EASL Clinical practical guidelines for HFE-Hemochromatosis

EASL – European Association for the Study of the Liver

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An international expert group developed in behalf of EASL (European Association for the Study of the liver) the guidelines after review of more than 6000 articles about HFE - HH to give – if possible- evidence based answers or recommendations to the following questions:

1. **What is the prevalence of C282Y homozygosity ?**

The frequency of the C282Y allele in the general population varies in different geographic European regions from the Northwest (10-12,8 in Ireland) to the Southeast (0-1,3).
The prevalence of homozygosity for C282Y in the HFE gene in clinically recognized haemochromatosis is 80,6 %, compound heterozygosity C282Y/H63D is 5,3%.

2. **What is the penetrance of C282Y homozygosity ?**

The penetrance varies in different studies due to the different definition of biochemical and disease penetrance. Three longitudinal (population screening) studies suggest that up to 38-50 % of C282Y homozygotes may develop iron overload, 10-33% eventually develop hemochromatosis –associated morbidity, with a generally higher penetrance in males.
Genetic screening for HFE-HC is **not** recommended in general population because disease penetrance is low.
HFE testing **should** be considered in patients with unexplained chronic liver disease, pre-selected for increased transferrin-saturation.
HFE testing **could** be considered in patients with: porphyria cutanea tarda, well-defined chondrocalcinosis, hepatocellular carcinoma, type 1 diabetes.
HFE testing is **not** recommended in patients with unexplained arthritis or arthralgia, type 2 diabetes.

3. **How should HFE-HC be diagnosed?**

The EASL CPG panel agreed on the following definition for diagnosis of HFE- HC: **C282Y-homozygosity <u>and</u> increased body iron stores with or without clinical symptoms.**

Increased body iron stores are good reflected by hyperferritinämia and MRI of the liver or SQUID (not widely available). Liver biopsy is no longer the gold standard for the diagnosis of HC since genotyping is available but still has a role for assessing liver fibrosis (Ferritin > 1000µg/l). Other tools to investigate liver fibrosis are serum hyaluronic acid and transient elastography of the liver.
Family screening is highly recommended for siblings of patients by measuring Serum-Ferritin and Transf-Sat. annually, ideally genetic testing after appropriate counseling.
Patients with suspected iron overload and elevated liver enzymes should first receive measurement of fasting Transf-sat. and S-Ferritin and only in case of increased Transf-Sat. HFE genetic testing.

The guidelines propose three algorithms, one for the diagnosis of genetic causes of hyper-ferritinemia, one for the diagnostic management of patients with C282Y homozygositiy and one for the diagnostic management of tissue iron overload.
In patients with high Serum-Ferritin levels it is mandatory to search for one of the following causes for Hyperferritinemia, which is identified in more than 90 % cases: chronic alcohol consumption, inflammation (check for CRP), cell necrosis (check for AST, ALT and CK), tumors, non-alcoholic fatty liver disease NAFLD and/or metabolic syndrome.

S-Ferritin should be checked once a year in (healthy) individuals with C282Y homozygositiy. In case of elevated S-Ferritin fasting blood glucose, Serum AST and ALT should be evaluated. According to the clinical features liver MRI, ECG, echocardiography or gonadotropic hormones should be tested.

4. How should HFE-HC be managed?

There are very few data which define the amount of tissue iron which leads to tissue damage.
Patients with HFE-HC and evidences of excess iron overload should be treated with phlebotomy which is the mainstay of treatment. 400-500 ml blood (200-250 mg iron) weekly or every two weeks should be removed, also in cases with liver fibrosis or cirrhosis.
Iron chelators can be an option in patients who are intolerant or when phlebotomy is contraindicated. Erythrocytapheresis is not widely practiced.

Complications of HC (diabetes, liver cirrhosis, arthropathy, endocrine deficiency like hypogonadism, hypothyroidism, cardiac diseases, osteoporosis, porphyria cut. tarda) should be assessed and treated regardless whether HFE-HC is the underlying cause or not. Immunization against Hepatitis A and B is recommended.

The benefit of iron depletion by phlebotomy has been established despite the absence of randomized controlled trials. Fatigue, elevated transaminases, the stage of liver fibrosis and skin pigmentation improves under phlebotomy treatment. Arthralgia is unlikely to improve whereas improvement of endocrinological disorders incl. diabetes mellitus and cardiological abnormalities vary related to the degree of tissue damage at the start of treatment.

Current empirical recommendations on the optimal start of venesection is a Serum-Ferritin above normal ranges. The standard clinical practice is to achieve a target of S-Ferritin less 50 µg/l. During maintainance therapy the advocated standard practice is to maintain the S-Ferritin at 50 – 100µg/l.
Some patients do not show re-accumualtion of iron. This may be caused by proton pump inhibitors or non-steroidal anti-inflammatory drugs. Clinicians should be alert to conditions of iron loss.

Dietary intervention has no additional beneficial effect on the outcome in patients undergoing venesection. Iron containing vitamin preparations and iron supplemented foods should be avoided. Ingestion of Vit. C supplements should be limited to 500mg/day. Important is to avoid excess alcohol consumption.
Screening for hepatocellular carcinoma by ultrasound and AFP every 6 month is highly and only recommended in HC-patients with cirrhoses .

Regarding the use of blood the EASL guidelines indicate that there is no medical reason to refuse blood taken from patients with HC at phlebotomy for blood transfusion and for the public good beside the accepted contraindication for blood donation.

The EASL CPG panel on HC advocates the full reimbursement of phenotypic and, where indicated, genetic testing for HFE-HC.

The cooperation of Patient-associations was appreciated explicitly.