Expert consensus guideline on the diagnosis of type 1 Gaucher disease in adult patients

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ABSTRACT

Gaucher disease (GD) is a rare genetic disorder characterized by glucocerebrosidase deficiency. Over 50% of patients with mild disease go undiagnosed, suggesting that GD diagnosis rates are still significantly low despite advancements in medical knowledge and diagnostic techniques. This guideline explores the potential settings in which patients with mild to moderate GD may present, providing professional guidance on diagnostic avenues and highlighting the necessity of raising awareness among medical professionals. Patients with undiagnosed GD may be seen in departments such as neurology, transfusion medicine, centers for hepatic disorders, orthopedics, hemostasis, thrombosis, benign and general hematology, and reference centers for these conditions. Therefore, for a timely diagnosis and appropriate management of this rare disorder, it is crucial that these specialties collaborate effectively and devise a path that avoids needless and invasive procedures.

IntroductionH

Gaucher disease (GD) is an autosomal lysosomal storage disorder caused by mutations in the GBA gene, leading to impaired activity of the enzyme glucocerebrosidase.[1] It manifests with a wide range of symptoms, including hepatosplenomegaly, anemia, thrombocytopenia, bone abnormalities, and neurologic involvement.[2-4] Early diagnosis is paramount for timely intervention and improved patient outcomes.[5]

GD prevalence at birth in the Caucasian population is estimated between 1:50.000 and 1:100.000;[6-8] evidence suggests a significant underdiagnosis of GD, particularly in patients with mild disease. This poses significant challenges in managing the burden of GD within the healthcare system. The reasons behind this underdiagnosis may include limited awareness among healthcare professionals, overlapping symptoms with other conditions, and the lack of routine screening protocols.[9-11]

In general, most of the efforts are placed in pediatric and high-symptoms burden populations,[12-14] and the adult setting often remains a white spot for diagnosis and treatment. An Italian study has already demonstrated that basic attention to peculiar signs and symptoms and remote history during the routine clinical examination may identify mild and mod-

erate GD patients with a likelihood of a genetic diagnosis of 3% within the clinically selected high-risk population.[15] A precise and prompt diagnosis plays a central role in improving a patient's journey and is highly sought after whenever patient input is gathered. In addition to addressing conventional objectives related to hematological, visceral, and skeletal aspects, patients focus on enhancing quality of life, managing fatigue, and promoting social engagement, alongside early identification of potential long-term complications or related illnesses.[9,16]

Given the diverse potential settings for GD diagnosis, establishing literacy and effective collaboration among different specialties is paramount.[17] Timely identification and referral of patients suspected to have GD can significantly improve patient outcomes and prevent unnecessary delays in diagnosis and treatment.[5,18] This multidisciplinary approach involves fostering communication and knowledge exchange among healthcare professionals in various departments, as well as promoting awareness and education regarding the clinical manifestations and diagnostic pathways of GD.

Materials and Methods

We employed a 2-round Delphi method to gather expert opinions and develop guidelines for the diagnosis of GD in the adult setting (Figure 1). A team of eight experts was selected based on their multidisciplinary expertise. The team comprised clinical hematologist experts specializing in neoplastic and benign hematology, experts in iron metabolism, experts in hemostasis and thrombosis, as well as experts in transfusion medicine. This diverse composition ensured that all relevant perspectives and areas of expertise were represented. The initial round of the Delphi method involved a round-table discussion among the experts. During this discussion, relevant opinions, experiences, and knowledge related to the diagnosis of GD and other enzymopathies were collected. This round served as a foundation for the subsequent survey.

Building upon the insights gathered from the round-table discussion, a survey was designed to quantify and qualify expert opinions and elicit specific arguments of interest and was conducted on RedCap.[19] The survey included 54 statements addressing various aspects of the diagnosis of GD, such as diagnostic criteria, laboratory tests, imaging techniques, and clinical presentation. The statements were carefully crafted to cover a wide range of diagnostic considerations and challenges. The survey was distributed to the panel of experts, who provided their responses based on their clinical experience and knowledge. The collected data was then pooled and analyzed. For ordinal or continuous statements where the responses followed a normal distribution, the median value was reported; in cases where the responses did not follow a normal distribution, the distribution pattern was specified. For nominal statements, responses were retained whenever approved by >70% of participants.

The statements and expert opinions were critically reviewed and compared with the current literature on GD diagnosis. The experts conducted an extensive literature review to ensure that the guidelines developed were in line with the latest evidence-based practices and recommendations. Based on the collective opinions, survey responses, and literature review, guidelines for the diagnosis of GD were formulated.

The guidelines represented a summation of the recommendations and consensus reached by the expert panel. The Delphi method employed in this study allowed for an iterative process, where the experts had the opportunity to revise and refine their opinions based on the collective feedback and discussion. This iterative approach contributed to the development of robust and consensus-driven guidelines for the diagnosis of GD and other enzymopathies with hematological manifestations.

Epidemiology

One of the significant challenges in understanding the epidemiology of GD is the underestimation of its prevalence. Up to 50% of patients with mild forms of the disease are estimated to remain undiagnosed. This phenomenon can be attributed to the variability in clinical presentation and the lack of awareness among healthcare professionals regarding the disease. In terms of healthcare settings, ref-

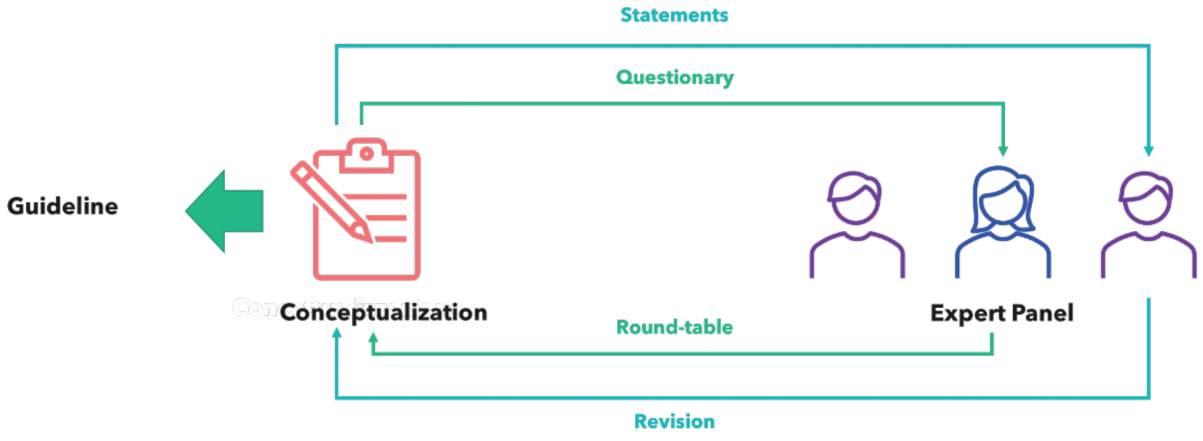

Figure 1. Delphi design.

erence centers specializing in iron metabolism, hemostasis and thrombosis, as well as benign and general hematology, play a crucial role in diagnosing and managing GD. These centers are likely to be the primary access points for patients experiencing the manifestations associated with the disease.

While reference centers and larger institutions are key settings for identifying GD patients, there are other departments where patients with undiagnosed GD may also present. These departments include neurology, transfusion medicine, centers for hepatic disorders, and orthopedics. Although the frequency of such discoveries in these departments is estimated to be rare, their inclusion highlights the need for a multidisciplinary approach to diagnosing and managing GD. Collaboration and communication between various specialties are crucial to ensure timely and accurate diagnoses, enabling appropriate treatment and support for patients.

Overall, the epidemiology of GD is marked by a significant rate of under-diagnosis, with a high proportion of patients, especially those with mild disease, remaining unidentified. Reference centers specialized in relevant fields are essential for identifying and managing GD patients, while departments outside these centers may occasionally encounter undiagnosed cases. Improving awareness among healthcare professionals and promoting interdisciplinary collaboration are crucial steps in addressing the challenges associated with the epidemiology of GD (Table 1).

Criteria to perform Gaucher screening test

Diagnostic criteria play a crucial role in identifying individuals who may be affected by GD. The most common manifestations of the disease, such as low platelet count, enlarged spleen, and elevated ferritin levels,[20] serve as the primary triggers for considering a differential diagnosis. These manifestations are present in over 80% of patients with GD, making them highly indicative of the condition.

In addition to the aforementioned manifestations, GD patients often present with a range of symptoms that can reinforce the suspicion of the disease. These symptoms include anemia, weakness, fatigue, bone lesions, coagulation disorders, hypergammaglobulinemia, monoclonal gammopathy of unknown significance, ecchymosis, osteopenia, constipation, dyspepsia, and hypersplenism. The presence of these symptoms, in combination with the common manifestations, further strengthens the diagnostic suspect for GD.

While certain manifestations are more prevalent in GD, there are other symptoms that are less frequently observed in affected individuals. These include bone pain, recurrent infections, enlarged liver, and neoplasms, including hematologic neoplasms. Thrombocytosis, active Parkinson's disease or Parkinson-like diseases, and leukopenia are also seen in a smaller proportion of patients. It is important to note that the presence of these less common manifestations does not exclusively indicate GD and may be present in other conditions as well (Table 2).

Obtaining a relevant family history is essential during the diagnostic process. It is not only important to inquire about diagnosed cases of GD within the family, but also to gather information about relevant symptoms, conditions, and laboratory abnormalities. This comprehensive evaluation of familial factors helps understand the inheritance pattern and potential predisposition to GD.

To guide the screening process for GD, the criteria in Figure 2 are suggested[21]:

- Patients with more than one major criterion.
- Patients with one major criterion and at least one minor criterion or two concomitant findings.
- Patients with at least two minor criteria or/and one concomitant finding.

Table 1. Statements on Gaucher disease epidemiology in adult patients.

Statements
The diagnosis of GD is underestimated, more than 50% of patients with mild disease may be unknown.
Reference centers for iron metabolism, hemostasis and thrombosis, and benign and general hematology represent the setting in which GD patients may likely access for the manifestations of their disease; it is expected more than a new patient per year in larger institutions.
A patient with undiagnosed GD may also be discovered in the neurology department, transfusion medicine department, center for hepatic disorders, or orthopedic department. This is estimated to be rare.

GD, Gaucher disease.

Table 2. Prevalence of findings in newly diagnosed adult Gaucher disease.

Low platelets, enlarged spleen, and augmented ferritin level are the most common manifestations of GD, and represent the most frequent trigger to carry differential diagnosis. >80% of patients with GD have one or more of these manifestations.
Anemia, weakness, fatigue, bone lesions, coagulation disorders, hypergammaglobulinemia, monoclonal gammopathy of unknown significance, ecchymosis, osteopenia, constipation, dyspepsia, and hypersplenism are common symptoms encountered in GD patients and may reinforce the diagnostic suspect.
Bone pain, recurrent infections, enlarged liver, neoplasms including hematologic neoplasms present in less than 50% of patients; thrombocytosis, active Parkinson or Parkinson-like diseases, and leukopenia present in less than 25% of patients; however, the presence of this manifestation are not exclusive of GD diagnosis.
A relevant familiar history should always be obtained, not only for diagnosed disease but also for relevant symptoms, conditions, and laboratory abnormalities

GD, Gaucher disease.

Importance of diagnosis in adult patients

The timely diagnosis of GD in adult patients is of paramount importance due to the potential for prolonged disease manifestation prior to clinical recognition. In many cases, the manifestations of GD appear several years before an accurate diagnosis is made, leading to a significant delay in initiating appropriate treatment. While appropriate therapy can effectively reverse most of the disease manifestations, individuals often experience residual effects from the untreated period of GD. It is estimated that up to 25% of disease manifestations may persist even in adult patients undergoing replacement therapy (Table 3).

However, it is crucial to emphasize that once replacement therapy is initiated, a remarkable improvement in patient outcomes can be achieved. More than 80% of GD-related morbidity can be avoided with the timely administration of appropriate therapy. Therefore, the early diagnosis of GD becomes pivotal in preventing further disease progression and reducing the burden of associated complications.[9]

Table 3. Statements on the importance of Gaucher disease diagnosis in adult patients.

Statement
In adult patients, manifestations of GD often precede the clinical diagnosis of more than 5 years
An appropriate therapy may revert most of the disease manifestation, however, the patient often has some sequelae from manifestations that developed while they were untreated for GD. We estimate that up to 25% of disease manifestations do not completely revert in adult patients in replacement therapy.
As soon as a replacement therapy begins, more than 80% of GD-related morbidity can be avoided.
GD must always be included in differential diagnosis of patients with low platelets, enlarged spleen, and/or augmented ferritin level.

GD, Gaucher disease.

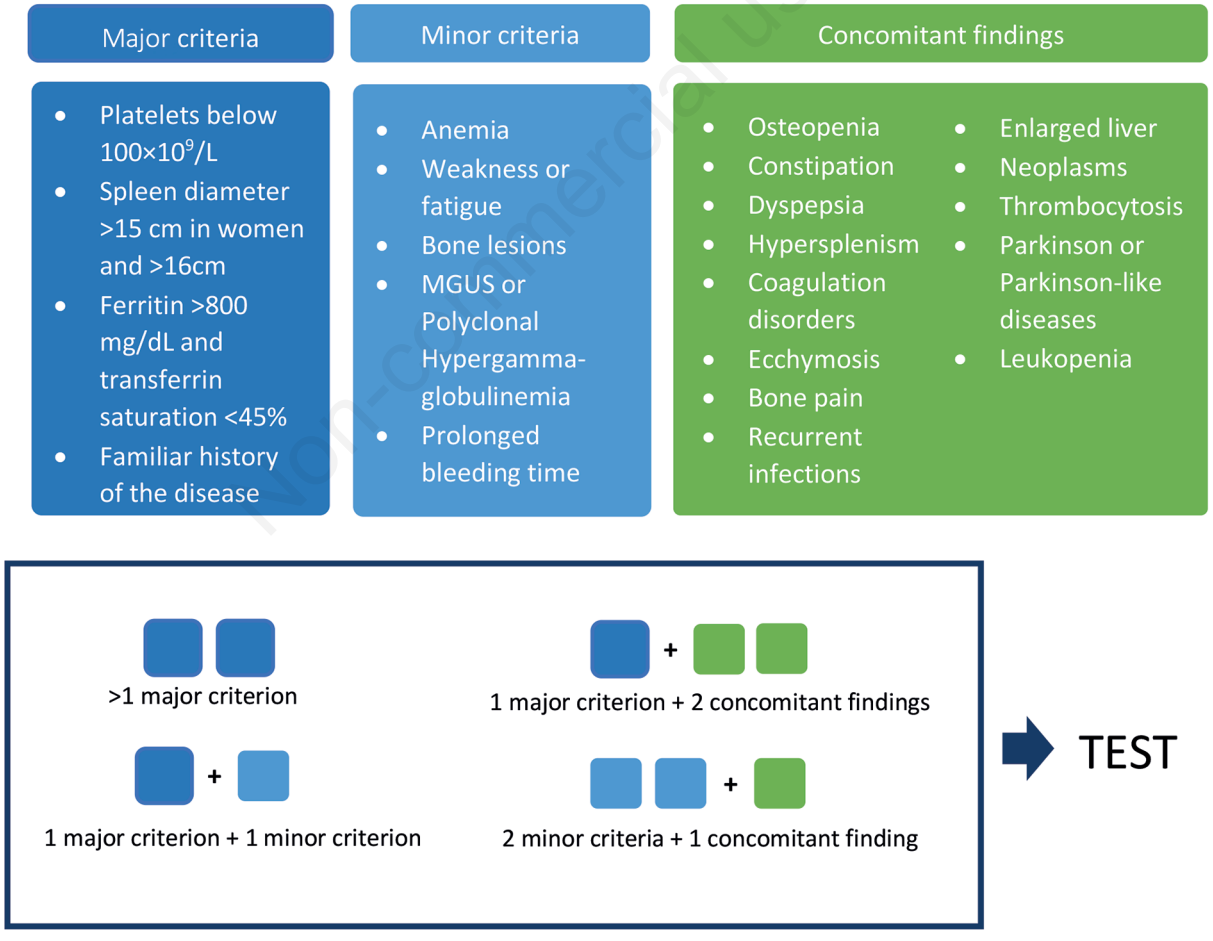

Figure 2. Criteria for Gaucher disease testing. (Adapted from Mehta *et al.*, 2019).[21]

Given the clinical presentation of GD, healthcare professionals should always consider it as part of the differential diagnosis when encountering patients with low platelet counts, an enlarged spleen, and/or elevated ferritin levels. These manifestations are among the most common and frequent triggers for considering GD, underscoring the need for heightened clinical suspicion. Prompt recognition and diagnosis enable the initiation of treatment at an earlier stage, thereby enhancing the chances of achieving better patient outcomes and minimizing the long-term consequences of the disease.

Invasive and high-cost/high-burden procedures

The avoidance of invasive and unnecessary procedures is crucial when evaluating patients with relevant clinical manifestations, as it pertains to differential diagnosis of GD. Splenectomy, for instance, should never be performed without prior GD screening, especially in cases of an enlarged spleen without a known cause or in the context of mild to moderate chronic cytopenia. Similarly, in patients with unexplained chronic platelet decrease, a bone marrow biopsy should be preceded by GD screening, except in cases of severe or sudden platelet count decrease (Table 4).

It is important to note that bone marrow biopsy alone has an accuracy rate of approximately 60 to 70% in GD diagnosis.[22,23] Therefore, relying solely on bone marrow biopsy to exclude GD from the differential diagnosis is not recommended. A negative bone marrow biopsy should not be used to avoid screening for GD and other enzymopathies, as it does not definitively rule out the possibility of these conditions.

In the case of augmented ferritin levels without a concomitant relevant increase in transferrin saturation, genomic testing should be requested from reference centers. However, it is crucial to always precede genomic testing with GD screening. GD testing is essential to ensure accurate interpretation and appropriate utilization of genomic testing results.

By adhering to these guidelines and avoiding unnecessary invasive procedures, healthcare providers can minimize patient discomfort, reduce the risk of complications, and optimize the diagnostic process for various conditions with clear benefits for patients ultimately diagnosed with GD. Implementing a systematic and informed approach that integrates Gaucher screening before considering invasive procedures or genomic testing helps ensure a comprehensive evaluation and appropriate management for patients presenting with relevant clinical manifestations.

Differential diagnosis in patients with enlarged spleen accounting for Gaucher disease

When encountering patients with an enlarged spleen, it is important to consider GD as a potential differential diagnosis. The size of the spleen can provide valuable information in the diagnostic workup. Generally, a spleen diameter of 15 cm in women and 16 cm in men is considered the minimum threshold that warrants further investigation, even if it is an isolated presentation. However, it is crucial to note that the absence of splenomegaly does not completely exclude the possibility of GD. In cases where the spleen size is mildly or borderline enlarged, special attention should be given, particularly when there is an association with coagulation disorders that cannot be attributed to any congenital or acquired causes, or when other typical Gaucher-related conditions are present. These signs may indicate an underlying GD, even in the absence of significant splenomegaly (Table 5).

To aid in the diagnostic process, a helpful resource is the algorithm depicted in Figure 3. This algorithm provides a step-by-step approach for the differential diagnosis of adult patients presenting with an enlarged spleen, with a specific focus on considering the possibility of GD. By following this algorithm, healthcare professionals can systematically evaluate and rule out other potential causes while keeping GD as a key consideration.

Table 4. Statements on invasive and high-cost procedures in adult patients with possible diagnosis of Gaucher disease.

Statement
Splenectomy for an enlarged spleen without any known cause must always be preceded by Gaucher screening. Splenectomy should be preceded by GD screening in the context of mild or moderate chronic cytopenia.
In patients with chronic platelet decrease without any known cause, bone marrow biopsy must always be preceded by Gaucher screening. This statement does not apply to severe or sudden decrease of the platelet count.
Bone marrow biopsy has an accuracy of between 60 and 70%. For this reason, bone marrow biopsy should not be used to exclude GD from the differential diagnosis
A negative bone marrow biopsy should not be used to avoid screening for GD and other enzymopathies.
Genomic testing for augmented ferritin without concomitant relevant augment of transferrin saturation must be demanded to reference centers and always preceded by GD testing.

GD, Gaucher disease.

Table 5. Statements on differential diagnosis in patients with enlarged spleen accounting for Gaucher disease.

Statement
15 cm in woman and 16 cm in man are the minimum diameter of the spleen that should require a diagnostic workup even if is an isolated presentation.
The absence of splenomegaly does not rule out GD. Mild or borderline augment in spleen size may require particular attention whenever associated to coagulation disorders (without any congenital or acquired cause) or other typical Gaucher-related conditions.

GD, Gaucher disease.

Differential diagnosis in patients with low platelets accounting for Gaucher disease

When encountering patients with low platelet counts, it is important to consider GD as a potential differential diagnosis. A platelet count of less than 100×10^9/L, in the absence of any known condition or pregnancy, should prompt a diagnostic workup, even if it is an isolated presentation. However, it is crucial to note that higher platelet values do not completely exclude the possibility of GD. Mild and borderline reductions in platelet count should receive particular attention, especially when there is an association with coagulation disorders that cannot be attributed to any congenital or acquired causes or when other typical Gaucher-related conditions are present. These additional signs may indicate an underlying GD, even in the presence of platelet values that may fall within the normal or higher range (Table 6).

To facilitate the diagnostic process, an algorithm designed for the differential diagnosis of adult patients with low platelets that accounts for possible GD can be followed. Figure 4 presents such an algorithm, which outlines a step-by-step approach to evaluate patients with low platelet counts while considering the potential involvement of GD. By utilizing this algorithm, healthcare professionals can systematically assess and eliminate other potential causes while maintaining a focus on GD.

Differential diagnosis in patients with augmented ferritin level accounting for Gaucher disease

When encountering patients with elevated ferritin levels, it is important to consider GD as a potential differential diagnosis. A ferritin level of 800 mg/dl is considered the threshold that should prompt a diagnostic workup, even if it is an isolated presentation. However, it is crucial to note that a normal ferritin value does not completely rule out the possibility of GD (Table 7).

Mild or borderline increases in ferritin levels should be given particular attention, especially when there is an association with coagulation disorders that cannot be attributed to any congenital or acquired causes or when other typical Gaucher-related conditions are present. These additional signs may indicate an underlying GD, even in the presence of ferritin levels that may fall within the normal range.

To assist in the diagnostic process, an algorithm specifically designed for the differential diagnosis of adult patients with augmented ferritin levels that accounts for possible GD

Table 6. Statement on differential diagnosis in patients with low platelets accounting for Gaucher disease.

Statement
Patients with less than 100×10^9 PLT/L in the absence of any known condition or pregnancy should require a diagnostic workup even if is an isolated presentation.
Higher platelet values do not rule out possible GD diagnosis. Mild and borderline reduction in platelet levels may require particular attention whenever associated with coagulation disorders (without any congenital or acquired cause) or other typical Gaucher-related conditions.

PLT, platelet; GD, Gaucher disease.

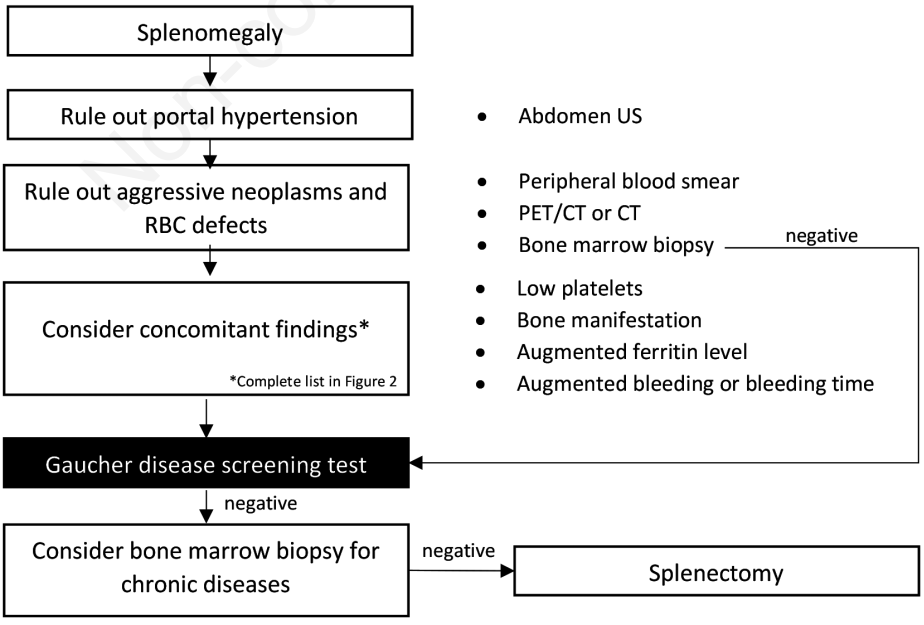

Figure 3. Algorithm for a differential diagnosis in adult patients with enlarged spleen that account for possible Gaucher disease. RBC, red blood cell; US, ultrasound; PET, Positron emission tomography; CT, computed tomography. (Modified from Mistry *et al.*, 2011).[23]

can be followed. Figure 5 depicts this algorithm, which provides a step-by-step approach for evaluating patients with elevated ferritin levels while considering the potential involvement of GD. By utilizing this algorithm, healthcare professionals can systematically assess and rule out other potential causes while maintaining a focus on GD.

Relevance of coagulation disorders

Coagulation disorders are frequently observed in GD patients, and various clotting abnormalities have been reported. Detection of prolonged prothrombin time and activated partial thromboplastin time should prompt further investigation of plasma levels of specific coagulation factors.[24] The reduction in clotting factors can be attributed to liver disease affecting synthesis, an enlarged spleen increasing clearance, elevated levels of circulating glucocerebroside, or the presence of antiphospholipid antibodies interfering with the clotting cascade. The consumption of clotting factors by low-grade intravascular coagulation and fibrinolysis, potentially triggered by cytokines secreted by Gaucher cells, may also contribute to clotting abnormalities.[25-27] Although coagulation defects are frequently observed at diagnosis, the complexity of their etiologies and the presence of confounding factors from both acquired and inherited clotting factor deficiencies make it challenging to create a diagnostic algorithm solely based on these abnormalities. Factors such as

Table 7. Statement on differential diagnosis in patients with augmented ferritin level accounting for Gaucher disease.

Statement
800 mg/dl is the ferritin level that should require a diagnostic workup even if is an isolated presentation.
Normal ferritin value does not rule out possible GD diagnosis. Mild or borderline rise in ferritin level may require particular attention whenever associated with coagulation disorders (without any congenital or acquired cause) or other typical Gaucher-related conditions.

GD, Gaucher disease.

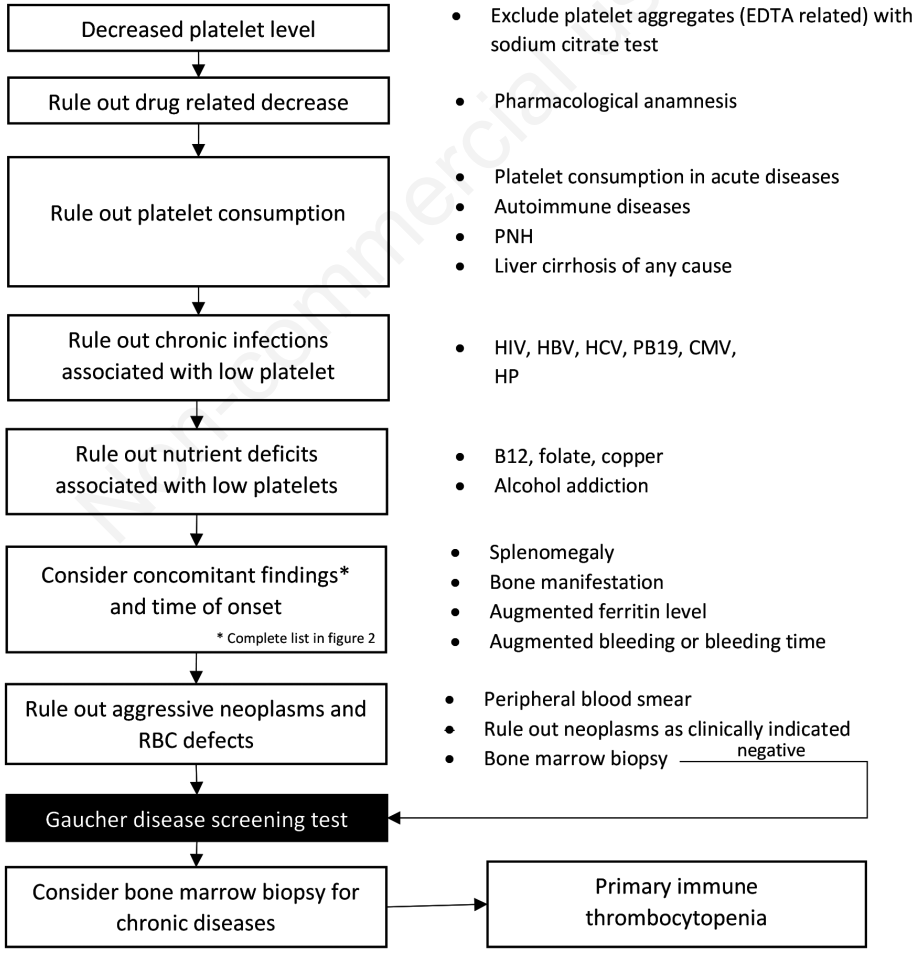

Figure 4. Algorithm for a differential diagnosis in adult patients with low platelets that account for possible Gaucher disease. RBC, red blood cell; EDTA, Ethylenediamine tetraacetic acid; PNH, Paroxysmal nocturnal hemoglobinuria; HBV, hepatitis B virus; HCV, hepatitis C virus; PB19, parvovirus B19; CMV, cytomegalovirus; HP, Helicobacter pylori.

Table 8. Statement on Gaucher disease screening.

Statement
The optimal time to obtain GD screening test results to incorporate in clinical practice is within 2 weeks.

GD, Gaucher disease.

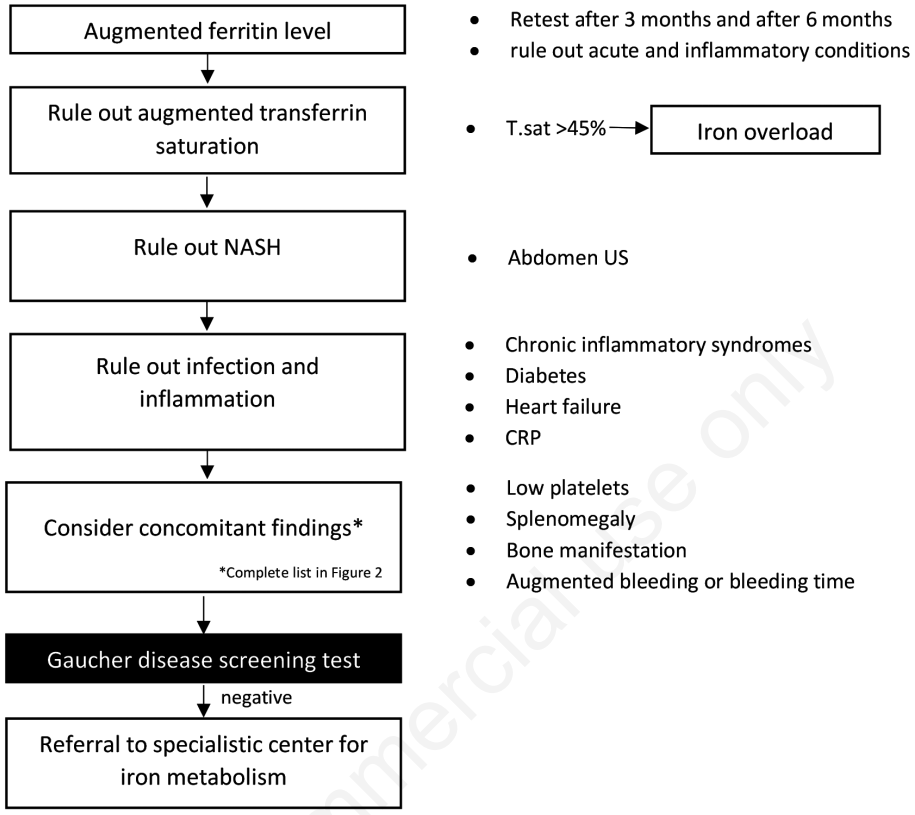

Figure 5. Algorithm for a differential diagnosis in adult patients with augmented ferritin levels that account for possible Gaucher disease. NASH, nonalcoholic steatohepatitis; T.sat., transferrin saturation; US, ultrasound; CRP, C-reactive protein.

factor XI deficiency with a high prevalence in the Ashkenazi Jewish population and von Willebrand factor deficiency with a prevalence of up to 1% in the Caucasian population further complicate the diagnostic process.[25,27-29]

Gaucher disease screening

Timely availability of test results plays a crucial role in facilitating early diagnosis and appropriate management of GD. A prompt turnaround time of 2 weeks allows healthcare providers to make informed decisions regarding patient care, including initiating necessary treatments or referrals to specialists. By obtaining screening test results within this timeframe, healthcare professionals can optimize patient outcomes and, of utmost importance, avoid unnecessary procedures (Table 8).

Conclusions

In conclusion, the diagnosis of GD remains an important health problem, despite the potential reduction in adult diagnoses with the implementation of neonatal screening over the next 50 years. It is crucial to recognize that GD exhibits a continuous spectrum of phenotypes, rather than being limited to the three classified types. This continuous phenotype is particularly important to consider as non-severe conditions related to sphingolipid accumulation can significantly impact the health of patients and potentially jeopardize other aspects of their well-being. Thus, accurate diagnosis becomes paramount in providing appropriate management and support for individuals with GD. While this consensus has certain limitations, such as reliance on a limited number of expert opinions through the Delphi method, efforts were made to mitigate bias and ensure the validity and applicability of the guidelines by involving a multidisciplinary expert panel and conducting an extensive literature review. It is hoped that the guidelines presented in this study will aid in improving the diagnosis and management of GD, thereby enhancing patient outcomes and quality of life.

Our work adds significant multidisciplinary to the GD diagnostic path. An informative flyer for physician literacy was generated based on this work (*Supplementary File 1*).

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Online supplementary material:

Supplementary File 1. Expert guideline on diagnosis of Gaucher disease in adult patients.