotes for the *HFE* C282Y mutation, a genotype seen in more than 90% of patients with typical hemochromatosis.<sup>12</sup> The highest reported prevalence for C282Y homozygosity is 1 in 83 people in Ireland.<sup>13</sup> Recently, it has become prevalent in the Hispanic population. The frequency is much lower among Hispanic persons (0.27 in 1,000), Asian American individuals (<0.001 per 1,000), Pacific Islanders (0.12 per 1,000), and black persons (0.14 per 1000); the Celtic population is affected most frequently.

**Sex**

Men are affected more often than women, with an estimated ratio of 1.8:1. Disease related to iron overload commonly develops in men (but not in women) who are homozygous for the C282Y mutation, especially when serum ferritin levels are 1000 µg/L or more. The increased prevalence of iron-overload-related disease in C282Y homozygous men, compared with that in women, is frequently ascribed to recurrent physiological blood loss and the resultant slower accumulation of iron in women.<sup>14</sup> However, disparate frequencies of HLA A\*03B\*07 haplotypes in men and women have been reported in hereditary hemochromatosis probands, which may be relevant to sex-specific phenotypic expression of this disease.<sup>15</sup> Studies of iron regulatory pathways in African American individuals have also suggested that serum ferritin levels may be genetically determined by sex differences as well as environmental factors.<sup>16</sup>

**Table I. Clinical manifestations**

Clinical manifestations associated with hemochromatosis	
• Liver disease	
• Skin pigmentation	
• Diabetes mellitus	
• Arthropathy	
• Impotence in males	
• Cardiac enlargement, with or without heart failure or conduction defects	

**Table II. Symptoms and signs of hemochromatosis**

<i>Symptoms</i>	<i>Signs</i>
Early	Hepatomegaly
Severe fatigue (74%)	Skin pigmentation
Impotence (45%)	Arthritis
Arthralgia (44%)	Abnormal liver function tests
	Susceptibility to bacterial infections
	Chondrocalcinosis of hand and wrists
Late	
Hyperpigmentation (70%)	
Diabetes mellitus (48%)	
Cirrhosis	
Asymptomatic (75%)	
Cardiomyopathy	
Dilated cardiomyopathy	
Hypogonadism	
Hypothyroidism	

**Age**

The disease usually becomes apparent after age 40 years in men and after age 50 years in women. Median age in women is 66 years. Median age in men is 51 years.

Clinically, the tetrad of cirrhosis, diabetes mellitus, hyperpigmentation of the skin, and cardiac failure may be evident. However, symptomatology of hereditary hemochromatosis has changed in recent years, and its full clinical expression is seen in only a minority of patients. In addition, any patient admitted to the hospital with an isolated case of asthenia or with arthralgia or hypertransaminasemia should be examined by means of transferrin-saturation testing.

Tables I and II reveal the associated signs and symptoms with hemochromatosis; however, in our cases the patients were asymptomatic with generalized burning sensation of the tongue.

**Differential diagnosis**

The macular diffuse slate gray pigmentation observed in hemochromatosis of the tongue may resemble early laterally spreading melanoma, diffuse tattoo, Addisonian pigmentation, and heavy metal ingestion.

A history of documentation of cirrhosis and bronzing of skin should arouse suspicion of hemochromatosis of tongue. A biopsy with demonstration of diffuse iron

deposition, in conjunction with clinical findings and elevated serum iron levels allows for definitive diagnosis.

## OTHER CONSIDERATIONS

### Biliary cirrhosis

*Alcoholic liver disease.* Patients include those who are heavy drinkers, perhaps of iron-containing fortified wines, who have cirrhosis. Liver biopsy in these patients may show a modest increase in iron; however, contrary to patients with hemochromatosis, the hepatic iron levels are relatively normal and iron stores are less than 4 g.

*Ineffective erythropoiesis with marrow hyperplasia.* Patients with hyperplastic erythroid marrow absorb an increased amount of iron to the point where they may have clinical iron overload. Examples include the hereditary sideroblastic anemias, severe alpha and beta thalassemia, and the myelodysplastic syndrome variants, such as refractory anemia with ringed sideroblasts.

*Iron overload associated with chronic anemia.* Patients have increased effective erythropoiesis and increased iron absorption. Examples include hereditary spherocytosis and acquired sideroblastic anemia.

*Multiple transfusions.* Hypertransfusion is performed in patients with beta thalassemia major, sickle cell anemia, refractory aplastic anemia, and myelodysplastic syndrome. Such patients may receive as many as 100 U of red cells, which contain as much as 20 to 25 g of iron, similar to or more than the amount retained in many symptomatic patients with hereditary hemochromatosis.

*Porphyria cutanea tarda (PCT).* PCT is primarily is a skin and liver disease that occurs in familial and sporadic forms. The cause of liver siderosis in sporadic PCT has not been established, but it may be related to a mutation in the *HFE* gene in most patients.

### Causes

Hereditary hemochromatosis is fairly common in whites and is a result of iron deposition in hepatocytes, myocardial fibers, and other visceral cells. Iron excess is known to be responsible for hypermelanosis; however, the mechanism is not fully understood. Tsuji<sup>17</sup> found that hyperpigmentation of the skin occurs after iron injections in hairless mice. This hyperpigmentation was accompanied by hemosiderin accumulation in the skin. Stronger pigmentation of the fascial skin rather than the dorsal skin corresponded with elevated iron accumulation in the fascial part of the skin. The study suggests that the brownish discoloration of the skin in hemochromatosis may be dependent to some degree on hemosiderin accumulation. Hemosiderin is supposed to increase activation of melanocytes. By contrast, Smith

et al<sup>18</sup> in 1978 found normal levels of immunoreactive beta-melanocyte-stimulating hormone (beta-MSH) in patients with hereditary hemochromatosis and concluded that elevation of beta-MSH played no role in the pathogenesis of hyperpigmentation.

## WORKUP

### Laboratory studies

Measuring serum iron has no value in the diagnosis, but measuring transferrin saturation is necessary. Transferrin saturation corresponds to the ratio of serum iron and total iron-binding capacity. Similar to iron, it is influenced by liver disease (other than hemochromatosis) and inflammation; therefore, it has limitations in the diagnostic workup.

Hemochromatosis is suggested by persistently elevated transferrin saturation in the absence of other causes of iron overload. It is the initial test of choice. The screening threshold for hemochromatosis is a fasting transferrin saturation of 45% to 50%. Approximately 30% of women younger than 30 years who have hemochromatosis do not have elevated transferrin saturation. High transferrin saturation is the earliest evidence of hemochromatosis. A value greater than 60% in men and 50% in women is highly specific.

Serum ferritin levels elevated higher than 200  $\mu\text{g/L}$  in premenopausal women and 300  $\mu\text{g/L}$  in men and postmenopausal women indicate primary iron overload attributable to hemochromatosis, especially when associated with high transferrin saturation and evidence of liver disease. The American College of Physicians found insufficient evidence to recommend for or against the use of transferrin saturation and serum ferritin levels to help identify the early stages of hereditary hemochromatosis.<sup>19</sup> Genetic testing for the *HFE* mutation is indicated in all first-degree relatives of patients with hemochromatosis and also in patients with evidence of iron overload<sup>20</sup> (e.g., elevated transferrin saturation, high serum ferritin levels, excess iron staining, or iron concentration on liver biopsy samples). This is particularly indicated in patients with known liver disease and evidence of iron overload, even if other causes of liver disease are present.<sup>21</sup>

### Treatment

The goal of therapy in patients with iron overload disorders is to remove the iron before it can produce irreversible parenchymal damage.<sup>22</sup> Because a normal life span can be expected if iron reduction is initiated before the development of cirrhosis, clinical suspicion and early diagnosis are essential. Once diagnosed, hemochromatosis is treated by phlebotomy to rid the body of excess iron and to maintain normal iron stores. Recently, deferasirox, which is a rationally designed



oral iron chelator, has been introduced to reduce chronic iron overload. In such patients, iron supplements should be avoided. Patients should limit alcohol consumption and should not eat raw oysters. In our patients, we initiated phlebotomy and after the symptoms subsided, advised adequate follow-up with regular consultation with the primary physician to avoid complications in the future.

## CONCLUSIONS

Hemochromatosis is the most common genetic disorder among white populations. Patients with hemochromatosis of the tongue are generally asymptomatic with generalized burning sensation of tongue. Patients may present with mild, nonspecific symptoms; evidence of organ damage; or at a preclinical stage when mild abnormalities are detected on routine laboratory tests. The key to successful management of hemochromatosis of the tongue is early recognition and prompt diagnosis. Transferrin saturation, ferritin levels, and genotyping can often establish the diagnosis. Adequate therapy before irreversible organ damage occurs is essentially curative, granting patients long-term survival similar to that of the general population. Iron depletion therapy with phlebotomy and deferasirox is helpful if initiated before organ damage occurs.

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