Recent advances in genetic iron overload-related disorders

Impact paragraph

Serum ferritin is one of the most frequently requested laboratory tests in both primary and secondary care. In 12% of the general population an increased serum ferritin level (hyperferritinemia) is found.[1] Hyperferritinemia can be caused by various conditions and for that reason, its interpretation is challenging for physicians and can lead to misdiagnoses. Therefore, it is important to raise awareness for hyperferritinemia and its different causes and to have diagnostic tools available which are easy to interpret.

In this thesis, an overview of the etiology of hyperferritinemia in non-alcoholic fatty liver disease (NAFLD) was given. NAFLD is associated with an unhealthy lifestyle and has a prevalence of 25%. Due to the ongoing obesity epidemic it is the main cause of chronic liver diseases in the Western world.[2,3] Hyperferritinemia is found in 30% of NAFLD patients[4], and is rarely caused by iron overload but mainly due to the chronic low grade systemic inflammation. The prevalence of both NAFLD and hyperferritinemia is expected to rise due to the growing global burden of diseases related to an unhealthy lifestyle.

Within NAFLD, there are several possible causes explaining hyperferritinemia with varying treatment options. With this thesis, clinicians' attention is drawn to the different causes of hyperferritinemia.

Measuring the liver iron concentration (LIC) with MRI, has an important role in the diagnostic work-up of hyperferritinemia. However, LIC values, and especially intermediate values, are difficult to interpret and do not always give a definite answer to the presence or absence of iron overload. The suggested liver iron index contributes to the correct interpretation of the MRI results and avoids misinterpretation of the results.

Less than half of hyperferritinemia cases referred to the outpatient clinic account for *HFE*-related hemochromatosis.[5] *HFE*-related hemochromatosis is the most common autosomal recessive disorder in the Northern European population. Due to the discovery of the *HFE* gene in 1996[6] the awareness of this condition improved and patients can be identified in an earlier state. The patients with `bronze diabetes`, the classical hallmark of severe advanced disease, or hemochromatosis-related mortality are seen less frequently.

To date, besides diabetes mellitus, liver cirrhosis and bronze skin, symptoms such as arthralgia, fatigue, cardiac complaints and impotence haven been linked to *HFE*-related hemochromatosis. However, not all of these associations were confirmed in case-control studies. Nevertheless these symptoms result in frequent testing of iron parameters (serum ferritin, serum iron, transferrin, transferrin saturation) by different types of physicians like rheumatologists, orthopedic surgeons, urologists, cardiologists or endocrinologists. And through the accessibility of *HFE* gene analysis, the diagnosis sometimes will be made in subjects with only very limited elevations of serum ferritin and transferrin saturation (biochemical iron overload) in the absence of clinical disease symptoms. To date, it is known that phenotypic expression of the disease is low and that not all patients require treatment at the time of diagnosis. With data from the Dutch South Limburg population-based cohort study an overview was given of the recent epidemiology, phenotypic expression and disease course bringing awareness to the disease and its course, not only for gastroenterologist and internist/hematologist but all physicians confronted with *HFE*-related hemochromatosis. In addition, an unexpected finding of a high number of non-cirrhotic hepatocellular carcinomas rises the need for future research.

The treatment of *HFE*-related hemochromatosis has remained the same for many decades. Phlebotomy is still the corner stone in the treatment but more recently erythrocytapheresis is becoming an attractive alternative. Through the more selective removal of erythrocytes, more iron can be removed with less procedures. Erythrocytapheresis is however less frequently used due to higher costs and is currently only performed in specialized centers.[7] With the modified iron avidity index patients who will benefit from a less frequent therapy like erythrocytapheresis can be selected to provide the optimal treatment for the patient.

This thesis has also given insight in still relatively unexplored pathways within iron homeostasis. Proton pump inhibitors (PPIs) are among the most frequently used drugs worldwide.[8] PPIs are also suggested as a treatment for *HFE*-related hemochromatosis since they can decrease iron absorption.[9] It is unclear why PPI use does not initiate an iron deficiency in the large population of chronic users without *HFE*-related hemochromatosis while they do decrease ferritin levels in *HFE*-related hemochromatosis. In this thesis the precise mechanism explaining this difference could not be established however the proof of concept study on iron absorption paved the way for future research requiring larger study populations.
Another relatively unexplored path analyzed in this thesis was the ability of hepcidin production, as a result of inflammation, in patients with *HFE*-related

hemochromatosis, through the JAK/STAT3 route. Based on the observations in this thesis, intervention via the JAK/STAT3 pathway deserves further exploration since it could reduce excess absorption and accumulation of iron in patients with *HFE*-related hemochromatosis and will lead to new treatment possibilities.

Lastly, a new treatment for hereditary aceruloplasminemia was introduced. Despite the fact that hereditary aceruloplasminemia is a very rare condition and therefore societal impact will be low, there is a need for a good treatment. Current therapeutic regimens are often associated with side-effects like aggravating anemia. Erythrocytapheresis has the ability to selectively remove erythrocytes, to return valuable blood components to the patient and closely monitor patients hemoglobin levels, thus preventing the aggravation of anemia.

In conclusion, this thesis will contribute to a better understanding of hyperferritinemia in NAFLD and to a better interpretation of liver iron concentrations measured by MRI used in the diagnostic work-up of hyperferritinemia and hemochromatosis. In addition, it provides insight in the current disease course of *HFE*-related hemochromatosis and relatively unexplored pathways within the iron homeostasis.

References

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