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Prevalence of Fabry Disease in Patients with Hypertrophic Cardiomyopathy in Saudi Arabia: A Multicenter Cross-Sectional Screening Study Protocol

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Abstract **Background:** Fabry disease (FD) is an X-linked lysosomal storage disorder caused by an inherited deficiency of the lysosomal enzyme Alpha galactosidase A (a-GAL A) due to mutations in the GLA gene. FD prevalence is increasing worldwide. The accurate FD prevalence data in Saudi Arabia lack to date. Therefore, this study aims to determine the prevalence of FD in high-risk groups of Hypertrophic cardiomyopathy (HCM) patients in Saudi Arabia. **Methods:** This cross-sectional, multicenter screening study will include HCM patients presenting with left ventricular hypertrophy (LVH) with no definitive cause over a period of 18 months. A total of 240 patients from seven centers in Saudi Arabia who fulfill the eligibility criteria will be enrolled. Each patient will be assessed for α-galactosidase A enzymatic activity using dried blood spot (DBS) samples, and diagnosis will be confirmed by genetic testing. **Results:** This protocol will be submitted for approval by the responsible ethics committee of the participating centers prior to patients' inclusion. We expect to collect data from 217 patients or more as determined by our sample size calculation. **Discussion:** With a high rate of consanguineous marriages, Saudi society is characterized by rapid population growth with an increased emergence of several genetic diseases. FD incidence in Saudi Arabia appears to be higher than in many other countries in the Arab world and Europe. In addition, there is a scarcity in the published literature regarding the prevalence, treatment patterns, and outcomes of FD in Saudi Arabia. **Trial Registration:** Not Applicable.

Keywords Fabry disease, Lysosomal storage disorders, Epidemiology, Saudi Arabia

1. Background

Fabry disease (FD) is a rare hereditary X-linked lysosomal storage disorder (LSD). This disease arises from mutations in the α-galactosidase A (GLA) gene leading to α-galactosidase A (α-Gal A) enzyme deficiency and subsequent accumulation of globotriaosylceramide in different parts of the body with a wide array of clinical presentations. It often leads to cell abnormalities, multiorgan dysfunction, significant impairment in quality of life, and premature death. FD is inherited as an X-linked recessive disease since GLA gene is located on the X-chromosome, and for this reason, symptoms developed tend to be more severe in males than females [1-4].

FD can be classified on the grounds of phenotypic features into two classes: the classic (type 1) and the later-onset (type 2) phenotypes [5]. With respect to the classic FD, the incidence in males is around 1 in 40,000 [6]. However, this range may extend from about ~1 in 18,000 to 1 in 95,000 based upon different newborn screening studies of different races and geographic areas [7-10]. Patients with classic phenotype have either tiny or no functional α-Gal A enzyme, alongside with pronounced accumulation of glycolipids in small blood vessels and capillaries leading to ischemia and infarction. Early symptoms usually manifest in childhood or adolescence, which include acroparesthesias, angiokeratomas, anhidrosis or Hypohidrosis, gastrointestinal symptoms (abdominal pain and cramping), and characteristic corneal dystrophy (seen by a slit-lamp as a star-burst pattern). With increasing age, the disease comes to a climax of life-threatening renal (proteinuria which progresses to renal failure), cardiac (myocardial infarction, arrhythmias, left ventricular hypertrophy (LVH), and hypertrophic cardiomyopathy (HCM)), cerebrovascular (transient ischemic attacks, hemiplegia, and strokes), and pulmonary (dyspnea and airflow obstruction) complications. Patients with this phenotype have an average life expectancy of 50 years [4]. On the other hand, the incidence of later-onset FD in males varies by ethnicity and race but is at least 5-10 times higher than that of the classic type males within the same race, ethnic group, and geographic region [11]. Patients with this phenotype have quite a few α-Gal A enzyme activity with no glycolipids accumulation in small blood vessels and

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capillaries, and therefore, they lack the early manifestations of the classic type. In this instance, renal and/or cardiac manifestations become evident in the 4th to 7th decades of life [12].

Recent studies have revealed that FD diagnosis is confronted by many challenges, and the disease is so far mis-diagnosed with other disorders or under-diagnosed with diagnostic delay of many years in vast majority of cases. The key challenges in FD diagnosis are; rarity of the disease along with lack of awareness across the vast number of specialists who evaluate patients initially; patients are actually presenting to different specializations; the clinical features of the disease are subjective in nature, highly diverse, and non-specific with a wide differential diagnosis. Several strategies have been advocated to improve this gap especially in patients with certain manifestations known to occur in FD patients such as: stroke, LVH, coronary insufficiency, chronic kidney disease, gastrointestinal and liver disease [13-16]. In this context, it should be recalled that ischemic heart disease, stroke, chronic kidney disease, and cirrhosis are among the top 10 causes of death in Saudi Arabia [17].

With regards to the entire Kingdom of Saudi Arabia, no accurate and comprehensive data is available on the prevalence of FD to date, especially in the high-risk group of patients [18]. However, a study conducted by Al-Sannaa et al. reported that the prevalence of FD males in the Eastern Province of Saudi Arabia who were born from January 1st, 1983 to December 31st, 2016 was 1.42 per 100,000 live births [19].

In both phenotypes, the cardiac variant is common in FD patients [20]. The prevalence of FD among patients with LVH is about 1–3%; out of 230 FD male patients, seven males were detected to have LVH [1,21]. In fact, cardiovascular symptoms are present in the majority of FD patients [22]. However, symptoms of cardiac FD are nonspecific, such as breathlessness, palpitations, chest pain, dizziness, and syncope [22]. In such case, globotriaosylceramide accumulation in cardiomyocytes leads to LVH that can mimic autosomal dominant HCM clinically and morphologically [20].

HCM is a relatively common monogenic disease with a prevalence of about 1 in 500 among the general population. Autosomal dominant inheritance is common in HCM patients, and the pathological hallmark in this case is the unexplained LVH. The distribution of LVH in HCM is asymmetric, heterogeneous, with no standard patterns of wall thickening, and no single morphologic feature is considered classic or typical. However, LVH in FD has a typical pattern of concentric thickening without left ventricular outflow tract obstruction. The presence of a thinned left ventricular posterior wall base with LVH is a characteristic feature of end-stage cardiac FD [1,21].

Recent studies have revealed that LVH, especially in the early stages, could be reversed to a significant extent with enzyme replacement therapy (ERT) [21]. Moreover, the initiation of ERT prior to the overt clinical disease has shown that could effectively mitigate organ damage, and this proactive approach could be a fundamental management strategy to remarkably improve outcomes in FD patients [23]. Additionally, FD has been considered a diagnostic challenge, and several studies have revealed that its prevalence is underestimated, and consequently, most FD patients suffer from a substantial delay until reaching the right diagnosis. Enhanced enzyme assays and genetic profiling in recent years paralleled with more targeted services for rare diseases, have invited a prompt growth in FD prevalence [21,22]. Thereby, this study proposes to screen patients with HCM of unknown cause with Dried Blood Spot (DBS) test as an early screening measure followed by genetic testing for confirmatory diagnosis in order to determine the prevalence of FD in patients with HCM in Saudi Arabia. These data will help change the local practice toward FD diagnosis and lead to subsequent early disease management.

2. Patients and Methods

2.1. Study Design and Participants

This study will be a cross-sectional, multicenter, screening study where patients will be recruited at an outpatient setting from different centers in Saudi Arabia. Targeted centers will be hospitals with specialty care for cardiology, which are having a fair experience with HCM patients.

Patients will be considered for eligibility in the study if they meet the following inclusion criteria; (1) males or females 18 ≤ 60 years of age, (2) patients with HCM of unknown origin or patients with unexplained LVH with a maximum LV wall thickness >13 mm in the absence of abnormal loading conditions, (3) patients willing to sign an informed consent, and (3) patients should meet at least one of the following criteria: (a) atypical HCM, (b) History or presence of documented arrhythmia, (c) short PR interval defined as <120 ms on electrocardiogram, and (d) symptoms of autonomic dysfunction (dizziness, fainting upon standing up, orthostatic hypotension, inability to alter heart rate with exercise, or exercise intolerance and sweating abnormalities (Hypohidrosis). While, patients with known FD, infiltrative cardiomyopathy (e.g. amyloidosis, sarcoidosis), known secondary hypertension (e.g. renal artery stenosis or hormonal excess), or who have been already DBS tested will be excluded from the study.

All eligible patients will visit the investigator for one visit and will sign the informed consent form. At the same visit data, and blood samples (DBS) for enzyme tests and genotyping will be collected by the investigator/designated person at the site. Afterward, the investigator will contact the patients later to share the results of the blood test. The study recruitment period will be opened for up to a maximum of 18 months.

2.2. Sample Size Calculation and Sampling Technique

The analyses of this study will be descriptive in nature, and the sample size has been chosen to allow collection of sufficient data to determine the FD prevalence in the high-risk group. Consequently, the sample size has not been assessed in terms of statistical power but rather in terms of precision based on the frequency (95% CI) that is expected.

The expected prevalence of FD worldwide is 1-5 patients in 10,000 subjects among the overall population. On the other hand, the expected prevalence of the high-risk group with HCM in Saudi is 0.2% (1:500 in the general population) [24]. Accordingly, we need to screen 20 patients with HCM of unknown origin aiming to identify one patient with FD. According to J Seo et al., the prevalence of FD in HCM population was 4.6% if at least one criterion was met using a screening method based on newly proposed criteria mentioned above [21], so that sample size could be adjusted to 217 HCM patients of unknown origin with at least one screening criterion to identify 10 FD patients with a 95% CI precision rate of 2.8% considering 5% alpha error plus an expected drop-out rate of 10% of ineligible data; thus a sample size of 240 patients will be appropriate to estimate FD prevalence in high-risk group.

2.3. Data Collection and Follow-up

The collected data from each patient will include: the socio-demographic profile, comorbidities, previous surgeries, family history of FD or any genetic diseases, currently used medications, treatment for FD (if applicable), laboratory data (if available), vital signs and physical examination findings, and the presenting symptoms. Data for both diagnosis (enzyme activity and DNA analysis genetic testing for male patients and this will be preceded by Lyso-GL3 test for female patients) and serious adverse events related to specific study procedure will be collected. A central laboratory (ARCHIMED Life Science Laboratories, Vienna) will provide DBS and genetic testing services to all sites in the study.

The data will be collected and managed by electronic case record forms (eCRF) using clinical data management system (CDMS). An independent contract research organization (CRO) will provide the study centers with the proper levels of access, grants, and privileges to eCRFs that will be filled by the investigator or the authorized designee. Data entry screen development, validation rules programming, and maintenance of the study database will be the responsibility of the independent CRO. The computerized handling of the data by the CRO may generate additional queries automatically identified through pre-programmed and tested validation rules. Validation rules will be detailed in the Data Validation Plan (DVP). In addition to automatic validation rules, medical review of data may generate further queries that will be raised on the system as well. Site staff will be responsible for resolving automatic and manual queries by confirming or modifying the data questioned through the Electronic data capture (EDC) system. Data collection and validation procedures will be detailed in an appropriate operational study manual.

2.4. Study Endpoints

The primary endpoint is the percentage of confirmed (positive result in enzyme assay test and genetic testing) FD subjects. Secondary endpoints include: (1) description of demographic and patient characteristics (including age, gender, risk factors, and ethnicity) in FD patients compared to other screened subjects, (2) therapeutic management of the disease in DBS test positive patients, and 3) frequency of comorbid conditions in patients with FD.

2.5. Statistical Methods

Descriptive analysis will be applied to analyze the collected data and will be performed by SPSS version 18 or higher. The analysis will be conducted on two populations:

(1) The eligible population: all subjects in high-risk group (patients with Hypertrophic Cardio-Myopathy of unknown cause) and fulfilling the inclusion and exclusion criteria, who came to the selected centers during the specified study period and signed an informed consent form; and
(2) The FD positive population: all patients from the eligible population for whom FD was diagnosed positive by DBS Test and genetic testing.

3. Results

Our protocol will be submitted for the approval from the responsible ethics committee prior to patients' inclusion. According to our sample size calculation, we expect at least 217 patients from different sites in Saudi Arabia to be enrolled to our study. The primary results will be the prevalence of FD described using counts and percentages with its 95% confidence interval (CI). This analysis will be descriptive and will be conducted on the eligible population. The secondary results will be: (1) patients' stratification as for the age, gender, risk factors of family history of FD and ethnicity of patients with confirmed FD, and will be compared to the rest of the population using Mann-Whitney-Wilcoxon tests for continuous parameters and Chi-square for categorical parameters. This analysis will be a comparative analysis and will be conducted between the FD positive population and the rest of the patients from the eligible population (Fabry disease negative population); (2) description of medical history and comorbidities using counts and percentages with its 95% CI. This analysis will be descriptive analysis and will be conducted on the Fabry disease positive population; (3) description of therapeutic management of patients using counts and percentages with its 95% CI. This analysis will be a descriptive analysis and will be conducted on the Fabry disease positive population.

4. Discussion

In the Arab patients collectively, genetic disorders are inherited through autosomal recessive pattern (around 64%), through autosomal dominant, and X-linked traits (26% and 6%, respectively) [26]. In light of a long Arabic tradition of marriage between relatives, many Arab countries demonstrate significant share of the highest rates of consanguineous marriages around the world. Interestingly, recent statistical data revealed that the percentage of first cousin marriages may range from 25% to 30% of all marriages in Arab countries. The major impact of consanguinity is revealed as a very high homozygotes rates for autosomal recessive genetic diseases [27].

Saudi Arabia is the second-largest Arab country that occupies about four-fifths of the Arab Peninsula, with an estimated population of 34,813,871 people in 2020 [19,25,28]. In respect to the Saudi community with a high rate of consanguineous marriages, it is characterized by a rapid population growth with an increased emergence of several genetic diseases among some families. With regards to LSDs, no accurate data for LSDs prevalence in Saudi Arabia has been reported [19]. In 1990, Ozand et al. had reported that King Faisal Specialist Hospital and Research Centre sees about 40 LSDs cases per year. Since the referral of patients was out of a population of 2-3 million people (in the central area of Saudi Arabia), this figure was mirroring a very high rate compared to other regions of the world [29].

In the United Arab Emirates (UAE), Al-Jasmi et al. reported a total of 119 confirmed LSDs cases between 1995 and 2010 (1995 and 2010 censuses in UAE were 2,415,090 and 8,549,988, respectively) [30]. In 2017, Al-Sannaa et al. revealed that LSDs prevalence in the Eastern Province alone of Saudi Arabia was 42.2 per 100,000 live births compared to 26.87 per 100,000, 12.9 per 100,000, 14 per 100,000, 12.25 per 100,000, and 25 per 100,000 live births in UAE, Australia, The Netherlands, Czech Republic, and Portugal, respectively [19].

With regards to FD, the investigators reported that FD male prevalence in the Eastern Province was 1.42 per 100,000 live births compared to 0.25 per 100,000, 0.86 per 100,000, 0.21 per 100,000, 0.52 per 100,000, and 0.21 per 100,000 live births in UAE, Australia, The Netherlands, Czech Republic, and Portugal, respectively [19]. Concerning the prevalence of FD among HCM patients, available data are limited and controversial [31]. Sachdev et al. reported that out of 79 men with late onset HCM (diagnosed at ≥ 40 years old), 5 patients (6.3%) were having low α-Gal A enzyme activity, and authors recommended that FD should be deemed in all cases of LVH with unknown cause [32]. However, other studies have been conducted on large cohorts of HCM European patients and reported that FD was the underlying cause in 0.5% - 1% of cases [31,33]. To the best of our knowledge, no data are available about the prevalence of FD in high-risk groups of HCM patients in Saudi Arabia or the Arab world to date.

The high prevalence of LSDs and FD in Saudi Arabia compared to other countries was anticipated since the Saudi community has a high degree of consanguinity [19]. In a study conducted by Warsy et al., they compared the prevalence of consanguinity in educated Saudi women to that of their parents. They aimed at assessing the impact of extensive educational activities that were targeting newer generations to inform them about the drawbacks of cousin marriages. Interestingly, the study results did not show any decrease in consanguinity prevalence; that is to say, it emphasized that marrying within the family is part of the culture in the Saudi community despite the increased awareness about the high susceptibility to certain genetic disorders [34].

From a different angle, FD is perceived as "a masquerader wearing several masks". It commonly imitates HCM since it manifests as LVH without outflow tract obstruction, alongside with nonspecific symptoms such as breathlessness, palpitations, dizziness, and syncope. These multi-directional manifestations often lead to delays between onset of symptoms and FD diagnosis, and accordingly, between FD diagnosis and initiation of therapy in the vast majority of patients [22,33,35]. In August 2013, Reisin et al. analyzed the "index patients" data extracted from the Fabry Outcome Survey (FOS) international registry [36]. The "index patients" is defined as the first patient diagnosed with FD from a family with several or no additional members registered in FOS [37]. The investigators revealed that the delay in diagnosis in all patients and in patients from Europe vs. the rest of the world did not improve in the period of 2001-2006 compared to 2007-2013 [36]. Nevertheless, early diagnosis is crucial to reduce mortality and morbidity, considering that cardiovascular complications are the leading cause of death in FD patients [38]. All these facts are emphasizing the need for precise data about FD prevalence, primarily in HCM patients, in order to pave the road for implementing effective strategies and screening programs which will support the early detection and management of the disease.

The recent evidence has encouraged a diagnostic approach involving a detailed history, family history, physical examination, clinical and biochemical findings, and genetic testing. In suspected FD males, α-Gal A enzyme activity should be measured, and enzyme activity < 1% is highly suggestive for FD diagnosis. In the case of FD females, the α-Gal A activity may be variable and can be normal even in the presence of clinically significant disease. Thus, confirmatory genetic testing is deemed mandatory for both males and females [38]. A recent prospective screening study was conducted by Sadasivan et al. on 266 patients with unexplained LVH using DBS testing as a screening tool. The investigators revealed that despite the challenges in FD diagnosis based on clinical presentation, the diagnosis could be made easily using DBS testing for both males and females. Moreover, an early FD diagnosis and ERT can reduce LVH before myocardial fibrosis is established, which is considered to be irreversible. The authors recommended

DBS testing as an effective screening tool in patients with unexplained LVH [39].

Declarations

- **Ethics approval and consent to participate:** The study's protocol is and will be submitted for approval by responsible ethics committee of the participating centers. Written informed consent is and will be obtained from every eligible patient prior to the sample withdrawal.

This study is conducted in accordance with the principles laid by the 18th World Medical Assembly (Helsinki, 1964) and all subsequent amendments.

This study is be conducted in accordance with the guidelines for Good Epidemiology Practice [US (1) & European, (2)]. All necessary regulatory submissions (eg, IRB/IEC) is performed in accordance with Saudi Arabia local regulations including local data protection regulations.

- **Consent for publication**: In case of any presentation of case reports, consent for publication will be obtained from that person, or in the case of children, their parent or legal guardian.
- **Conflicts of interests:** Aly Ezzat, Marwan ElBagoury, Sherif Roushdy, and Yahia Aktham are employees of Sanofi Genzyme and may hold shares and/or stock options in the company'.

Disclaimer

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