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ORIGINAL ARTICLE

Prevalence of Gaucher disease in patients with unknown cause of splenomegaly and/or thrombocytopenia in Saudi Arabia

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ABSTRACT

Background: Many uncommon metabolic disorders have a high prevalence in Arab countries due to the high rate of consanguineous marriages. This study aimed to assess the prevalence of Gaucher disease (GD) in patients with splenomegaly and/or thrombocytopenia of unknown cause in Saudi Arabia.

Methods: This screening study was conducted in 13 hematology and hematopathology centers in Saudi Arabia over 2 years. Patients with splenomegaly and/or thrombocytopenia of unknown cause for at least a year were included. Enzyme activity in eligible patients was assessed using a dried blood spot sample.

Results: Out of 390 patients, 87.4% had thrombocytopenia. In comparison, 8.8% had a history of splenectomy, and nearly 67.7% had splenomegaly. Fatigue, bone crises, and abdominal pain were commonly reported among adult patients. Anemia was the most common symptom among pediatric patients, followed by splenomegaly and easy bruising or bleeding. One patient was found to have GD. She was a Saudi toddler with no family history of GD, acid sphingomyelinase deficiency, or other genetic abnormalities. The GD patient's neurological, cardiac, and skeletal examinations were normal.

Conclusion: This screening study paves the way for GD screening in Saudi Arabia. It also emphasizes the importance of early diagnosis, proper care, and positive outcomes for GD.

Keywords: Gaucher Disease, splenomegaly, thrombocytopenia, Saudi Arabia.

Introduction

Gaucher disease (GD), the commonest type of lysosomal storage disease (LSD), is an autosomal recessive disorder that occurs secondarily to biallelic mutations in the glucocerebrosidase (GBA1) gene. In return, affected patients present with defective lysosomal acid-β-glucosidase activity, resulting in lysosomal accumulation of glucocerebroside lipids, mainly in the spleen, liver, and bone marrow (1). According to recent figures from the Gaucher Institute, the estimated GD prevalence ranges between 0.70 and 1.75 per 100,000 population worldwide (2). Regarding ethnic variation and geographic distribution, the estimated incidence varies from 0.39 to 5.80 per 100,000 live births (3). Clinically, GD is classified into three phenotypes; type 1(GD1; 230800) is the commonest form characterized by a wide range of age at onset from childhood throughout life and various clinical manifestations like osteopenia, anemia, thrombocytopenia, and hepatosplenomegaly but without neurological manifestations. Type 2 (GD2; 230900) is characterized by being a very progressive type affecting the central nervous system and leading to death by the

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age of 4 years; meanwhile, type 3 (GD3; 231000) also affects the nervous system but in a less severe manner with a slow progression, allowing survival to 40 years (4).

Nonetheless, the clinical presentations of GD overlap among all forms and can even differ amongst patients having the same genetic variant (5). Hepatosplenomegaly, with or without hypersplenism, is a common presentation among different types of GD (6). Due to the effect of GD on multiple organs, non-invasive images are the suitable approach to evaluate and follow up on the organs' status. Computed tomography (CT) is one of the most commonly used methods of imaging, helping to investigate the organs' condition and estimate their volumes. CD scans can detect the presence of different types of lesions as well as focal changes in the spleen. According to the published Gaucher registry assessing demographics of 1,698 patients with GD, the most predominant signs of GD in the main three phenotypes were the presence of splenomegaly and thrombocytopenia, which presented in 85% and 68% of the cases, respectively (7). However, it was found that only 20% of healthcare practitioners consider GD in patients with thrombocytopenia and hepatosplenomegaly, which can lead to under or delayed diagnosis (8,9). Early identification and prompt initiation of treatment of GD patients have become crucial, particularly with Enzyme replacement therapy (ERT); ERT has proven to be well tolerated and significantly effective in improving clinical manifestation and the quality of life of GD patients (10,11). Before the discovery of ERT, only symptomatic treatments were available for Gaucher's patients. In 1990, Imiglucerase, the first discovered ERT, was used intravenously as a replacement for the defective acid β-glucosidase, helping in breaking glucosylceramide (GLC) into glucose and ceramide. Unfortunately, due to the side effects of Imiglucerase, especially the sensitivity reactions, other treatments like velaglucerase alfa, and taliglucerase alfa were developed. ERT was shown to be very effective in reversing visceral and hematologic manifestations but with no effect on neurological manifestations.

Substrate reduction therapy is another option available now for patients who cannot tolerate ERT. Substrate reduction therapy is orally administrated and inhibits the GLC-synthase enzyme, reducing the GLC amount in the body. Thus, long diagnostic delays that may result from the lack of awareness of GD among healthcare practitioners seeing patients with thrombocytopenia and hepatosplenomegaly can worsen the prognosis of the patients (9).

Acid sphingomyelinase deficiency (ASMD) is an inherited LSD with a birth prevalence of nearly 0.4-0.6 per 100,000 live births (12). The development of ASMD occurs secondarily to genetic mutations in the sphingomyelin phosphodiesterase 1 (SMPD1) gene, leading to defective lysosomal acid sphingomyelinase (ASM) enzymatic activity and accumulation of sphingomyelin and other lipids in the mononuclear phagocytic system and hepatocytes. In return, patients with ASMD present with organomegaly and multiple organ failure (13). ASMD has three different subtypes: Type A, Type A/B, and Type B. Type A (SMPD1; 607608), also known as infantile neurovisceral, causes visceral manifestations and neurodegeneration, leading to death at a very young age, mainly due to respiratory system complications. Type B (SMPD1; 607616) and Type A/B are mainly characterized by visceral manifestations, including delayed growth, interstitial lung disease, hepatosplenomegaly, thrombocytopenia, and breath shortness. Although Type A/B could cause neurological manifestations, they are much less severe than those of Type A. In ASMD patients, pulmonary and hepatic complications could endanger their lives (1). Historically, the differentiation between ASMD and GD remained difficult until 1967, when Kampine and colleagues discriminated between these disorders by respective peripheral blood leukocytes' enzymatic activities (14).

The prevalence of rare metabolic disorders is comparatively higher in the Arab countries than in the rest of the world due to the high rate of consanguinity marriage (15). There is a lack of published registries assessing GD prevalence in Saudi Arabia. The only published report stated that GD accounted for 6% of all genetic and metabolic disorders in Saudi Arabia (16). However, the incidence of GD is expected to be higher due to the misdiagnosis or underdiagnosis of the disease among high-risk groups. Thus, we conducted the present study to determine the prevalence of GD and ASMD amongst patients presenting with splenomegaly and/or thrombocytopenia of unknown cause in Saudi Arabia.

Subjects and Methods

The present study gained the ethical approval of the local ethics committee of participating centers (Supplementary Table 1). We confirm that all study procedures adhere to the principles of the latest version of the Declaration of Helsinki (17) and applicable local regulatory laws. Eligible patients or their legal guardians were required to sign the informed consent before the study's enrollment.

The present study was a multicenter national screening study conducted over 2 years in 13 hematology and haemato-pathology centers across Saudi Arabia. Only the patients who met the following criteria were eligible to be included to the study: Female or male subject with age 2-75 years (Including Saudi and non-Saudi patients). All patients presenting with clinical, instrumental or laboratory signs of splenomegaly or thrombocytopenia over a period of 12 months should be evaluated, patients with at least one of the following characteristics should be tested for acid β-glucosidase and ASM enzymes activity on dried blood spot (DBS) samples; Splenomegaly: defined as the palpable spleen at ≥ 1cm from the costal margin or diagnosed by ultrasound scans, magnetic resonance imaging (MRI) or CT of the spleen, thrombocytopenia (<150,000/mm3) suspected to be immune thrombocytopenia, thrombocytopenia (<150000/mm3) with at least 1 of the following conditions: history of bone or joint abnormality - pain, pathological fractures, arthritis, radiological bone disease, joint stiffness, hemarthrosis, monoclonal gammopathy of unknown significance

(MGUS), polyclonal gammopathy in subjects ≤30 years, Hb <12 g/dl in men and <11 g/dl in women, History of Splenectomy. We excluded patients with splenomegaly and/or thrombocytopenia having been confirmed with a diagnosis including GD/ASMD or any other definitive disorder, splenomegaly due to portal hypertension (documented by an abdomen ultrasound scan or another instrumental test). Hematological malignancies (documented by a positive result in physical examination + peripheral blood smear or bone marrow fine needle aspiration or bone-marrow biopsy), hemolytic anemia, and thalassemia except for sickle cell anemia, subjects who have already undergone DBS testing. Eligible patients were tested for acid β-glucosidase and ASM enzymes activity using DBS sample techniques. A genetic test followed the DBS tests to confirm the results.

Data were collected from eligible patients using an electronic data collection form. The collected data included sociodemographic characteristics, ethnicity, presence of comorbidities, anthropometric measures, heart rate, blood pressure, concomitant medications, clinical presentation, spleen length and volume, diagnostic procedure type, and DBS test findings. The DBS tests were performed in a central laboratory (ARCHIMED Life Science Laboratories, Vienna); the cut-off value for the diagnosis of GD was B- GBA1 < 1.5 and ASM < 1.2. The DBS tests were followed by confirmatory genetic testing. The primary outcome of the present study was the prevalence of confirmed (positive result in enzyme assay test and genetic testing) GD subjects amongst patients presenting with splenomegaly and/or thrombocytopenia of unknown cause. The secondary outcomes included the prevalence of confirmed ASMD, demographic profile and patient characteristics of the GD/ASMD population, and the associated comorbid conditions in patients with GD and ASMD. The statistical analyses were conducted using the SAS Software version 9.2. The quantitative variables were summarized using the mean and standard deviation (SD). While the qualitative variables were summarized using counts and percentages. The prevalence of GD and ASMD was described using counts and percentages with a 95% confidence interval (CI).

Results

A total of 390 patients were enrolled in the study from May 2019 to June 2021. The study was conducted in 13 active sites throughout Saudi Arabia, all included in the full analysis set.

The mean age of the patients in the study was 30.11 ± 18.13 years old. Nearly 53.6% of the patients were females, and 69.5% were from urban areas. Most patients (n = 385, 98.7%) were Arab; Saudi individuals accounted for 97.4%. About 46.2% of the patients were unemployed with secondary education (30.4%). The vast majority (87.18%) had health insurance, mainly public health insurance (95%). The mean body mass index (BMI) was 25 ± 6.81kg/m^2. Besides, 77.7% of the patients had a medical history of comorbidities. Of them, 51.8% had sickle cell anemia, and 16.83% had hepatobiliary disorders. At the same time, 15.51% had autoimmune diseases and obesity each. More than two-thirds of the patients (70.8%) received concomitant medications. Analgesics were the most frequently reported class (82.97%), followed by multivitamins (76.09%) and mineral supplements (60.87%). Table 1 shows the characteristics of the included patients.

Most patients (87.4%) had thrombocytopenia; 66.86% presented with anemia, and 59.82% had bone pain. In comparison, 8.8% had a history of splenectomy. On the other hand, nearly 67.7% had splenomegaly with a mean spleen length of 11.11 ± 5.45 cm. Additionally, most of the patients underwent diagnostic procedures for measuring spleen volume (87.5%), and the most frequently used tool was an ultrasound scan (94.7%), followed by CT (14.02%) and MRI (4.67%), Table 2.

In adults, the commonly reported symptoms were fatigue (68.21%), followed by bone pain or bone crisis (49.74%) and abdominal pain (48.72%). Besides, the proportion of easy bruising or bleeding and hepatomegaly were 34.1% and 32.05%, respectively. Nonetheless, out of 66 pediatric patients, anemia was the most frequent symptom (16.92%), followed by marked splenomegaly (13.33%) and easy bruising or bleeding (8.46%), Figures 1 and 2.

Table 1. *Demographic and clinical characteristics of the included patients.*

Variable (N = 390)		Count (%) or Mean (SD)
Age (years)		30.11 (18.13)
Gender	Female	209 (53.6)
Residence	Urban	271 (69.5)
Race /Ethnicity	Arab	385 (98.7)
	Asian	4 (1.03)
	Black	1 (0.3)
Employment (N = 372)	Unemployed	172 (46.2)
	Employed	84 (22.6)
	Retired	6 (1.6)
	NA	110 (29.6)

Continued

Table 1. Continued...

Variable (N = 390)		Count (%) or Mean (SD)
Education (N = 372)	Secondary	113 (30.4)
	College graduate/ Higher	83 (22.3)
	Basic/ Primary	58 (15.6)
	None	23 (6.2)
	NA	95 (25.5)
Health insurance	Yes	340 (87.18)
	• Public Health Insurance	323 (95)
	• *Public + Private Health Insurance*	8 (2.35)
	• *Private Health Insurance*	7 (2.06)
	Missing	2 (0.59)
	No	50 (12.82)
Weight (kg), (N = 377)		61.97 (25.15)
Height (cm), (N = 372)		152.73 (23.82)
Waist circumference (cm), (N = 183)		76.87 (22.24)
BMI (kg/m2), (N = 243)		25 (6.8)
Heart Rate (beats/minute), (N = 320)		87.12 (11.21)
SBP (mmHg), (N = 367)		120.92 (13.12)
DBP (mmHg), (N = 367)		74.43 (9.35)
Medical history/Comorbidities	No	87 (22.3)
	Yes	303 (77.7)
	Sickle cell anemia	157 (51.8)
	Hepatobiliary disorders	51 (16.83)
	Autoimmune disease	47 (15.51)
	Obesity	47 (15.51)
	Cardiovascular disorders	40 (13.2)
	Nervous system disorders	37 (12.21)
	Dyslipidemia	36 (11.88)
	Diabetes mellitus II	34 (11.22)
	Musculoskeletal disorders	18 (5.94)
	GI disorders	18 (5.94)
	Infections	18 (5.94)
	Diabetes mellitus I	5 (1.65)
	Other	51 (16.8)
	Surgery	58 (19.14)
Patients taking concomitant medication(s)	Yes	276 (70.8)
	No	114 (29.2)
Concomitant medications list (N = 276)	Analgesics	229 (82.97)
	Vitamin/ Multivitamins	210 (76.09)
	Mineral supplements	168 (60.87)
	Corticosteroids	46 (16.67)
	Antihypertensive drugs	36 (13.04)
	Thrombocytopenia classes (Including whole blood & platelet transfusion)	35 (12.68)
	Oral hypoglycaemic medication(s)	26 (9.42)
	Antihyperlipidemic medication(s)	21 (7.61)
	Oral Anticoagulant(s)	20 (7.25)
	Erythropoietin (rhEPO) therapy	18 (6.52)

SD: Standard deviation; BMI: Body mass index: SBP: Systolic blood pressure; DBP: Diastolic blood pressure; GI: Gastrointestinal.

* Note: Patients may have more than one concomitant medication and have more than one concomitant disease.

Table 2. *Assessment of thrombocytopenia and splenomegaly of the included patients.*

Variable (*N* = 390)		Count (%) or Mean (SD)
Presence of thrombocytopenia	Yes	341 (87.4)
	• Hb <12 g/dl in men and <11 g/dl in women	228 (66.86)
	• Bone pain	204 (59.82)
	• History of Splenectomy	30 (8.8)
	• Monoclonal Gammopathy of unknown significance (MGUS)	1 (0.29)
	• Polyclonal Gammopathy in subjects ≤ 30 years	1 (0.29)
	No	49 (12.6)
Presence of splenomegaly	Yes	264 (67.7)
	No	126 (32.3)
Spleen length (cm), (256)		11.11 (5.45)
Diagnostic procedures for spleen volume*, (*N* = 367)	Yes	321 (87.5)
	Ultrasound scan result	304 (94.7)
	Normal	58 (19.08)
	Abnormal	246 (80.92)
	CT result	45 (14.02)
	Normal	24 (53.33)
	Abnormal	21 (46.67)
	Magnetic resonance imaging (MRI) results	15 (4.67)
	Normal	9 (60)
	Abnormal	6 (40)
	No	46 (12.5)

SD: Standard deviation; Hb: Hemoglobin.

* Patients who underwent diagnostic procedures may have more than one.

Out of 390 patients, one female patient was found to have GD (0.26%). She was a Saudi toddler girl, aged 2 years and 7 months, with no known family history of GD, ASMD, or other genetic disorders. No abnormalities were detected regarding the neurological, cardiac, or skeletal examination. Table 3 shows GD case laboratory tests and physical examinations. No ASMD cases were found in our study.

Discussion

Since the high rate of consanguineous marriage among Arab countries, the urge to conduct screening programs and epidemiological studies for genetic disorders to increase awareness among physicians and the population has evolved. The proportion of consanguineous marriage, especially with the first-cousin type, is most frequent in the Middle East [18]. In Saudi Arabia, El-Mouzan et al. reported the prevalence of consanguinity amongst Saudi families was 56% (18). As a result, genetic diseases (including metabolic and blood disorders) are more common in Saudi Arabia (16,19). Although the presumed high prevalence of genetic disorders, including GD, in Saudi Arabia, there is a lack of registries highlighting the actual prevalence of the disease since there are multiple missed diagnosed patients. In line with that, the report of the 17th Annual Meeting of the Saudi Society of Hematology 2019 highlighted the high prevalence of misdiagnosis and late diagnosis of GD cases. The report emphasized that the hallmark characteristic for diagnosing GD is splenomegaly in adults. In pediatrics, the presence of splenomegaly with thrombocytopenia should be considered an important sign for subsequent hematological assessment. Additionally, they highlighted the significant impact of raising GD awareness by developing screening programs for any individual presenting with thrombocytopenia with or without splenomegaly. Furthermore, the report confirmed the importance of genetic testing and enzyme assay to help early diagnosis and management of GD (20).

Owing to the rare nature of GD, together with a wide range of clinical presentations and disease severity, the diagnosis became challenging. A published study by Mehta et al. [21] which included two surveys evaluating GD diagnosis' journey from both physician and patient perspectives, showed that one out of a total of six patients with a confirmed diagnosis of GD experienced delayed diagnosis or misdiagnosis. Besides, there is a long referral history across various specialties such as hematology or hematology-oncology, pediatrics, or even primary care

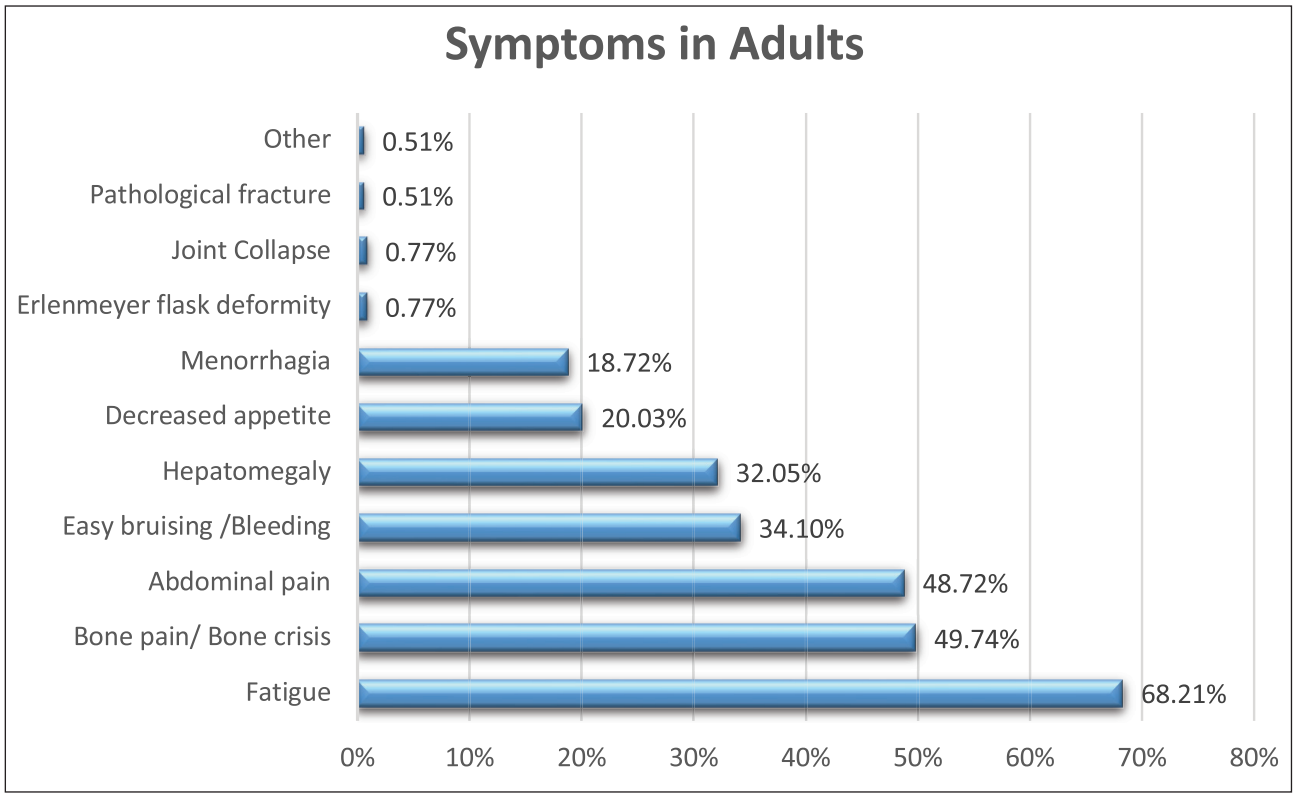

Figure 1. *Percentage of presenting symptoms in adults.*

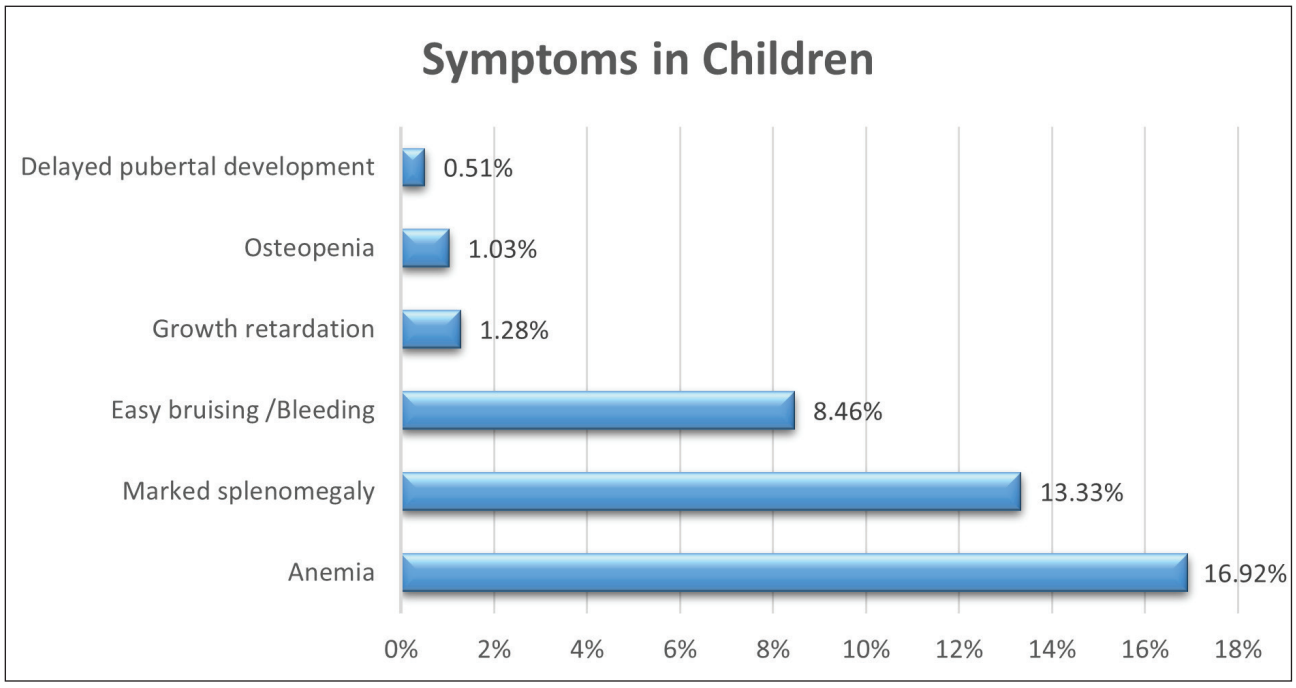

Figure 2. *Percentage of presenting symptoms in pediatrics.*

units before obtaining a definitive diagnosis of GD (22). The present study represents a small screening study for GD conducted in clinics where patients with GD clinical presentations are usually present.

A total of 390 patients were screened in our study. One patient had GD (0.26%), a Saudi toddler girl aged 2 years and 7 months. She had no family history of GD, ASMD, or any other genetic disorders. Notably, the main presenting sign was hepatosplenomegaly without any bone manifestations. Concerning hematological profile, the patient had a normal hemoglobin level (11 g/dl, with the normal range for children aged 1-6 years of age being 9.5-14 g/dl) and a high ferritin level (202.3 mg/

Table 3. *Laboratory tests and other examinations for the patient with GD.*

Lab test	Value
Hematological/biochemical	
Hemoglobin (Hb) (g/dl)	11
Platelet count (× 10^3/mm^3)	86
(RBCs) count (× 10^6/mm^3)	4.9
(WBCs) count (× 10^3/mm^3)	4
Ferritin (ng/ml)	202.3
PT (seconds)	14.1
APTT (seconds)	40
Liver function tests	
AST (U/l)	62
Lipid profile	
Total cholesterol (mg/dl)	117.5
LDL (mg/dl)	77
HDL (mg/dl)	22
Triglyceride (mg/dl)	123
Radiological examination	
Hepatosplenomegaly	
Neurological examination	
Unremarkable	
Pulmonary examination	
Unremarkable	
Cardiac examination	
Unremarkable	
Skeletal examination	
Unremarkable	

RBCs: Red blood cells; WBCs: White blood cells; PT: Prothrombin time; APTT: Activated partial thromboplastin clotting time; AST: Aspartate aminotransferase; LDL: Low-density lipoproteins; HDL: High-density lipoproteins.

dl; with the normal range for children aged six months and 15 years being 7-142 ng/ml), based on Mosby's Diagnostic and Laboratory Test Reference (22). At the same time, she had abnormal levels of triglycerides (≥ 100 mg/dl) and HDL-C (<40 mg/dl); and acceptable LDL-C level (<110 mg/dl), according to the cholesterol clinical practice guidelines by the American College of Cardiology/American Heart Association Task Force (23). These findings are in accordance with GD diagnostic features; GD is characterized by large amounts of lipid-storing macrophages associated with iron accumulation, with high ferritin levels being the hallmark of the disease. Regenboog et al. (24) explained the findings mentioned above as the chronic low-grade inflammation state associated with GD results in high ferritin levels due to increased hepcidin transcription and subsequent ferritin trapping in macrophages. Stein et al. revealed in their analysis that HDL-C acts as a biomarker for assessing GD severity (25). In addition, there was a strong correlation between HDL-C level and the size of the spleen and liver, where lower HDL-C levels were correlated with severe hepatomegaly and splenomegaly, which, in turn, highlighted the benefit of using HDL-C as a significant biomarker for monitoring GD progression, what was called as "biomarker basket" (25) ERT has proven a notable improvement in altered lipid profiles (25,26).

Conclusion

In conclusion, this screening study paved the way for an effective GD screening program in Saudi Arabia. Furthermore, it emphasized the significant impact on early diagnosis and adequate management of GD and subsequent worthwhile outcomes.

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List of Abbreviations

ASM	Acid sphingomyelinase
ASMD	Acid sphingomyelinase deficiency
DBS	Dry blood spot
ERT	Enzyme replacement therapy
GBA1	Glucocerebrosidase
GD	Gaucher disease
LSDs	Lysosomal storage diseases
MGUS	Monoclonal gammopathy of unknown significance
SD	Standard deviation
SMPD1	Sphingomyelin phosphodiesterase 1

Declaration of conflicting interests

The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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The study is conducted by Sanofi, Saudi Arabia. Sanofi provided investigator fees to the investigators according to the study's agreement. Sanofi provided the needed materials for all study steps, including protocol formation, data collection, medical writing, and manuscript submission. Furthermore, according to local and international regulations, Sanofi Saudi Arabia provided all the required resources for the study to be conducted and published. The study protocol has been peer-reviewed by the representative of Sanofi before submission.

Consent to participate

Informed consent was obtained from the patients

Ethical approval

The present study gained the ethical approval of the local ethics committee and intuitional review boards (IRBs) of participating centers.

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Supplementary Table 1. *Ethical approval reference numbers.*

Affiliations	Reference No#
Qatif Central Hospital, Qatif, Saudi Arabia	19-242E6
Prince Sultan Military Medical City, Riyadh, Saudi Arabia	1284
Asir Central Hospital, Abha, Saudi Arabia	19-242E7
Prince Saud Bin Jalawi Hospital, City, Saudi Arabia	19-242E9
East Jeddah Hospital, Jeddah, Saudi Arabia	19-242E5
National Guard - Health Affairs, Hofuf, Saudi Arabia	CT19/018/A
King Faisal Specialist Hospital, Jeddah, Saudi Arabia	IRB 2019-66
King Fahd Hospital, Hofuf, Saudi Arabia	19-242E10
King Fahad Medical City, Riyadh, Saudi Arabia	19-242
King Fahd Hospital, Medina, Saudi Arabia	19-242E8
Al Noor Specialist hospital, Mecca, Saudi Arabia	19-242E2
Maternity and Children Hospital, Mecca, Saudi Arabia	19-242E11
National Guard - Health Affairs, Riyadh, Saudi Arabia	CT19/018/R