Original Paper

Screening for Fabry Disease in Kidney Disease: a Cross-Sectional Study in Males and Females

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Key Words

Brazil • Fabry disease • Kidney diseases • Prevalence • Screening

Abstract

Background/Aims: Evaluate the prevalence of Fabry disease in men and women with kidney disease; and observe the presence and importance of the main signs and symptoms in patients with kidney disease. **Methods:** A cross-sectional analysis of secondary data from a multicenter project of Clinical and Epidemiological Analysis of Fabry Disease in 854 Dialysis Centers. A total of 36,442 patients underwent the questionnaire and algorithm; of them, 28,284 were discarded for not presenting signs and symptoms of Fabry disease, while the other 8,087 submitted to blood collection and analysis. All participants signed a Free and Informed Consent Form and a questionnaire was applied. The questionnaire data were analyzed using a computerized algorithm. This program/algorithm analyzes and separates patients into: discarded, patients unlikely to have Fabry disease; suspect, patients who submitted to blood collection. The blood of suspect patients was collected on filter paper for enzyme measurement and genetic testing. A descriptive data analysis was performed and the likelihood ratio was determined. **Results:** The general prevalence was 0.19% and after use of algorithm was 0.87%. Although more men were screened (59.3%), the prevalence was higher in women (65.1%). The most prevalent signs and symptoms were: heart disease (60.6%), decreased or lack of sweating (42.3%), heat and cold intolerance (28.2%), and pain crises spreading throughout the body (26.8%). **Conclusion:** The prevalence was higher in women, and the most prevalent symptom was heart diseases.

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Introduction

Fabry disease (FD) is a lysosomal storage disease, which is a genetic, hereditary, chronic, progressive, and multisystem diseases linked to region Xq22 of the X chromosome. FD is

an inborn error of the glycosphingolipid metabolism. Acid α -galactosidase A (α -Gal A) deficiency interferes with the decomposition of globotriaosylceramide (Gb3), an adipose-like substance. Gb3 accumulates in lysosomes throughout the body and affects the function of several organs [1-3].

This can be an important problem in body parts that depend on small blood vessels for vascularization since they can become obstructed by the accumulated Gb3. The areas most affected by occlusion of the small blood vessels are the kidneys, heart, nervous system, brain, and skin, leading to several important signs and symptoms and high morbidity and mortality rates. Because FD affects only a very small percentage of the general population, it also received another important classification of being a rare or orphan disease [1-3]. Its estimated incidence worldwide is 1:40000 and 1:117000 [4].

In men, FD can be diagnosed by low α -Gal A activity in the plasma and/or leukocytes. In women, the measurement of α -Gal A activity does not always allow FD identification in heterozygous females, in which cases diagnosis through identification of the gene mutation by genetic testing is advised [4].

One of the main consequences of FD is chronic kidney disease (CKD), a slow and progressive loss of kidney function based on three components: anatomical or structural (kidney damage markers), functional (glomerular filtration rate [GFR]), and temporal (abnormalities present for > 3 months). Carriers of CKD are all individuals who, independently of the cause, present with a GFR < 60 mL/min/1.73 m² or GFR < 60 mL/min/1.73 m² and the presence of at least one renal parenchymal damage marker (proteinuria) for at least 3 months [5, 6]. This is almost always discovered late through abnormal laboratory analyses instead of symptoms [4].

The first symptoms of FD usually appear during the first decade of life and consist of acroparesthesia, abdominal pain, postprandial diarrhea, and postprandial pain. Angiokeratoma is the most characteristic clinical symptom. Hypohydrosis is caused by the accumulation of Gb3 in the sweat glands and associated blood vessels [3, 4, 7-9]. Several other organs can be affected, such as the cardiovascular system [4, 7-9], hearing system, circulatory system, visual system, and urinary system [3, 4, 7-9].

Most studies reporting FD prevalence studied populations with CKD receiving dialysis treatment and screened only men in risk populations without the use of specific tools [10-15].

The aims of the present study were to evaluate the prevalence of FD in men and women with kidney disease receiving treatment in dialysis centers in Brazil and observe the presence and importance of the main FD symptoms in this population.

Materials and Methods

The study received approval from the human research and ethics committee (number 18029513.0.0000.5244) and adhered to the principles of the Declaration of Helsinki.

The present study consists of a cross-sectional analysis of secondary data from the multicenter Clinical and Epidemiological Analysis of Fabry Disease in Dialysis Centers in Brazil - Project Kidney Fabry Brazil. A total of 854 dialysis centers located throughout Brazil were included in the study (Fig. 1). A questionnaire was provided to 36,442 patients who signed a Free and Informed Consent Form. The participating centers received no financial compensation. The data were introduced into a computer program. When patients were selected, their blood was collected on filter paper for enzyme measurement and genetic testing.

The questionnaire of the KIDNEYFABRYBRAZIL Datagenno© project contains the following data:

Participating Center Data: Company name, Full address, National Register of Legal Entity (Cadastro Nacional de Pessoa Jurídica - CNPJ), Responsible doctor, and Responsible for the medical records Patient Data: Number and name initials, Age, Birth date, Sex, Full address, Contact telephone number Signs and symptoms: Obesity, Diabetes Mellitus and time of diagnosis, Systemic Arterial Hypertension and time of diagnosis, Rheumatoid Arthritis with positive or negative rheumatoid test, Polycystic Kidney, Berger Disease

Fig. 1. Participating dialysis centers (854).

Other Symptoms: Do you have renal disease? Chronic renal insufficiency? How long have you been receiving dialysis? Other renal diseases: Family history of renal disease? Father, Mother, Brother, Sister, Uncle, Aunt, Grandfather, Grandmother. Which renal disease? Presents proteinuria on a 24-hour exam? Presents high creatinine? Presents cardiac disease, left ventricular hypertrophy, or other cardiac diseases? Family history of cardiac disease? Father, Mother, Brother, Sister, Uncle, Aunt, Grandfather, Grandmother? Which cardiac disease? Presents precordialgia and/or palpitations, Recurrent fever without apparent cause, heat and cold intolerance, intolerance to physical exercise, burning feeling in hands and feet, unilateral, bilateral, pain crises spreading throughout the body, numbness or tingling sensation in hands and feet, unilateral, bilateral, decrease or absence of sweating, increased sweating, depression? Family history of depression or behavioral disturbances? Father, Mother, Brother, Sister, Uncle, Aunt, Grandfather, Grandmother? Hearing problems, uses diuretics (hydrochlorothiazide – Lasix)? Since when? Abdominal pain after eating, diarrhea after eating, cerebrovascular disease (AVC or transient ischemic attack)? Family history of cerebrovascular disease? Father, Mother, Brother, Sister, Uncle, Aunt, Grandfather, Grandmother? Cornea verticillata, with ophthalmologist report, without ophthalmologist report? Angiokeratoma, with dermatologist report, discovered through biopsy?

After applying the questionnaire, the data were run through the algorithm and separated into discarded, suspect, and doubtful groups. Discarded: no signs or symptoms indicating FD; suspect: signs and symptoms indicative of FD; doubtful: the algorithm results were doubtful, requiring human intervention to classify them as discarded or suspect. Blood from suspect patients was collected onto filter paper for DNA analysis and measurement of α -Gal A activity by tandem mass spectrometry, a screening technology with

Table 1. Population with kidney disease by age category

		Total	Positive	Negative	Discarded
Age group	n	36,442	71	8,087	28,284
≤44 years	%	25.7	56.3	45.2	20.1
45-55 years	%	23.5	26.8	28.4	22.1
56-66 years	%	26.3	12.7	18.7	28.5
>66 years	%	24.5	4.2	7.6	29.4
Average	%	54.81	41.42	46	57.36

sensitivity and specificity of 96%. It is not as sensitive as a biochemical or specific genetic test, and genetic counseling is recommended for patients and other relevant family members. Enzymatic activities < 2.6 μmol/L/h were considered low.

The FD prevalence was calculated, a descriptive data analysis was performed, and likelihood ratios of signs, symptoms, and comorbidities were calculated.

Results

Of the total 36, 442 patients screened using the Datagenno© questionnaire from the KIDNEYFABRYBRAZIL project, 28, 284 were discarded, 8, 087 were tested, and 71 tested positive for FD (Fig. 2).

The overall average age of the study participants was 54.81 years, while that of the FD-positive patients was 41.2 years (Table 1). Regarding sex, 40.2% of the overall study participants and 63.4% of the FD-positive patients were female (Table 2). Regarding renal insufficiency cause, 7.3% of the individuals had polycystic kidney, while 0.2% had Berger disease. Of the patients with kidney disease and FD, 60.6% had cardiac diseases, 42.3% had decreased or absent sweating, 28.2% had heat and cold intolerance, 26.8% had a pain crisis spreading throughout the body, 25.4% had cerebrovascular disease, 23.9% had a burning sensation in the hands and feet, 23.9% had postprandial abdominal pain, 22.5% had numbness in the hands and feet, 16.9% had recurrent fever, 12.7% had angiokeratoma, and 7% had eye diseases.

Regarding the likelihood ratio between patients with and without FD, the signs, symptoms, and comorbidities presenting

Fig. 2. Screening fluxogram.

Table 2. Population with kidney disease by gender

		Total	Positive	Negative	Discarded
Gender	n	36,442	71	8,087	28,284
Female	%	40.2	63.4	47.2	38.2
Male	%	59.8	36.6	52.8	61.8

Fig. 3. Likelihood ratio – positive and negative Fabry results.

a significant likelihood ratio (LR > 1) were: angiokeratoma (14.1), recurrent fever (3.8), postprandial abdominal pain (3.1), decreased or absent sweating (2.3), cornea verticillata (2.2), pain crisis spreading throughout the body (1.7), hearing problems (1.6), heat and cold intolerance (1.4), rheumatoid arthritis (1.1), and depression (1.1) (Fig. 3).

Discussion

The aims of the present study were to evaluate the prevalence of FD in men and women receiving treatment in dialysis centers in Brazil and observe the presence and importance of the main symptoms of FD in this population.

The FD prevalence estimated in the present study was 0.19% and after algorithm was considered, prevalence increased to 0.87%, was close to that previously reported [10-20]. Studies performed in Brazil by Marinho et al. in 2007 reported an FD prevalence of 0.52% for the city of Natal in the state of Rio Grande do Norte and Vale et al. found 0.57% in the state of Piauí [13, 14]. Porsch et al. observed a prevalence of 0.36% in the state of Rio Grande do Sul in 2013 [15]. These studies only screened men and used no tools to select higher-risk cases [13-15]. Kabalan et al. screened men receiving hemodialysis in Lebanon in 2013 and found

nine FD cases among 275 patients [12].

Saito et al. (2015) performed a national study of 8,547 patients in Japan and found a prevalence of 0.02% [19]. A more encompassing study was performed in Italy that investigated the presence of rare genetic disorders in general in kidney transplant recipients and found a prevalence of 4.32% but only one case of FD [20].

Of the kidney disease patients screened, 25.7% were up to 44 years old, 49.8% were 45–66 years old, and 24.5% were > 66 years old with an overall mean age of 54.81 years. According to the Brazilian dialysis census, 24% of dialysis patients are up to 44 years old, 42.2% are 45–64 years, and 33.7% are > 65 years old, showing age equivalence [21]. In addition, most screened patients were men (59.3%), which is in accordance with the 58% reported in the Brazilian dialysis census [21].

Among the cited studies, the screening criteria varied, were usually not described, and were based on clinical suspicion by the assisting doctors. In other studies, the dialysis patients were screened without defined criteria. A recent report by KDIGO reinforces the importance of screening and early diagnosis for achieving better treatment results [22].

It is evident in published studies that women have been overlooked in FD screenings [10–15]. However, we found a higher FD prevalence in women. Even though more men were screened, there were more women with FD in the population. This is in contrast with previous reports that FD is more prevalent in men [8, 10–15]. We believe that women are not screened because the diagnostic test for women consists of a more expensive DNA analysis versus that in men, an enzyme measurement that is less expensive [4].

Regarding CKD, after category three, complications inherent to the disease begin appearing. These complications affect several organs and systems and result in multiple non-specific symptoms that can be easily confused with other pathologies [5]. Similarly, FD presents non-specific symptoms that may overlap with CKD, making diagnostic suspicion difficult [1, 4, 7, 8, 19].

The fact that arterial hypertension and diabetes mellitus were frequent in patients with FD is probably related to the fact that these pathologies are the most frequent causes of CKD [23]. Diabetes mellitus presents multiple symptoms that may overlap with those of FD and result in diagnostic confusion [23].

Regarding symptoms, it should be highlighted that some signs and symptoms are not part of the usual anamnesis and should be included when CKD patients are evaluated, namely heat and cold intolerance, burning sensation in the hands and feet, decreased or absent sweating, all of which were frequently observed in the patients with CKD and FD in our study [3, 4, 7, 8, 19, 24]. Depression symptoms are frequent in patients with FD [3, 7]. In the present study, the overall prevalence of depression was 28.2%. Angiokeratoma and cornea verticillata are pathognomonic symptoms of FD [1, 2] and were present in 12.7% of the population with renal disease and 7% of the population with FD in the current study.

The screening of family members is also required. The importance of early diagnosis to begin treatment as early as possible has been reported [17, 25–28]. Zarate and Hopkin (2008) reported that there is no known ethnic predisposition for FD but that there are some regional pockets with higher FD incidence, including Nova Scotia in Canada and Virginia in the USA [4].

A limitation to the present study is the fact that the questionnaire was self-reported and administered by several different researchers. Because of the low FD prevalence, it would be very expensive to test all patients to obtain a false negative rate. Another limitation is about the absence of the ethnicity data, considering it is known that Brazil has one of the most heterogeneous populations in the world.

FD is a rare disease with a low prevalence and is difficult to diagnose, but all patients should be treated equally. As stated in the Brazilian Federal Constitution, health is a right of all the people and a duty of the State. Although it is a rare disease, it should not be forgotten by the concerned medical authorities [29].

Conclusion

We observed FD prevalence 0.19% was close to the previously reported values. When the questionnaire and algorithm were considered, the FD prevalence increased to 0.87%. We also found a higher FD prevalence in women. We hypothesized that the finding of the highest prevalence in women is probably due to the non-screening of women in other studies, since in X-linked heirs, a higher prevalence in men is expected. Another possibility is that men present more severe forms and there is a negative selection bias in this population on dialysis, with men with severe phenotypes having died before initiating replacement renal therapy.

The highest likelihood ratios were observed for the following signs/symptoms/comorbidities: angiokeratoma 14.1, recurrent fever 3.8, postprandial abdominal pain 3.1, decreased or absent sweating 2.3, and cornea verticillata 2.2.

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Disclosure Statement

None.

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