El-Beshlawy *et al.*
Egyptian Journal of Medical Human Genetics (2024) 25:88
https://doi.org/10.1186/s43042-024-00552-z

Egyptian Journal of Medical Human Genetics

REVIEW

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Diagnosis and management of patients with Gaucher disease: an Egyptian expert opinion

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Abstract

Background Gaucher disease (GD), an autosomal recessive, lysosomal storage disorder, is caused due to mutations in the glucocerebrosidase (*GBA*) gene. GD can occur at any age and is classified as type 1 (non-neurologic), type 2 (infantile form, with acute early neurologic manifestation), and type 3 (subacute/chronic neuropathic form). The rarity of the disease and its overlapping symptoms with other diseases increase the delay in diagnosis. The Egyptian cohort of patients with GD is specifically different regarding the prevalence of type 3 as well as the severity and progression of the disease. The unavailability of precise diagnostic tests and lack of awareness among clinicians are the current challenges associated with diagnosing and managing GD in Egypt.

Method An expert panel meeting was convened with 19 experts from Egypt to address the current unmet challenges in the diagnosis and management of GD from the region and to develop country-specific diagnostic algorithms based on the existing literature for pediatric and adult groups. In addition, management strategies and preventive measures were also discussed.

Result The algorithms presented in this review can be implemented in clinical practice for the timely diagnosis of patients with GD in Egypt. Early diagnosis is crucial in selecting the best treatment for patients with GD, and evidence suggests that early initiation of therapy can result in better outcomes.

Conclusion The evidence-based expert opinion presented in this review will help clinicians in the early initial diagnosis of GD in Egypt, leading to appropriate management of the disease.

Keywords Gaucher disease, Egypt, Diagnosis, Management, Expert opinion

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Introduction and rationale

Gaucher disease (GD), a rare genetic disorder inherited via the autosomal recessive mode, is the most prevalent lysosomal storage disorder. Mutations in the glucocerebrosidase (*GBA*) gene lead to the manifestations of GD. To date, nearly 300 mutations have been identified, including missense, nonsense, splice junction, deletion, insertion, gene fusion, and downstream pseudogene, which can be linked to GD [1, 2].

Although GD is pan-ethnic, its presentation in Egypt reveals some ethnicity-specific characteristics. Hence, it is essential to identify prevalent alleles among Egyptian patients with GD to assess their frequency, help in prenatal diagnosis, screen carriers, and provide genetic counseling.

Patients usually manifest splenomegaly and thrombocytopenia; hence, GD has a relatively high representation in a hematology setting. GD is classified as non-neuronopathic or type 1 (OMIM 230800) and neuronopathic or type 2 (OMIM 230900) or type 3 (OMIM 231000) forms [2]. Nevertheless, clinicians commonly overlook GD in the differential diagnosis due to its rarity, and patients frequently go through unnecessary investigations or are inadequately managed [3, 4].

Delay in diagnosis hinders timely and effective treatment and increases the risk of morbidity and irreversible disability. Therefore, it is important to devise a simple but effective protocol for diagnosing GD promptly.

In a previous study conducted in Egypt, consanguinity between parents was reported in 88.8% of patients, and interestingly, type 3 GD was found among the majority (66.67%) of patients [5]. It has been observed that the Egyptian cohort of patients with GD is unique based on the prevalence of type 3 as well as the severity and progression of the disease [5]. Moreover, in Egypt, diagnostic tests are not widely available, and reasonable justifications are required to recommend tests for GD. Therefore, the current review aims to bring out the challenges in GD diagnosis and management by developing precise diagnostic algorithms.

Methods

To address the current unmet challenges of GD in Egypt, expert panel meetings involving 19 experts from Egypt were convened. The discussions from the four expert panel meetings held in April 2019, September 2019, November 2019, and April 2021 were compiled, and based on previous literature, algorithms for the diagnosis and management (including prevention) of pediatric and adult patients with GD were developed. These algorithms can be implemented clinically in Egypt to promptly diagnose and manage patients with GD.

Results

Epidemiology

Worldwide incidence and carrier rate

Generally, the estimated prevalence of GD is between 1:50,000 and 1:100,000. GD risk escalates due to consanguineous unions, geographic isolates, or inbreeding, with worldwide birth incidence ranging from 0.39 to 5.80 per 100,000 and a prevalence rate between 0.70 and 1.75 per 100,000 [6, 7].

Type 1 GD is highly prevalent (1 in 350 to 450 live births) among Ashkenazi Jews compared to the general population (1 in 40,000 to 50,000). The neuronopathic forms of GD are rare, with an approximate incidence of < 1 in 100,000 live births [8]. Type 3 GD is predominantly reported in East Asia, Egypt, and Northern Europe, and a particular geographic isolate is seen in the Norrbotten County of Sweden [8].

GD in the Egyptian population In a cohort of 216 patients from eight treatment centers in Egypt, the percentage of type 1, type 2, and type 3 GD was reported to be 30.5%, 7.5%, and 62%, respectively. The average age of presentation was 4.5 years. Hepatosplenomegaly was present in 77% of patients at presentation, and bleeding tendency was present in 21% of patients [5, 9, 10]. Fateen et al. tested 5128 suspected cases over a period of 25 years and observed that 882 (17%) had GD [10]. The most common disease-causing mutations identified in Egypt were L444P, followed by N370S [5, 9, 10]. The homozygous L444P pathogenic variant is the most prevalent and usually indicates a type 3 phenotype with a neurologic disease of variable severity [5, 9, 11]. The characteristics of patients with GD in the Egyptian population are described in Table 1 [12–14].

Pathogenesis of GD

Deficiency in the GBA enzyme causes the accumulation of glucocerebroside and other glycolipids within the lysosomes in the macrophages/monocytes in different tissues, and their levels may increase by 20–100 times the normal levels [15]. The elevated levels of deacylated glucosylsphingosine and glucosylceramide may have a role in neurodegeneration [7].

The macrophages loaded with lipids accumulate in the liver, bone marrow, spleen, bones, and other tissues associated with an inflammatory and hyperplastic cellular response, resulting in the clinical manifestation of GD [16]. Gaucher cells and neighboring macrophages overexpress and secrete lysosomal proteases and cytokines, including cathepsins, interleukins 6, 8, and 10, and macrophage inflammatory proteins 1α and 1β [17, 18]. Gaucher cells correspond to the typical M2

Table 1 Characteristics of patients with GD in Egypt [12–14]

S no	Author/year	Study design	Location	Patient characteristics
1	El-Beshlawy et al.[12]	A cohort study with a long follow-up period of 20 years with 85 pediatric patients with GD type 3 enrolled	Cairo, Egypt	Consanguinity between the patient's parents was observed in 85.9% of patients
				A family history of GD was reported in 515 patients
				Hemato-visceral involvement observed: Anemia (75.6%), moderate-to-severe thrombocytopenia (21.7%), severe splenomegaly (49.2%), severe hepatomegaly (10.8%), oculomotor apraxia (48.6%), squint (30.6%), and bulbar symptoms (29.4%)
				Bone marrow aspirate was performed in 57.6% of patients
				Overall survival rate was 71% at 20 years
				Mortality due to pulmonary and neurologic disease in 23.5% of the patients
2	Saleem et al. [13]	A cross-sectional study of 26 pediatric patients with GD (Type 1 and 3)	Qena, Upper Egypt	Consanguinity between the patient's parents was observed in 73.1% of the patients
				Developmental delay was reported in 15.4% of patients
				Hepatosplenomegaly was found in 88.5% of patients
				Hemato-visceral involvement observed: Splenectomy (3.8%), musculoskeletal involvement (73.1%), neurologic involvement (23.1%), pallor (76.9%), abdominal distension (61.5%)
3	El-Beshlawy et al. [14]	A cross-sectional study carried out on 22 Egyptian children with GD	Cairo, Egypt	Bone involvement was detected in 73% of patients
				High rate (68%) of consanguinity among parents of children with GD
				Around 36% percent of the patients had at least one sibling who was affected
				Prior splenectomy was observed in 13.6% patients due to hypersplenism and pressure symptoms

subpopulation of macrophages from an alternate differentiation pathway and are linked to chronic inflammation, healing, and fibrosis [16].

Manifestations of GD

Manifestation of GD involves multiple organs; thus, it could be defined as a multisystem disease presenting a broad range of symptoms. The organs involved may present varying disease severity and clinical phenotypes, with type 2 being the most severe and lethal among postnatal cases [8].

Table 2 summarizes the different types of GD along with associated symptoms, clinical presentation, and management [19–21].

Clinical manifestations

Organomegaly

One of the causes of splenomegaly, as well as mild hepatomegaly, is the accumulation of glucosylceramide-laden macrophages in the liver and spleen. Splenic infarction and rupture can cause acute pain in the abdomen with serious complications [20, 22].

Hematologic manifestations

Cytopenia is found in almost all patients with GD. Thrombocytopenia, anemia, and, less commonly, leukopenia may be observed concomitantly or independently [23]. Anemia and thrombocytopenia may occur due to multiple factors, and the degree of splenomegaly may not necessarily be a predictive factor for the same [24, 25].

Table 2 Clinical classification of Gaucher disease [19–21]

Type	Name	Dominant clinical manifestation	Predilections mutation/ethnicity	Age of onset	Life expectancy	Treatment
I	Chronic, non-neuronopathic	Skeletal disorders, such as AVN and anomalies in growth, hematologic abnormalities, and visceral organ involvement	N370S mutations pan-ethnic common in Ashkenazi jews	Between childhood and early adulthood	Normal to almost normal	ERT or SRT for symptomatic patients
II	Acute, neuronopathic	Serious neurologic involvement, such as strabismus, supranuclear gaze palsy, and opisthotonos; lung disorder	None pan-ethnic	Between neonate and infant	Poor (death in early years)	Supportive
III	Subacute–chronic, neuronopathic	Increasing neurologic dysfunctions and cognitive impairment, including supranuclear gaze palsy and myoclonic seizures; visceral involvement of varying degree	L444P, D409H mutations pan-ethnic more in Arab, Southeast Asia, Japan, and Norrbotten population in Sweden	Between childhood and adulthood	Shortened (childhood–early/mid-adulthood)	ERT for visceral involvement
Type III: subgroup 3a	Norrbottnian Gaucher	Progressive dementia, ataxia, and myoclonus	Norrbottnian region of Northern Sweden	Childhood or adolescence	Shortened (childhood or early adulthood)	ERT
Type III: subgroup 3b	Neuronopathic Gaucher disease (Norrbottnian Gaucher)	Extensive visceral and bone involvement with central nervous system involvement limited to supranuclear gaze palsy	Panethnic	Early childhood	Shortened (childhood or early adulthood)	ERT
Type III: subgroup 3c	Neuronopathic Gaucher disease	Supranuclear gaze palsy, corneal opacity, and cardiovascular calcification, with little visceral disease	Panethnic	Childhood or adolescence	Shortened (childhood or early adulthood)	ERT

AVN: Avascular necrosis; ERT: Enzyme replacement therapy; SRT: Substrate reduction therapy

Bleeding could result from deficiencies in platelet functions or coagulation factors [24]. A significantly high risk of coexisting, alarming hematologic disorders has been reported in patients with GD, including multiple myeloma and B-cell lymphomas [24, 25].

Skeletal manifestations

It is possible to detect the invasive Gaucher cells in the bone marrow in most type 1 patients with GD as well as in a proportion of patients with type 3 GD (type 3B and the Norrbotten variant), which underlies the skeletal pathology seen in the disease and affects both the inner (marrow) and outer (mineralized) bone components [26–28]. Approximately 20% of patients with GD with skeletal involvement have impaired mobility [28].

Common skeletal findings include a decline in bone mineral density, lytic bone lesions, bone crisis, osteonecrosis, increased risk of fractures, osteosclerosis, erosion of the cortical bone, Erlenmeyer flask deformity, and rarely acute osteomyelitis. The risk of bone complications is common in all patients with type 1 GD, irrespective of their age, genotype, and presence and severity of visceral or hematologic disorders. Delayed puberty and growth retardation are observed in children [29].

Infiltration of Gaucher cells alters bone vascularity and initiates inflammatory processes that result in bone infarcts. Bone crises cause extreme pain and present signs of systemic and/or acute local inflammation. The bone crisis increases the risk of osteonecrosis in the future, especially during pregnancy [29].

However, bone infarcts may occur without any symptoms or with mild pain or acute severe localized pain, which may be the first feature of osteonecrosis. Spontaneous bacterial osteomyelitis is rare in GD, and it is difficult or rather impossible to differentiate between aseptic (bone crisis) and pyogenic osteomyelitis if this is the presenting manifestation of GD [30].

Neurologic symptoms

Neurologic manifestations are the hallmark of neuronopathic type 2 and 3 GD and can present at any time in the patient's life. Horizontal supranuclear gaze palsy, the most prevalent neurologic symptom, is sometimes the only neurologic manifestation. Some patients develop additional neurologic symptoms, which include myoclonus, seizures, and escalating myoclonic epilepsy [31].

Type 1 GD is non-neuronopathic; however, a secondary effect on the nervous system could be observed due to the involvement of the vertebral system caused by severe skeletal and hematologic anomalies. Although there are no primary neurologic manifestations in type 1 GD, specific neurologic presentations, such as Parkinson's disease and peripheral neuropathy, have been reported [28, 32].

Neurologic manifestations in neuropathic GD

Type 3 GD—Subacute/Chronic Neuropathic Slow horizontal saccadic eye movement is the only neurologic manifestation presented by some type 3 patients with GD, whereas other patients present a slowly progressive neurologic condition displaying organomegaly of mild-to-moderate grade and generalized or myoclonic seizures. In some patients, severe organ involvement is observed along with bone disorders. The *D409H* mutation within the *GBA* gene leads to a rare type of GD manifestation presented with cardiac disorders, deficiencies in the saccadic movement of eyes, and sometimes skeletal deformities and hydrocephalus. Developmental delays, dementia, and disability in learning and communication are seen in some type 3 patients with GD. However, sometimes a remarkably high verbal intelligence quotient score is reported in some patients with type 3 GD [33, 34].

Type 2 GD—acute neuropathic Type 2 GD is a progressive neurodegenerative disease that commonly causes fatality by age 1–3 years. Neurologic declines are common among this type of patient with GD. However, a variation in clinical presentation is observed. In the early years of life, type 2 patients with GD display symptoms of irritability, hypokinesia, supranuclear gaze palsy, and hypertonia, demonstrating brainstem dysfunction. Later, these children with type 2 GD show rapid deterioration of the brainstem, manifesting dysphagia, laryngeal obstruction, and apnea. These patients also present several other symptoms, such as seizures, microcephaly, cognitive impairment, arthrogryposis, rigidity, myoclonic jerks, developmental delays, and opisthotonos [8, 34].

GD and parkinsonism

The connecting link between the presence of *GBA1* variants, mainly *N370S* and *L444P*, as well as other mutations, and an elevated risk of parkinsonism was noticed more than two decades ago in the GD clinics. Moreover, the prevalence of parkinsonism was also found to be higher among patients with GD and their relatives who carried a *GBA1* mutation than others. Some patients with GD may exhibit resting tremors and bradykinesia with variable levodopa responses. Atypical features and nonmotor manifestations, such as supranuclear oculomotor signs, sleep disturbances, hallucinations, dementia, cognitive dysfunction, and apraxia, have also been presented in patients with *GBA1* mutations. Usually, GBA1-linked parkinsonism manifests earlier than parkinsonism not associated with GBA1 and demonstrates a more severe cognitive impairment [8, 35].

Liver diseases

Hepatomegaly is a common manifestation of GD. It has varying severity and clinical significance, with manifestations such as subclinical liver fibrosis and liver cirrhosis and related complications such as elevated transaminases, portal hypertension, hepatic decompensation, cholelithiasis, hepatic steatosis, hepatocellular carcinoma (HCC), non-HCC focal liver lesions, and Budd–Chiari and portopulmonary syndromes [29, 36, 37]. The degree of liver involvement might affect the treatment prioritization [38].

Pulmonary disorders

Patients with GD present a broad range of pulmonary symptoms ranging from clinically asymptomatic to severe symptoms. These are confirmed by radiologic changes, which may be either normal or present as mild or marked radiographic changes [39]. Invasion of Gaucher cells in the pulmonary vasculature, interstitium, alveoli, or bronchi leads to the development of symptoms involving the lungs [40]. Pulmonary hypertension is clinically evident in less than 1% of adult patients with GD, mainly in those splenectomized. Hepatopulmonary syndrome is rarely described [41].

Cardiac disorders

Gaucher cells may accumulate in the pericardium or myocardium, resulting in pericarditis or restrictive cardiomyopathy, respectively [42]. It may also lead to valvular calcification or extensive pericardial calcification, mostly in the *D409H* genotype [5]. Only a few cases have been reported with massive hemopericardium and cardiac tamponade with pulmonary hypertension [43].

Genetics of GD

GD results from a biallelic pathogenic variant in the *GBA* gene, located on chromosome 1q21, and has 11 exons [44]. Most pathogenic variants for GD are rare, but four of them have significant frequencies in various populations: *c.1226A > G*, p.p.Asn409Ser (previously N370S); *c.1448 T > C*, p.p.Leu483Pro (previously L444P); *c.115 + 1G > A* (previously *IVS2 + 1G > A*); and *c.84dupG*, p.p.Leu29AlafsTer18 (previously *84 GG* [*84-85insG*]). In the Egyptian population, the *L444P* mutant allele was detected in 50%–60% of cases, as reported in different studies [5, 45]. However, this pathogenic variant had a lower frequency (18.5%–25%) in some populations [46–48].

Further, one study reported the prevalence of recombinant alleles (*Rec*) as 38.1% in a cohort of Egyptian type 1 GD [45]. Worldwide, the frequency of Rec alleles was shown to be 9.5%–21% [48, 49].

Genotype–phenotype correlation

The level of residual GBA enzyme cannot confirm the type and severity of GD. Genotype–phenotype correlation in GD is not uniform with interfamilial and intrafamilial variabilities, which were noted in patients with GD in Egypt [50].

Most GD pathogenic variants were studied in Egypt. The most common pathogenic variant detected is *L444P* in heterozygous or homozygous form (47.8%–60%). This pathogenic variant, especially in the homozygous form, is usually associated with type 2 and type 3 phenotypes [5, 9] and less often with type 1 [4]. These type 1 patients should be closely monitored for a subtle course as pathogenic variants are present in heterozygous combination with N370S in some patients [50].

The patient's age at presentation determines the severity of the disease in cases homozygous for *L444P*. The severity of splenomegaly and hepatomegaly is also negatively correlated with the age of presentation [51]. Moreover, it is likely that patients with the *L444P/L444P* genotype and presenting as type 1 GD phenotype develop neuropathic symptoms with aging or due to modification of the onset of phenotype after treatment with enzyme replacement therapy (ERT) [5, 50].

Patients with *L444P/L444P* genotype present the complete clinical spectrum of this genotype from a normal neurologic phenotype (20%) to a severe neurologic phenotype. Patients usually present with neurodevelopmental delay, behavioral disorders, epilepsy, bulbar palsy, and even sudden unexpected death. In Egypt, patients with the *L444P/L444P* genotype report a more severe phenotype than patients with the same mutation found in other countries [52]. Despite having the most prevalent *GBA* genotype, linked to neuropathic GD, Egyptian patients with type 3 GD present a milder phenotype and a better clinical outcome with ERT, thus indicating that putative modifying genes of the ethnic group of Egypt may support better clinical prognosis upon treatment (Egyptian Gaucher Working Group Experience) [53]. In Egyptian studies, parental consanguinity varied from 60 to 88% [5, 9].

Diagnosis

As discussed in previous sections, GD manifests a broad range of clinical symptoms overlapping with several other childhood diseases, which delays the diagnosis of GD, emphasizing the importance of differential diagnosis.

Diagnostic testing

Baseline enzyme activity of β-GBA This enzyme assay can be performed in blood leukocytes obtained from fresh blood or dried blood spot (the sample should be collected in ethylenediaminetetraacetic acid).

Plasma chitotriosidase It is the most used biomarker in GD. Chitotriosidase activity can be evaluated at baseline and as per the requirement to evaluate the severity of the disease and monitor response to treatment. It showed elevated levels at diagnosis in 99% of patients with GD [10]. The drawbacks of using plasma chitotriosidase as a biomarker are that homozygosity with the chitotriosidase variant has been observed in 6% of the population and these patients exhibited a deficiency in chitotriosidase activity, and heterogeneity has been observed in 35% of the population for the null chitotriosidase variant and these patients demonstrated only half the chitotriosidase activity as compared to patients with the wild type. Additionally, the test for this biomarker is complicated to perform and standardization varies across laboratories [54].

Genotyping/DNA mutational analysis (confirmatory GD diagnosis and type prediction) Molecular testing and identification of the *GBA* mutation can confirm the diagnosis of GD. In addition, the genotype reflects the disease type, severity, and prognosis. It also helps in carrier testing and prenatal diagnosis [55].

The most common worldwide mutation reported in the International Collaborative Gaucher Group is due to the *N370S* substitution in alleles [56]. Compound heterozygous patients who present L444P substitution or *84 GG* substitution in alleles account for the second and the third most frequent mutations observed in GD [57]. Studies revealed that L444P, *IVS2* (*IVS2+1G>A*), N370S, and D409H are the most prevalent mutations among Egyptian patients [11, 58].

New biomarkers Glucosylsphingosine (Lyso-Gb1) is considered mainly as a monitoring biomarker, and based on clinical evidence, it can also be used as a prognostic biomarker for GD [59].

Associated biomarkers Serum ferritin may be assessed as hyperferritinemia has been reported concurrently with GD [60].

Bone marrow examination (not a mandatory method) Gaucher cells' presence in the bone marrow is a definitive marker of GD. However, the status of bone marrow invasion by Gaucher cells cannot confirm the presence of GD. Additionally, the role of pseudo-Gaucher cells has been established in a few diseases unrelated to GD [55].

Baseline laboratory assessment

Baseline laboratory assessments conducted to identify the impact of the disease are complete blood count, including prothrombin time and partial thromboplastin time, renal and liver functions, 25-hydroxyvitamin D and serum calcium, and screening for hepatitis viruses [53, 55].

Prenatal diagnosis

It is conducted by an enzyme assay or molecular testing for more rapid results. This can be performed through either chorionic villus sampling during the 12th week of gestation or amniotic fluid sampling during the 16th week of gestation. An Egyptian study demonstrated that the *L444P/L444P* mutation was the most common in fetuses of pregnant mothers with a previous child with GD as determined by prenatal genotyping [61].

Egyptian algorithm for the diagnosis of GD

Developing country-specific diagnostic and management algorithms is common and addresses region-specific diagnostic gaps. Generally, the diagnostic algorithm of GD should highlight clinically similar diseases that share some of the indicators of GD and use the best approach to reach a final diagnosis by using the least investigations in the shortest time.

It is important to know that:

- Diagnosis of GD is easier if the physician is aware of the features of the disease.
- Algorithms will only help those with awareness of GD.
- Increasing awareness may be a better approach to decrease the time and effort spent till a diagnosis is reached [3, 5, 62, 63].

Figures 1 and 2 depict suggested algorithms [3, 5, 63–66] for the early diagnosis of GD in pediatric and adult patients, respectively, in Egypt.

Management

The heterogeneous clinical spectrum of GD requires a multidisciplinary approach in management. The multidisciplinary team would comprise a hematologist, pediatrician, geneticist, neurologist, cardiologist, psychiatrist, gastroenterologist, occupational therapist, and orthopedic surgeon. The management plan should be individualized for each patient depending on a

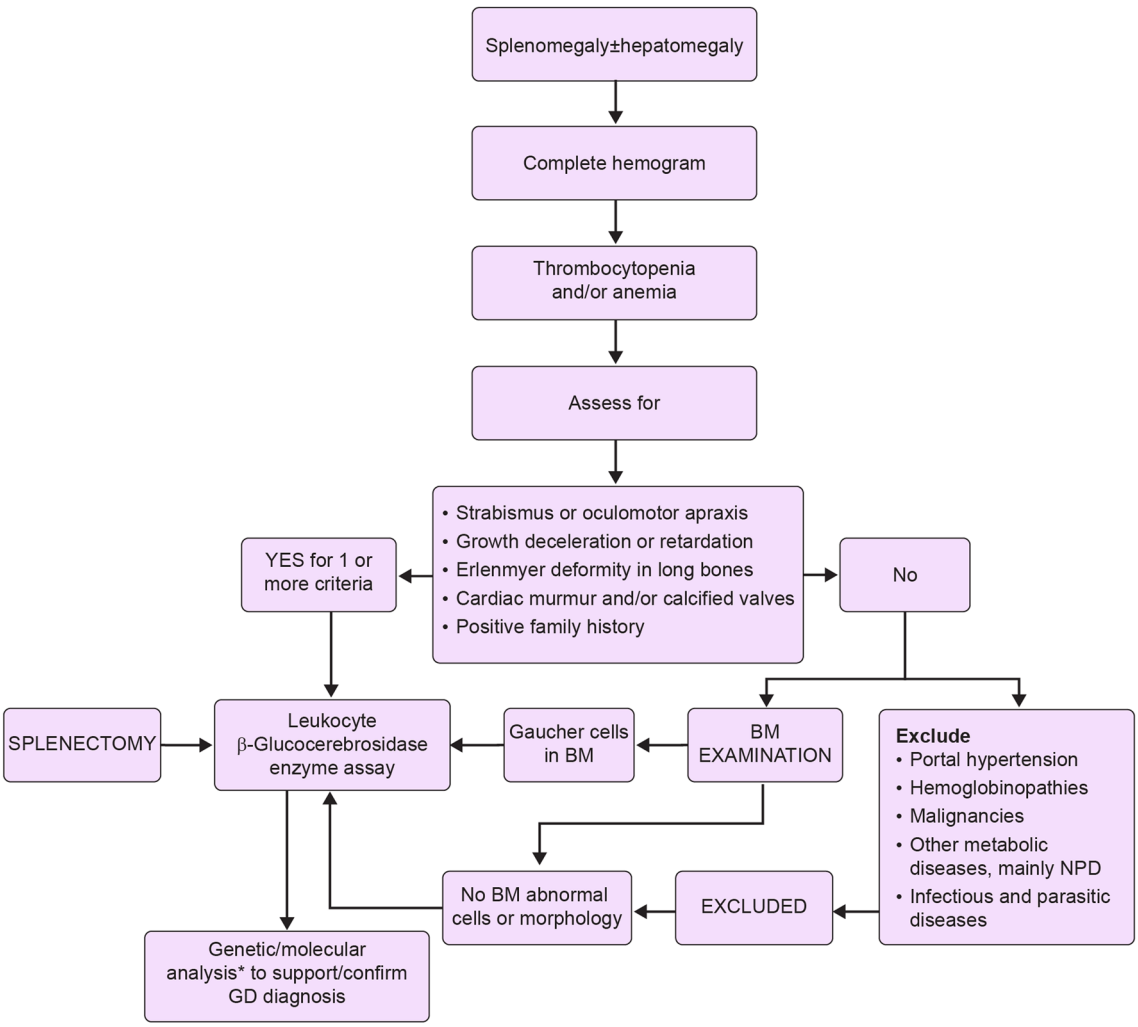

Fig. 1 Algorithm for early diagnosis of Gaucher disease in the pediatric age-group in Egypt [3, 5, 63–66]. BM: Bone marrow; GD: Gaucher's disease; NPD: Niemann–Pick disease

thorough baseline and continuous monitoring to identify disease severity [67, 68].

Disease-specific management

The targeted management of GD comprises ERT, substrate reduction therapy (SRT), and chaperone therapy.

Enzyme replacement therapy After GD came to be recognized as a disease entity, patients were treated entirely with supportive measures for a long time [69]. In 1991, the first intravenous ERT alglucerase (Ceredase®; Genzyme Corporation, Cambridge, Massachusetts) was produced [69]. In 1994, Genzyme introduced imiglucerase (Cerezyme®; Genzyme Corporation, Cambridge, Massachusetts) as a recombinant analog of GBA [69]. Later, velaglucerase alfa (VPRIV™; Takeda Pharmaceuticals International AG/Pharma AG, Opfikon, Zurich, Switzerland) and taliglucerase alfa (ELELYSO™; Protalix Karmiel, Israel, and Pfizer, New York) were produced [16, 69]. There are some differences in the structure of amino acids and glycosylation of these three agents. A significant improvement in organomegaly and hematologic disorders is observed upon treatment with ERT [8, 70]. It also inhibits the development of avascular necrosis, improves skeletal manifestations, and reverses growth failure in type 1 and type 3 patients with GD [16]. The development and availability of ERT in Egypt since 1998 have transformed the management of patients with GD.

ERT Regimen: All pediatric type 1 and type 3 patients with GD should start ERT at a recommended dose of 60 U/kg every other week. In adults with type 1 disease, the initial standard dose of ERT is 30–60 U/kg body weight every 2 weeks based on the disease severity scoring [70–72]. Depending on the patient's prognosis,

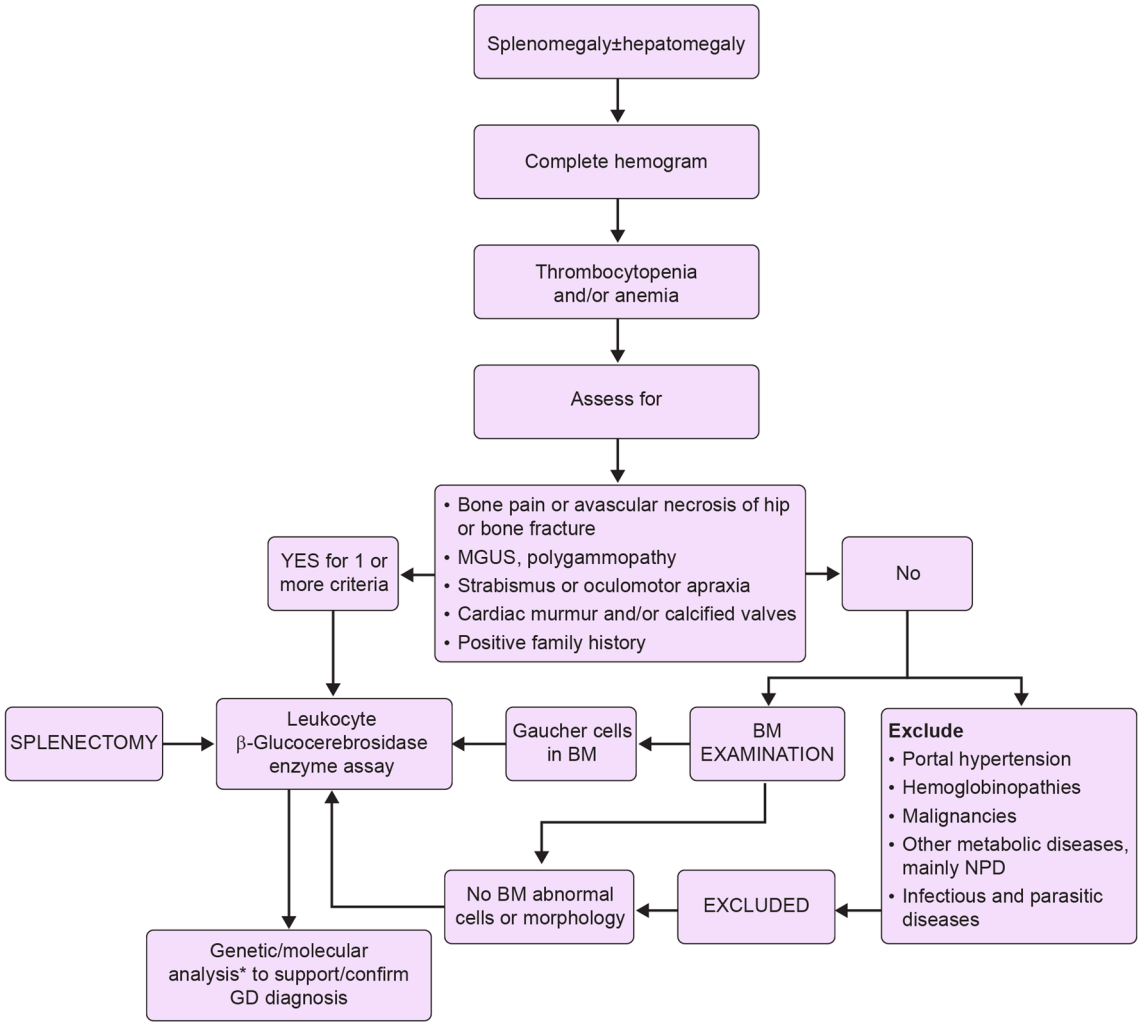

Fig. 2 Algorithm for early diagnosis of Gaucher disease in the adult age-group in Egypt [3, 5, 63–66]. BM: Bone marrow; GD: Gaucher's disease; MGUS: Monoclonal gammopathy of undetermined significance; NPD: Niemann–Pick disease

individual dose adjustments should be made. Treatment is administered intravenously once every 2 weeks as lifelong therapy. Treatment with ERT in presymptomatic pediatric patients with GD should be considered for siblings of patients with severe neuropathic disease.

A few patients with GD on ERT develop antibodies to the enzyme protein, most of which are non-neutralizing antibodies. In some cases, significant allergic reactions can be observed, which can be controlled by administering antihistamine, hydrocortisone, or both as premedication [73].

Multisystem involvement in GD necessitates early intervention. A delay in treatment initiation might lead to a limited response to therapies and a poor prognosis [74]. The criteria for initiation of ERT are outlined in Table 3 [69, 74–77].

Table 3 Criteria for initiation of enzyme replacement therapy [69, 74–77]

1. Any child with disease manifestations
2. All type 3 patients should receive immediate treatment
3. All symptomatic adults with one or more of the following features:
History of progressive organomegaly (hepatosplenomegaly)
Cytopenia (bicytopenia at least): clinically significant thrombocytopenia or anemia
Bone anomalies
Previous splenectomy
Abnormal growth and delay in puberty
Pulmonary dysfunctions
Deterioration in physical growth and quality of life
4. Presymptomatic siblings of type 3 disease

Table 4 Indications for Cessation of ERT75

After discussion with patients and the multidisciplinary team, the decision to cease ERT can be taken under the below-mentioned conditions:
When there are intolerable and unavoidable adverse effects
In type 2 patients with GD as there is no significant benefit due to ERT
Lack of responsiveness to therapy after at least 6 months of ERT at an appropriate dose. This occurs in cases where the quality of life of the patient is extremely poor, the patient is unresponsive to treatment, and irreversible disease progression mostly shows neurologic symptoms
Social support should be provided to patients. It is recommended that the decision of treatment cessation must be taken by an expert panel (Egyptian Gaucher Committee)

ERT: Enzyme replacement therapy; GD: Gaucher disease

Considering the high cost of ERT, patient selection and disease monitoring are mandatory. The indications to cease ERT are shown in Table 4 [75].

Substrate reduction therapy The SRT for GD utilizes the inhibitor of glucosylceramide synthase to balance the glucosylceramidase level. The Food and Drug Administration has approved two oral SRTs for the treatment of GD: miglustat (Zavesca®; Actelion Pharmaceuticals, Allschwil, Switzerland) in 2003 and eliglustat tartrate (Cerdelga®; Sanofi Genzyme, Cambridge, Massachusetts) in 2014. Miglustat is indicated in adult type 1 patients with GD with mild-to-moderate involvement who are intolerant to ERT [78]. Eliglustat is indicated in adult type 1 patients with GD and administered orally with dose adjustment depending on the CYP2D6 poor metabolizers, intermediate metabolizers, and extensive metabolizers [79]. However, eliglustat is not yet licensed in Egypt, and both oral SRTs are not approved in type 3 GD and the pediatric population.

Molecular chaperone therapy Molecular chaperones can potentially restore the functionality of the mutant *GBA* by facilitating the production of functional enzymes. Utilizing molecular chaperones to treat GD is still in the initial phases of development. However, the pilot studies on ambroxol suggest the effectiveness of this therapy and call for further research [31, 80].

Treatment goals for GD

The treatment of choice aims at addressing certain symptoms or complications of GD directly, which is identified as a short-term effect and/or maintenance of the long-term effect. Details of the treatment goals are presented in Table 5 [5, 65, 67–69, 76, 77, 81–87] and Table 6 [77, 83–85].

Table 5 Short-term goals of treatment in patients with GD to improve outcomes and decrease morbidity [5, 65, 76, 77, 87676869818283848586]

1. Anemia: Eliminate blood transfusion dependency and increase Hb levels within 12–24 months to > 11.0 g/dL in women and children and > 12.0 g/dL in men
In severely diseased patients (Hb < 8.0 g/dL), ERT is expected to show a marked increase in Hb levels within the first 6 months of treatment initiation
2. Bleeding tendency: To reduce the risk of spontaneous bleeding and the need for surgical and obstetric interventions within the first year of ERT, it is aimed at increasing the platelet count
Restore the platelet count within 1 year of treatment in splenectomy patients
In patients with an intact spleen, achieve a platelet count of ≥ 100,000/mm^3 by 3 years of treatment
3. Visceral complication: To prevent splenectomy, reduce symptoms caused by splenomegaly, prevent new infarction of the spleen, and eradicate hypersplenism
4. Reduce splenic volume: Contract the volume of the spleen (2–8 times less than normal) or reduce the size of the spleen by 1–2 years based on the baseline volume of the spleen. Similarly, reduce the volume of the liver to 1.0–1.5 times than normal or restore the liver to normal size within 1–2 years based on the initial volume of the liver. In cases with massive splenomegaly, it is difficult to normalize the spleen volume
5. Pulmonary involvement: Avoid pulmonary disease, correct hepatopulmonary syndrome, reduce oxygen dependency, and improve pulmonary hypertension
6. Treatment goals for skeletal pathology: Reduce or abolish bone pain early (within 1–2 years), avoid the risk of osteonecrosis and bone crisis, prevent subchondral joint collapse, and improvise BMD in all patients under ERT. In pediatric patients, the goals include attaining normal or ideal peak skeletal mass and increasing cortical and trabecular BMD by 2 years, whereas in adults, increasing the BMD by 3–5 years. [6]
7. Treatment goals for growth: Normalize growth within 3 years of ERT in children with GD and assist them in reaching normal heights based on population standards and support the timely attainment of puberty
8. General well-being: Attain better scores in comparison with baseline by using standard quality of life instrument within 2–3 years or less, reduce fatigue, and restore or enhance physical function to conduct daily activities and fulfill functional roles

BMD: Bone mineral density; ERT: Enzyme replacement therapy; GD: Gaucher disease; Hb: Hemoglobin

Table 6 Long-term goals of treatment in patients with GD to improve outcomes and decrease morbidity [77, 83–85]

1. Maintenance of improved values of hemoglobin, which was achieved after initiation of treatment for 12–24 months
2. Maintenance of platelet count of ≥ 100,000/mm^3 and reduction in increased bleeding
3. Prevention of bone complications: Avascular necrosis, bone crisis, bone infarcts, and pathologic fracture
Prevention of osteopenia and osteoporosis (i.e., maintain BMD T-scores [DEXA] of − 1)
Prevention of chronic usage of analgesic medication for bone pain
Maintenance of normal mobility or, if impaired at diagnosis, improvement of mobility
Increment in physical activity
4. Maintenance of the spleen volume of 2–8 times than normal after 1–2 years
Maintenance of (near) normal liver volume after 1–2 years
Prevention of liver fibrosis, cirrhosis, and portal hypertension
5. Prevention or improvement of pulmonary diseases, such as pulmonary hypertension and hepatopulmonary syndrome
6. Maintenance of good quality of life as evaluated by standard instruments. Maintenance of normal participation in school and workplace, and reduction in the psychosocial burden of lifelong treatment
7. Attainment of puberty on time
8. Normalization of life expectancy
9. Protection from GD-related complications during pregnancy and delivery

BMD: Bone mineral density; DEXA: Dual-energy X-ray absorptiometry; GD: Gaucher disease

Table 7 Recommended assessment at baseline and on follow-up in patients With GD [60, 76]

Assessment	Baseline (diagnosis)	Every 6 months	Yearly	As indicated
Hepatic and splenic size*	Ultrasonography	Ultrasonography		MRI
Complete blood count	√	√		
Neurologic evaluation	√		√ (If type 3)	
Electroencephalogram**	√		√	
Neuropsychiatric assessment	√			√
Dual-energy X-ray absorptiometry (for adults)				Every 3 years
Radiographs of spine and pelvis***	√			√
MRI of the spine and femoral neck (optional)				√
Chitotriosidase	√		√	
Pulmonary function test****	√			√
Cardiac (2D echocardiography)*****	√		√	
Chest radiography******				√

* Assessment of splenic and hepatic sizes can be performed by PAUS or MRI abdomen

** Yearly EEG for all type 3 patients

*** Radiography of the spine and pelvis using plain X-ray or MRI of the spine and neck of the femur

**** Pulmonary function test for patients aged above 6 years

***** In patients with the D409H genotype and for those with suspected pulmonary arterial hypertension

****** Using plain chest X-ray or high-resolution CT chest

CT: Computed tomography, EEG: Electroencephalogram, GD: Gaucher disease, MRI: Magnetic resonance imaging; PAUS: Perianal ultrasound

Patient monitoring

The size of the liver and spleen is measured using ultrasonography or magnetic resonance imaging at initial diagnosis and every 6 months. A complete blood count is carried out to assess cytopenia initially and every 6 months. The recommended assessment conducted at baseline and on follow-up in patients with GD is presented in Table 7 [60, 76].

In the routine monitoring of patients with GD, liver enzyme testing is usually not conducted. A minor increase in liver enzyme levels may be encountered, even in mildly affected patients. However, if jaundice or abnormal hepatocellular function is diagnosed, patients should be recommended for a complete evaluation of the liver function [37, 38]. The coagulation profile should be monitored at presentation and then

as indicated in patients with GD who are found to have coagulopathy [16, 88].

Full neurologic assessment and electroencephalogram are performed for all patients initially and then as appropriate for the clinical status of type 3 patients with GD. A complete psychological examination should also be conducted initially and followed up based on the clinical status [35, 89, 90]. For patients > 8 years, bone assessment with dual-energy X-ray absorptiometry must be made every 3 years after the initial assessment (radiographs of the femur, spine, and pelvis must be taken initially and then as indicated) [91].

Chest radiography, such as plain chest X-ray or high-resolution computed tomography of the chest, should be taken at presentation and then yearly for patients with clinical pulmonary involvement. Pulmonary function tests should be conducted at presentation for cooperative patients who are more than 6 years old, and this should be repeated yearly as indicated [7, 39].

Assessment of biomarkers for GD includes assessing the levels of glucosyl sphingosine, plasma chitotriosidase, angiotensin-converting enzyme, total acid phosphatase, and ferritin. These biomarkers are typically elevated during an active GD condition. However, all these biomarkers are nonspecific to GD. Monitoring the levels of these markers might be useful in monitoring disease activity [92].

Other lines of management

Watchful waiting Adult patients who usually carry the *N370S* homozygous genotype present very mild or sometimes even no symptoms of the disease; therefore, they might not require any GD-specific treatments. However, these patients should be regularly monitored at an interval of 6 months to detect poor prognosis early and thus avoid irreversible damage. Interestingly, sometimes these patients, though asymptomatic, may develop serious complications, such as cytopenia, osteopenia, or splenomegaly, which would require appropriate treatment [93].

Supportive therapy It focuses on resolving issues of nutritional anemia or deficiency of vitamin D, thereby strengthening the nutritional status of patients. Oral or intravenous bisphosphonate therapy may be effective for adult patients. Mobility aids are helpful when bones are affected. The national guidelines should be followed for immunization with vaccines, especially for splenectomized patients [75, 94].

Adjuvant therapy Specific case-based management includes the use of blood products for patients with significant cytopenia, specific pain management protocols, antiepileptics for seizures, antipsychotics for psychosis, treatment of dental caries, and medical treatment for pulmonary hypertension [75, 95–101].

Surgical management Surgery is a common intervention in patients with GD to manage various ailments. For example, cholecystectomy is useful for gallstones prevalent in patients with GD. On the contrary, perioperative medical management of patients with GD is essential, especially in asplenic patients with a high risk of infection, patients with thrombocytopenia and/or platelet dysfunction and coagulopathies, and those who have a high risk of bleeding. Splenectomy is rarely indicated in the management of GD [7].

Bone marrow transplantation It appears to have little or no effect on the neuronopathic aspects of GD, and because of its inherent high morbidity and mortality risks, this procedure is generally not recommended for patients with GD with advanced neurologic symptoms. Since the introduction of ERTs and SRTs, bone marrow transplantation is rarely advocated for patients with GD [20].

Treatment of special cases

Bone crisis In times of growth, a bone crisis may occasionally occur, causing infarcts. Bone infarcts and avascular necrosis of the hip are uncommon in patients with GD stabilized on ERT. The bone crisis may be treated by ERT together with nonsteroidal anti-inflammatory drugs, steroids, and other analgesics [91].

Splenic infarcts and splenic rupture On identifying subcapsular splenic infarcts by magnetic resonance imaging, ERT is initiated. Limited utilization of splenectomy is recorded in patients with GD. In cases with severe hypersplenism or massive infarcts, splenectomy is performed while maintaining ERT [20].

Liver cirrhosis It is a rare complication seen in patients with GD on ERT and requires further investigation for additional comorbidities (e.g., viral hepatitis) [20].

Pulmonary infiltration Several pathophysiological mechanisms are involved, as previously described. ERT is effective in most patients, although improvement in radiologic findings may take several years; however, a poor response is observed in severely affected patients with pulmonary fibrosis [39, 102, 103].

Cardiac involvement In patients homozygous for *D409H*, the disease is associated with myocardial and valve calcification, which hinders responsiveness to ERT. In such patients, valve replacement or cardiac transplantation may be the only therapeutic option [104, 105].

However, cardiomyopathy and pericardial effusion have been reported in non-*D409H* patients with GD, mainly with *L444P* pathogenic variants, who were reported to respond to ERT [5, 106].

Immunologic abnormalities *Patients with GD exhibit immunologic disorders, such as impaired neutrophil chemotaxis, T-lymphocyte abnormalities in the spleen, and hypergammaglobulinemia* [107]. Prompt measures to prevent infection and accurate early introduction of antibiotics should be sought in patients with GD. In addition, immunization against common infections with vaccines, such as the annual influenza vaccine, pneumococcal vaccine, *Haemophilus influenza* vaccine, and meningococcal vaccine, is recommended in patients with GD.

Preventive measures

Genetic counseling

It should be provided to all families with a child with GD because it is the most potent method to decrease the incidence rate of GD in Egypt.

Carrier detection

Disease gene carrier frequency for GD in Egypt is unknown; however, genetic testing should be offered to extended families and relatives to identify the familial pathogenic variant. This is of utmost importance, considering the high rates of consanguineous marriage in Egypt, which are reported to vary between 29 and 39% in different studies [108]. Enzyme activity is not a reliable test to detect carriers because of the significant overlap between carriers and noncarriers; hence, molecular genetic testing is the method of choice to diagnose carriers [60, 109]. A carrier screening program is recommended in Egypt, and it is reasonable to test for the most common pathogenic variants among the Egyptian population (*L444P* and *N370S*) [5, 9].

Conclusion

GD is not rare among the Egyptian population, which has a high rate of consanguinity; however, the prevalence is not known due to the lack of a national Gaucher registry.

The clinical presentations and the complications of GD are variable in different patients; therefore, a multidisciplinary approach is important for the early diagnosis of the disease, monitoring of the treatment regimen, and anticipation of potential complications to prevent irreversible damage.

Expert opinion

In Egypt, the prevalence of type 3 GD is higher than that of type 1, whereas the prevalence of type 2 disease is rare, and the most common pathogenic variant detected is *L444P* in heterozygous or homozygous form (47.8%–80.0%). Considering the diversity of mutant alleles in the Egyptian population and the heterogeneous presentation with multisystem involvement, a region-specific diagnostic algorithm, as suggested previously, could aid in the appropriate early diagnosis and early management of patients with GD in Egypt. The multiple organ involvement in GD and the disease complications that continue to develop as patients age necessitate an expert multidisciplinary approach and a regularly planned follow-up of patients. There is marked heterogenicity in clinical phenotype deciding the response to ERT, severity, and outcome, even within identical genotypes and among siblings with GD. However, *L444P* homozygosity is associated with neuropathic GD or severe type 1 disease, and *D409H* homozygosity, although uncommon, is mostly linked to cardiac calcification. Currently, the targeted management of GD available in Egypt is ERT for all type 3 patients with GD and symptomatic type 1 patients under well-defined criteria.

Interestingly, although type 3 patients with GD in Egypt have the most common severe *GBA* genotype *L444P/L444P*, which is established to be linked to neuropathic GD, these patients showed variable clinical improvement with ERT, unlike other populations. The long-term follow-up of patients with GD on ERT allows the identification of pathologic problems developing and/or progressing with aging and the identification of different pathologic problems' responses to ERT and whether other lines of therapy are indicated. Furthermore, the monitoring of follow-up of patients with GD on ERT allows the identification of risk factors associated with poor response and higher morbidity. Monitoring the schedule of patients should be standardized and affordable to ensure long-term continuity. Shortly, it is expected that SRT will be available in Egypt for adults with type 1 GD, and it has been suggested that SRT alone or combined with ERT could be a more effective therapy in patients with GD of types 1 or 3 complicated by significant abdominal lymphadenopathy and pulmonary disease; this is an important field for further studies. The experts hope that Egyptian type 3 patients will be included in clinical trials of neuropathic GD targeting the neurologic outcome with new drugs, including SRT (venglustat) and chaperone therapy clinical trials. Preventive measures are also important for the management of GD. There is no national GD registry, and the mutated gene carrier frequency for GD in Egypt is unknown, but genetic testing should be offered to extended families and relatives to identify the familial pathogenic variant. With the increasing awareness about GD in the medical community in Egypt, government-supported availability of ERT in the last decade, and NGO support over the

last two decades, there has been marked improvement in outcomes and earlier presentation and diagnosis of patients, thereby reinforcing better outcomes. Medical, social, and administrative communities should maintain and actively support these efforts of awareness and sustainability of drug availability to ensure improved quality of life for patients.

Abbreviations

GD	Gaucher disease
GBA	Glucocerebrosidase gene
HCC	Hepatocellular carcinoma
Rec	Recombinant alleles
ERT	Enzyme replacement therapy
Lyso-Gb1	Glucosylsphingosine

Acknowledgements
The authors thank Sanofi Egypt for the support in accomplishing this work and for funding BioQuest Solutions for writing and editorial assistance.

Author contributions
All the authors were involved in the conception of the idea; design of the study; acquisition, analysis, and interpretation of data; and drafting of the article.

Funding
The authors received editorial/writing support in the preparation of this manuscript, funded by Sanofi Egypt.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Availability of data and materials
Not applicable.

Competing interests
The authors have no conflicts of interest.

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Received: 4 September 2023 Accepted: 10 July 2024
Published online: 31 July 2024

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