Ironing out pathophysiological aspects of Gaucher disease

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Summary
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The studies described in this thesis focus on the role of iron in the pathophysiology and imaging of Gaucher disease (GD), and elucidate a potential link of iron-related pathophysiological changes to the occurrence of associated conditions in this rare lysosomal storage disorder.

In chapter 2 a literature review on iron metabolism in GD was performed. A total number of 37 studies that reported on hyperferritinemia and/or iron metabolism in GD were included. Evidence for the presence of iron particles in Gaucher cells is described in pathology studies from 1960 and the years thereafter. Several studies focusing on the presence of hyperferritinemia in GD are summarized. No clear-cut explanation for a possible distortion in iron metabolism could be extracted from literature, although several hypotheses have been proposed. For example, hepcidin upregulation has frequently been suggested as a factor contributing to trapping of iron in GD. With respect to the contribution of these mechanisms to iron dysregulation in GD, we hypothesize the following:

1. The altered macrophage membrane structure of Gaucher cells affects the expression of the main cellular iron-exporter ferroportin, leading to a block of iron export and subsequent ‘iron trapping’ in Gaucher macrophages.

2. The chronic low-grade inflammatory state in GD leads to disturbances in iron regulation, with the balance between a pro-inflammatory environment (classically activated macrophages) and anti-inflammatory factors (alternatively activated macrophages) determining the net effect on iron flow in each individual GD patient.

Furthermore, potential pathophysiological implications of iron storage in GD are described. With regard to the occurrence of associated conditions such as Parkinson’s disease, liver injury and malignancies, iron is considered as possible contributing factor.

The hypothesis drawn in chapter 2 serves as the basis of further studies described in this thesis. In chapter 3 we report a study on the use of magnetic resonance imaging (MRI) to visualize iron in a cohort of 40 GD patients in comparison to healthy volunteers. A whole-body MRI protocol was developed, with the aim to assess the distribution of (excess) iron in GD patients. We showed that GD patients have significantly higher $R_2^*$ levels, reflecting the presence of iron, as compared to healthy controls. Those differences were only found
in liver and bone marrow (femoral and vertebral); key sites involved in glucocerebroside storage in GD. The spleen also showed significant higher iron levels in GD patients, but mainly in focal Gaucher lesions known as Gaucheroma. Elevated serum ferritin levels correlated with increased MRI-measured iron levels.

A study of laboratory parameters of iron status including hepcidin analysis in the same cohort as described in chapter 3 is provided in chapter 4. We did not find the assumed elevated hepcidin levels in our GD population; there is no difference in absolute hepcidin levels between (treated) patients and healthy controls in this study. The hepcidin-ferritin ratio is significantly lower in GD patients. We hypothesize that the low hepcidin-ferritin ratios indicate insufficient hepcidin upregulation in response to iron loading. Another important finding is the absence of a correlation between chitotriosidase and ferritin. Chitotriosidase, a well-established marker of residual GD, is therefore less suitable in assessing the risk of iron-related complications. Serum ferritin was shown to reflect iron loading and as such is proposed as important laboratory parameter in follow-up of GD patients.

Chapter 5 covers an international case series describing 16 GD patients with hepatocellular carcinoma (HCC). In a subset of these cases, the presence of iron loading was confirmed on histopathological examination of the liver. Risk factors for HCC development in GD are discussed, with the aim to better define patients at risk in the future and propose recommendations for screening. Screening for HCC is recommended in GD patients with a history of splenectomy, presence of liver fibrosis/cirrhosis, persistent hyperferritinemia and/or chronic hepatitis B or C.

The focal splenic and hepatic lesions commonly seen in GD patients are known as Gaucheroma (also discussed in chapter 3). A retrospective study on the occurrence and imaging characteristics of these focal lesions in liver and spleen is described in chapter 6. In the studied 95 GD1 patients from the Dutch cohort, 40% had focal hepatic and/or splenic abnormalities on radiology examination. The differential diagnosis of the lesions includes simple cysts, haemangioma, focal nodular hyperplasia (FNH), Gaucheroma and HCC. Distinguishing those anomalies based on imaging characteristics is often challenging. A decision-making algorithm is proposed to aid in case of a reported focal lesion in a GD patient.