Ironing out pathophysiological aspects of Gaucher disease

Regenboog, M.

Citation for published version (APA):
Hyperferritinemia and iron metabolism in Gaucher disease: potential pathophysiological implications

Martine Regenboog, André BP van Kuilenburg, Joanne Verheij, Dorine W Swinkels, Carla EM Hollak

Blood Reviews 2016; 30:431-437
Chapter 2

Abstract

Gaucher Disease (GD) is characterized by large amounts of lipid-storing macrophages and is associated with accumulation of iron. High levels of ferritin are a hallmark of the disease. The precise mechanism underlying the changes in iron metabolism has not been elucidated. A systematic search was conducted to summarize available evidence from the literature on iron metabolism in GD and its potential pathophysiological implications. We conclude that in GD, a chronic low grade inflammation state can lead to high ferritin levels and increased hepcidin transcription with subsequent trapping of ferritin in macrophages. Extensive GD manifestations with severe anemia or extreme splenomegaly can lead to a situation of iron-overload resembling haemochromatosis. We hypothesize that specifically this latter situation carries a risk for the occurrence of associated conditions such as the increased cancer risk, metabolic syndrome and neurodegeneration.
Introduction

Gaucher disease (GD; OMIM #230800) is a rare lysosomal storage disorder in which a deficiency of the lysosomal enzyme glucocerebrosidase (EC 3.2.1.45) leads to accumulation of its substrate glucosylceramide [1]. Accumulation of glucosylceramide occurs primarily in macrophages and this storage leads to the appearance of so-called ‘Gaucher cells’. These lipid-laden macrophages are mainly found in spleen, liver and bone marrow resulting in a complex disorder with a heterogeneous clinical picture [2].

GD is classically categorized in three phenotypic variants, based on the presence (type 2 and 3) or absence (type 1) of central nervous system involvement. Type 1 GD (GD1) is the most common variant, accounting for approximately 94% of the GD patients [3]. Infiltration of Gaucher cells in spleen, liver and bone marrow leads to cytopenia, hepatosplenomegaly and bone disease. The spectrum of symptoms can range from mild to severe and can have a debilitating effect on quality of life [4]. Type 1 GD is extremely variable in its expression of disease manifestations between individuals. Even within families, the phenotypic differences are vast, so genotype-phenotype correlation is limited [5]. Presumably, genetic, epigenetic and environmental factors contribute to the presence and severity of clinical symptoms.

Until the 1990s splenectomy was the only treatment option in GD patients suffering from splenomegaly and its accompanying symptoms. Nowadays, the disease is treatable with enzyme replacement therapy (ERT), based upon intravenous administration of purified glucocerebrosidase, or substrate reduction therapy (SRT), the latter partially inhibiting glucosylceramide synthesis. ERT has completely altered the lives of GD patients and does not only improve key clinical symptoms but can prevent splenectomy and severe bone disease [6-10]. Because of its effectiveness, it can be hypothesized that the occurrence of other complications and associated conditions can be altered as well [11]. These long term complications and associated conditions of GD have been extensively described [12-15]. The increased susceptibility of patients with GD for malignancies, in particular, multiple myeloma and other hematological malignancies, is remarkable. In addition, several cases of hepatocellular carcinoma have been reported [16-20]. Factors contributing to this increased cancer risk are largely unknown. A better understanding of the pathophysiological processes involved in carcinogenesis in GD may lead to a more optimized follow-up of individual patients at risk and might result in prevention of complications later in life. Insulin resistance and Parkinson’s disease are more prevalent in GD as well [12, 14].
One possible factor implicated in the pathophysiology of conditions associated to GD is the accumulation of redox-active iron. Iron is an essential element in the human body and important for normal cellular functioning with most of the total body iron being present in hemoglobin and myoglobin. Apart from its role in oxygen transport, iron is required for heme and iron-sulfur synthesis, which are essential cofactors of enzymes of the mitochondrial respiratory chain, adequate electron transport and iron serves as an important co-factor for a number of enzymes involved in metabolism including neurotransmitter synthesis [21]. However, the facile interconversion between Fe(II) to Fe(III) makes it hazardous if present in free form and can result in the production of reactive oxygen radicals and ultimately cellular death [22, 23]. Storage of excess iron in ferritin is essential to prevent iron-mediated oxidative processes. Serum ferritin is reported to be elevated in the majority of GD patients [24, 25]. Since, serum ferritin levels reflect both macrophage and parenchymal iron stores [26] this suggests abnormal storage of iron in either macrophages, hepatocytes or other parenchymal cells. Overall, parenchymal iron is considered to be more toxic than macrophage system overload, as evidenced by the relatively clinically mild iron overload observed in loss of function ferroportin disease compared to the more severe iron overload observed in HFE-hemochromatosis [27, 28]. In the liver, iron overload can provoke lipid peroxidation resulting in cell damage with induction of fibrosis, which is a risk factor for development of hepatocellular carcinoma [29]. Fibrosis may occur in Gaucher disease in the liver, bone marrow and spleen [30]. Disrupted iron metabolism may also be partly responsible for the increased cancer risk in GD. Furthermore, Parkinson’s disease as well as metabolic syndrome have been associated with GD. In these conditions, a possible pathophysiological effect of iron metabolism disturbances could be considered.

This review discusses currently available literature with respect to iron metabolism in GD with the aim to formulate a hypothesis on the pathophysiological implications of altered iron metabolism.

**Methods**

A PubMed search was performed, which consisted of the following Medical Subject Headings (MeSH) terms: Gaucher Disease, Iron, Iron Compounds, Iron Metabolism Disorders, Iron-Binding proteins, Iron-Regulatory Proteins, Ferritins in combination with the following non-MeSH terms: Gaucher, acid-beta-glucosidase deficiency, cerebroside lipidosis syndrome, glucocerebrosidase deficiency, glucosylceramide beta-
glucosidase deficiency, GBA deficiency, iron, ferritin, apoferritin, isoferritin, transferrin, hyperferritinemia. An EMBASE search was also performed, stratified for all possible synonyms for Gaucher disease, iron and hyperferritinemia. Reference lists of relevant articles were screened for possible additional literature. Date of last search: 4 December 2014.

Studies reporting on hyperferritinemia and/or iron metabolism in GD and studies describing a possible link between iron metabolism and associated conditions in GD were included in this review.

Exclusion criteria were: language (article not written in English or Dutch), no full text available, content not related to inclusion criteria.

**Results**

The search resulted in 225 articles from which title and abstract were screened. One hundred thirty-two studies did not fulfil the inclusion criteria. The remaining 93 studies were selected for full-text reading. After full-text reading of these studies, another fifty-eight articles did not fulfil the inclusion criteria and were excluded. Screening of reference lists of the included articles yielded two additional studies, resulting in thirty-seven studies for review. See figure 1 for a flowchart.
Pathology studies

As already published by Lorber in 1960 [31] iron particles can be found in the pathological Gaucher cells. Bone marrow aspirates of five GD type 1 (GD1) patients showed many iron-containing structures in the Prussian-blue stain. This finding was strengthened by studies performed in the following years. Lee et al [32] studied tissues from twelve patients using light- and electron microscopy and found iron storage in Gaucher cells in eleven of these patients in samples from bone marrow, spleen, liver and lymph nodes. Using light microscopy, only some Gaucher cells stained positive for iron particles. This finding was in contrast to that observed using electron microscopy, in which all Gaucher cells were found to contain iron. Subsequently, ferritin was identified as the iron-storing compound in the Gaucher cells [33]. In a later study, Lorber observed in seven spleens and a bone marrow aspirate from GD patients that not every storage cell stained positive with Prussian blue [34].

While most additional case reports described positive staining for iron in Gaucher cells [35-39], other pathology studies challenged this: in a case series in which five immunohistochemical and ultrastructural features of Gaucher cells were examined, none of the typical Gaucher cells stained positive for iron [40]. However, splenic macrophages
or bone marrow showed brown granules of hemosiderin. In a perinatal lethal form of GD [41] extreme hyperferritinemia was found with hemosiderin depositions throughout the macrophage system on pathological examination. It is not clear whether the Gaucher cells in this case accumulated hemosiderin as well (aggregated, partially deproteinized ferritin that is formed when ferritin is partially degraded). It was postulated that intravascular ferritin release from damaged hepatocytes due to extensive hepatic infiltration with Gaucher cells was the source of the extremely high circulating ferritin levels. Apparently, parenchymal cells surrounding Gaucher cells can show iron storage: Stein et al [25] performed liver biopsies in three GD patients, treated with enzyme replacement therapy, with evidence of iron overload based on elevated transferrin saturations and/or imaging. These biopsies showed up to grade 3-4 hepatocyte siderosis, mainly found in hepatocytes and Kupffer cells; the Gaucher cells did not show excessive iron accumulation.

An investigational technique to identify metallic elements present in tissue is laser microprobe mass analysis (LAMMA). This technique was used to study Gaucher cells and cultured Gaucher fibroblasts and their elemental content [42]. A high iron-related signal in the Gaucher cell cytoplasm from liver tissue was found. By electron microscopy abundant ferritin particles and hemosiderin in the cytosol were proven to be the main source of this iron-signal in Gaucher cells. Occasional membrane-limited organelles containing iron-rich ferritin particles (siderosomes) were also observed. No excess iron was found in the surrounding hepatocytes. It was postulated that due to the absence of excess iron in cultured skin fibroblasts of Gaucher patients the stored iron should have had an extrinsic origin, presumably erythrophagocytosis.

Together, these studies support the hypothesis that excessive iron storage can be present in GD. However, iron storage is not always confined to Gaucher cells and can be observed in other cellular iron storage sites, such as hepatocytes or Kupffer cells; the Gaucher cells did not show excessive iron accumulation.

**Ferrokinetic studies**

Using radioactive iron, rapid disappearance of radio-iron from plasma was observed in GD [34]. Slightly more radioactivity was measured in regions where Gaucher disease manifestations were present, supporting the hypothesis that iron was taken up by Gaucher cells. In a series described by Lee et al [32], erythrokinetic studies and measurements of iron stores were performed. They also observed a rapid plasma iron disappearance in three out of four patients. In two patients, the distribution of intravenously administered
radio-iron was studied. After accumulation of radioactivity in the sacrum a slight increase in radio-iron was measured in the spleen. All studied patients showed a decreased iron incorporation in red cells, with grossly normal red cell volume. Haematology values, total serum iron and iron binding capacity remained normal in these patients. Three patients were reported to have increased iron stores, based on increased urinary iron excretion after administering an iron chelator. In vitro studies of bone marrow of a GD patient showed markedly positive iron-staining Gaucher cells, which decreased in time, indicative of iron exit from Gaucher cells [34]. In summary, these studies showed a rapid distribution of iron out of plasma, most likely to sites of storage macrophages.

**Biochemical studies**

**Hyperferritinemia**

The presence of high levels of serum ferritin is a well-known feature of GD [24, 25, 43-47]. A ferritin-decreasing effect of ERT has been described and as such this marker is used to monitor response to therapy [24, 25].

Ferritin is a protein complex composed of 24 protein subunits of 2 types, H- and L-ferritin, which assemble to make a hollow spherical shell, which can take up 4500 atoms of intracellular stored iron [48]. Its main function is binding of iron in a redox-inactive form, preventing cellular damage to be caused by free iron [49]. The ferroxidase activity of H-ferritin converts ferrous iron (Fe^{2+}) to ferric iron (Fe^{3+}), which is necessary for iron deposition in the nanocage [48]. L-ferritin induces iron nucleation. Serum ferritin concentration is a useful clinical parameter in determining the amount of iron storage in the human body. However, several disorders are associated with increased ferritin levels, i.e. inflammatory disorders, metabolic syndrome and cancer [27]. The precise source and secretory pathway of serum ferritin remains to be elucidated, although animal studies suggest that macrophages contribute significantly to serum ferritin concentrations [50]. It is possible that cells actively secrete ferritin into the circulation, or that damaged cells leak ferritin and thereby causing ferritin levels to increase [49, 51]. Serum ferritin differs from tissue ferritin in that it is glycosylated, contains mostly L-chains and is iron poor [27]. Subtyping of the different ferritin forms is performed in several hyperferritinemic conditions. In adult-onset Still’s disease for example, the percentage of glycosylated ferritin is <20%, whereas normal adults have a percentage of 50-80% of circulating ferritin which is glycosylated [52, 53]. Stirnemann et al. investigated ferritin glycoforms in patients with GD and found significantly lower glycosylated ferritin percentages in untreated GD patients when compared to patients on enzyme replacement therapy [54]. Absolute concentrations
of non-glycosylated ferritin forms significantly decreased on ERT, but glycosylated ferritin concentration was not significantly altered, suggesting that an increased non-glycosylated ferritin is a reflection of enhanced ferritin release via cell lysis.

Mekinian et al. [24] reported a frequency of hyperferritinemia in treatment-naïve patients of 87%, while other iron-status parameters were normal. This pattern in GD could show some similarities to the pathogenesis of macrophage activation syndrome (MAS), an acquired form of hemophagocytic lymphohistiocytosis (HLH). This hemophagocytic syndrome is characterized by high levels of ferritin and the presence of several inflammatory cytokines [55]. A chronic inflammatory state as is seen in GD, with the upregulation of IL-6, IL-10 [56] and macrophage inflammatory proteins [57], may lead to increasing circulating ferritin levels through modulation of hepcidin as described below.

**Hepcidin**

In the past decades, our understanding of human iron homeostasis has greatly improved due to unraveling of key mechanisms involved in this process. Iron metabolism is fine-tuned by two regulatory mechanisms; a system involving regulation by the hormone hepcidin and a cellular control mechanism via iron-regulatory proteins (IRP1 and IRP2), for review see [51].

Hepcidin is a 25 amino acid peptide produced mainly by the liver. Binding of this hormone to the cellular iron exporter ferroportin leads to internalization and degradation of this exporter. As a result, intracellular iron levels increase, less dietary iron will be absorbed and consequently, plasma iron concentration decreases. Main regulators of hepcidin expression are body iron status, erythropoietic activity, hypoxia and inflammation. The hemochromatosis iron protein (HFE) is an important regulatory factor in hepcidin transcription. Defects in the HFE-gene causes downregulation of hepcidin secretion and leads to disproportional dietary iron absorption and the release of intracellular stored iron. This finally results in an iron overload disorder known as hereditary hemochromatosis.

It has been suggested that there could be a role for hepcidin in the occurrence of hyperferritinemia in GD [24, 25]. For example, interleukin-6 is a regulator of hepcidin synthesis in the liver [58] and this pro-inflammatory cytokine can be increased in GD [56]. The multisystemic inflammatory reaction as observed in GD with accompanying production of cytokines may contribute to the elevation of hepcidin levels and consequently to intracellular iron trapping [25, 59]. Indeed, Medrano-Engay et al. [60] found elevated
hepcidin levels in mildly affected GD patients. They studied the effect of two different iron chelator therapies in eight GD1 patients with a serum ferritin level > 700 ng/ml. Five of these patients were treated with SRT and three were untreated. The main findings of this study were the significant reduction of mean serum ferritin concentration after four months of iron chelation therapy and a significant decrease in mean hepcidin concentration. Interestingly, ferritin reduction and hepcidin showed a high positive correlation ($r^2=0.976$). In addition, an increase in pro-inflammatory cytokines (MIP-1$\alpha$, MIP-1$\beta$ and TNF-$\alpha$) was observed in all patients.

Discussion

Studies published more than fifty years ago already reported signs of iron storage in the typical Gaucher macrophages [31-34, 36-39]. The iron mainly consists of ferritin particles, the storage form of iron, presumably as a result of erythrophagocytosis. However, iron storage was also found in cellular storage sites other than the Gaucher cells, for example in non-Gaucher macrophages in spleen and bone marrow or Kupffer cells in the liver [25, 35, 40, 41]. Ferrokinetic studies demonstrated a rapid plasma turnover of iron, signs of iron-uptake by Gaucher cells and decreased incorporation of iron in erythrocytes [32, 34]. In the years thereafter, increasing evidence became available regarding the frequently found elevated ferritin levels in GD. Macrophage activation leading to a state of low-grade inflammation due to glucosylceramide accumulation has been described as one possible explanation for increasing ferritin levels [24]. In line with this is the finding of increased hepcidin levels in GD, due to the presence of inflammatory mediators. As a consequence, ferroportin exporters will become less available for iron export out of the cells, which results in higher intracellular iron levels [60].

Cohen et al [50] studied the possible source of serum ferritin in mice and concluded that serum ferritin is a reflection of macrophage iron status. It is proposed that serum ferritin represents a subpopulation of intracellular ferritin that has translocated to the lysosomal compartment. Inherent to its vital role in the degradation of organelles and macro-molecules, several iron-containing elements are degraded by lysosomes. For example, senescent erythrocytes are endocytosed in the lysosomes of macrophages and heme, a complex of hemoglobin-haptoglobin is delivered to the macrophage through the CD163-receptor. Iron in lysosomes mostly occurs in the ferrous form ($Fe^{2+}$), due to the acidic environment and presence of reducing molecules [61]. This redox-active form of iron may lead to oxidative stress in the lysosome and can ultimately destabilize the organelle
Iron in its free form can easily transport electrons and lead to oxygen radical formation. Oxidative damage to lysosomes and subsequently to cells is avoided by storing iron in a non-redox-active form in the cytosol as ferritin. Release of iron from ferritin may occur through transport to the plasma compartment, as L-ferritin, or through lysosomal degradation [65]. However, ferritin can also become autophagocytosed and degraded [66]. In situations of high iron load, for example in hereditary haemochromatosis, hepcidin levels are inappropriately low for the body iron status, leading to a relative excess uptake of dietary iron. This results in increased saturation of transferrin in plasma and the generation of so called toxic iron species non-transferrin bound iron (NTBI) that are readily taken up by parenchymal cells [67, 68]. In this situation, serum ferritin levels are increased and the concomitant elevated transferrin saturation can serve as a marker of (parenchymal) iron overload and risk of cellular toxicity and organ damage [69].

In Gaucher disease, secondary hypersplenism due to splenomegaly is one of the mechanisms which contributes to the occurrence of cytopenias [70]. Splenectomies were often performed in the past followed by immediate increases in hemoglobin levels and thrombocyte counts [71]. These effects, albeit more slowly, are now observed in patients on enzyme replacement therapy [72] as well. Morphological changes in red blood cells (RBCs) in GD patients favor erythrophagocytosis and result in enhanced splenic turnover of RBCs [73]. Thus, in case of enhanced red cell destruction, an increase in iron supply to be handled by the macrophage system occurs. In addition, we hypothesize that in GD the following factors contribute to a possible dysregulation in the storage of iron.

First of all, a direct effect of altered macrophage membrane structure on ferroportin expression could mimic the consequences of the so-called ferroportin disease with loss of function from the cellular iron-exporter. In this situation, iron-release from macrophages is blocked. Transferrin saturation is normal and iron is sequestered and can be demonstrated in macrophages [28]. To our knowledge, data concerning changes in ferroportin expression on Gaucher macrophages is not published, but would be of high interest to investigate.

Secondly, the chronic low-grade inflammatory state present in GD could lead to disturbances in ferroportin expression. Gaucher cells secrete pro- as well as anti-inflammatory cytokines and proteins into the circulation [44, 56, 57]. While mature Gaucher cells resemble alternatively activated M2 macrophages, smaller surrounding cells have been identified as possessing a more classically activated, M1 signature [74]. Previous studies have shown that these macrophage sub-types display a different expression profile.
of genes involved in iron storage [75]. The M1, pro-inflammatory macrophages have low ferroportin expression and are therefore contributing to the iron sequestration in these cells. Inflammation leads to upregulation of hepcidin, but hepcidin-independent downregulation of ferroportin through stimulation of toll-like receptors enhances this effect [76]. Conversely, the M2 macrophages show an upregulation in ferroportin expression leading to increased iron release out of the cells. The balance between the M1 and M2 macrophages in GD may lead to differential, predominantly pro- or anti-inflammatory effects on the surrounding tissues and beyond. We hypothesize that this balance is dependent on the disease activity and amount of Gaucher cells present in each individual patient. A similar mechanism as is seen in the macrophage disorder hemophagocytic lymphohistiocytosis is hypothesized: in this disease, several pro-inflammatory cytokines are secreted and excessive activation of macrophages takes place. As a result of this, growth differentiation factor 15 (GDF15) is abundantly secreted by pro-inflammatory macrophages with the aim to suppress further activation of these cells [77]. Increasing GDF15 levels are associated with the M2 macrophage phenotype and result in enhanced ferroportin expression because it is a negative regulator of hepcidin production [77]. This could lead to efflux of trapped iron from macrophages into the circulation and hence toxicity to surrounding tissue. Ineffective or increased erythropoiesis challenges the macrophage system as well. It has been reported that GDF15, twisted gastrulation (TWSG1) and erythroferrone (ERFE) levels from erythroblasts in situations of ineffective or increased erythropoiesis lead to suppression of hepcidin production in the liver [78, 79].

Hence, we hypothesize that in mild GD, the pro-inflammatory classically activated (M1) macrophage is the major storage cell, entrapping iron as is seen in other pro-inflammatory diseases. In more excessive, long-standing storage, an anti-inflammatory response is induced, leading to larger numbers of alternatively activated M2-type Gaucher cells, that leak iron to parenchymal cells and non-GD macrophages, with subsequent damage due to oxidative stress. Figure 2 shows a schematic representation of this hypothesis.

Interestingly, iron has been implicated in the pathophysiology of several disorders which are associated with GD, for example Parkinson's disease, cancer and insulin resistance [2, 12, 16, 17]. Parkinson's disease (PD), a disorder characterized by progressive neurodegeneration and loss of dopaminergic neurons in the substantia nigra together with the production of Lewy bodies, is considered a complex multifactorial disease. In the last decade, increasing evidence became available indicating that free iron and the formation of
reactive oxygen species are one of the important pathophysiological mechanisms involved [80].

The increased risk of developing malignancies in GD is another major topic of interest [16-20]. Several possible pathophysiological mechanisms can contribute to this malignancy risk and disruption in iron metabolism may be one of these [81]. Iron can be toxic and carcinogenic in several ways. As described above, the production of oxygen radicals and subsequent oxidative stress can lead to cell damage. Iron overload leads to increasing levels of non-transferrin bound iron which in turn can have a direct damaging effect on DNA. Also, a disturbing effect of high iron levels on the normal functioning of immune surveillance has been acknowledged, which may lead to the development of cancer [82]. As suggested by Bassan et al. [83] it could well be due that the high ferritin levels in GD itself have an inhibiting effect on T-lymphocytes and thereby inducing a malfunctioning immune system, leading to a higher risk of developing cancers in GD patients. In the liver, iron overload can provoke lipid peroxidation resulting in cell damage with induction of fibrosis, which is a risk factor for development of hepatocellular carcinoma (HCC) [29]. Parenchymal iron storage itself, which is described earlier in this report, is also associated with organ toxicity and as such can have a direct effect on HCC evolution. Removal of the spleen might induce a redistribution of iron towards liver parenchyma. This in turn can lead to an increased risk of HCC in patients who underwent splenectomy.

Iron has also been recognized as a possible inducer of insulin resistance and an association between iron metabolism and diabetes has become clear [84]. Glucose and iron metabolism could show interaction via different pathways [85-87].

In conclusion, in mild cases of GD, the chronic inflammation presumably contributes to a pattern of iron storage as seen in other inflammatory conditions: high ferritin levels with increased levels of hepcidin and trapping of ferritin in macrophages [88, 89]. However, in more severe cases, possibly enhanced by multiple blood transfusions, the iron supply to the lysosomes exceeds the iron handling capacity of the macrophages. This can lead to cellular damage and a possible iron-shift to parenchymal cells. The latter situations may be noticed by increasing transferrin saturation levels in addition to the high ferritin levels. These patients may be prone to oxidative stress, cell death, fibrosis and ultimately development of malignancies. We suggest that the measurement of levels of hepcidin, ferritin and transferrin saturation might altogether be of clinical use in the prediction of iron-related complications.
Practice Points

- High ferritin levels occur in most patients with GD and can be used as disease related markers.
- Different patterns of disturbed iron metabolism exist in GD, presumably due to individual differences in the balance between classically and alternatively activated Gaucher macrophages.
- GD patients with signs of iron overload, including high transferrin saturation, may have an increased risk for liver injury, fibrosis and cancer.

Research Agenda

- Expression of ferroportin on classically and alternatively activated Gaucher macrophages.
- Hepcidin levels in relation to patterns of iron storage and inflammation in GD.
- Iron storage in the pathophysiology of associated conditions in GD.
Figure 2. Schematic representation of iron flow in the normal macrophage (A), a classically activated pro-inflammatory macrophage in mild GD (B) and an alternatively anti-inflammatory activated macrophage in severe GD (C).

A. a.) Phagocytosis of senescent erythrocytes. b.) Endocytosis of heme groups by CD163-receptor. c.) Hemoglobin proteolysis leads to release of heme, degradation of heme by heme oxygenase 1 (HO-1) leads to iron (mainly in ferrous form in lysosomes), export of iron by the divalent metal transporter 1 (DMT1). d.) Iron stored in ferritin, some iron used for metabolic purposes. e.) When iron demand is present, ferritin is degraded and ferrous iron exported by ferroportin. This feedback loop is controlled by hepcidin and other factors on transcriptional and translational level (not depicted). f.) Ferrous iron is oxidized by the ferroxidase ceruloplasmin. Ferric iron can be transported by transferrin.

B. In mild Gaucher disease, a predominance of classically activated, pro-inflammatory macrophages is present. Enhanced turnover of erythrocytes leads to increasing iron supplies to macrophages, with increased lysosomal handling of iron. Storage in ferritin takes place. Upregulation of hepcidin limits iron export through ferroportin.

C. In long-standing, severe Gaucher disease, a predominance of alternatively activated, pro-inflammatory macrophages is present. If iron supply exceeds the normal handling capacity of the macrophage, ferrous iron can provoke the production of hydroxyl radicals (HO•) and lysosomal destabilization can occur. Growth differentiation factor 15 (GDF15) secretion by macrophages and/or erythroblasts may limit hepcidin synthesis in hepatocytes with consequent increasing ferroportin expression, leading to efflux of iron to the circulation. Transferrin saturation increases, toxic iron species that are formed and readily taken up by parenchymal tissues, leading to organ damage.
References


22. Kell DB. Towards a unifying, systems biology understanding of large-scale cellular death and destruction caused by poorly liganded iron: Parkinson’s, Huntington’s, Alzheimer’s, prions, bactericides, chemical toxicity and others as examples. Arch Toxicol. 2010;84:825-89.


36. Mandlebaum FS. A contribution to the pathology of primary splenomegaly (Gaucher type), with the report of an autopsy on a male child four and one half years of age. J Exp Med. 1912;16:797-821.


