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SOLVING CLINICAL PROBLEMS IN BLOOD DISEASES

A physician or group of physicians considers presentation and evolution of a real clinical case, reacting to clinical information and data (boldface type). This is followed by a discussion/commentary

Hyperferritinemia and diagnosis of type 1 Gaucher disease

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1 | CASE PRESENTATION

A 61-year-old Caucasian man presented with persistent hyperferritinemia known since his forties in the presence of components of metabolic syndrome. History revealed longstanding obesity, with maximum weight and BMI of 100 kg and 32 kg/m^2, respectively. At the age of 45 years, routine blood examination showed marked hyperferritinemia (1738 μg/L) with normal transferrin saturation (TSat 41%), very mild thrombocytopenia (140 × 10^9/L), normal Hb (139 g/L) and white blood cell count (8.93 × 10^9/L), and polyclonal hypergammaglobulinemia (21.5%). He also had low HDL cholesterol (0.8 mmol/L), mild hypertriglyceridemia (2.33 mmol/L), impaired fasting glucose (5.66 mmol/L), and oral glucose tolerance test (OGTT) consistent with glucose intolerance (glucose 9.49 mmol/L at 2 hours). Liver function tests were normal, as well as C-reactive protein, coagulation, renal and thyroid function tests. At that time, he reported an unbalanced diet with moderate alcohol consumption, sedentariness, and positive family history for type 2 diabetes mellitus. Abdominal ultrasonography (US) showed mild liver enlargement with increased echogenicity consistent with moderate steatosis; the major diameter of the spleen was 12.4 cm; no signs of portal hypertension were detected. Liver biopsy demonstrated micro-macrovesicular steatosis in 50% of hepatocytes, and hypertrophic Kupffer cells with mild siderosis (Figure 1).

A first-level genetic test for *HFE*-hemochromatosis was negative, only showing heterozygosity for the H63D variant. Sequencing of the *SLC40A1* gene (encoding ferroportin) did not reveal pathogenic mutations. A provisional diagnosis of dysmetabolic iron overload syndrome (DIOS) was suggested, and lifestyle changes as well as alcohol withdrawal were recommended.

Initially, Gaucher disease (GD) was not suspected. The patient had ≥2 alterations of the metabolic syndrome, liver steatosis and normal TSat, fitting the criteria for the diagnosis of DIOS,[1] which represents a far more frequent cause of hyperferritinemia than GD. A possible Ferroportin Disease, suggested by iron accumulation in Kupffer cells,[2] was ruled out by *SLC40A1* sequencing.

In the following 15 years, the patient lost weight (8 kg, leading to BMI reduction to 28 kg/m^2), and substantially improved his metabolic profile (fasting glucose 4.88 mmol/L, OGTT normalization, HDL cholesterol 1.39 mmol/L, triglycerides 0.93 mmol/L); he also underwent irregular phlebotomies (total *n* = 12). Nonetheless, serum ferritin was only mildly reduced (1056 μg/L). Of note, hypergammaglobulinemia (21%) was confirmed, and platelet count further decreased

[§]Alberto Piperno and Domenico Girelli equally contributed to the work.

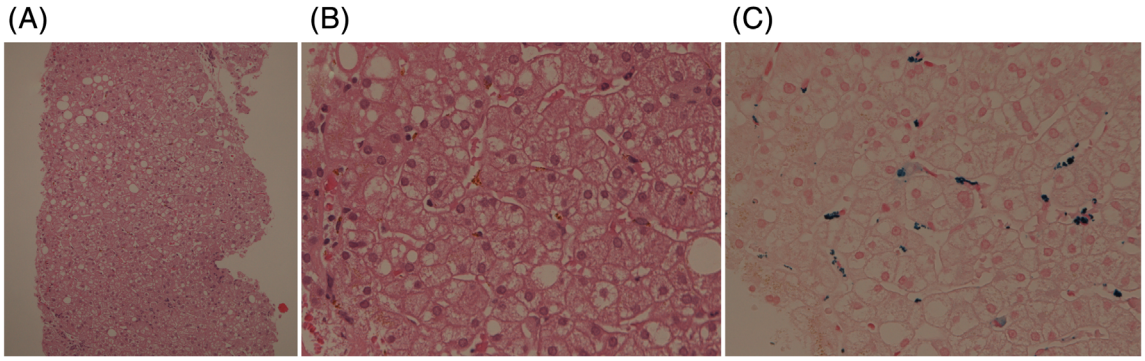


FIGURE 1 Liver histology in hematoxylin–eosin 4x (A) and 40x (B) and in Perls staining 40x (C). Preserved acinar structure with micro-macrovescicular steatosis in 50% of hepatocytes (A, B). Hypertrophic Kupffer cells with siderosis (Brissot grade 3/20) (C) [Color figure can be viewed at wileyonlinelibrary.com]

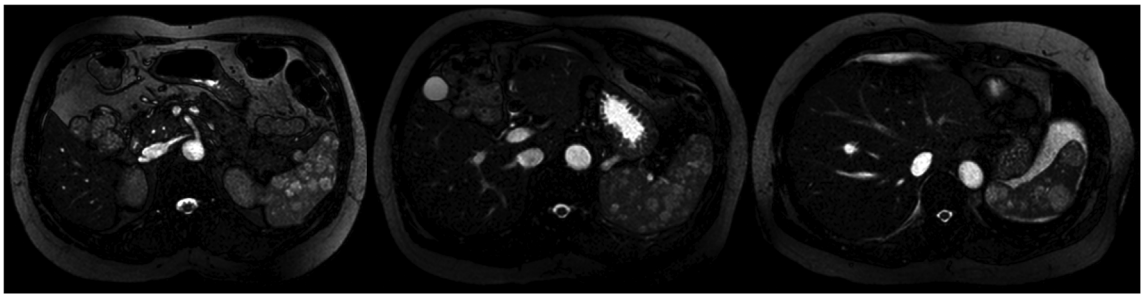


FIGURE 2 MRI T2-weighted sections showing hepatomegaly and splenomegaly with multiple Gaucheromas

(111 × 10^9/L), notwithstanding persistently normal liver function tests. The patient reported worsening back and knee pain. Lumbar spine MRI revealed diffuse bone marrow infiltration, multiple bulging disks, and osteophytosis.

The initial diagnosis of DIOS was questioned since a more pronounced decrease of serum ferritin would have been expected due to the substantial metabolic improvement. Considering the whole clinical phenotype characterized by worsening thrombocytopenia, polyclonal gammopathy, and bone pain, GD was eventually suspected and confirmed by the reduced β-glucocerebrosidase activity, on both dried blood spot (DBS) and leukocytes (0.6 nmol/mg/h; normal range 10-30). *GBA1* sequencing detected homozygosity for the pathogenic N370S mutation. A critical revision of the liver biopsy allowed re-defining the "hypertrophic" Kupffer cells as Gaucher cells. Abdominal MRI showed hepatomegaly (2043 mL; normal value <2000), normal liver iron concentration (35 ± 20 μmol/g, normalvalue <36), and mild splenomegaly (510 mL; normalvalue 110-340) with several nodular lesions (the so-called "Gaucheromas") (Figure 2).

Further disease staging revealed increased chitotriosidase (493 nmol/mL/h, normalvalue 43 ± 23) and glucosylsphingosine (93 ng/mL; normalvalue <4.8) levels. Femoral and pelvic MRI showed diffuse bone marrow infiltration similar to that observed in the lumbar spine, and consistent with the pain sites reported by the patient. Lumbar and femoral densitometry excluded osteoporosis and osteopenia. Enzyme replacement therapy (ERT) was started and, after 18 months, skeletal and visceral involvement improved, platelet count was 167 × 10^9/L, ferritin levels decreased to 430 μg/L (without further phlebotomies), and gammaglobulin to 19.2%.

Gaucher Disease is frequently underdiagnosed because of lack of awareness, even when all typical clinical signs and symptoms are present.[3] This case was challenging since the classical hematological signs of GD were initially mild and incomplete (normal Hb, barely detectable thrombocytopenia and splenomegaly). Over the 15 years follow-up, the platelet count dropped and the patient developed severe and symptomatic bone marrow infiltration, justifying the starting of ERT.[4,5] Regarding hyperferritinemia, it was initially attributed to metabolic syndrome, and improvement of lifestyle was recommended. Of note, obesity is uncommon in untreated GD patients.[6] Although liver biopsy and normal TSat substantially excluded a true iron overload (IO), the patient was initially treated by unnecessary phlebotomies.

We subsequently collected 8 GD type 1 (GD1) patients referred to four Italian specialized centers for iron disorders, because of "unexplained hyperferritinemia" (Table 1). All subjects were Caucasians, with a median age at diagnosis of 45 years. Both sexes were represented (five males and three females). At least one N370S mutation was present in seven out of eight patients. Median ferritin was 1285 μg/L, median TSat was 27%, and only one of the patients had evidence of significant IO, in line with previous case series.[7,8] Noteworthy, the classical GD hematological alterations were mild or even absent at first evaluation, underscoring the need for a high degree of suspicion. Thrombocytopenia and splenomegaly were present in all patients, but were both mild in the majority. In particular, splenomegaly was barely noticeable (spleen longitudinal diameter ranging from 12 to 13 cm by

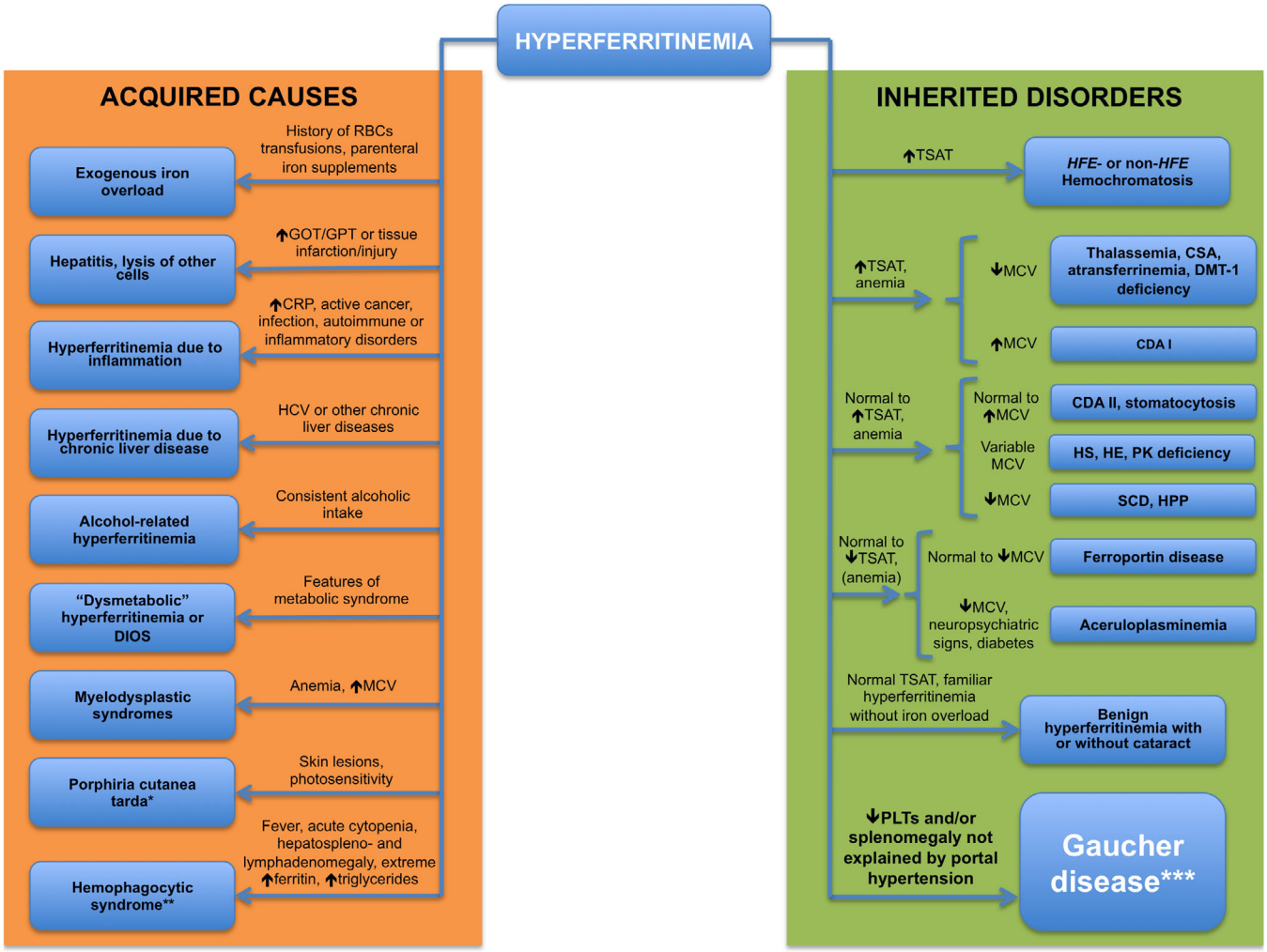
TABLE 1 Details of patients in the case series: diagnosis of GD in patients initially referred for "unexplained hyperferritinemia" in four Italian referral centers for iron disorders: MO = Modena; VR = Verona; MZ = Monza; MI = Milan. ^ normal beta-glucocerebrosidase activity: 18.4 ± 6.8 nmol/mg/hr. § underwent iron depletion by phlebotomies (3-4 per month, total iron removed 7 g)

Pt ID	GD genotype	Gender	Age at GD diagnosis; age at first detection of hyper-ferritinemia	Ferritin (μg/L); TSAT	*HFE*	LIC at MRI	Liver biopsy	Splenomegaly (MRI-spleen volume; US-maximum diameter)	PLTs (x 10^9/L)	Hb (g/L)	Other GD manifestations	Other concurrent medical conditions
MO1	N370S/ N370S	M	61; 45	1738 (age 45), 1056 (age 61); 41%	H63D hetero	Normal (35 ± 20 μM/g) (after therapeutic phlebotomy 15 years earlier)	Hypertrophic Kupffer cells with mild siderosis	510 mL; 12.4	140-111	139	Nodular splenomegaly, hepatomegaly, polyclonal gammopathy, fatigue, bone pain and bone marrow infiltration	Obesity, metabolic syndrome, liver steatosis
VR1	N370S/ N370S	M	60; 56	1470; 35%	S65C hetero	80 ± 30 μM/g pre-SRT, 47 ± 30 after 1 year of SRT	NA	371 mL; 12.7 cm	116	144	Mild hepatomegaly, Parkinson, fatigue, chronic bone pain, bone marrow infiltration	Type 2 diabetes, hypercholesterolemia (anamnestic)
VR2	N370S/ N370S	F	23; 22	600; 15%	Wild type	<36 μM/g pre-SRT	NA	400 mL; 13.9 cm	118	121	Hepatomegaly, reduced bone mass, fatigue	none
MZ1	N370S/ F213I	M	55; 55	1965; 28%	Wild type	NA	Mixed iron overload, prevalent in Kupffer cells§, presence of Gaucher cells	NA; 14 cm	112	138	Hepatomegaly	alcohol intake 30 g/day
MZ2	N370S/x (enzyme activity 1.1 nmol/mg/hr)^	F	48; 45	928; 25%	Wild type	NA	Unremarkable except forpresence of Gaucher cells	NA; 12 cm	109	123	Hepatomegaly	mild overweight
MZ3	N370S/ Q362*	M	42; 40	1101; 18%	Wild type	NA	NA	NA; 19 cm	42	125	Leucopenia 3.11×10^9/L; hepatomegaly	liver steatosis
MI1	N370S/ G377S	F	33; 27	443; 26%	NA	NA	NA	NA; 13 cm	130	112	Bone marrow infiltration	none
MI2	L444P/ A456P	M	23; 22	1800; 33% (age 22). 1387; 17% (age 23)	Wild type	40 ± 20 μM/g	NA	NA; 13 cm	140	141	Bone marrow infiltration	none

US) in five out of eight patients. Hepatomegaly was present in six out of eight patients, but in five cases co-factors for liver disease were detected. Anemia was present only in two out of eight patients and was mild in both cases. Only two out of eight patients reported bone pain at diagnosis, while bone involvement was demonstrated with subsequent imaging examinations in six out of eight patients.

2 | DISCUSSION

Gaucher Disease is a pleiotropic lysosomal storage disorder due to biallelic mutations in the *GBA1* gene (1q21), or, in exceedingly rare cases, in the *PSAP* gene, which encodes for its activator protein (saposin C). Reduced or absent activity of β-glucocerebrosidase results in the accumulation of glucocerebroside in macrophages of several organs, mainly the spleen, liver, and bone marrow.[9] The current phenotypic classification of GD into different subtypes is likely an oversimplification of a continuum of the same enzymatic defect that can be variably severe and clinically expressed. Such classification is based on the presence of central nervous system involvement, being type 1 the "non-neuronopathic", type 2 the "acute neuronopathic", and type 3 the "chronic neuronopathic" form of the disease.[10] A certain degree of overlap is possible, particularly regarding the occurrence of Parkinsonism in GD1 patients.[11] Gaucher Disease type 1 accounts for about 90% of all GD cases, and has a heterogeneous clinical expression, ranging from overt visceral and bone involvement in childhood/early-adulthood to more faded manifestations in late-adulthood. Unrecognized GD often leads to significant disability due to bone pain, fractures, and bleeding. N370S homozygosity in *GBA1*, the most common genotype in Ashkenazi Jewish, and the second most common one in European non-Jewish patients, is traditionally related to a mild phenotype but a clear genotype-phenotype correlation is lacking, and acquired factors can also influence the phenotype.[12,13] The prevalence of GD, previously estimated at around 1:59000 [Meikle, JAMA 1999], has been recently questioned by data from newborn screening programs, suggesting a prevalence of near 1:22000, at least in North-



* Can be an inherited disorder. ** Can be a genetic condition in pediatric age. *** Also other inherited metabolic disorders can have hyperferritinemia with hepatosplenomegaly, for example acid sphingomyelinase deficiency and lysinuric protein intolerance. CSA: congenital sideroblastic anemia. CDA: congenital dyserythropoietic anemia. HS: hereditary spherocytosis. HE: hereditary elliptocytosis. PK: pyruvate kinase. SCD: sickle cell disease. HPP: hereditary pyropoikilocytosis.

FIGURE 3 Flow-chart for the differential diagnosis of hyperferritinemia based on clinical evaluation and first level tests: when to suspect a Gaucher Disease [Color figure can be viewed at wileyonlinelibrary.com]

East Italy.[14] Indeed, such new findings have corroborated the belief that the disease is often under-recognized. The increasing availability of "dried blood spot" tools for widespread first-level analysis of enzymatic activity represents a useful help in the diagnostic process.[15] The confirmation of low enzymatic activity is virtually diagnostic, and has almost completely superseded bone marrow examination,[16] which could still be needed only when the clinical differential diagnosis includes a hematological malignancy.[17] Noteworthy, effective treatments are available for GD1 and for non-neurological manifestations of GD3, that is, enzyme replacement therapy (ERT) and substrate-reduction therapy (SRT).[10]

In such a context, it is essential to increase the awareness of the disease in order to make the right diagnosis as early as possible, hence reducing the disability burden. Hematologists are the specialists more likely involved in the diagnosis of GD, but, even when all classical clinical features are present, only a minority (~20%) of them consider GD in the differential diagnosis.[3,18] Consultation of several specialists, misdiagnosis, and diagnostic delay are frequent features of the patient's journey towards the correct diagnosis of GD, eventually resulting in a poor quality of life, complications, and sometimes irreversible disabilities.[18] Common misdiagnoses include hematological malignancies, immune thrombocytopenic purpura, autoimmune disease, liver cirrhosis, idiopathic avascular necrosis, and "idiopathic" splenomegaly.[18]

Since hematologic findings like splenomegaly, thrombocytopenia and anemia are among the most prevalent signs of GD, diagnostic algorithms starting from these findings have been proposed, with dedicated algorithms for subjects of Jewish ancestry due to the higher prevalence of GD.[19] For example, the application of one of these algorithms to patients referred to Italian hematology outpatient clinics because of splenomegaly and/or thrombocytopenia detected GD in 7 out of 196 cases (prevalence 3.6%).[20] Nonetheless, because of phenotypic heterogeneity and lack of awareness, other "high-risk patterns" need to be considered. Biochemical abnormalities commonly found in GD include hyperferritinemia, hypolipidemia with low HDL-cholesterol levels, low vitamin B12, polyclonal hypergammaglobulinemia, and MGUS.[6,7]

Hyperferritinemia is a frequent finding in clinical practice, potentially associated with many different etiologies.[21,22] Sometimes, it is due to IO, which may be genetic (eg, hereditary hemochromatosis caused by mutations in the *HFE* gene or in other genes involved in

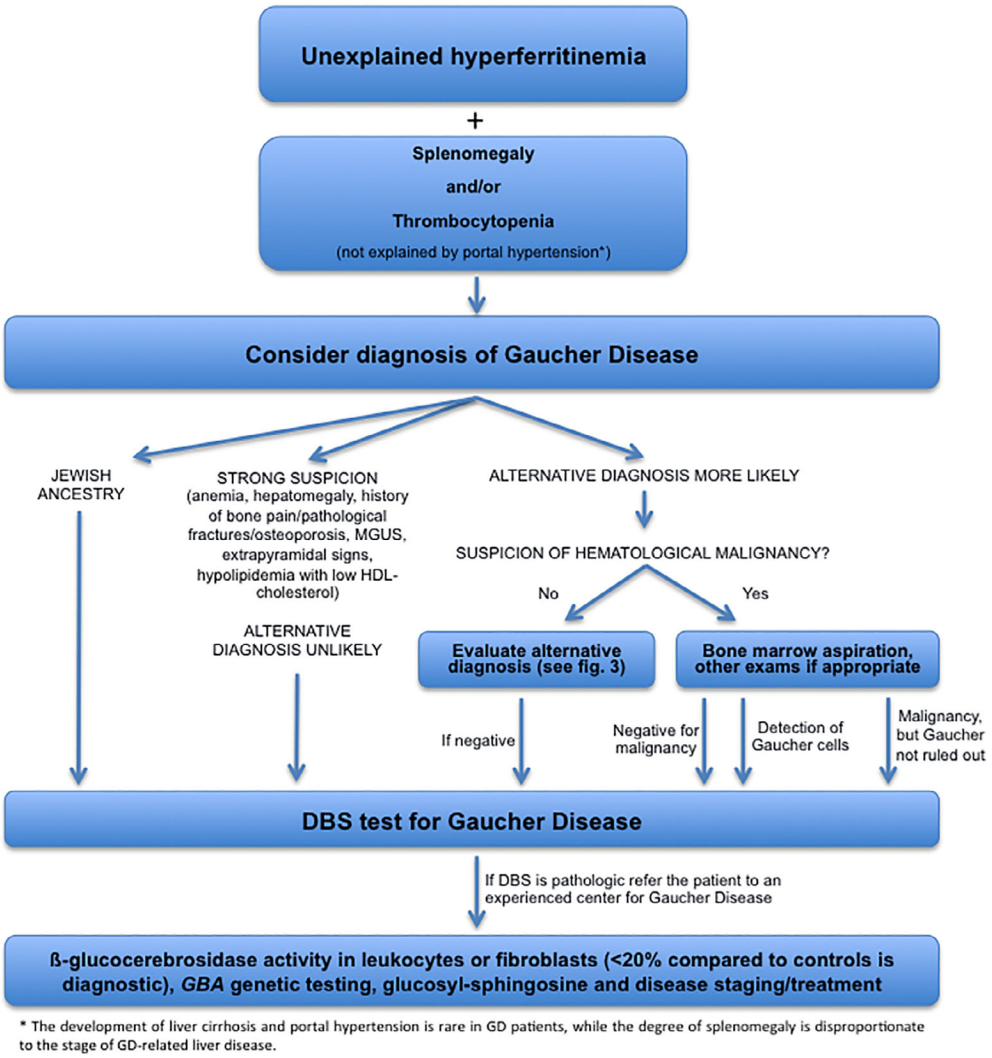


FIGURE 4 Gaucher-focused flow-chart for appropriate diagnosis of GD starting from hyperferritinemia: how to pursuit the diagnosis [Color figure can be viewed at wileyonlinelibrary.com]

iron homeostasis), generally associated with increased TSat, or acquired (eg, due to repeated blood transfusions). More frequently, hyperferritinemia does not reflect a true IO, but it is due to inflammation, chronic liver disease, excessive alcohol intake, components of metabolic syndrome or malignancies. In these cases, TSat is usually normal. To make the correct diagnosis is essential because the management depends on the underlying disorder. Investigations of raised serum ferritin (ie, >200 μg/L in females, >300 μg/L in males) should include an accurate collection of patient's medical history and some simple laboratory test, as summarized in Figure 3. In some cases, liver MRI or biopsy can be useful to assess liver iron stores. If hereditary hemochromatosis is suspected, a genetic analysis is recommended, including rare mutations in *HFE* and non-*HFE* genes (eg, *HAMP*, *HJV*, *TFR2*, *BMP6*, etc.) when a first-level genetic test is negative. Among the different causes of hyperferritinemia, GD is often overlooked. Hyperferritinemia (mean elevation 3-4 x upper limit of normal) with normal TSat is a common finding in naïve patients with type 1 GD.[23] Recent case series reported a prevalence of 63-81%.[7,8] While ferritin levels in GD patients can be markedly elevated, they are typically disproportioned with respect to liver iron accumulation, which is usually absent or unremarkable.[23] For this reason, hyperferritinemia per se is not an indication for phlebotomies in GD patients, who may even experience worsening anemia and fatigue. Only sporadic cases reports in literature described significant iron deposits in GD patients, generally associated with cofactors like *HFE* mutations or chronic hepatitis C virus infection.[23] An elevated TSat or liver iron accumulation at MRI can be of value in these rare cases.

Pathophysiology of hyperferritinemia in GD is still debated, and several explanations have been proposed, including long-lasting low-grade chronic inflammation, impaired function of macrophages involved in iron recycling, and local dysregulation of the hepcidin-ferroportin axis.[7] Ferritin levels typically decrease during treatment, and have been proposed as a biomarker of disease activity,[17] although not as meaningful as glucosylsphingosine, which directly reflects substrate accumulation.[24] The GD specific treatment with ERT or SRT must be initiated according to international recommendations and consensus, not solely on the basis of mutation analysis and regardless of the ferritin levels.

Our series of 8 GD cases diagnosed at different Italian referral centers for iron disorders highlights the possibility of diagnosing GD starting from hyperferritinemia. In this context, even mild or incomplete classical manifestations of GD (ie, thrombocytopenia, splenomegaly, anemia, bone involvement) should lead to include GD in the differential diagnosis. Of note, our series shows that clinically mild phenotypes are not restricted to N370S homozygotes. In Figure 3 we propose a diagnostic flow-chart that could help physicians to detect GD when facing patients presenting with apparently "unexplained hyperferritinemia". The combination of a careful clinical history with simple first level investigations may be sufficient for guiding a differential diagnosis, also including rare conditions, like GD. When GD is suspected, subsequent investigations should be tailored according to the strength of clinical suspicion. A DBS testing could be used as a first-line screening strategy, followed by confirmatory diagnostic approaches in the case of pathologic DBS results (Figure 4). Bone marrow examination may still play a role in the diagnostic process, particularly considering that GD per se is a risk factor for the development of hematological malignancies.

3 | CONCLUSIONS

Given the difficulties in diagnosis of type 1 GD in adults because of disease heterogeneity and lack of awareness, appropriate diagnostic algorithms or flow-charts starting from non-specific findings may help. Further studies may establish the usefulness of our proposed flow-chart in patients presenting with "unexplained hyperferritinemia".

CONFLICT OF INTEREST

Giacomo Marchi has received fees for lectures from Shire-Takeda. Fabio Nascimbeni and Francesca Carubbi have received fees for consultancy or lectures from Sanofi-Genzyme and Shire-Takeda. Irene Motta has received honoraria and is a member of the advisory board for Sanofi-Genzyme. Maria Domenica Cappellini is a member of Vifor, Sanofi-Genzyme, Celgene, Novartis and Bluebird advisory board. Alberto Piperno has received fees for consultancy and lectures from Shire-Takeda. Domenico Girelli has received fees for lectures from Sanofi-Genzyme and Shire-Takeda. Fabiana Busti, Antonello Pietrangelo and Elena Corradini have nothing to declare.

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