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Review Article

Liver involvement in Gaucher disease: A practical review for the hepatologist and the gastroenterologist

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ABSTRACT

Gaucher disease (GD), a rare lysosomal storage disorder caused by deficient glucocerebrosidase activity and consequent accumulation of glycosphingolipids in the mononuclear phagocyte system, may progress to disabling and potentially life-threatening complications when left undiagnosed and untreated. Unfortunately, because of non-specific signs and symptoms and lack of awareness, patients with type 1 GD, the most common non-neuropathic variant, frequently experience diagnostic delays. Since splenomegaly and thrombocytopenia are the dominant clinical features in many GD patients leading to first medical contact, the hepatologist and the gastroenterologist need to be aware of this condition. Liver involvement has been reported in the majority of GD patients, and comprises hepatomegaly, with or without liver enzymes alteration, fibrosis/cirrhosis, portal hypertension, focal liver lesions, and cholelithiasis. Moreover, GD is associated with several biochemical alterations of potential interest for the hepatologist and the gastroenterologist, including hypergammaglobulinemia, hyperferritinemia and metabolic abnormalities, that may lead to misdiagnoses with chronic liver diseases of common etiology, such as primary hemochromatosis, autoimmune liver diseases or nonalcoholic fatty liver disease. This comprehensive review, based on the collaborative experience of physicians managing patients with GD, provides practical information on the clinical, histological and radiological hepatic manifestations of GD aiming at facilitating the diagnosis of GD for the hepatologist and the gastroenterologist.

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1. Introduction

Gaucher disease (GD) is a rare autosomal recessive disease with an estimated incidence of 1:22.000 newborns due to deficient lysosomal glucocerebrosidase (GBA) enzyme activity leading to glycosphingolipid storage in cells of the mononuclear phagocyte system [1]. It is a chronic progressive multisystem disorder, whose clinical spectrum encompasses hepato-splenomegaly, bone marrow infiltration with thrombocytopenia and anemia, bleeding diathesis, bone disease ranging from osteopenia/osteoporosis to bone pain/bone crisis, lytic lesions/fractures, osteonecrosis and skeletal deformities, and variable central nervous system

involvement [2–5]. GD is conventionally categorized in three main phenotypes on the ground of neurologic involvement: type 1 GD, the most common, frequently adult-onset, non-neuropathic variant; type 2 GD, the lethal infantile, acute neuropathic form; and type 3 GD, the severe chronic neuro-visceral form [2,4]. However, this classification is somewhat artificial, since GD actually manifests as a clinical continuum; indeed, it is now clear that also type 1 GD may be associated with neurologic manifestations, in particular movement disorders and Parkinson disease [4,6]. Few genotype–phenotype correlations have been identified. The most recognized correlation concerns patients who carry the common N370S mutation on at least one allele of the GBA gene. N370S mutation is encountered only in subjects with type 1 GD and is protective for the development of the neurological involvement characteristic of type 2 and type 3 GD. Subjects who are homozygous for the N370S mutation can also remain poorly symptomatic until adulthood and can escape medical attention [7]. Other clinical features of GD are: immunological alterations,

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including polyclonal and monoclonal gammopathy, high prevalence of autoantibodies and increased risk of malignancies, notably including multiple myeloma and hepatocellular carcinoma (HCC) [8–10]. Metabolic abnormalities, due to chronic inflammation and characterized by hypercatabolic state with growth retardation, chronic fatigue and reduced body mass, dyslipidemia with low high-density lipoprotein (HDL) cholesterol and hyperferritinemia without significant iron overload could also be present [11,12]. Finally, cardio-pulmonary involvement, with interstitial lung disease, pulmonary hypertension and valvulopathies, has also been described in most severe cases [13,14].

Since hepato-splenomegaly and thrombocytopenia are the dominant clinical features in many GD patients leading to first medical contact, the hepatologist and the gastroenterologist need to be aware of this condition in their routine practice. Moreover, misdiagnoses with other chronic liver diseases, such as primary hemochromatosis, autoimmune liver diseases or nonalcoholic fatty liver disease (NAFLD), may be possible due to the abovementioned association of GD with hyperferritinemia, hypergammaglobulinemia and metabolic abnormalities [15,16].

Surveys of patients and medical specialists have clearly shown that, because of non-specific symptoms and lack of awareness, prolonged diagnostic delays are very common in GD and may result in severe disease complications, disabilities and potentially life-threatening manifestations [5,17,18]. Physician education may increase the likelihood of prompt detection of GD and allow its correct management with specific treatment, such as enzyme replacement therapy (ERT) or substrate reduction therapy (SRT), that are effective in preventing or reversing GD-related complications. Three recombinant glucocerebrosidase preparations, imiglucerase, velaglucerase alfa and taliglucerase alfa, are currently available. These ERT, which are administered i.v. once every two weeks, have been shown to improve hematological, visceral and skeletal manifestations of GD, and the quality of life of affected patients. The SRT eliglustat, based on the inhibition of glucosylceramide synthase, is now an alternative oral first-line therapeutic option, whose efficacy is comparable to that of ERT [19,20]. Screening strategies for GD by using simple diagnostic algorithms in selected high-risk populations, such as pediatric or adult subjects with splenomegaly and/or thrombocytopenia, have proven feasible and effective in helping pediatricians and hematologists in promoting a timely diagnosis [21,22]. Of note, due to the high GD prevalence among Ashkenazi Jews, Mistry et al. have even proposed to screen for GD as a first-line investigation in Ashkenazi patients presenting with splenomegaly [2].

This comprehensive review, based on the collaborative experience of physicians managing patients with GD and chronic liver diseases of various etiology, provides practical information on the clinical, histological and radiological hepatic manifestations of GD aiming at facilitating the diagnosis of GD for the hepatologist and the gastroenterologist.

2. Hepatic manifestations of Gaucher disease

A certain degree of liver involvement with a wide variability in clinical presentation has been reported in the majority of GD patients [23]. Hepatic manifestations of GD comprise hepatomegaly, with or without liver enzymes alteration, fibrosis, cirrhosis and portal hypertension, HCC and non-HCC focal liver lesions and cholelithiasis. Moreover, GD is associated with several biochemical abnormalities that may be of potential interest for the hepatologists/gastroenterologists, such as hypergammaglobulinemia and hyperferritinemia. Finally, concurrent chronic liver diseases, such as liver steatosis, chronic viral hepatitis and vascular liver diseases may be frequently found in GD patients, making the diagnosis of GD more difficult.

2.1. Hepatomegaly and liver enzymes abnormalities

Liver volume, measured by imaging techniques, is conventionally reported in multiples of normal size predicted for body weight, which is 2.5% of total body weight in kilograms [24]. Moderate hepatomegaly is defined as a liver volume >1.25 and ≤ 2.5 multiples of normal and severe hepatomegaly as a liver volume >2.5 multiples of normal [25]. Some degree of liver enlargement is found in nearly all GD patients as a consequence of intra-hepatic accumulation of Gaucher cells and secondary inflammatory response. However, since liver enlargement is usually less severe than spleen enlargement, if hepatomegaly outweighs splenomegaly, then a careful evaluation for other causes of liver disease is necessary. Data from the International Collaborative Gaucher Group Registry show that moderate or severe hepatomegaly is present in at least 80% of patients with type 1 GD at the time of first infusion of ERT; of note, in non-splenectomized subjects mean liver volume is 1.8 multiples of normal whereas mean spleen volume is 19.4 multiples of normal [25]. Liver volume is higher in patients with more severe GD and in splenectomized patients. Therapy for GD, both ERT and SRT, is effective in reducing or normalizing liver volume; however, hepatomegaly may persist despite treatment when severe and nodular hepatomegaly, significant liver fibrosis or splenectomy are present [19,20,25,26].

Liver enzymes, particularly aminotransferases and alkaline phosphatase, may be elevated in GD patients. However, the increase in liver enzymes is usually mild or moderate, and does not correlate with hepatomegaly or severity of liver involvement [27].

2.2. Liver histology in Gaucher disease

Only few studies have provided detailed histologic descriptions of liver abnormalities in GD. James et al., who described the liver histopathological findings of 22 untreated GD patients, showed a wide range of pathologic changes spanning from the presence of scattered foci of storage cells with little structural abnormalities of the liver to cirrhosis with extensive replacement of the liver by storage cells [28]. Storage cells, defined as Gaucher cells, are sphingolipid-laden macrophages displaying small round vesicular nuclei and abundant lightly eosinophilic cytoplasm with a wrinkled or striated appearance, and may virtually be found in every liver biopsy of GD patients. In the majority of GD patients, Gaucher cells have a zonal distribution, with central zones (zone 3) showing the highest abundance, portal and periportal regions (zone 1) showing mild to moderate presence, and midzones presenting only occasional scattered foci of storage cells [28]. Gaucher cells often present a slight accumulation of iron. Hepatocytes, which do not accumulate the storage material, may present degenerative changes and atrophy when are adjacent to or within large collections of Gaucher cells. Inflammatory changes are mild to moderate and are closely associated with Gaucher cells. At least pericellular liver fibrosis is present in nearly all GD patients, and a significant proportion may develop severe fibrosis with thick fibrous septa, predominantly originating from the central zones where the storage of Gaucher cells is more represented, or cirrhosis [28]. The severity of histologic liver involvement is associated with the presence of severe extra-hepatic complications of GD and splenectomy [28].

2.3. Liver fibrosis and cirrhosis

Liver fibrosis is a serious complication of GD, since its severity is the main driver for the development of long-term liver-related events, such as cirrhosis, portal hypertension and HCC [10,29]. Although cirrhosis has been only anecdotally reported, significant liver fibrosis is largely underestimated and seems to be common

in GD patients. In past years, the systematic evaluation of liver fibrosis by liver biopsy in GD patients has been hampered by the fear of an increased bleeding tendency. With the advent of imaging techniques, such as ultrasound (US)-based elastography or magnetic resonance (MR) elastography, which allow a non-invasive and accurate evaluation of liver fibrosis, recent studies were able to provide some estimate of the prevalence of clinically relevant liver fibrosis in GD, ranging from 20% to 50% [29–31]. These studies found that splenectomy, the severity of extrahepatic manifestations of GD, and non-N370S GBA genotypes (i.e. genotypes commonly associated with more severe disease), were all associated with the presence and severity of liver fibrosis [29–31]. The severe extreme of the spectrum of GD-related liver involvement has been described by Lachmann et al. in their case series of 4 splenectomized patients with severe multi-organ involvement [32]. All these patients had portal hypertension, decompensated liver failure and severe hepatic parenchymal disease histologically and radiologically characterized by massive confluent fibrosis with focal calcifications occupying the central region of the liver [32]. The mechanism of liver fibrosis in GD may be multifactorial. In the early steps of fibrosis development, the accumulation of Gaucher cells in the liver, which is more marked in severe GD and may be worsened by splenectomy, may act through local release of cytotoxic, proinflammatory and fibrogenic factors. Subsequently, once dense fibrous bands have developed, episodes of ischemia and infarction may play a part in the pathophysiology of liver fibrosis progression, as substantiated by the finding of calcifications within areas of massive fibrosis [28,32]. Of note, one study found that the length of ERT is inversely correlated with liver fibrosis [29], and another study showed that, even when fibrosis is advanced, the institution of ERT can reduce the numbers of Gaucher cells infiltrating the liver parenchyma, ameliorate the severity of portal hypertension and prevent variceal bleeding and hepatic decompensation [32], suggesting a beneficial effect of ERT on progression of GD-related liver disease.

2.4. Portal hypertension

Portal hypertension may be a rare complication of severe cases of GD and may become clinically significant with development of esophageal varices and occurrence of life-threatening bleeding [32]. Of note, gastrointestinal bleeding and liver failure were among the leading causes of premature death of GD patients in the pre-ERT era, but nowadays are increasingly rare with earlier diagnosis and timely institution of appropriate GD treatment [33,34]. Portal hypertension in GD is not just secondary to the presence of liver cirrhosis, since the overflow in the portal system secondary to splenomegaly or the massive infiltration of Gaucher cells in liver parenchyma especially in splenectomized patients have also been reported as potential underlying mechanisms [23]. Even if splenectomy was performed in the past as a therapeutic option for massive splenomegaly with life-threatening pre-hepatic portal hypertension, now this procedure should be discouraged since it may lead to worsening of liver and bone disease and systemic GD complications. Here it is worth acknowledging that splenomegaly and cytopenia in GD are not necessarily associated with chronic liver disease and portal hypertension, rather they are the consequence of the accumulation of Gaucher cells and chronic inflammatory infiltrates in the spleen and bone marrow. As such, splenomegaly and thrombocytopenia are almost invariably present in GD patients independently of the presence of liver disease and portal hypertension.

2.5. HCC and non-HCC focal liver lesions

Focal splenic and hepatic lesions are common in GD patients and are closely associated with GD severity. The reported prevalence

of splenic lesions in several GD cohorts ranges from 18% to 33%; the vast majority of focal splenic abnormalities is represented by Gaucheromas, benign clusters of Gaucher cells associated with areas of fibrosis and iron accumulation [35,36]. The prevalence of hepatic lesions is reported to be slightly lower ranging from 6% to 25%; the differential diagnosis of focal liver abnormalities is much more complex. Indeed, although focal liver lesions are mostly Gaucheromas, they may represent a diagnostic challenge due to the variable radiological features, which can mimic malignant liver lesions, in particular HCC [35,37]. Of note, GD is associated with an increased risk of malignancies, including HCC, as a consequence of immune dysregulation and chronic macrophage activation with increased release of cytokines and cellular dysfunction due to accumulation of glycosphingolipids [38,39]. It has been shown that GD patients with previous splenectomy, advanced fibrosis/cirrhosis, iron overload and concurrent causes of chronic liver disease (i.e. alcohol, viral hepatitis) are those at the highest risk of HCC occurrence and those who may benefit more from surveillance strategies [10,37].

2.6. Cholelithiasis

Patients with GD have been found to have a 5-fold excess risk of gallstones as compared to the general population [40]; the prevalence of cholelithiasis in several GD cohorts ranges from 25% to 46% and is associated with age, female sex, previous splenectomy and GD severity [40–43]. Of note, bile lipid analyses in GD patients with cholelithiasis has revealed that gallstones are composed predominantly of cholesterol, whereas pigment stones are an exception; moreover, bile lipid composition in GD patients is abnormal and contains glucosylceramide [40].

2.7. Other GD-related alterations of potential interest for the hepatologists/gastroenterologists

2.7.1. Hypergammaglobulinemia and autoantibodies

The presence of polyclonal gammopathy and autoantibodies is quite common in GD patients, independently of GD severity and splenectomy. The reported prevalence of hypergammaglobulinemia ranges from 14% to 64% [44,45]; similarly, the prevalence of autoantibodies has been reported as much as 60% [46,47]. Importantly, the presence of autoantibodies is not associated with an increased prevalence of clinically manifested autoimmune diseases [47].

2.7.2. Hyperferritinemia

Hyperferritinemia is very common in GD patients, affecting up to 87% of untreated subjects. Ferritin levels are correlated with GD severity and splenectomy and significantly decrease during GD treatment [48–50]. Hyperferritinemia is not associated with systemic iron overload in GD, unless genetic (HFE mutations) or acquired/environmental (splenectomy, alcohol, metabolic syndrome, chronic viral hepatitis, malignancies) concurrent causes of iron storage are present [30,48]. The mechanisms underlying hyperferritinemia, which are not yet completely defined, include chronic low-grade inflammation, impaired macrophages functions and local dysregulation in hepcidin-ferroportin axis [51].

2.7.3. Concurrent liver diseases

The presence of concurrent liver diseases in GD patients is common. Chronic viral hepatitis and vascular liver diseases are frequent due to splenectomy, often required in the past for the management of severe splenomegaly, other surgical procedures, including gallbladder removal, and blood transfusions for cytopenia [23,29]. Historically, transfusional iron overload has been an important

cofactor for liver disease progression in GD patients. Liver steatosis is also a prevalent finding in GD patients due to metabolic abnormalities, such as insulin resistance and increased adiposity, associated with GD itself and unhealthy lifestyle habits [11,23]. Moreover, long-term treatment with ERT has been associated with a significant weight gain [11,52].

3. Imaging characteristics of liver involvement in Gaucher disease

As detailed above, liver involvement in GD exhibits a wide clinical spectrum with variable severity and an unpredictable natural course. Furthermore, apart from the primary involvement of the liver due to GD, patients may also suffer from other comorbidities involving the liver, thus making the diagnosis and/or the assessment more difficult. Differently from the past, in which US, computed tomography (CT) and/or MR imaging techniques were mainly used to evaluate the increase in organ volume [24], currently the indications to perform imaging techniques in the assessment of liver involvement in GD are: 1) the identification of early tissue damage and the evaluation of liver disease severity; 2) the differentiation of Gaucheromas from other benign or malignant focal liver lesions; 3) monitoring the response to ERT or SRT.

3.1. Identification of early tissue damage and evaluation of the severity of liver disease

US-based methods are the cheapest and most widely available imaging techniques proposed to non-invasively evaluate the degree of tissue damage in GD. US can recognize diffuse irregular liver texture, expression of chronic liver damage, as well as hepatic steatosis. The latter can be frequently detected in GD patients on long-term ERT and with concurrent metabolic syndrome and is probably related to the concomitant presence of NAFLD, rather than being the consequence of glycosphingolipid storage in macrophages [11,29,52]. Doppler US may help in evaluating the severity of liver disease and portal hypertension. Promising results are provided by US-based elastography techniques, transient elastography with Fibroscan® being the most popular one. Several studies have demonstrated the feasibility of Fibroscan® for the evaluation of liver stiffness in GD patients and have suggested that significant fibrosis is an overlooked complication of GD and is strongly associated with GD severity [29–31]. Of note, an interesting study showed that combined liver and spleen elastography, using either Fibroscan® or 2-dimensional shear wave elastography, is a useful tool for differentiating GD patients from cirrhotic patients of different etiology among subjects with splenomegaly [31].

MR imaging techniques outweigh the performance of US methods in identifying early tissue damage and evaluating the severity of liver disease. Diffusion-weighted and chemical shift MR imaging have been proposed for the detection and quantification of hepatic and splenic infiltration in GD and have been associated with GD severity [53,54]. Some MR imaging protocols, such as T2* and relaxation rate R2* measurements, or the Gandon methods, are able to provide reliable estimates of liver iron concentrations. Bohte et al. found an association between liver iron concentration measured through MR and splenectomy in GD patients [30]. The use of whole-body MR R2* measurements has also been proposed in GD patients; a study showed that the presence of increased R2* values in liver, bone marrow and splenic Gaucheromas was quite common in GD, was associated with ferritin levels and presumably indicated elevated tissue iron concentrations [55]. Liver stiffness measurement by MR elastography is considered a reliable non-invasive tool to quantify liver fibrosis in patients with chronic viral hepatitis or NAFLD [56–58]; however, the use of these MR techniques in clin-

ical practice is still limited and data on GD patients are scanty. In a small cohort of adult patients with GD, liver stiffness values, as measured by both Fibroscan® and MR elastography, were associated with GD severity and splenectomy [30]. A larger recent study confirmed that MR elastography may be a useful tool for monitoring disease severity and progression by showing a positive correlation with GD severity scoring system GD-DS3 [59].

3.2. Differentiation of Gaucheromas from other benign or malignant focal liver lesions

The prevalence of focal liver lesions has been reported to range from 6% to 25% [35,60], and is more frequent in patients with more severe GD [35]. Further to the classic benign (hemangiomas, cysts, focal nodular hyperplasia) and malignant focal liver lesions (HCC), single or multiple nodules in GD patients may be the expression of clusters of Gaucher cells conglomerated in the liver (Gaucheromas). Regenboog et al. [35] reported the imaging characteristics of all focal lesions in liver and spleen in the Dutch GD cohort. Of 95 type 1 GD patients, 40% had focal splenic and/or hepatic lesions (24% had splenic lesions, 25% had liver lesions and 9% patients had both). Liver lesions identified as Gaucheromas had variable imaging characteristics: hyper- or hypoechoic with calcifications on US, hyper- to hypo-intense on MR, and hypodense on CT usually without contrast enhancement [35]. These non-specific radiological features make difficult to distinguish Gaucheromas from hemangiomas, focal nodular hyperplasia or HCC by conventional US, CT or MR. Dynamic contrast-enhanced studies and, in case of inconclusive results, percutaneous imaging-guided biopsy, are necessary to further characterize indeterminate focal liver lesions. Given the reported increased risk of HCC development in GD [10], US is widely recommended for regular routine follow-up in high-risk patients (i.e. those with liver cirrhosis, concurrent chronic liver diseases, and/or splenectomy).

3.3. Monitoring the response to enzyme replacement therapy or substrate reduction therapy

ERT and SRT are very effective in reducing hepatic and splenic volumes within 1–2 years [20,25]. Imaging techniques that evaluate liver and spleen volumes are used for monitoring disease activity and facilitating treatment decision-making. Although US is not very accurate in evaluating organ volumes, a good correlation between liver volume and hepatic longitudinal diameter evaluated by US has been found in patients with GD, making this method useful for routine monitoring when MR imaging techniques are not available [23,61]. CT is not suitable for regular follow-up of GD patients since it is associated with exposure to ionizing radiation. Despite its high costs, MR is considered the gold standard technique in assessing therapeutic efficacy since it allows to have, at the same time, information on the reduction of organ volumes and on the evolution of bone disease by evaluating the severity of bone marrow infiltration and/or the presence of bone lesions or osteonecrosis [62].

4. Diagnostic hints of GD for the hepatologist and the gastroenterologist

Subjects with hepatomegaly or splenomegaly often consult the hepatologist and/or the gastroenterologist for the suspicion of chronic liver disease. Splenomegaly with or without hepatomegaly is the most common feature of GD; however, this lysosomal disorder is rarely considered as a differential diagnosis in patients with unexplained splenomegaly. To facilitate the potential diagnosis of GD in adult patients presenting to the hepatologist and the gastroenterologist with splenomegaly (or previous splenectomy), here

Table 1

Diagnostic hints of Gaucher disease for the hepatologist and the gastroenterologist.

Unexplained splenomegaly (or previous splenectomy) plus one or more of these factors may increase clinical suspicion for Gaucher disease:

Thrombocytopenia
Anemia
Bleeding diathesis
History of growth retardation/chronic fatigue
Hepatomegaly
Spleen nodules/lesions
Gallstones
Low HDL cholesterol
Increased ferritin levels
Policlonal gammopathy
Monoclonal gammopathy, including MGUS
Bone involvement*
Parkinsonism
Family history of Parkinson disease

HDL: High-density lipoprotein; MGUS: Monoclonal gammopathy of unknown significance.

* Includes: Reduction of bone mineral density, chronic bone pain, acute bone crisis, pathologic fractures, lytic lesions, osteonecrosis, Erlenmeyer flask deformity.

we provide several hints based on the presence/absence of several peculiar signs or symptoms of GD, which must be evaluated when more common causes of splenomegaly have been excluded (Table 1).

When GD is suspected, the first step in the diagnostic work-up is the detection of a reduced GBA activity that can be evaluated on dried blood spots (DBS). DBS assay is a quick, not expensive and accurate screening test; it can be easily performed in any outpatient service and it has been validated in a large number of patients [63]. A pathologic result on DBS should be confirmed by evaluating GBA enzymatic activity in blood leukocytes or cell cultures and DNA sequencing with evidence of biallelic GBA pathogenic mutations.

5. Conclusions and future perspectives

GD is a chronic and multisystem disease which may progress to severe disabling and potentially life-threatening complications when left undiagnosed and untreated [17,18]. Several diagnostic algorithms for GD have previously been proposed for hematologists and pediatricians, with the aims of increasing awareness and favoring an early diagnosis [21,22]. Liver involvement in GD is non-specific and variable [11,23]; as a consequence, GD is frequently misdiagnosed with other highly prevalent chronic liver diseases of different etiologies [15,16]. Splenomegaly with or without hepatomegaly is a nearly universal finding; as such, GD should be considered as a differential diagnosis in patients with unexplained splenomegaly referred to the hepatologist or the gastroenterologist. Other peculiar findings that should increase the suspicion of GD are the presence of bone involvement, gammopathy, hyperferritinemia, hepatomegaly, hepatic and splenic nodules, gallstones, low HDL cholesterol, thrombocytopenia, anemia, bleeding diathesis, chronic fatigue, familial or personal history of parkinsonism [2,4,5]. In this paper, we have provided a comprehensive and practical review of liver involvement in GD aimed at facilitating a prompt diagnosis of GD for the hepatologist and the gastroenterologist.

Conflict of interest

All authors are members of Sanofi-Genzyme advisory boards.

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References

- [1] Burlina AB, Polo G, Salviati L, Duro G, Zizzo C, Dardis A, et al. Newborn screening for lysosomal storage disorders by tandem mass spectrometry in North East Italy. *J Inher Metab Dis* 2018;41:209–19.
- [2] Mistry PK, Cappellini MD, Lukina E, Ozsan H, Mach Pascual S, Rosenbaum H, et al. A reappraisal of Gaucher disease-diagnosis and disease management algorithms. *Am J Hematol* 2011;86:110–5.
- [3] Hughes D, Mikosch P, Belmatoug N, Carubbi F, Cox T, Goker-Alpan O, et al. Gaucher disease in bone: from pathophysiology to practice. *J Bone Miner Res* 2019;34:996–1013.
- [4] Mistry PK, Lopez G, Schiffmann R, Barton NW, Weinreb NJ, Sidransky E. Gaucher disease: progress and ongoing challenges. *Mol Genet Metab* 2017;120:8–21.
- [5] Mehta A, Kuter DJ, Salek SS, Belmatoug N, Bembi B, Bright J, et al. Presenting signs and patient co-variables in Gaucher disease: outcome of the Gaucher Earlier Diagnosis Consensus (GED-C) Delphi initiative. *Intern Med J* 2019;49:578–91.
- [6] Aharon-Peretz J, Rosenbaum H, Gershoni-Baruch R. Mutations in the glucocerebrosidase gene and Parkinson's disease in Ashkenazi Jews. *N Engl J Med* 2004;351:1972–7.
- [7] Hruska KS, LaMarca ME, Scott CR, Sidransky E. Gaucher disease: mutation and polymorphism spectrum in the glucocerebrosidase gene (GBA). *Human Mutat* 2008;29:567–83.
- [8] Arends M, van Dussen L, Biegstraaten M, Hollak CE. Malignancies and monoclonal gammopathy in Gaucher disease; a systematic review of the literature. *Br J Haematol* 2013;161:832–42.
- [9] Nair S, Branagan AR, Liu J, Boddupalli CS, Mistry PK, Dhodapkar MV. Clonal immunoglobulin against lysolipids in the origin of myeloma. *N Engl J Med* 2016;374:555–61.
- [10] Regenboog M, van Dussen L, Verheij J, Weinreb NJ, Santosa D, Vom Dahl S, et al. Hepatocellular carcinoma in Gaucher disease: an international case series. *J Inher Metab Dis* 2018;41:819–27.
- [11] Nascimbeni F, Dalla Salda A, Carubbi F. Energy balance, glucose and lipid metabolism, cardiovascular risk and liver disease burden in adult patients with type 1 Gaucher disease. *Blood Cells Mol Dis* 2018;68:74–80.
- [12] Regenboog M, van Kuilenburg AB, Verheij J, Swinkels DW, Hollak CE. Hyperferritinemia and iron metabolism in Gaucher disease: potential pathophysiological implications. *Blood Rev* 2016;30:431–7.
- [13] Miller A, Brown LK, Pastores GM, Desnick RJ. Pulmonary involvement in type 1 Gaucher disease: functional and exercise findings in patients with and without clinical interstitial lung disease. *Clin Genet* 2003;63:368–76.
- [14] Mistry PK, Sirrs S, Chan A, Pritzker MR, Duffy TP, Grace ME, et al. Pulmonary hypertension in type 1 Gaucher's disease: genetic and epigenetic determinants of phenotype and response to therapy. *Mol Genet Metab* 2002;77:91–8.
- [15] Saadi T, Rosenbaum H, Veitsman E, Baruch Y. Gaucher's disease type I: a disease masked by the presence of abnormal laboratory tests common to primary liver disease. *Eur J Gastroenterol Hepatol* 2010;22:1019–21.
- [16] vom Dahl S, Mengel E. Lysosomal storage diseases as differential diagnosis of hepatosplenomegaly. *Best Pract Res Clin Gastroenterol* 2010;24:619–28.
- [17] Mistry PK, Sadan S, Yang R, Yee J, Yang M. Consequences of diagnostic delays in type 1 Gaucher disease: the need for greater awareness among hematologists-oncologists and an opportunity for early diagnosis and intervention. *Am J Hematol* 2007;82:697–701.
- [18] Mehta A, Belmatoug N, Bembi B, Deegan P, Elstein D, Goker-Alpan O, et al. Exploring the patient journey to diagnosis of Gaucher disease from the perspective of 212 patients with Gaucher disease and 16 Gaucher expert physicians. *Mol Genet Metab* 2017;122:122–9.
- [19] Mistry PK, Batista JL, Andersson HC, Balwani M, Burrow TA, Charrow J, et al. Transformation in pretreatment manifestations of Gaucher disease type 1 during two decades of alglucerase/imiglucerase enzyme replacement therapy in the International Collaborative Gaucher Group (ICGG) Gaucher Registry. *Am J Hematol* 2017;92:929–39.
- [20] Lukina E, Watman N, Dragosky M, Lau H, Avila Arreguin E, Rosenbaum H, et al. Outcomes after 8 years of eliglustat therapy for Gaucher disease type 1: final results from the Phase 2 trial. *Am J Hematol* 2019;94:29–38.
- [21] Motta I, Filocamo M, Poggiali E, Stroppiano M, Dragani A, Consonni D, et al. A multicentre observational study for early diagnosis of Gaucher disease in patients with Splenomegaly and/or Thrombocytopenia. *Eur J Haematol* 2016;96:352–9.
- [22] Di Rocco M, Andria G, Deodato F, Giona F, Micalizzi C, Pession A. Early diagnosis of Gaucher disease in pediatric patients: proposal for a diagnostic algorithm. *Pediatr Blood Cancer* 2014;61:1905–9.
- [23] Adar T, Ilan Y, Elstein D, Zimran A. Liver involvement in Gaucher disease – review and clinical approach. *Blood Cells Mol Dis* 2018;68:66–73.
- [24] Elstein D, Hadas-Halpern I, Azuri Y, Abrahamov A, Bar-Ziv Y, Zimran A. Accuracy of ultrasonography in assessing spleen and liver size in patients with Gaucher disease: comparison to computed tomographic measurements. *J Ultrasound Med* 1997;16:209–11.
- [25] Weinreb NJ, Goldblatt J, Villalobos J, Charrow J, Cole JA, Kerstenetzky M, et al. Long-term clinical outcomes in type 1 Gaucher disease following 10 years of imiglucerase treatment. *J Inher Metab Dis* 2013;36:543–53.
- [26] Shemesh E, Deroma L, Bembi B, Deegan P, Hollak C, Weinreb NJ, et al. Enzyme replacement and substrate reduction therapy for Gaucher disease. *Cochrane Database Syst Rev* 2015:CD010324.

- [27] Zimran A, Kay A, Gelbart T, Garver P, Thurston D, Saven A, et al. Gaucher disease. Clinical, laboratory, radiologic, and genetic features of 53 patients. *Medicine* 1992;71:337–53.
- [28] James SP, Stromeyer FW, Chang C, Barranger JA. Liver abnormalities in patients with Gaucher's disease. *Gastroenterology* 1981;80:126–33.
- [29] Nascimbeni F, Cassinerio E, Dalla Salda A, Motta I, Bursi S, Donatiello S, et al. Prevalence and predictors of liver fibrosis evaluated by vibration controlled transient elastography in type 1 Gaucher disease. *Mol Genet Metab* 2018;125:64–72.
- [30] Bohte AE, van Dussen L, Akkerman EM, Nederveen AJ, Sinkus R, Jansen PL, et al. Liver fibrosis in type I Gaucher disease: magnetic resonance imaging, transient elastography and parameters of iron storage. *PLoS One* 2013;8:e57507.
- [31] Webb M, Zimran A, Dinur T, Shibolet O, Levit S, Steinberg DM, et al. Are transient and shear wave elastography useful tools in Gaucher disease? *Blood Cells Mol Dis* 2018;68:143–7.
- [32] Lachmann RH, Wight DG, Lomas DJ, Fisher NC, Schofield JP, Elias E, et al. Massive hepatic fibrosis in Gaucher's disease: clinico-pathological and radiological features. *QJM* 2000;93:237–44.
- [33] Weinreb NJ, Barbooth DS, Lee RE. Causes of death in 184 patients with type 1 Gaucher disease from the United States who were never treated with enzyme replacement therapy. *Blood Cells Mol Dis* 2018;68:211–7.
- [34] Weinreb NJ, Deegan P, Kacena KA, Mistry P, Pastores GM, Velentgas P, et al. Life expectancy in Gaucher disease type 1. *Am J Hematol* 2008;83:896–900.
- [35] Regenboog M, Bohte AE, Somers I, van Delden OM, Maas M, Hollak CE. Imaging characteristics of focal splenic and hepatic lesions in type 1 Gaucher disease. *Blood Cells Mol Dis* 2016;60:49–57.
- [36] Stein P, Malhotra A, Haims A, Pastores GM, Mistry PK. Focal splenic lesions in type I Gaucher disease are associated with poor platelet and splenic response to macrophage-targeted enzyme replacement therapy. *J Inher Metab Dis* 2010;33:769–74.
- [37] Starosta RT, Pinto EVF, Dornelles AD, Cerski CTS, Alvares-da-Silva MR, Schwartz IVD. Hepatocellular carcinoma in Gaucher disease: reinforcing the proposed guidelines. *Blood Cells Mol Dis* 2019;74:34–6.
- [38] de Fost M, Vom Dahl S, Weverling GJ, Brill N, Brett S, Haussinger D, et al. Increased incidence of cancer in adult Gaucher disease in Western Europe. *Blood Cells Mol Dis* 2006;36:53–8.
- [39] Weinreb NJ, Lee RE. Causes of death due to hematological and non-hematological cancers in 57 US patients with type 1 Gaucher disease who were never treated with enzyme replacement therapy. *Crit Rev Oncol* 2013;18:177–95.
- [40] Taddei TH, Dziura J, Chen S, Yang R, Hyogo H, Sullards C, et al. High incidence of cholesterol gallstone disease in type 1 Gaucher disease: characterizing the biliary phenotype of type 1 Gaucher disease. *J Inher Metab Dis* 2010;33:291–300.
- [41] Ben Harosh-Katz M, Patlas M, Hadas-Halpern I, Zimran A, Elstein D. Increased prevalence of cholelithiasis in Gaucher disease: association with splenectomy but not with gilbert syndrome. *J Clin Gastroenterol* 2004;38:586–9.
- [42] Rosenbaum H, Sidransky E. Cholelithiasis in patients with Gaucher disease. *Blood Cells Mol Dis* 2002;28:21–7.
- [43] Zimmermann A, Popp RA, Al-Khazouz C, Bucerzan S, Nascu I, Leucuta D, et al. Cholelithiasis in patients with Gaucher disease type 1: risk factors and the role of ABCG5/ABCG8 gene variants. *J Gastrointest Liver Dis* 2016;25:447–55.
- [44] Brautbar A, Elstein D, Pines G, Abrahamov A, Zimran A. Effect of enzyme replacement therapy on gammopathies in Gaucher disease. *Blood Cells Mol Dis* 2004;32:214–7.
- [45] de Fost M, Out TA, de Wilde FA, Tjin EP, Pals ST, van Oers MH, et al. Immunoglobulin and free light chain abnormalities in Gaucher disease type I: data from an adult cohort of 63 patients and review of the literature. *Ann Hematol* 2008;87:439–49.
- [46] Shoenfeld Y, Beresovski A, Zharhary D, Tomer Y, Swissa M, Sela E, et al. Natural autoantibodies in sera of patients with Gaucher's disease. *J Clinical Immunol* 1995;15:363–72.
- [47] Serratrice C, Bensalah N, Penaranda G, Bardin N, Belmatoug N, Masseau A, et al. Prevalence of autoantibodies in the course of Gaucher disease type 1: a multicenter study comparing Gaucher disease patients to healthy subjects. *Joint Bone Spine* 2018;85:71–7.
- [48] Stein P, Yu H, Jain D, Mistry PK. Hyperferritinemia and iron overload in type 1 Gaucher disease. *Am J Hematol* 2010;85:472–6.
- [49] Mekinian A, Stirnemann J, Belmatoug N, Heraoui D, Fantin B, Fain O, et al. Ferritinemia during type 1 Gaucher disease: mechanisms and progression under treatment. *Blood Cells Mol Dis* 2012;49:53–7.
- [50] Lorenz F, Pawlowicz E, Klimkowska M, Beshara S, Bulanda Brustad A, Skotnicki AB, et al. Ferritinemia and serum inflammatory cytokines in Swedish adults with Gaucher disease type 1. *Blood Cells Mol Dis* 2018;68:35–42.
- [51] Lefebvre T, Reihani N, Daher R, de Villemeur TB, Belmatoug N, Rose C, et al. Involvement of hepcidin in iron metabolism dysregulation in Gaucher disease. *Haematologica* 2018;103:587–96.
- [52] Langeveld M, de Fost M, Aerts JM, Sauerwein HP, Hollak CE. Overweight, insulin resistance and type II diabetes in type I Gaucher disease patients in relation to enzyme replacement therapy. *Blood Cells Mol Dis* 2008;40:428–32.
- [53] Razeq A, Abdalla A, Barakat T, El-Taher H, Ali K. Assessment of the liver and spleen in children with Gaucher disease type I with diffusion-weighted MR imaging. *Blood Cells Mol Dis* 2018;68:139–42.
- [54] Abdel Razeq AAK, Barakat T, Ali K. Assessment of liver and spleen in children with Gaucher disease type 1 with chemical shift imaging. *J Comput Assist Tomogr* 2019;43:183–6.
- [55] Regenboog M, Bohte AE, Akkerman EM, Stoker J, Hollak CEM. Iron storage in liver, bone marrow and splenic Gaucheroma reflects residual disease in type 1 Gaucher disease patients on treatment. *Br J Haematol* 2017;179:635–47.
- [56] Huwart L, Sempoux C, Vicaud E, Salameh N, Annet L, Danse E, et al. Magnetic resonance elastography for the noninvasive staging of liver fibrosis. *Gastroenterology* 2008;135:32–40.
- [57] Yin M, Talwalkar JA, Glaser KJ, Manduca A, Grimm RC, Rossman PJ, et al. Assessment of hepatic fibrosis with magnetic resonance elastography. *Clin Gastroenterol Hepatol* 2007;1213:e1202.
- [58] Singh S, Venkatesh SK, Wang Z, Miller FH, Motosugi U, Low RN, et al. Diagnostic performance of magnetic resonance elastography in staging liver fibrosis: a systematic review and meta-analysis of individual participant data. *Clin Gastroenterol Hepatol* 2015;451, 440–451 e446.
- [59] Serai SD, Naidu AP, Andrew Burrow T, Prada CE, Xanthakos S, Towbin AJ. Correlating liver stiffness with disease severity scoring system (DS3) values in Gaucher disease type 1 (GD1) patients. *Mol Genet Metab* 2018;123:357–63.
- [60] Neudorfer O, Hadas-Halpern I, Elstein D, Abrahamov A, Zimran A. Abdominal ultrasound findings mimicking hematological malignancies in a study of 218 Gaucher patients. *Am J Hematol* 1997;55:28–34.
- [61] Elstein D, Tiomkin M, Hadas-Halpern I, Zimran A. Organ volume by computed tomography correlates with longitudinal axis on ultrasound in patients with Gaucher disease. *Ultrasound Q* 2011;27:225–8.
- [62] Poll LW, Cox ML, Godehardt E, Steinhof V, vom Dahl S. Whole body MRI in type I Gaucher patients: evaluation of skeletal involvement. *Blood Cells Mol Dis* 2011;46:53–9.
- [63] Stroppiano M, Calevo MG, Corsolini F, Cassanello M, Cassinerio E, Lanza F, et al. Validity of beta-D-glucosidase activity measured in dried blood samples for detection of potential Gaucher disease patients. *Clin Biochem* 2014;47:1293–6.