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Synopsis of the Dutch multidisciplinary guideline for the diagnosis and treatment of hereditary haemochromatosis

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ABSTRACT

Hereditary haemochromatosis (HH) is a disease related to mutations in the *HFE* gene and can lead to progressive iron accumulation, especially in the liver, eventually resulting in organ damage. We have developed guidelines for the diagnosis and treatment of this disease according to CBO methodology (Dutch Institute for Healthcare Quality). The prevalence of clinical symptoms such as fatigue, arthropathies, impotence and diabetes mellitus among homozygotes was similar to that in a control population. Nevertheless, we recommend the assessment of serum iron indices when these symptoms remain unexplained. When transferrin saturation is >45% and ferritin exceeds local reference ranges, *HFE* mutations should be investigated. Homozygosity for the C282Y mutation or combined C282Y/H63D mutation confirms the diagnosis of *HFE*-related HH.

Liver biopsy is recommended when ferritin exceeds 1000 µg/l to establish the presence or absence of cirrhosis, which will affect prognosis and management. Iron accumulation confirmed by magnetic resonance imaging (MRI) in the absence of the homozygous C282Y mutation or the combined C282Y/H63D genotype may justify a search for rare hereditary forms of non-*HFE* HH in a specialised centre. The literature supports the benefits of adequate phlebotomy and the screening of first-degree relatives of index patients with clinically overt HH. Overall, the guidelines presented here are to a great extent based on the expert opinion of the working party, as the quantity of evidence that met predefined criteria posed by the evidence-based approach was small. We therefore recommend world-wide efforts to collaboratively address these remaining issues.

METHODOLOGY

Development method

The working group adopted the CBO (the Dutch Institute for Healthcare Quality, www.cbo.nl) method of evidence-based guideline development for answering a number of predefined clinical questions. A literature search exploiting MESH/(thesaurus) terms and free text in the databases Medline, Embase, and the Cochrane library was performed until mid 2005. Next to literature from systematic searches, additional articles were acquired by bibliographies of key reviews and included studies. Furthermore, relevant studies that appeared later than 2005 were included, as well as (inter)national guidelines.¹⁻⁶

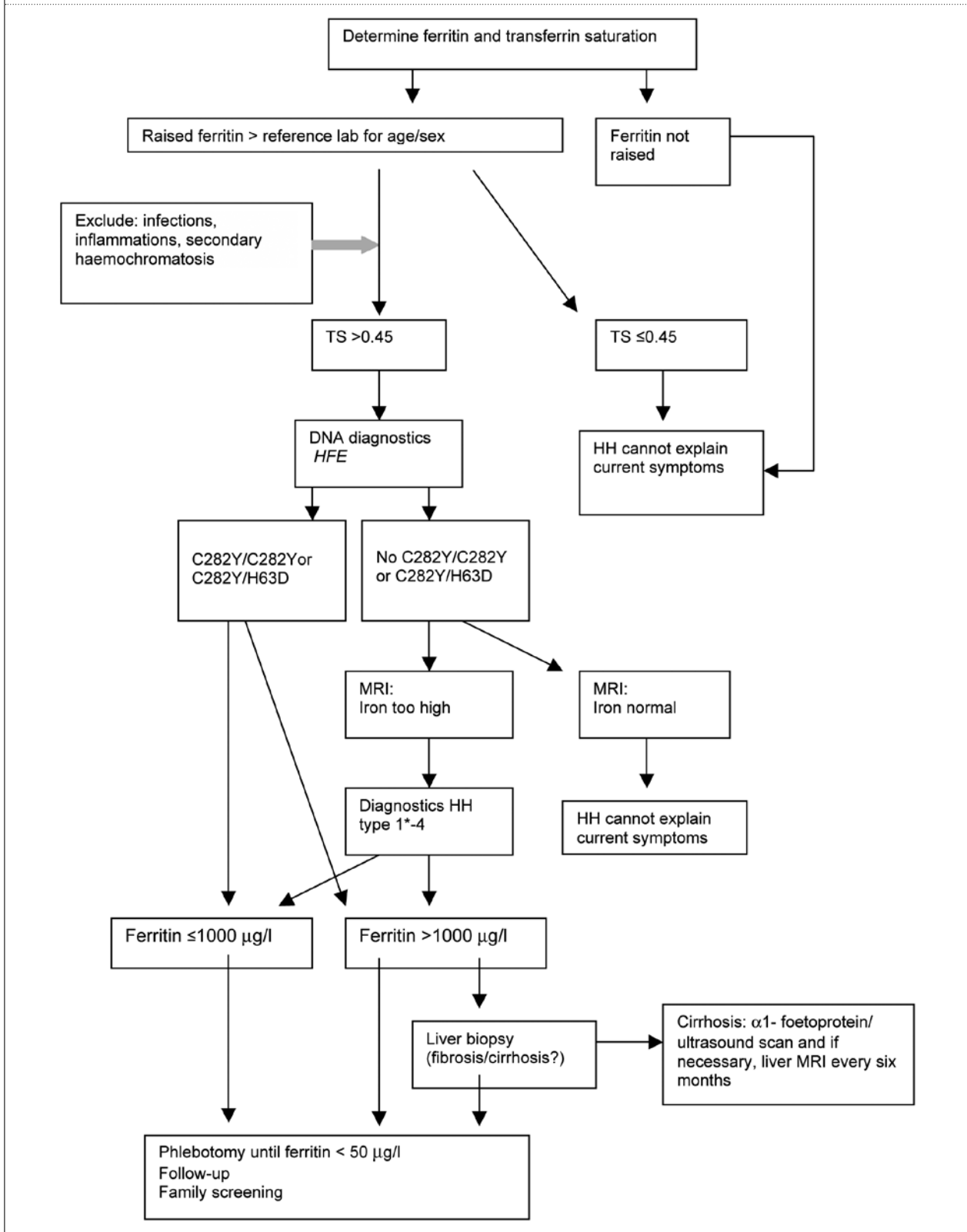
Procedures

The concepts of the chapters of the guideline prepared by individual members of the working party on the basis of the best available evidence were discussed and amended in plenary sessions. Literature was reviewed and evidence was classified according to the CBO rating scheme. The members abstracted studies into evidence tables using condition definitions and diagnostic criteria. If scientific evidence was lacking, issues were discussed until the working party members agreed upon text and recommendations.

The draft guideline was sent to the representing professional societies for comments. These comments were discussed by the working group and incorporated in the final version of the guideline. Two years after the first meeting of the working party, the guideline was approved by the boards of the participating scientific associations in May and June 2007 and made available on line along with the evidence tables (in Dutch:

<http://www.internisten.nl/home/richtlijnen/niv/niv/hemochromatose-niv/nvkc>)

Figure 1. Diagnostic diagram for suspected iron accumulation



TS = transferrin saturation; HH = hereditary haemochromatosis; MRI = magnetic resonance imaging.

*Type 1 diagnostics consists of testing the gene for rare mutations (i.e., not the frequent C282Y and H63D mutations).

In addition to the information in the diagram, the diagnostic route taken may depend on:

- Clinical presentation
- Haemoglobin (low in secondary types of iron accumulation and in some forms of ferroportin disease)
- Family history (hereditary disease)
- Concomitant clinical pictures (hepatitis, alcohol abuse)
- Age upon presentation (young in the case of juvenile haemochromatosis)

SUMMARY OF THE GUIDELINE

Epidemiology

Hereditary haemochromatosis (HH) is a disease that is characterised by progressive iron accumulation, especially in the liver, eventually resulting in organ damage. HH is a frequent hereditary condition. In Northern Europe, 0.5 to 1.0% of the population is homozygous for the C282Y mutation and 1 to 3% has the combined C282Y/H63D genotype. However, the relation between genotype and the biochemical and clinical expression (reviewed in references 7-10) remains unclear.

Morbidity

Iron accumulation results in a number of nonspecific symptoms, e.g. general health disturbance, joint problems, diabetes mellitus, fatigue, abdominal symptoms, impotence, cardiovascular diseases and skin pigmentation. However, none of these individual symptoms have been proved to occur more frequently among subjects with the genetic condition of HH than among control subjects. The occurrence of any of these symptoms, therefore, does not justify the performance of diagnostic tests for HH in first-line care. However, in accordance with international guidelines, the working group believes that assessment of the serum iron status should be considered in patients of Northern European descent who have been referred to a specialist after at least six months of unexplained symptoms as described above. The diagnostic diagram in *figure 1* outlines the subsequent diagnostic and therapeutic strategies.

Diagnostic strategy

Serum iron indices

During the first diagnostic phase, the combined measurement of serum iron, transferrin (and the calculation of transferrin saturation (TS)) and ferritin, offers a simple and reliable approach for determining the amount of iron in the body. When TS is >45% and ferritin levels exceed the reference laboratory values, *HFE* mutations should be investigated. However, hyperferritinaemia and raised TS are observed both in HH and in secondary haemosiderosis with anaemia. Conditions with increased TS or ferritin but without significant iron accumulation including infections and inflammations, excessive alcohol use, hepatic disorders and metabolic syndrome should be considered.

Genotypic testing

During the second diagnostic phase, homozygosity for the C282Y mutation or the combined C282Y/H63D genotype confirms an *HFE*-related form of HH.

Role of liver biopsy and MRI

To diagnose cirrhosis a liver biopsy remains the gold standard and is recommended when serum ferritin is >1000 µg/l. In case of raised serum iron parameters without homozygosity

for the C282Y mutation or the combined C282Y/H63D genotype, an MRI can be performed as a semiquantitative assessment of iron in the liver. MRI-confirmed iron accumulation in the absence of the C282Y mutation or the combined C282Y/H63D genotype justifies a search for rare hereditary forms of non-*HFE* HH in a specialised centre.

FAMILY SCREENING

In the third diagnostic phase, relatives to the first degree must be evaluated on the basis of iron parameters and, in the event of an *HFE*-related form of HH, on the basis of *HFE* genotyping as well. An index patient's siblings and his children/parents have a 25 and 5% chance, respectively, of being predisposed to HH.

TREATMENT

The treatment of haemochromatosis involves phlebotomy, which can prevent and possibly reverse tissue damage. During the depletion phase, weekly 500 ml bloodlettings are performed based on haemoglobin and serum ferritin, until ferritin levels are less than 50 µg/l. During the maintenance phase, ferritin levels are kept within reference values, which may involve several phlebotomies per year.

DISCUSSION

Despite the wealth of information about this disease that has accumulated over the years, diagnostic and therapeutic strategies that are recommended in the various reviews throughout the literature as well in our and other guidelines appear to lack solid evidence and are to a great extent based on expert opinions.

During the development of the guidelines, we identified the following parts in the work-up and treatment of patients that in our opinion urgently need a more solid scientific basis:

- the natural history of the relation between genotype and phenotype in the disease, with respect to sex, age, and genetic and environmental factors;
- determination of the optimal approach to screening for iron overload;
- the level of the serum iron indices above which disease manifestations as fatigue and arthritis are likely to occur;
- the substantial interlaboratory variation of the ferritin value;
- the target value of the serum iron indices during both the depletion and the maintenance phase of phlebotomy treatment.

We therefore recommend world-wide efforts to collaboratively address these issues.

NOTE

The guideline development was initiated by the Netherlands Association of Internal Medicine (NIV), the Netherlands Society of Clinical Chemistry and the Laboratory Medicine (NVKC) and Laboratory Diagnostic Practitioners Association (VAL).

The guidelines were developed within the framework of the EBRO (Evidence Based Guideline Development) Programme of the Order of Medical Specialists in association with the Dutch Society for Gastroenterology (MDL), Dutch College of General Practitioners (NHG), Dutch Blood Transfusion Society (NVB), Dutch Society for Haematology (NVvH), Dutch Society for Pathology (NVVP), Dutch Society for Radiology (NVvR), Dutch Society for Rheumatology (NVvR), Dutch Society for Clinical Genetics (VKGn) and the Haemochromatosis Society the Netherlands (HVN). Support was provided by the Committee for Guideline Development of the Netherlands Association of Internal Medicine and the Dutch Institute for Healthcare Quality CBO.

The target audience for this guideline is the Dutch professionals in their management of patients and their relatives with hereditary haemochromatosis, including general practitioners, internists, gastroenterologists, rheumatologists, radiologists, haematologists, clinical pathologists, clinical chemists and clinical geneticists.

The working party consisted of the following people:

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