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Prevalence of Fabry Disease in Chronic Kidney Disease Patients in Saudi Arabia: A Multicenter, Cross-sectional, Study Protocol

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Abstract **Background:** Fabry disease (FD) is a form of lysosomal storage disorders (LSDs) that occurs due to reduction in α-galactosidase A (α-Gal A) activity which leads to accumulation of glycolipids in different body tissues. More than 25% of FD patients have chronic kidney disease (CKD) that eventually progresses to end-stage renal disease (ESRD). Renal biopsy is the gold standard of ESRD diagnosis; however, it is not performed in most cases. Since undiagnosed FD cases can be discovered in ESRD patients, we are conducting this multicenter, cross-sectional study to detect the prevalence of FD in the high-risk group (male patients with CKD stage 3–4 of unknown cause) in Saudi Arabia. **Methods:** This cross-sectional, multicenter screening study will include male patients with unknown cause CKD (stage 3 or 4) with comorbid conditions. A total of 580 patients or more will be included from different hospitals with specialty care centers for nephrology across Saudi Arabia from September 2019 to March 2021. Each patient will be assessed for the fulfillment of the eligibility criteria prior to inclusion. All eligible patients will be assessed by renal function parameters (including albumin creatinine ratio and estimated glomerular filtration rate), left ventricular mass thickness, and enzymatic activity by the dried blood spot 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 580 patients or more as determined by our sample size calculation. **Discussion:** The early introduction of enzyme replacement therapy has lessened the disease severity, risk of heart failure, and preserved renal functions. Early diagnosis of FD is a challenging process due to its rare presentation and multisystem affection nature. The incidence of FD in Saudi Arabia is higher than in many other countries in the Arab world and Europe. Also, published data about FD prevalence, comorbidities, and outcomes are very scarce in the literature.

Keywords Fabry Disease, Chronic Kidney Disease, Epidemiology, Saudi Arabia

1. Background

Fabry's disease (FD) is an X-linked lysosomal storage disorder caused by a mutation in the Galactosidase Alpha (GLA) gene, leading to a marked reduction in α-galactosidase A (α-Gal A) activity. This is followed by a progressive build-up of glycolipids in a myriad of cells and tissues around the body; primarily in the form of globotriaosylceramide (Gb_3), and its deacylated form globotriaosylsphingosine (lyso-GL-3). The accumulation of these compounds leads to multi-systemic effects and functional debilitations [1–3]. Hence, the nature of the disease to target multiple organs can be attributed to glycolipid accumulations in the kidney, eyes, heart, nervous system, vascular endothelium, and skin.

The incidence of FD in the general population is estimated to be around 1:117,000 [4], with the reported incidence in males being around 1/40,000 males [5]. The severity of FD manifestation depends on the sex, with males suffering from more severe phenotypes than females [6]. The heightened severity in males can be explained by the very low residual function of α-Gal A in males [5]. On the other hand, manifestations of FD in heterozygous females may be asymptomatic (except for corneal opacities) or exhibit similar severity to males due to lyonization or random X-chromosome inactivation in the female embryos [2,5].

The initial description of FD detailed the severe "classical" manifestation, which stems from absent or severely reduced α-Gal A activity (less than 1% of mean normal), followed by marked Gb_3 accumulation in vascular endothelial cells, cardiomyocytes, smooth muscle cells, and podocytes [1,7]. This is later translated into childhood or adolescent onset of symptoms; characterized by sweating irregularities (hyper/hypo-hydrosis), cornea verticillata, angiokeratoma, acroparesthesia, in addition to cardiovascular, cerebrovascular diseases, renal disorders, and eventually death [2). Renal involvement is frequently encountered in

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patients with FD, affecting nearly all men and the majority of the women with this rare disorder; according to the Fabry Outcome Survey, more than one-fourth of the FD patients had stage 3-5 chronic kidney disease (CKD), which ultimately progress to end-stage renal disease (ESRD) [8]. Besides, it has been shown that FD accounts for 0.0167% of all ESRD cases [9]. Although renal biopsy is the gold standard for the diagnosis of kidney diseases, patients are usually labelled by physicians as ESRD and assigned to dialysis or renal transplantation without obtaining a renal biopsy. Therefore, undiagnosed FD can be found in ESRD patients with other diagnoses of kidney disease [10].

Therefore, the primary objective of this study is to determine the prevalence of FD in the high-risk group (male patients with CKD stage 3–4 of unknown cause) in Saudi Arabia. The secondary objectives are to describe the demographic profile and clinical characteristics of patients with FD; to describe other co-morbid conditions in patients with FD; to record the therapeutic management of CKD in this high-risk group.

2. Methods

Study design and Participants

A multicenter, cross-sectional, study will be conducted through the period from September 2019 to March 2021 at different hospitals with specialty care centers for nephrology across Saudi Arabia; only hospitals with a fair experience with patients having a CKD stage 3-4 will be selected. Patients will be deemed eligible if they meet the following criteria: (1) male aged between18 and 50 years old; (2) patients with stage 3 or stage 4 CKD defined as glomerular filtration rate (GFR) of 30-44 mL/min/1.73m^2 and 15-29 mL/min/1.73m^2, respectively; (3) patients with no definitive aetiology of CKD; and (4) patients with one of the following: left ventricular hypertrophy, cerebrovascular accident/strokes in anamnesis, neuropathic pain, angiokeratoma, cornea verticillata, family history of FD, Hypohidrosis, and/or heat/cold intolerance. We will exclude diabetic patients, patients with ESRD (defined as GFR <15 mL/min/1.73m^2), and/or patients who have already undergone DBS testing. All eligible patients will be tested after signing the written informed consent.

Sample Size Calculation and Sampling Technique

The primary objective of this study is to determine FD prevalence in the high-risk group (patients with CKD stage 3-4 of unknown cause). The expected prevalence of FD worldwide is 1-5 patients in 10,000 subjects among the overall population [4]. On the other hand, the expected prevalence of the high-risk group with CKD is 5.7% [11]. Accordingly, we need to screen 570 patients with CKD stage 3-4 of unknown cause aiming to explore 1-5 patients with FD. Based on the TURKFAB Study results, 0.95% of CKD patients were diagnosed with FD, this sample size could be adjusted to 526 CKD patients to explore 5 FD patients with a 95% CI precision rate of 0.83% considering 5% alpha error plus an expected drop-out rate of 10% of ineligible data [12]. Thus, a sample size of 580 patients will be appropriate to estimate FD prevalence in the high-risk group.

Data collection

The following data will be collected from each patient: the socio-demographic profile, vital signs, anthropometric measures, history of comorbidities, family history of FD or other inborn errors of metabolism, presenting symptoms, the current treatment of included aCKD, concomitant medications, renal function parameters albumin/creatinine ratio and eGFR, left ventricular mass thickness, and findings of DBS screening. A central laboratory will provide DBS and genetic tests service to all sites in the study (ARCHIMED Life Science Laboratories, Vienna). All patient data (except the result of the investigation) will be collected in a single visit. Each enrolled patient will visit the investigator for a baseline visit. The investigators will complete the electronic Case Report Form (eCRF) soon after the baseline visit. Upon receiving the test results, investigators are required to report in the eCRF (within five days) that the results which will be provided to their respective patient.

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 according to the complete guidelines. 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, a manual/ 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 the operational study manual.

Study Endpoints

The primary endpoint is the prevalence of FD tested by enzyme activity DBS testing. Other endpoints include a description of demographic profile and patient characteristics, frequency of co-morbid conditions in patients with FD, and therapeutic management of CKD in this high-risk group.

Statistical methods

All data collected during the study will be analyzed in the appropriate descriptive analysis. Statistical analysis will be performed by SPSS version 18 or higher. The prevalence of FD will be described using counts and percentages with a 95% confidence interval. Other variables will be described using mean ± standard deviation for continuous variables

and counts for categorical variables. Patients' variables will be compared using Mann-Whitney-Wilcoxon tests for continuous parameters and Chi-square for categorical parameters. A probability value (P-value) of less than 5% will be considered significant.

3. Results

We will submit the study protocol to the responsible ethics committee for approval prior to patients' recruitment. Regarding the sample size calculation, we will include at least 580 male patients with unknown cause CKD from different hospitals and nephrology centers across Saudi Arabia. The yielded manuscript will present patients' demographics and other collected data.

4. Discussion

FD is a progressive, inherent, disorder that is characterized by a wide, heterogeneous, spectrum of phenotypes; such presentations can range from asymptomatic course to classic, severe, multi-organ involvements in adult males [2]. The critical importance of early diagnosis of FD cannot be overstated, especially following the introduction of enzyme replacement therapy (ERT); early introduction of ERT was linked to a significant reduction in symptomatic severity, durable preservation of renal function, and decrease in the risk heart failure and cerebrovascular events [7]. Besides, early diagnosis of FD pursued by early treatment can have a huge impact on the patient's quality of life [13]. However, owing to the multisystem nature of the disease, early diagnosis of FD is challenging, particularly in the case of atypical variants such as renal variants [14]. Male adults can present with the renal disorder as the sole manifestation of FD, renal involvement in FD can include proteinuria, crescentic glomerulonephritis, chronic renal insufficiency, and ESRD [15]. In the pivotal Japanese study by Nakao et al. [14], it was demonstrated that 1.2% of haemodialysis patients, who were previously diagnosed as chronic glomerulonephritis, had FD. Other reports showed FD prevalence rate of 0.6% [16]. In Saudi Arabia, the prevalence of CKD was reported to range from 5.7 – 9.4% amongst Saudi selected from primary health centers [17,18]. Other reports showed that nearly 20% of Saudi CKD patients had unidentified causes [19]. Recently, Salwa et al. [20], assessed the prevalence of FD among Saudi patients on haemodialysis. This prospective study was conducted in 3 major hospitals in the Kingdom of Saudi Arabia among ESRD patients. The prevalence of FD in this cohort was 4.8 per 1000 patients.

It is widely thought that Arab countries had a higher prevalence of genetic disorders, compared to other parts of the world. These high figures were postulated to stem from a higher incidence of congenital and genetic diseases in the Arab world compared to other parts of the world [29], high consanguinity rates which reach up to 60% in some regions, high prevalence of hemoglobinopathies, and metabolic disorders, relatively high maternal and parental age and lack of proper genetic screening [29–31] Reports from Saudi Arabia showed a higher incidence of FD, as compared to the global reports. The first retrospective study from Saudi Arabia reported that the incidence of FD was 5 per 100,000 live births [25].

Newborn screening programs (NSP) have been widely conducted for early detection of inborn error of metabolisms, including FD, at various parts of the world [7]. As previously stated, early detection of FD is of paramount importance for optimal outcomes of ERT [32]. The detection of FD is based on measuring alpha-galactosidase A enzyme activity in dry blood spot (DBS) using either tandem mass spectrometry (MS/MS) or fluorimetry [33]. Over the past two decades, the diagnostic utility of DBS-based enzymatic assays has dramatically improved and it is now widely considered a valid and reliable tool for the detection of lysosomal storage disease [34,35]. Moreover, DBS has the practical advantage in universal screening In Saudi Arabia, there are established national NSP since 2005 that cover inborn error of metabolism, endocrine disorders, congenital heart defects, and hearing loss [36]. A recent 7-years retrospective study in 139 hospitals reported a high rate of inborn error of metabolism in Saudi Arabia compared to other parts of the world [37]. However, the inclusion of LSD, including FD, in the program has not been discussed yet.

List of Abbreviations

CRO: Contract research organization
DBS: Dried blood spot
DVP: Data Validation Plan
eCRF: Electronic Case Report Form
ERT: Enzyme replacement therapy
FD: Fabry Disease
US: United States

Declarations

- **Ethics approval and consent to participate:** The study's protocol is and will be submitted for approval by the 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 being conducted in accordance with the guidelines for Good Epidemiology Practice [US (1) & European, (2)]. All necessary regulatory submissions (eg, IRB/IEC) are performed in accordance with Saudi Arabia's 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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