University of Sistan and Baluchestan

Journal of Epigenetics

Online ISSN: 2676 - 4350

Homepage: https://jep.usb.ac.ir

Iranian Genetics Society

The Practicality of Family screening for Gaucher disease among first- and second-degree relatives: an effective diagnostic approach in high consanguinity

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ARTICLE INFO

Article type:
Research Article

Article history:
Received: 29 January 2023
Revised: 15 August 2023
Accepted: 3 September 2023

Keywords:
Gaucher's Disease; family screening; family history; cost-effectiveness; genetic counseling; genome sequencing;.

A B S T R A C T

Gaucher Disease occurs more frequently in the offspring of familial marriages. With a wide variety of presentations, the long list of tests required to confirm GD in addition to those needed to rule out others puts a heavy financial burden on the patients, especially in regions where the majority live below the poverty line. Thus, in this study, we provide a familial screening method in patients whose relatives are confirmed GD cases, assuming that this approach might ease up the process.

In this study, 26 patients out of 217, whose family members were GD patients and had symptoms associated with GD were selected. Enzyme assay levels using Dried-Blood Samples from 3ml of samples were measured. Those with low levels of enzyme assay were further tested with *GBA* gene sequencing to confirm the diagnosis. The results of the sequencing revealed 5 carriers and 1 GD patient. Genetic counseling for GD on a personalized level is novel in the region, which all our patients received and responded positively to. In conclusion this process eases the diagnosis and reduces the overall burden of GD while keeping genetic counseling for the patients, which provides better care and opens up the possibilities of a registry system for GD patients and susceptible individuals in low-income countries.

Introduction

Gaucher Disease (GD) (OMIM: #230800, OMIM: #230900, OMIM: #231000) is a rare autosomal recessive (AR) lysosomal storage disease caused by the mutation of the *GBA1* gene located on chromosome 1 (1q21). It was first described as

DOI: https://doi.org/10.22111/JEP.2023.44665.1050

Publisher: University of Sistan and Baluchestan

How to Cite: Naderi, M., Mirzaei, I., Yaghoubi, S., & Azizi, Gh. (2023). The Practicality of Family screening for Gaucher disease among first- and second-degree relatives: an effective diagnostic approach in high consanguinity. *Journal of Epigenetics*, 4(1), 15-23. https://doi.org/10.22111/JEP.2023.44665.1050

massive hepatosplenomegaly without leukemia (1). Clinical presentation is as follows; hepatosplenomegaly, thrombocytopenia, bone crises, and neurological impairments (1). The disease incidence is around 1 in every 40,000 to 60,000 births in the general population, and much higher in the Ashkenazi Jewish population, at 1 in every 800 births (2). Despite its phenotypic heterogeneity, the AR inheritance of GD means it tends to occur more often in regions where familial marriages happen more often (3).

Sistan and Baluchestan is the southeastern province of Iran, with Zahedan as its capital, housing more than 600,000 people. The entire province of Sistan and Baluchestan is considered an underprivileged area, with more than 70% of its population below the poverty line and having limited access to education, health care, and insurance. The hospital and health-allied institutions are not well-equipped enough to deal with the research and lab-heavy procedures required to diagnose GD. Familial marriages are more common in the region due to people's reliance on religious traditions (4). Thus, one expects to see an abundance of rare diseases, particularly those with an autosomal recessive inheritance pattern, such as GD (1, 5), making it a decent location to screen suspicious individuals for the condition (6).

Neurologic disorders like parkinsonism are also common (except for in type 1) (1). The clinical presentation, decreased glucocerebroside enzyme activity to 15% of its normal value, and identification of biallelic *GBA* gene mutation (homozygotes) on molecular testing are all part of the diagnostic process (5, 7). The crumpled tissue paper appearance of the macrophages is characteristic of GD (1). Given that GD is considered a rare disease, it lies way down the differential list of physicians, even in regions where it is more prevalent. Another issue is the financial aspect of GD, whether it is the diagnostic process, ruling out other conditions or the management, patients living in under-privileged regions struggle to keep up with every aspect of the condition.

Carrier screening for GD has been done before (8, 9) but, as the name suggests, it is aimed at finding the carriers or the heterozygotes for the disease. Moreover, the screening studies done so far were either conducted in an economically stable country or were aimed at providing genetic counseling to the carriers rather than finding GD cases. Besides, different classifications of GD present quite differently, with type 1 having more hematologic findings while type 2 and 3 have more neurologic abnormalities like cognitive impairment and seizures respectively. In this study we decided to factor in all the various problems we faced in diagnosing GD, including the widely non-specific presentation of the condition, and see whether familial screening is a feasible approach or not. Therefore, we selected the first- and second-degree family members of our GD patients and tested them for GD.

Material and Methods

Study Design

In this descriptive, non-interventional, diagnostic, clinical study, we selected GD patients from the southeastern region of Iran, Sistan and Baluchestan province, to ask the details of their family members and the presence of any other familial conditions. The selected patients were all from Sistan and Baluchestan whose documents were stored in Ali-Asghar Hospital Repository. Their primary care center was established in Ali Asghar Hospital, Zahedan, Sistan and Baluchestan, Iran.

We gathered the details of 217 individuals (23 families) of our GD patients and contacted them regarding their consent to participate in our study. 6 families were excluded on account of already having GD confirmed, and 4 families refused to participate in our study. Of the remaining 93 individuals (13 families) we contacted, 49 had no complaints regarding their health status, 18 disclosed symptoms irrelevant to our work or another diagnosis and finally, 26 patients fell into our inclusion criteria. The population sampling method for this study was a non-probability convenience sampling.

Selection Criteria

The selection criteria for this study includes any presenting symptom associated with GD (regardless of its type). These include hepatosplenomegaly, growth abnormalities, bone pains, pulmonary diseases, neurologic conditions, leukopenia, thrombocytopenia (platelet count <120,000), anemia (including anemia resistant to treatment), and liver function tests (LFTs). (1, 5). In table 1, it is shown the numbers of patients with

their conditions regarding our selection criteria. The most concomitant presentations were anemia, leukopenia, and thrombocytopenia (pancytopenia). As for the neurologic manifestations; 5 patients had tremors, 1 Parkinsonism, 1 abnormal gait. Growth abnormalities refer to conditions of short stature, facial or skeletal deformities, and intellectual disabilities.

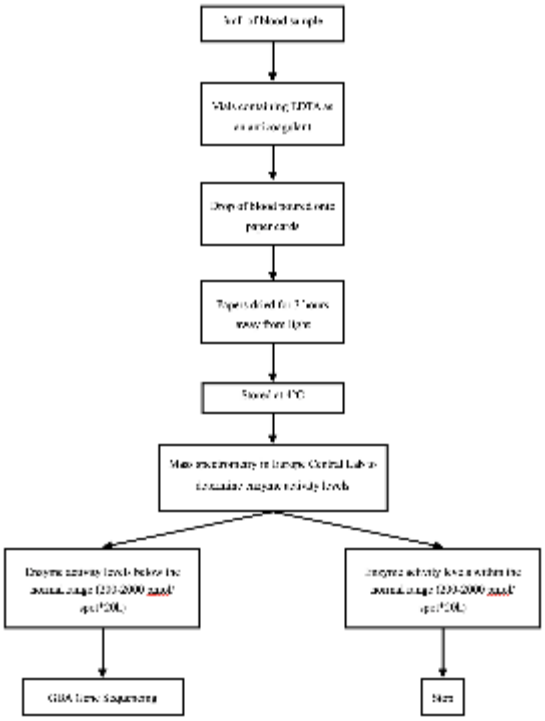
Table 1: The evaluated conditions with numbers of presentations. Most patients had more than one condition at a time.

Condition	Number
Anemia	6
Bone Pain	13
Growth Abnormalities	10
Hepatosplenomegaly	5
Neurologic Conditions	7
Leukopenia	3
Thrombocytopenia	4
Pulmonary Disease	1
Elevated Liver Function Tests	9

Lab Studies and Diagnostic method

The patients initially had all their symptoms confirmed via complete physical exams, thorough histories and lab analyses (CBCs, Complete Biochemistry, etc.). Then an enzyme assay test was performed for the glucocerebrosidase enzyme activity on a Dried-Blood Sample. We used whole blood samples utilized for the CBC test to implement enzyme assay. Whole blood samples (3 mL) were taken in vials containing EDTA as an anticoagulant. Simultaneously, a drop of blood was poured onto the paper cards (Whatman, Schleicher & Schuell, Keene, New Hampshire, United States) in the middle of the circle using a needle to fill the circle's surface. Paper cards were dried for 3 hours away from light and were stored at 4°C. *GBA* activity level was evaluated by mass-spectrometry in the central laboratory in Europe. A decreased activity to less than 15% of normal is suggestive of GD (5). In table 2, it is shown the details of patients whose enzyme assay levels were below normal values. Patients with decreased enzyme activity were then tested for *GBA* gene mutations via gene sequencing. According to the manufacturer's instructions, the DNA of all samples was extracted by QIAamp DNA Mini kit (Qiagen, Hilden, Germany, CAT Number: 104 364 000), and the samples with enzyme activity levels below 15% were sent to the National Institutes of Health to sequence all exons, introns, and flanking regions of the *GBA* gene. Sequencing of all exons and flanking intronic regions of the glucocerebrosidase gene (GBA) was performed on the seven genomic DNA samples using a 3130 Genetic Analyzer (Applied Biosystems, Foster City, CA). The data was analyzed using Sequencing Analysis v.5.1.1 and SeqScape v.2.1.1 (Applied Biosystems, Foster City, CA). In figure 1, we have shown a stepwise approach to the laboratory method of this study. The *GBA* sequencing method goes beyond the scopes of this article, but for the more interested readers, we suggest the methods section of the research by Ortiz-Cabrera et al. in which they have described the different genetic analysis methods for the *GBA* gene (10).

Figure 1: The laboratory method for using Dried-Blood Samples to determine the GBA enzyme assay levels



Ethics and IRB statement

This study took place in Ali-Asghar Hospital in Zahedan in 2019-2020. It was authorized by the Zahedan University of Medical Sciences research and ethics committee under the ethics code: IR.ZAUMS.REC.1398.434. Approval of this study was done by the ethics committee of Zahedan University of Medical Sciences in accordance to Iranian Ministry of Health Ethics Codes and all of the affiliates and ethical associations in agreement with the ministry, which includes the Helsinki declaration of ethics.

Results

Six patients out of the original 26 had low enzyme activity levels. Their beta-glucosidase enzyme activity levels and symptoms at presentation are shown in table 2. All of these patients then underwent *GBA* gene sequencing to determine whether they have GD (homozygote) or not (heterozygote or carriers) by looking *for c1246G>A* mutation. Five of these patients were only carriers, i.e., heterozygotes for GD, but one patient was homozygote for GD. Figure 2 shows the *GBA* gene sequencing done for these six patients, with section A representing a heterozygote mutation and section B representing the homozygote mutation with a full missense mutation (A surge in the location of the mutation).

This patient was an 18-months old female who initially presented with bone pains and mild hepatosplenomegaly. Her cousin (second-degree relative) is a known GD case of ours. Her parents are blood-related, and so are the parents of her cousin. (Figure 3)

A more detailed metabolic profile was requested for further evaluation to rule out other similar lysosomal storage diseases (LSDs), which are in table 3. Her low beta-glucosidase activity indicates GD, while normal values for the other enzymes rule out other lysosomal storage diseases like Niemann-Pick disease. The presence of c1246G>A mutation was confirmed in the patient. The early presentation of the condition, bone pain and organomegaly in the absence of neurologic manifestations makes this a type 1 GD case.

In summary, the result of this study shows that familial presentations of GD -despite the rarity of the condition- is not unlikely. More objectively, out of the 26 patients with complaints similar to GD presentations and a positive family history, 5 were carriers and 1 had GD.

The 21 non-GD patients, given their family history, were given oral genetic counseling regarding the possibility of GD in their children. The 5 carriers had formal, written or recorded genetic counseling for GD, covering the basics of the inheritance to the possible presentations, associations with other conditions and, treatment. These patients were specifically instructed to look out for hepatosplenomegaly, bleeding diatheses, skeletal abnormalities and, neurologic manifestations such as parkinsonism in their children. The GD patient was promptly started on enzyme replacement therapy, her family were informed as to how the condition had passed on and were given genetic counseling accordingly, with more emphasis on treatment and management.

Table 1: The detailed enzyme activity levels of our GD patient. The test was done on a dried-blood sample. Normal value of Acid sphingomyelinase

rules out Niemann-Pick Disease, leaving Gaucher Disease the only possible diagnosis.

Lysosome Enzymes	Result	Reference Range
Beta-Glucosidase	35.30	200-2000 pmol/spot*20h
Acid Sphingomyelinase	242	200-3500 pmol/spot*20h
Beta-Galactosidase	0.51	0.5-3.2 pmol/spot*21h

Table 2: The details of the patients with low beta-glucosidase enzyme activity levels. The normal range for beta-glucosidase activity is 200-2000 pmol/spot*20 h. Low activity is suggestive of GD.

pmol/spot*20h: pico-mol/spot in 20 hours. Represents the value of enzyme activity in 20 hours.

Age	Gender	Enzyme (pmol/spot *20h)	Conditions under examination	Degree of relationship
2 Years -old	Male	121	Mild Hepatospleno megaly	First degree
10.5 Years -old	Female	180	Mild Hepatospleno megaly and Delayed Growth	First degree
18 Months	Female	35.30	Mild Hepatospleno megaly and Bone Pain	Second degree
6 Months	Male	90	Hepatospleno megaly, pancytopenia, myoclonus	Second degree
25 Years -old	Female	122	Bone pain and Low Height	First degree
35 Years -old	Male	118	Short stature, Avascular Necrosis, and Tremor	Second degree

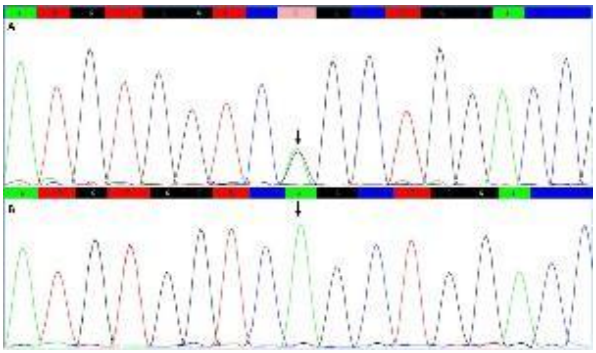


Figure 2: The result of GBA sequencing on exon 9 for the missense mutation of c1246G>A. A: The arrow indicates a heterozygote mutation, noted by a slight shift in the peak. B: The arrow indicates a homozygote mutation for the disease, noted by a surge in A nucleotide and a lack of variability with the original G nucleotide.

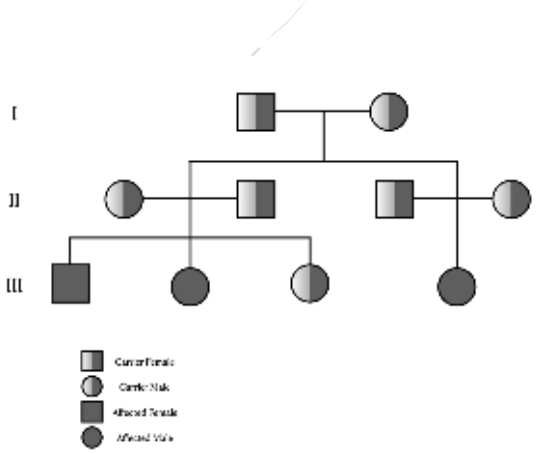


Figure 3: Family pedigree of the GD patient. She was a second-grade relative of a previously confirmed GD patient, with the rest of her family members being carriers for GD. Though not shown in the figure, all the marriages in this family tree were between blood relatives.

Discussion

In this investigation, we discovered that five people were carriers and one had GD, out of a total of 26 people (all of whom had a family relative with GD). Positive family history for GD among relatives is a reliable factor to base the diagnosis on, especially for low-income settings, as this eliminates the general concept of a vague presentation, vast differentials and excluding enough causes until GD is the only one left. In addition, this method saves cost, which is a huge burden as discussed later, organizes genetic

counseling methods, and most importantly, opens up the path to the establishment of a registry for GD patients, carriers and family members in these regions. Therefore, in this section we discuss other screening studies, and their results as well as the different methods of screening done so far. Then we mention our genetic counseling obstacles and methods for our patients, a mutually difficult task in regions similar to ours. finally, we explain the financial aspects of GD and why this screening tool, despite its apparent simplicity is extremely useful in these challenging settings. In the end, we discuss the limitations we had for this study, and our approach to mitigating them to the possible extent.

So far, GD screening has been conducted in three formats, which we shall address in the following order: 1-a study of a certain group of people 2-variations in the presentations and 3-newborn screening. Zuckerman et al. presented the largest and most significant carrier screening study for GD in 2007. Over the course of eight years, the researchers evaluated 28,893 people for GD in this study. Their findings suggest that the condition had an impact on the patients' pregnancies and birthing decisions (6). Ashkenazi Jewish population is the most studied population when it comes to GD. Beside the screening study from 2007, many other studies have screened for GD within the population, specifically when it comes to the co-occurrence of different presentations. Even different types of screenings have been compared in this population, as American College of Medical Genetics and Genomics (ACMG) guidelines suggests Ashkenazi Jews be screened for 9 conditions including GD. Pan-ethnic and ethnic-based carrier based screening is a good example of screening process done only for the Ashkenazi Jews, which is a reasonable study given that the highest prevalence of GD is among this population (11). However, epidemiological evidence is lacking in whether regions like Sistan and Baluchestan, where this study is done, have similar prevalence of GD or not. Other countries have established screening processes of their own based on the presence of GD in their regions. A study in Japan used dried-blood samples to assess enzyme activity levels in 155,442 neonates to screen for GD, an approach similar to ours but in newborns (9). Another multi-center study from Japan examined patients based on their symptoms and discovered a platelet count of fewer than 120,000/L. The researchers then evaluated the patients' enzyme activity levels and discovered that 11 had GD, with one patient requiring genetic testing to be properly confirmed. DBS is a less complicated way for diagnosing GD, according to the study's findings (12). A similar strategy was used in another study known as the Delphi consensus, in which the authors tested babies for GD. The difference is that they also took into account the family's history. As a result, the researcher exclusively chose neonates with Ashkenazi Jewish ancestry with symptoms of GD, which is a methodologically similar approach to ours (8). They showed that the usefulness of family screening for GD is not confined to low-income areas. Lastly, Chiong et al. studied the genetic and clinical characteristics of GD in 14 Filipino patients. They concluded that in their population, type 3 GD more commonly presents with hepatosplenomegaly (13). A study from China by Kang et al. screened newborns for GD via fluorometric assays. However, the assay was performed in the last step, after the low enzyme assay, dried blood spot and gene analysis were performed. The authors conclude the fluorometric as a feasible screening method for the newborn (14).

The second screening method was based on variations of the presentations. GD is a phenotypically variable condition, even among siblings with the same mutations, so co-inheritances and diverse presentations are very likely (15-17). Co-inheritance with alpha-thalassemia has been seen, both of which are more common in familial marriages (18). Splenomegaly and thrombocytopenia require high-risk screening as they are the most common presentations of GD with enzyme activity levels cutoffs of 3.0 pmol/punch/hr, following which Sanger sequencing of the *GBA* gene is a great confirmatory tool (19). A study detected four GD cases out of 73 enrolled children in a screening program that primarily focused on high-risk children (20). An essential point to remember is cascade screening, which is best shown in a case report by Hannah-Shmouni et al. describing three cases of colon cancer and GD, particularly in consanguineous situations (21). Another case report states the occurrence of Diffuse Large B-Cell Lymphoma in 2 GD patients, further

emphasizing the importance of cascade screening and thus family screening (22). Neurological symptoms have been used as an indicator to high-risk screening for types 2 and 3 of GD. Of the two patients in the study by Momosaki et al. one patient, despite being a compound heterozygote, had neurological manifestations along with their mutation. In this study, of the 102 patients studied, only 2 had GD, and the authors recognized DBS sampling an early diagnostic method in high-risk patients too (23).

Most studies, as mentioned, focused on co-occurrence or specific presentations of the condition. Those that implemented family history only screened newborns. In our method, we excluded age as a factor and only relied on a positive family history of GD and relevant presentation. In this study we aimed to ease the process in challenging settings with what was available to us, and the screening we did, improved many negative aspects our patients experienced until GD was confirmed or ruled out.

The treatment for GD, generally includes enzyme replacement therapy (ERT) and substrate reduction therapy. The drugs of choice for GD type 1 are imiglucerase and velaglucerase as enzyme replacements. Substrate reduction therapy is considered the second-line treatment of choice when ERT is no longer an option, with miglustat as the medication of choice (1, 24). GCase enhancers have been described as potential candidates for treating GD, especially in GD types with neurological manifestations (25). Of note, one must always focus on the hematological parameters when treating GD (26). Hematopoietic stem cell transplantation is another, riskier option that has been recently discussed, that while used as a more permanent solution, still requires further research (27).

One of the most challenging components when it comes to GD is the cost. Multiple studies have estimated to cost of the illness, which boils down to 48,000$ per year at minimum, but even above 100,000$ in average in China (28). Treatment alone exceeds 258,000 euros in the Netherlands. (29). The cost of care for Gaucher Disease in Iran was estimated around 1,473,818$ based on documentations in 2014-2015 in which 95.2% of the cost belonged to medications alone (30). A more recent study from 2018 states that the average cost of treating GD in Iran is ranged from 40,941.1$ to 69,176.5$ per year, and 3,477,710.8$ in lifetime with treatment with ERT. Without ERT the cost in a lifetime is 87.855.4$. With all the efforts the Quality Adjust Life Years (QALY) goes from 39.67 to 50.45. (31) However, one should consider the economic damages the sanctions have caused since 2019. The referred amounts are conversion of USD to IRR based on the relative prices back then, which has gone up roughly 10 times since 2019 and fluctuates at a highly unpredictable rate (32). This means a hefty increase in the prices of treatment alone, which in addition to the increased costs of the living in all aspects and the insurance companies' reluctance to alleviate these issues puts part of the burden on the physicians' shoulders to attempt to ease the process. In Iran, insurance companies only pay a fraction of the price of prescriptions and diagnostic procedures. The percentage is determined by the family's background, location, economic situation, and, in some situations, income. Regardless, out-of-pocket expenses are still considered expensive (33). The screening process among family members with GD is a decent approach in doing so as it is a short diagnostic process, avoids the waste of time on other causes, shortens the duration of admission to the hospital and excludes additional unnecessary testing.

As new and more regional studies are published and more specific mutations for each region are being defined, screening riskier population, be it based on their symptoms, family histories, or a combination of both, is becoming more and more of a routine. An example of these mutation is a Norrbottnian variation found in Italy, with a c1448T>G mutation (34). Finding symptomatic associations with each mutation is a clear way for further enhancing our understanding of GD and its presentations. The most further reaching implication of such studies is the establishment of registries in more under-privileged regions. However, a more plausible attempt is to repeat this study with more patients, and possibly on a more international level, to more accurately evaluate the practicality of the family screening method.

The most noticeable limitation of this study was the population sample. Despite that, GD is considered a rare disease, thus a low population sample is not problematic. In considering this study, one must include the context to avoid biases. The family screening method is useful in

underprivileged areas where registries are not utilized, regions where otherwise patients will go unnoticed. The reasons for our low samples are as follows: 1- Patients were reluctant to travel for the study, 2- The fear of diagnosis, 3- a lack of education about inherited disorders.

The second limitation we faced was the inconsistent price of US Dollars to Iranian Rials due to the sanctions which, prevented us to appropriately present the cost of diagnosis and treatment and how much this method exactly saved patients (which is quite significant when calculating in Iranian Rials).

Conclusion

In conclusion, providing a screening process for individuals with family members with GD is helpful in not only providing some relief to the families, but alleviating the financial and mental burdens of the disease. This is in addition to the diagnostic and therapeutic advantages that come with an earlier diagnosis. The appropriate genetic and medical counseling that follows can really ease the process of living with an already difficult and costly condition. The success of this study implies the possibility of a registry system for GD patients in countries and hopefully in other under-privileged areas which can significantly improve the quality of life of GD patients.

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