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FABRY DISEASE AMONG MAINTENANCE HEMODIALYSIS PATIENTS IN MOSUL

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ABSTRACT

Background: Fabry disease is an X-linked disorder causing lysosomal storage issues in males due to a deficiency in alpha-galactosidase A, causing inflammation and cellular necrosis. It affects endothelial cells and pericytes, primarily affecting males and heterozygous females. **Aim:** To determine the prevalence of Fabry disease among hemodialysis patients screened for Fabry disease in Mosul City. **Patients and Methods:** The study involved 93 patients with unknown end-stage kidney disease (ESKD) in Ibn-Sina Teaching Hospital and Al-Salam Hospital in Mosul, Iraq. Patients were measured for enzyme activity and lyso-Gl3 using a negative cutoff value. Genetic testing was conducted for all female patients and those with equivocal results in males. Positive results were defined as positive enzyme activity and lyso-Gl3 tests. **Results:** 36.6% of the 93 patients included were females and 63.4% were males. The average age of the male participants was 31.11 ± 16.79 years, whereas the average age of the female participants was 25.11 ± 16.90 years. P = 0.101 indicates that there was no statistically significant difference between the two groups. Just 4 patients tested positive for Fabry disease; all four of these patients were female. Of the 89 patients tested negative for the condition. The four individuals that tested positive were all female and had positive results for lyso-GL3, enzyme activity, and genetic research. **Conclusion:** Fabry disease affecting female patients undergoing maintenance hemodialysis in Mosul, is more prevalent in females than males, necessitating further research and a multidisciplinary approach for accurate diagnosis and treatment.

KEYWORDS: Fabry Disease, Hemodialysis.

INTRODUCTION

Fabry disease is an X-linked disorder considered a lysosomal storage disease that results from a deficiency of the enzyme alpha-galactosidase A, which causes the accumulation of glycosphingolipids, particularly globotriaosylceramide (Gb3).[1] The intracellular accumulation of Gb3 within the lysosome leads to subsequent inflammation and cellular necrosis.[2] The prevalence of Fabry disease ranges from 1:8,454 to 1:117,000 in males.[3-5] Fabry disease is often underestimated due to the rarity of the condition and its nonspecific clinical manifestations.[5,6] Misdiagnosis can sometimes occur[7], and some patients present with the disease later in life.[8]

Fabry disease affects males more frequently than females, though females can still develop the disease, typically in a milder form and with a later onset.[9,10] The disease is now recognized to be more common than previously thought, with classical disease prevalence estimated at 1:22,000 to 1:4,000[8-11] and atypical variants at 1:6,000 to 1:4,000 in females and 1:1,000 to 1:3,000 in males.[8, 11-15]

The most common mutation associated with Fabry disease is A143T.[16] The deficiency of alpha-galactosidase A below the required level to catalyze Gb3 results in its accumulation in the lysosome, leading to cell death.[16-19] The severity of clinical manifestations is determined by the level of enzyme activity.[2, 20] The most commonly affected cell types include endothelial cells, vascular smooth muscle cells, and pericytes.[3, 19, 21]

Fabry disease can lead to end-stage kidney disease (ESKD).[22] Renal involvement can affect glomerular, tubular, and interstitial cells.[23] Fabry disease follows an X-linked mode of inheritance, and the mutation of the alpha-galactosidase A gene on the long arm of the X

chromosome (Xq22.1) predominantly affects males, who exhibit more severe and earlier clinical presentations. Heterozygous females can also be affected, with varying degrees of severity due to skewed non-random X-chromosome inactivation.[9, 24-26] Thousands of variants can affect the alpha-galactosidase A gene, resulting in enzyme deficiency.[27, 28]

Clinically, renal manifestations include an insidious onset of proteinuria, primarily subnephrotic, microscopic hematuria, and ESKD occurring around the third to sixth decade of life.[28] Cardiac manifestations can range from left ventricular hypertrophy, heart block, arrhythmia, and myocardial infarction.[29] Neurological presentations may include hypohidrosis, acral paresthesia, hemiparesis, vertigo, dysarthria, nystagmus, and ataxia.[30-32] Skin manifestations include angiokeratomas located on the lower trunk, buttocks, hips, and upper thighs.[33] Corneal verticillata, visible in both males and females, can be observed through slit-lamp examination as white radiations from the center of the cornea, giving a whorl-like discoloration.[34] The diagnosis of Fabry disease is based on clinical features, slit-lamp examination, measurement of alpha-galactosidase A enzyme activity in the serum, leukocytes, fibroblasts, and tissue biopsy. A positive test is diagnostic in males, while genetic testing is indicated for female patients and borderline male cases.[34] Treatment with recombinant alpha-galactosidase A enzyme (alpha-Gal-A) has revolutionized the management of Fabry disease.[35]

AIM OF THE STUDY

To determine the prevalence of Fabry disease among hemodialysis patients screened for Fabry disease in Mosul City.

PATIENTS AND METHODS

This observational study was conducted from January 2021 to September 2023 in the hemodialysis units of Ibn-Sina Teaching Hospital and Al-Salam Hospital in Mosul, Iraq. The total number of patients included was 93, with 60 males and 33 females.

Inclusion criteria included patients with end-stage kidney disease (ESKD) of unknown cause. Exclusion criteria included secondary causes of ESKD such as diabetes, hypertension, immunological diseases, cystic kidney disease, and a history of nephrotoxic medication use.

Alpha-galactosidase A enzyme activity was measured for all patients, with a negative cutoff value >2.8 micromol/liter/hour, and lyso-Gl3 as indicated by the referral laboratory. Genetic testing was conducted for all female patients and in cases of equivocal results in males. All tests were performed at MEDICAL LABORATORY ARCHIMED Life Science in Vienna, Austria (E-mail: info@archimed.com).

Positive results were defined as follows: for male patients, a positive enzyme activity test and lyso-Gl3 test (optional, based on referral laboratory) supported by genetic study; for all females and cases with equivocal results in males, positive genetic study results were required.

RESULTS

The distribution of the studied sample according to sex is shown in Figure 1. Among the 93 patients included, 63.4% were male and 36.6% were female.

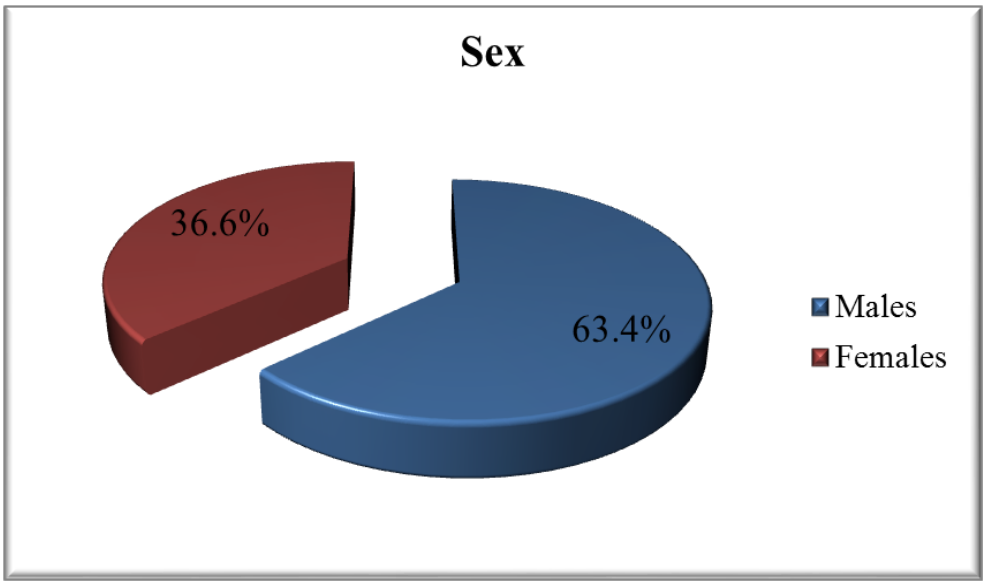

Figure 1: Distribution of the studied sample according to sex.

The comparison of the mean age of the patients by sex is detailed in Table 1. The mean age of the males was 31.11

± 16.79 years, while the mean age of the females was 25.11 ± 16.90 years. The difference between the two groups was not statistically significant (p = 0.101).

Table (1): Comparison of the mean age of the patients according to sex.

Age in years Mean ±SD	Males (n=59)	Females (n=34)	p-value*	95% Confidence Interval of the Difference	
				Lower	Upper
	31.11±16.790	25.11±16.896	0.101	-1.196	13.198
*Independent t-test for two means					

The characteristics of the studied sample according to sex are shown in Figure 2. The majority of patients were negative for Fabry disease (89 patients), while only four patients were positive; all of these positive patients were female.

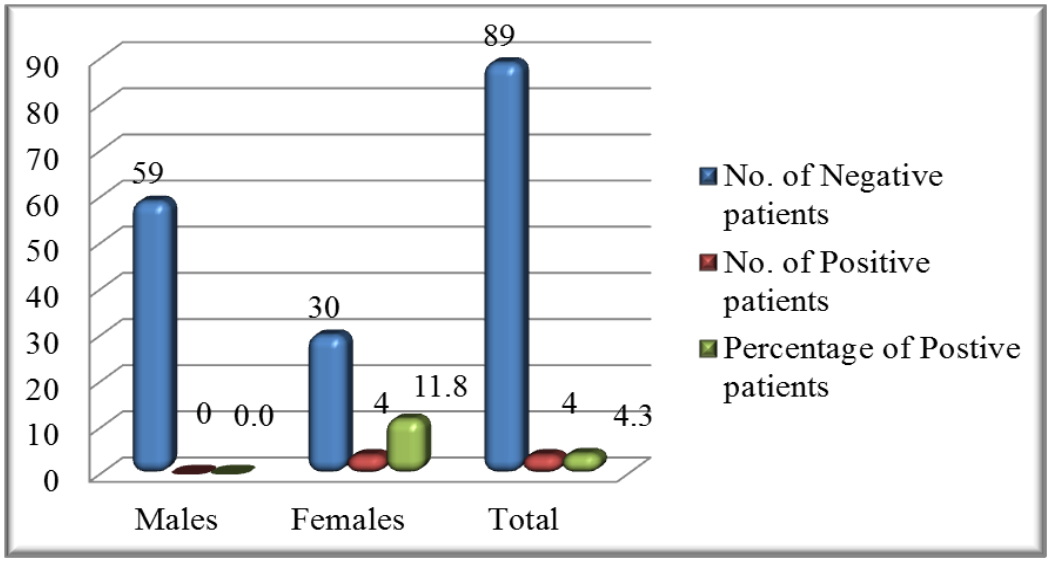

Figure 2: Characteristics of the studied sample according to sex.

The characteristics of the positive patients for Fabry disease are detailed in Table 2. All four positive patients were female and tested positive for enzyme activity, lyso-GL3, and genetic studies.

Table (2): Characteristics of positive patients for Fabry disease.

Positive patients	No.	%
Male patients	**0**	**0.0**
Female patients	**4**	**100.0**
Enzyme activity	**4**	**100.0**
Lyso-GL3	**4**	**100.0**
Genetic study	**4**	**100.0**

DISCUSSION

Fabry disease can affect both males and females, as it is genetically inherited, although the symptoms and their severity may differ significantly between the sexes.[36] The current study found that females were affected more than males, which contrasts with some studies showing a higher prevalence of cardiac outcomes in males with Fabry disease compared to females.[37] However, more research is needed to draw definitive conclusions about the sex-specific impact of the disease on cardiac outcomes.[38]

It is crucial to note that generalizations may not accurately represent each individual patient's experience with Fabry disease, as symptoms and severity can vary widely.[39]

In this study, males were older than females. Age at diagnosis for Fabry disease can vary significantly and is influenced by factors such as gender and disease severity. While the exact age at diagnosis can be challenging to pinpoint, a pattern of diagnosis in young adulthood is common. For example, one study reported the mean age of diagnosis for male patients to be around 21.9 years[40], while female patients were diagnosed

approximately a decade later.[21] The disease can also manifest earlier in males, with some developing left ventricular hypertrophy as early as 20 years of age.[21] In some cases, Fabry disease can be diagnosed as early as 6 years of age[41], though symptoms at this early age might be less common. In the context of maintenance hemodialysis care, the mean age of patients with Fabry disease differs between males and females, with males experiencing symptoms and diagnosis at an earlier age. According to one study, the mean age at diagnosis for self-identified Black individuals and White individuals was 40 years and 45.5 years, respectively.[42] However, specific information on the mean age at diagnosis for patients with Fabry disease undergoing maintenance hemodialysis is not readily available. Studies have shown that male Fabry patients often experience an earlier onset of the disease. For instance, in a large cohort study of Fabry cardiomyopathy, the mean age of symptom onset was 9 years for males.[43] The influence of sex and disease phenotype on the occurrence of cardiac events in Fabry disease has also been explored, with some studies finding that female Fabry patients have a later onset of the disease, with a median age at symptom onset of 13 years.[43]

In maintenance hemodialysis management for patients with Fabry disease, monitoring Lyso-GL3 levels is essential. This biomarker, also known as Lyso-Gb3, is an effective indicator for diagnosing Fabry disease and assessing treatment response.[46-48] Elevated levels of Lyso-GL3 in patients with Fabry disease make it a valuable marker for distinguishing between classic and non-classic forms of the disease, as well as for monitoring disease progression and treatment response.[46-48]

Fabry disease is a genetic disorder caused by mutations in the GLA gene, affecting multiple systems in the body, including the heart and kidneys. Symptoms can vary widely among patients and may be misdiagnosed due to their similarity to other conditions. In maintenance hemodialysis, it is important to consider Fabry disease in patients with unexplained conditions, as dried blood spot (DBS) testing can help detect the disease in potentially affected individuals.[49] Fabry cardiomyopathy can significantly impair heart function, and patients may require specific management strategies.[50]

Screening for Fabry disease is recommended for all female patients due to its X-linked inheritance.[51] Gene sequencing is the preferred method for screening, with enzymatic activity testing as a secondary measure. A systematic review on screening for Fabry disease highlights the importance of identifying individuals with genetic variants of unknown significance.[52]

Currently, enzyme replacement therapy (ERT) and chaperone therapy are the primary treatment options for Fabry disease.[37,53,54] Future treatment options may include gene therapy, which is still in preclinical stages.[54] In terms of hemodynamic management, it is advisable to follow established guidelines and avoid specific anesthesia agents, such as melphalan, that might exacerbate Fabry symptoms.[55]

Modern diagnostics can help identify and manage Fabry disease in patients, potentially improving prognosis and quality of life. However, the complexity of the disease and the need for specialized testing underscore the importance of a multidisciplinary approach in its management.[37]

CONCLUSION

This study highlights the prevalence and demographic characteristics of Fabry disease among patients undergoing maintenance hemodialysis in Mosul. The findings reveal that Fabry disease disproportionately affects females in this cohort, contrasting with some existing literature that indicates a higher prevalence of cardiac outcomes in males. This discrepancy underscores the need for further research to elucidate sex-specific differences in disease presentation and outcomes.

The study confirms that Fabry disease can manifest at an early age, with males often presenting symptoms earlier than females. Monitoring biomarkers such as Lyso-GL3 is crucial in diagnosing and managing the disease, as it provides valuable insights into disease severity and treatment efficacy. The variation in age at diagnosis and symptom onset between sexes highlights the importance of tailored diagnostic and management approaches.

Screening for Fabry disease should be a standard practice in patients with unexplained renal conditions undergoing hemodialysis, particularly due to its X-linked inheritance pattern and the availability of effective diagnostic tools. Gene sequencing and enzyme activity tests are essential for accurate diagnosis and treatment planning.

Enzyme replacement therapy and chaperone therapy remain the cornerstone of treatment, with emerging gene therapy approaches showing promise for future management. The findings emphasize the necessity of a multidisciplinary approach to manage Fabry disease effectively, considering its complex interplay with multiple organ systems and the potential for severe complications.

Overall, this study contributes to the understanding of Fabry disease prevalence and management in a specific patient population and underscores the need for ongoing research to refine diagnostic and therapeutic strategies.

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