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Liver involvement in Gaucher disease – Review and clinical approach

Tomer Adar [a,*], Yaron Ilan [b], Deborah Elstein [c], Ari Zimran [c]

[a] Digestive Diseases Institute, Shaare Zedek Medical Center (SZMC), Hebrew University, Jerusalem, Israel
[b] Department of Medicine, Hebrew University-Hadassah Medical Center, Jerusalem, Israel
[c] Gaucher Clinic, Shaare Zedek Medical Center (SZMC), Hebrew University, Jerusalem, Israel

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ABSTRACT

Gaucher disease (GD), one of the most prevalent lysosomal storage diseases, is associated with glucocerebroside accumulation in cells of the monocyte-macrophage system in various organs, including the liver.
Evaluating and managing liver disease in patients with Gaucher disease may be challenging. While hepatic involvement is common in Gaucher disease, its severity, and clinical significance span a wide spectrum, ranging from sub-clinical involvement to liver cirrhosis with its associated complications including portal hypertension. Apart from liver involvement in Gaucher disease, patients with may also suffer from other comorbidities involving the liver. That Gaucher disease itself can mimic hepatic lesions, affect laboratory tests used to characterize liver disease, and may be associated with non-cirrhotic portal hypertension, complicates the diagnostic approach even more.
Better understanding of liver involvement in Gaucher disease can spare patients unnecessary invasive testing, and assist physicians in decision making when evaluating patients with Gaucher disease suspected for significant liver disease.
This review describes the various clinical manifestations, laboratory and imaging abnormalities that may be encountered when following patients with Gaucher disease for liver involvement. The mechanism for liver disease are discussed, as well as the possible hepato-protective effect of glucocerebroside, and the a diagnostic and treatment approaches.

1. Introduction

Gaucher disease (GD), an autosomal recessive disorder that is one of the most prevalent lysosomal storage diseases, results from mutations in the β-glucocerebrosidase gene (1q21), leading to reduced enzyme activity and accumulation of glucocerebroside in cells of the monocyte-macrophage system ("Gaucher cells") throughout the body, but mainly in specific target end-organs including spleen, bone marrow and liver (Fig. 1) [1,2]. In the liver, several patterns of Gaucher cell infiltration have been reported, including scattered foci, prominent centrilobular infiltration and extensive replacement of liver parenchyma with Gaucher cells [3].

Gaucher disease has traditionally been divided into 3 clinical forms: non-neuronopathic type 1 disease, where the features are primarily visceral and skeletal, with the presence of at least one mutation that is putatively protective of neurological involvement; and the neuronopathic forms which are marked by various genotypes that include two severe and/or one severe and one null mutations: type 2 has been termed "infantile" because it is characterized by an unabated progression of neurological signs and symptoms until death typically before the age of 4 years; and type 3 which is sub-acute and was once considered "juvenile" because of a more slowly evolution of neurological signs and symptoms in addition to varying degrees of visceral involvement [2,4].

Liver enlargement is usually noted in GD, sometimes only by imaging when the liver is not palpable [5]. In patients who had undergone splenectomy before Gaucher-specific therapy became available, the liver may become enormously enlarged. In these splenectomized and most severely affected patients, liver cirrhosis has been reported. However, symptoms are only rarely described [6]. Liver function tests (LFTs) tend to be within the normal range for most patients, and severe abnormalities are, again, more likely to be seen in splenectomized patients. It has been posited that when there is relatively more profound hepatomegaly than splenomegaly in a patient with GD, the liver findings are most probably due to a concurrent morbidity [7].

Thus, in appraising hepatic manifestations in patients with GD, disease-specific considerations should be taken into account including the need for an extensive baseline evaluation, choice of diagnostic modality, frequency of follow-up, management of portal hypertension (p-

* Corresponding author at: Digestive Diseases Institute, Shaare Zedek Medical Center, 12 Bayit Street, Jerusalem 91031, Israel.
E-mail address: adartom@szmc.org.il (T. Adar).

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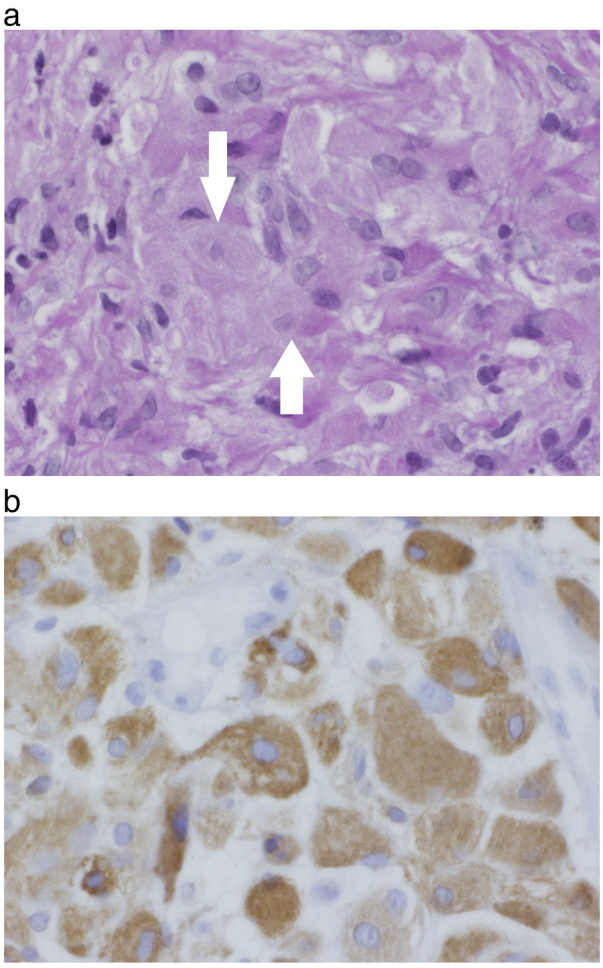

Fig. 1. Histopathological appearance of liver involvement in Gaucher disease. a: Gaucher cells (arrowheads) infiltrating the liver parenchyma (LMx100, H&E stain). 1b: anti CD68 stain may help to demonstrate "Gaucher" cells.

HTN) if present, and the possible impact (if any) of hepatic involvement on GD-specific therapeutic options, particularly enzyme replacement therapy (ERT).

2. Elevated glucocerebroside levels may be hepatoprotective

There is a high prevalence of GD among the Ashkenazi Jewish (AJ) population, specifically that of two different disease producing alleles, the null 84GG that exists exclusively among AJ, and the N370S, which is the most common mutation among AJ patients. The rate of carriership, 1:17 of the N370S mutation within this ethnic group, along with a higher prevalence of other LSDs (such as Tay-Sachs disease), have led to the speculation, that there may be an evolutionary advantage; although evidence of the benefit of carriership for GD remains unknown [8,9].

Our group has recently hypothesized, based on clinical and laboratory findings in patients having GD and hepatitis C [9] that the selective advantage might be because of elevated circulatory levels of GC; it is further hypothesized that this increased concentration induces anti-inflammatory and beneficial immunoregulatory changes, that specifically with regard to the liver would also be hepatoprotective as reported in animal models [9]. GC has been found to alleviate concanavalin A (ConA)-induced hepatitis in mice, an effect associated low serum levels of interferon (IFN)-γ and a reduced expression of the transcription factor STAT1 [10]. In mice with hepatocellular carcinoma (HCC), GC administration resulted in a Th1 immune shift that was associated with the suppression of tumor growth and improved survival [9,11]. GC treatment was effective in alleviating the liver damage in a model of semi-allogeneic acute and chronic graft-versus-host disease (GVHD) in mice [12]. GC was also shown to exert a potent immune modulatory adjuvant effect alleviating the insulin resistance and liver damage in animal models of NASH and type 2 diabetes [9,13,14]. A beneficial effect has also been noted in the Cohen diabetic-sensitive (CDS) rat, a lean model of non-insulin resistant, nutritionally induced fatty liver disease [15], and in the sand rat model [16].

GC increased the immune response against hepatitis B virus (HBV) in association with altered distribution of NKT cells and CD8 cells, suggesting that GC could be used as a potent adjuvant for overcoming non-responsiveness to HBV vaccine, and augmenting the antiviral immune response [9,17].

Several mechanisms have been suggested to explain the hepatoprotective effect of GC. These include GC serving as a glycolipid ligand, presented to NKT cells and dendritic cells (DCs) via CD1 molecules. GC can exert an immunomodulatory effect directly on these target cells or indirectly by altering the cross-talk between these cells and other subsets of cells of the immune system. Altering the plasticity of NKT cells either by functioning as their natural ligand or replacing their yet-undefined natural ligand(s); promoting regulatory T lymphocytes; altering lipid rafts, intracellular signaling machinery or DC function; acting as an adjuvant for antigens to improve immunogenicity; functioning as a metabolic intermediate in insulin resistance and promoting immune dependent mucosal mechanisms [9].

B-structured glycosphingolipid (including beta-galactosyl-ceramide, β-GalCer) are normal constituents of the cell membrane [18–20]. There is anecdotal evidence from studies of GD patients suggesting GC is involved in NKT cell regulation [21]. Patients with GD have altered humoral and cellular immune profiles, including altered NKT cell number and function [9]. This suggests a direct effect of β-GalCer on the cell membrane. Some patients have increased red blood cell aggregation due, in part, to changes in properties of the cell membrane [22]. The administration of naturally occurring β-GalCer can alter the lipid rafts composition and structure, thereby affecting the intracellular signaling machinery [23,24]. It has been reported that β-GalCer can stimulate NKT cells [25]. Recent studies have suggested that the glycosphingolipids can promote regulatory T cells (Tregs). This effect can be mediated via DCs or by cross-talk between NKT cells and Tregs [26,27].

Preliminary human data suggests that GC can exert a beneficial effect in humans with chronic liver disease [28]. It should be noted that the hepatoprotective effects of β-glycolipids are in contrast to the hepatotoxic effect of α-glycolipids [29,30].

3. Manifestations of hepatic involvement in patients with GD

The more typical clinical and imaging findings of liver involvement in GD include hepatomegaly non-HCC focal liver lesions and fibrosis; severely affected patients may develop cirrhosis, portal hypertension and potentially HCC.

3.1. Hepatomegaly and abnormalities in liver function tests

Hepatomegaly is generally conceded to be defined as liver mass > 1.25 times the estimated normal volume which is 2.5% of total body weight [31] and has been described as a common finding in patients with GD. Nonetheless, hepatomegaly is relatively less massive than GD splenomegaly [2–4,32]. The reported incidence of hepatomegaly may sometimes be inaccurate because of the modality of assessment of organ size. Using ultrasonography, Patlas et al. reported 100% prevalence of hepatomegaly in a cohort of 103 pediatric patients [33]. Similarly, using Magnetic Resonance Imaging, (MRI), in a cohort of 46 adult patients, all were noted to have some degree of liver enlargement [34] (the two modalities have been reported to comparably estimate liver

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