

## Generalized Pruritus Revealing Hereditary Haemochromatosis

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Sir,

Hereditary haemochromatosis (HH) is an autosomal recessive disorder characterized by iron accumulation in various organs of the body (1). Pruritus has seldom been reported as a disclosing symptom of iron overload without cholestasis (2–3). We present here a case of generalized pruritus that revealed HH and was improved by regular phlebotomies.

### CASE REPORT

A 47-year-old woman was seen for a 1-year history of severe generalized pruritus resistant to antihistamine treatment. Her past medical history was notable for sigmoidectomy in 1989, resection of benign colonic polyps in 2001 and osteoarthritis of the hands. She denied taking any drug. At presentation, she complained of weakness, chronic fatigue and unexplained weight loss of 3 kg. Except hand osteoarthritis, physical examination was unremarkable. Skin or mucosal hyperpigmentation, cardiac symptoms, hepatosplenomegaly and loss of libido were absent. Laboratory investigations including full blood cell and eosinophil counts, erythrocyte sedimentation rate, C-reactive protein, serum protein electrophoresis, kidney and liver function tests, calcium, phosphorus, fasting blood glucose, thyroid stimulating hormone, follicle-stimulating hormone, luteinizing hormone, oestradiol, cortisolaemia, hepatitis B, hepatitis C and HIV serologies proved either normal or negative. Serum iron, ferritin and transferrin saturation values were elevated to 34  $\mu\text{mol/l}$  (normal <27  $\mu\text{mol/l}$ ), 430 ng/ml (normal <185 ng/ml) and 68% (normal <45%), respectively. Molecular analysis confirmed the HH diagnosis with a homozygous C282Y mutation of the *HFE* gene. Chest X-ray and abdominal ultrasound showed no anomaly. Hand radiographs did not show characteristic changes of HH arthropathy. Hepatic magnetic resonance imaging assessed iron overload estimated to 290 $\pm$ 50  $\mu\text{mol/g}$  (normal <36  $\mu\text{mol/g}$ ). The liver had a homogenous appearance; no dilatation of the main bile duct and the intrahepatic bile ducts was noted. Of note, there was no family history of HH. Regular phlebotomy therapy was initiated at the dose of 400 ml once every other week during 10 months. The patient reported improvement in pruritus even though it did not completely disappear. The phlebotomies resulted in iron depletion with normalization of serum iron, ferritin and transferrin saturation values, 22  $\mu\text{mol/l}$ , 156 ng/ml and 42%, respectively. Maintenance regimen of phlebotomy was then started once every other month, which resulted in the elevation of ferritin level (266 ng/ml). The patient denied any flare up of the pruritus.

### DISCUSSION

Generalized pruritus is an unusual presentation of haemochromatosis only reported twice (2–3). Pruritus is more frequently caused by iron deficiency (4). Arguments that support a correlation between pruritus and HH in the above case include: (i) onset before diagnosis of HH; (ii) absence of other causes of itching, especially cholestasis, chronic renal failure, iron deficiency,

hypothyroidism and lymphoma (4); (iii) improvement with phlebotomies and normalization of ferritin and transferrin saturation levels.

HH diagnosis in case of generalized pruritus could be underestimated. The variability of HH presentation makes its diagnosis difficult and pruritus might be related to a direct complication of HH at an advanced stage of the disease, such as hypothyroidism, or, more rarely, to cholestasis. Transferrin saturation is the best screening test for HH, whereas serum ferritin screening has a low sensitivity of 50% to detect C282Y homozygotes (1, 5). Therefore, when exploring pruritus sine materia, patients should be tested for transferrin saturation and ferritin in order not to miss either iron deficiency or iron overload. Elevated transferrin saturation should then prompt genetic testing for *HFE* mutation as secondary causes of iron overload should be ruled out (1). According to EASL International Consensus Conference on Haemochromatosis (6), normal transferrin saturation varies according to gender and ranges from 20% to 40% for men and from 15% to 25% for women. Transferrin saturation is usually calculated as iron concentration  $\times$  100 divided by total iron-binding capacity. But other methods are used according to the habits of each laboratory (7) and normal ranges differ from each other.

The pathogenesis of pruritus related to haemochromatosis remains unknown. It might be due to direct stimulation of C class fibres by iron deposits in the skin, or iron deposits might be responsible for the local release of histamine from tissue mast cells (2–3).

We believe that generalized pruritus should be added to the list of early manifestations of HH.

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