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REVIEW

Hyperferritinemia and iron metabolism in Gaucher disease: Potential pathophysiological implications

Martine Regenboog [a,1], André B.P. van Kuilenburg [b,2], Joanne Verheij [c,3], Dorine W. Swinkels [d,4], Carla E.M. Hollak [a,1]

[a] Department of Internal Medicine, division of Endocrinology and Metabolism, Academic Medical Center Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands
[b] Laboratory Genetic Metabolic Diseases, Academic Medical Center Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands
[c] Department of Pathology, Academic Medical Center Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands
[d] Department of Laboratory Medicine, Translational Metabolic Laboratory, Radboud University Medical Center, Nijmegen, The Netherlands

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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 hemochromatosis. 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.

1. 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 the 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 (types 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 the 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].

E-mail addresses: m.regenboog@amc.uva.nl (M. Regenboog), a.b.vankuilenburg@amc.uva.nl (A.B.P. van Kuilenburg), j.verheij@amc.uva.nl (J. Verheij), dorine.swinkels@radboudumc.nl (D.W. Swinkels), c.e.hollak@amc.uva.nl (C.E.M. Hollak).
[1] Tel.: +31 20 5662432; fax: +31206917682.
[2] Tel.: +31 20 5665958.
[3] Tel.: +31 20 5665650.
[4] Tel.: + 31 24 3618957.

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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.

2. 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.

3. Results

The search resulted in 225 articles from which title and abstract were screened. One hundred thirty-two studies did not fulfill 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 fulfill 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 Fig. 1 for a flowchart.

3.1. 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, instead of the Gaucher macrophages.

3.2. 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

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