Original Article

Screening for Fabry disease in patients on Hemodialysis

Gaurav Batta, R. Vishnuprasad[1], Anshita Batta[2], D. Santhanalakshmi[3], Aradhana Dwivedi[4]

Department of Nephrology, Command Hospital, [2]Clinical Validator, Regional Centre ECHS, Chandimandir, Haryana, [1]Department of Community Medicine, Military Hospital, Jodhpur, Rajasthan, [3]Department of Physiology, Sri Venkateshwaraa Medical College, Hospital and Research Center, Puducherry, [4]Division of Clinical Genetics, Department of Paediatrics, Army Hospital Research and Referral, New Delhi, India

Abstract

Background: Fabry disease is an under-recognized X-linked lysosomal storage disorder characterized by the accumulation of trihexosylceramides in multifarious tissues, leading to end-organ damage, including progressive renal failure. Antecedent screening studies worldwide have shown inconsistent prevalence in the hemodialysis population. We conducted this study to screen for Fabry disease in patients undergoing dialysis at a tertiary care hospital. **Materials and Methods:** All patients undergoing dialysis were screened with a gal assay using dried blood spots (DBS) on filter paper using the fluorescence method. Patients with positive DBS test results were further tested for underlying mutations. **Results:** A total of 112 patients (64.3% males and 35.7% females) on dialysis were screened. Nineteen patients (13 males and 6 females) were found to have low enzyme activity on DBS. Further mutation analysis confirmed that one female patient had Fabry disease. The mutation detected was a heterozygous missense variation in exon 7 of the GLA gene, which resulted in the amino acid substitution of histidine for arginine at codon 363 (p.Arg363His). Subsequent screening of the family members revealed that the son of the patient was asymptomatic and carried the same genotypic mutation. Genetic counseling was performed, and enzyme replacement therapy was offered to both patients. **Conclusions:** Fabry disease remains underdiagnosed, especially in high-risk populations such as those undergoing dialysis. DBS is a convenient and effective screening tool for Fabry disease. Facilities should be augmented for similar screening studies in the dialysis population.

Keywords: *Dialysis, Fabry disease, genetic diseases*

Introduction

Chronic kidney disease (CKD) is a gradually progressive disease that has serious social, financial, and health implications. When a nephrologist declares a patient suffering from end stage renal disease (ESRD), it is devastating news for the patient and his family. There is a significant proportion of patients that are initiated on hemodialysis (HD) without a firm diagnosis. The two major registries the European Renal Association–European Dialysis and Transplant Association[1] and the United States Renal Data System[2] have mentioned that 27% and 22% of patients respectively are put on dialysis with the basic diagnosis as unknown.

Inherited kidney diseases (IKDs) remain largely undiagnosed[3] in the adult population, being more common in the pediatric age group. Adult nephrologists are not perceptive enough to suspect and in turn, diagnose genetic diseases effectively. Although the incidence of individual IKD may be low but collectively as a cohort, they weigh about 10% of adult patients on HD[4] and majority of pediatric patients on HD.

Fabry disease is one of the IKDs, which is an under-recognized, X-linked recessive, lysosomal storage disorder and results from deficient activity of the enzyme a-galactosidase (a-Gal A). The first description of this disease was given by Fabry[5] and Anderson[6] in 1898. Since then, the understanding of this disease has evolved from being a mere dermatological disorder to a progressive multisystem disease.

The incidence[7] of Fabry disease has been estimated at one in 40,000 to one in 117,000 and there is no ethnic or racial predisposition. Various studies[8,9] worldwide have reported variable prevalence of Fabry disease in high-risk populations such as dialysis. There are no studies from India on its prevalence. Depending on the group of patients screened, the range of prevalence has been 0.2%–1.2% in patients on

How to cite this article: Batta G, Vishnuprasad R, Batta A, Santhanalakshmi D, Dwivedi A. Screening for Fabry disease in patients on hemodialysis. Int J App Basic Med Res 2024;14:187-92.

Submitted: 10-Apr-2024
Revised: 11-Jul-2024
Accepted: 05-Aug-2024
Published: 24-Aug-2024

Address for correspondence:
Dr. Gaurav Batta, Command Hospital, Chandimandir, Haryana, India. E-mail: gauravbatta99@gmail.com

Access this article online

Website: https://journals.lww.com/IJAB

DOI: 10.4103/ijabmr.ijabmr_161_24

Quick Response Code:

HD[10] and as high as 3%–4% in adult male patients with cryptogenic stroke[11] and unexplained LVH.[12]

The deficiency of the enzyme a-Gal A leads to the accumulation of its substrates, typically Globotriaosylceramide (Gb3) and galactosylceramide in vast variety of tissues lysosomes.[13] This multifarious deposition of Gb3 leads to cellular dysfunction and fibrosis at various levels and leads to protean manifestations and multisystem involvement[14] of predominantly cardiovascular, renal, and central nervous systems.

The X-linked inheritance results in broadly three typical clinical scenarios of the disease. The Classical disease, being substantially more common in males[15] presents early in childhood with features of acroparaesthesias, angiokeratomas, hypohidrosis, characteristic corneal and lenticular opacities, and proteinuria. In other scenarios of heterozygous females, symptoms may vary from either asymptomatic to a less severe pattern or full-blown disease. Third scenarios is of late-onset variants of either cardiac or renal variants in which the presence of residual enzyme activity[13] of more than 5%–10% delays phenotypic expression.

The gene coding A Gal A has been well studied[16] and localized to chromosomal region Xq22. To date, more than 1000 variants have been described[17] with most mutations being restricted within a single family and de novo mutations are rare.

The diagnosis in male patients speculated to have Fabry disease is confirmed by measuring a gal activity assay[18] either using plasma samples, peripheral blood leucocytes, or a simple dried blood spot (DBS). In female patients, measuring enzyme activity can be unreliable;[19] hence, gene sequencing and identification of disease-causing mutation are required to confirm the diagnosis.

Out of several treatment approaches,[20] the one that is widely available is the enzyme replacement therapy to be given as biweekly infusions lifelong. It is ultra-expensive and formidable therapy for many.

Materials and Methods

This study was conducted for 2 years, at the dialysis center of a tertiary care hospital in North India. The hospital caters to defense personnel and their dependent family members, from various districts in Punjab, Himachal Pradesh, and Jammu and Kashmir states. The department provides comprehensive nephrology care to CKD patients at all stages of CKD. The patients are offered renal replacement therapy as and when they reach ESRD. The choice of RRT such as dialysis (HD or peritoneal dialysis) and renal transplantation is discussed with each patient before initiating the therapy. Kidney transplant is not being done at this center and patients who are willing and have prospective donors are referred to other transplant centers for further management.

This center has a workload of approximately 60 patients on regular HD and every month 5–7 New patients are initiated on HD. The aim was to screen all patients for Fabry disease and identify its potential associated factors. This was an observational, prospective study, undertaken on all patients diagnosed with ESRD and were undergoing dialysis at our hospital or initiated on dialysis between March 2020 and June 2022. The study was approved by the Institutional Ethics Committee. Informed written consent was obtained from all participants. Good clinical care guidelines and guidelines as per the Declaration of Helsinki were followed. The patients were classified into different clinical diagnosis based on history, investigations, and kidney biopsy wherever indicated. The high-risk features suggestive of genetic diseases, and in particular for Fabry disease, were noted. Blood samples were taken from all patients undergoing HD irrespective of their clinical diagnosis. One drop of blood per circle on DBS card was applied with caution that it covers the whole circle on the inside. These cards were then dried at room temperature for 4 h and stored at 2°C –8°C. Further, they were sent for analysis to the Sir Ganga Ram Hospital in New Delhi by courier. The DBSs were analyzed using a fluorescence-based high throughput microplate method. The BSS test result was defined as positive if the α-Gal A activity was found below the threshold of 3 nmol/h/ml, which represents approximately 30% of the α-Gal A activity in healthy controls. All patients, whose enzyme levels were lower than the lower prescribed range, were subjected to mutations study after repeat written informed consent and requisite counseling. The sample for mutation analysis was collected in Heparin tube (3 mL) and was sent to Med Genome Laboratory, Bengaluru. The suggested Schematic flow chart to diagnose Fabry disease is shown in Figure 1.

Statistical analysis

Data entry was carried out using MS Excel 2016, and analysis of the data were done using IBM SPSS Version 21.0 (Armonk, NY, USA). Means and proportions were calculated for continuous and categorical data. Differences in proportions was tested for statistical significance using Chi square test. A P <0.05 was considered statistically significant.

Results

Patients were divided into four age groups as shown in Table 1. Mean age of the patients was 52.44 ± 14.6 years, maximum number of patients, 42%, was in 46–60 years, and majority of the patients, 64.3% were males. Patients with diabetic kidney disease and presumed Contrast-induced nephropathy CKD (CIN CKD) were 24.6%, the most common clinical diagnosis [Table 1].

The DBS test was done on 112 patients, and it revealed that 19 patients had low enzyme activity. Out of the 19 patients, 6 were females, and subsequently, one of them was found to be positive for mutation pathogenic for Fabry disease, as shown in Figure 2.

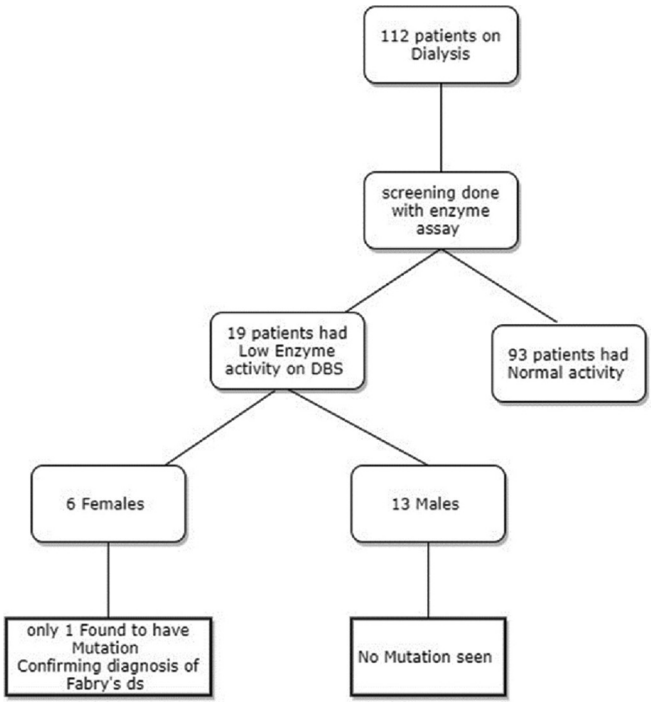

Figure 1: Schematic flow chart to diagnose Fabry disease

The 19 patients (13 males, 6 females) who were DBS positive were further studied [Table 2]. The mean age of onset of renal dysfunction was 46.11 ± 16 years and the majority of them were males (68%). The most common diagnosis was diabetic kidney disease (26%), followed by presumed chronic glomerulonephritis CKD (21%) and presumed CIN CKD (21%). Amongst the DBS-positive patients, 15.8% had a history of consanguineous marriage and 10.5% had family history of kidney disease.

Patients with positive DBS tests were further compared for any association with typical features of Fabry disease [Table 3]. It was found that of the positive DBS test, 21.1% had reported pain/paresthesia in hands and feet as compared to 11.8% among those with negative DBS test (P = 0.282). Similarly, intolerance to heat was 15.8% versus 9.7% (P = 0.433), history of CVA was 10.5% versus 8.6% (P = 0.677), and LVH on ECG was 42.1% versus 22.6% (P = 0.077); but none of these associations were found to be statistically significant

Out of 19 patients with low enzyme activity, the study found one confirmed case of Fabry disease on mutation analysis. The mutation was a heterozygous missense variation in exon 7 of the GLA gene (p.Arg363His). The patient confirmed to have Fabry disease was an 82-years-old female. The pedigree chart of the index patient is shown in Figure 3.

Discussion

The diagnosis of Fabry disease is often delayed for many years due to diverse phenotypes, and it is an underrecognized cause of renal failure in the dialysis population. Hence, many guidelines[21] have now included the screening of Fabry disease as one of the recommendations. This is the first precision medicine screening study for Fabry disease in India. In this study, of the 112 patients on dialysis, only one was a confirmed patient of Fabry disease.

The 112 patients were divided into four age groups, and it was found that majority of the patients were in the age

Table 1: Demographic characteristics of patients screened for Fabry disease (*n*=112)

Parameter	Frequency (%)
Age at the time of enrollment (years)	
10–30	9 (8.0)
31–45	26 (23.2)
46–60	45 (40.2)
>60	32 (28.6)
Age at the time of onset of renal dysfunction (years)	
<16	1 (0.9)
16–30	15 (13.4)
31–45	32 (28.6)
46–60	47 (42.0)
>60	17 (15.2)
Sex	
Female	40 (35.7)
Male	72 (64.3)
Clinical diagnosis of basic disease	
ADPKD	5 (4.5)
CAKUT	7 (6.3)
CGN CKD	18 (16.1)
Diabetic kidney disease	27 (24.1)
Presumed CGN CKD	22 (19.6)
Presumed CIN CKD	27 (24.1)
Stone-related CIN CKD	6 (5.4)
Total	112 (100.0)

ADPKD: Autosomal dominant polycystic kidney disease; CAKUT: Congenital anomalies of the kidney and urinary tract; CGN: Chronic glomerulonephritis; CKD: Chronic kidney disease; CIN: Cervical intraepithelial neoplasia

Table 2: Characteristics of patients with positive dried blood spot test

Characteristics	Values
DBS value lower than the reference range	Total patients *n*=19
Mean age (years)	50.53±15.8
Mean age at onset	46.11±16
Males, *n* (%)	13 (68)
Females, *n* (%)	6 (32)
Clinical diagnosis, *n* (%)	
CGN CKD	4 (21)
DKD	6 (26)
Presumed CGN CKD	4 (21)
Presumed CIN CKD	4 (21)
Stone-related CIN CKD	1 (5)
Consanguinity, *n* (%)	3 (15.8)
Family history of kidney disease, *n* (%)	2 (10.5)

CGN: Chronic glomerulonephritis; CKD: Chronic kidney disease; CIN: Cervical intraepithelial neoplasia; DBS: Dried blood spot

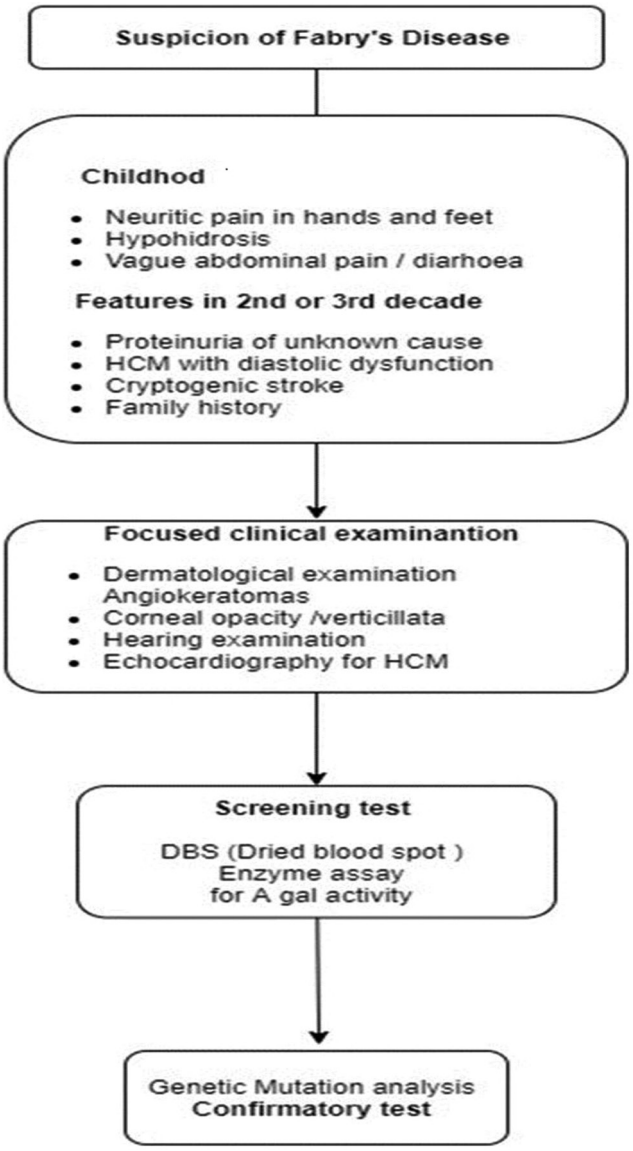

Figure 2: Results of screening test and confirmatory test

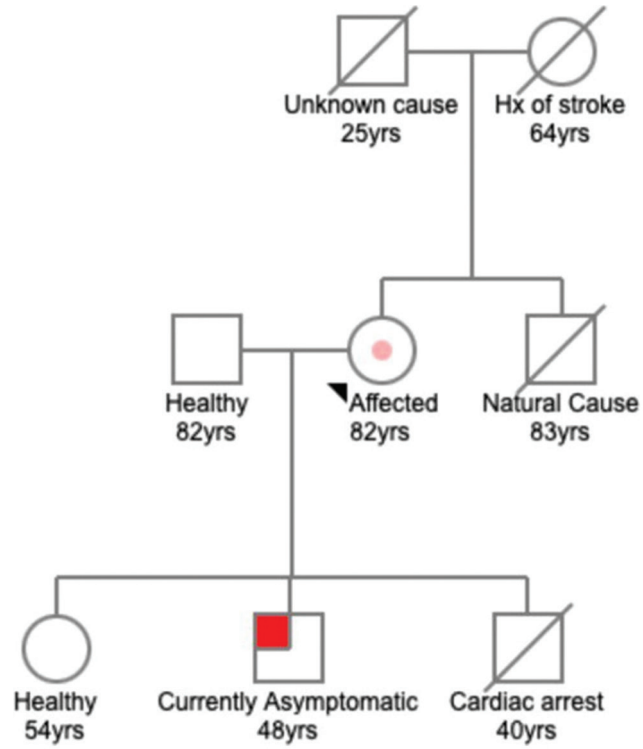

Figure 3: Pedigree chart of index patient of Fabry disease

group of 46–60 years. Similar result was also seen in large Indian CKD study[22] which found the mean age of patients suffering from mild-to-moderate CKD across 11 centers in India to be 50.3 ± 11.3 years. It is a matter of concern that the most productive age group is crippled with the burden of dialysis. In our study, the predominant cause of ESRD was Diabetic kidney disease and Presumed CIN CKD (24.1%). These results are congruent with other Indian studies[22-24] which also found the diabetes as leading cause of ESRD.

There are various methods to screen for Fabry disease. Screening studies worldwide have used different assays, which include either plasma/whole blood based or leukocytes or DBS method. In this study, the DBS method has been used.

In one of the largest prospective screening studies[8] (n = 9604) using DBS samples of all male patients undergoing HD in Argentina, Frabasil *et al*. [Table 4] confirmed 22 undiagnosed Fabry disease cases and concluded the prevalence rate of 0.23% for Fabry disease in HD population. Similarly, other studies[8-10,25-27] have found the prevalence rate of Fabry disease in the HD population to be ranging from 0.16% to 0.58%. This study found 19 patients with enzyme activity lesser than the normal range, of which 13 were males and 6 were females. However, the mutation analysis confirmed only one patient with Fabry disease, making the prevalence of Fabry disease 0.89% in this study, which is more than the frequency observed in other studies mentioned in Table 4. Our results are congruent with studies[8,9] that support the potential benefit of screening Fabry disease in high-risk population such as dialysis. In contrast, the Dutch study by Linthorst *et al*.[28] has advised to use caution for screening Fabry disease in view of lacunae in the screening tests and the paucity of treatment options subsequently.

Fabry disease can be diagnosed in affected males by demonstrating a deficiency of α-galactosidase A enzyme in plasma samples, leukocytes, or DBS fairly accurately, However, enzyme assay is an unreliable test for females.[19] In our study, 13 males and 6 females (total 19) patients had low enzyme activity on DBS. However, the mutation testing confirmed FD in only one female patient. Similar result was seen in nationwide Screening study[9] which reported 117 positive DBS patients and only 4 confirmed FD cases subsequently. In contrast,[8] this study confirmed 22 Fabry disease patients out of 24 patients with Positive DBS test. Overall DBS is accepted as an effective screening method

Table 3: Association between dried blood spots result and features of Fabry disease (*n*=112)

Parameter	DBS enzyme assay		Total, *n* (%)	*P**
	<3 nmol/h/mL (*n*=19), *n* (%)	≥3 nmol/h/mL (*n*=93), *n* (%)		
Pain/paraesthesia in hands/feet				
Yes	4 (21.1)	11 (11.8)	15 (13.4)	0.282
No	15 (78.9)	82 (88.2)	97 (86.6)	
Intolerance to heat and cold				
Yes	3 (15.8)	9 (9.7)	12 (10.7)	0.433
No	16 (84.2)	84 (90.3)	100 (89.3)	
Hypohidrosis				
Yes	1 (5.3)	6 (6.5)	7 (6.3)	1.0
No	18 (94.7)	87 (93.5)	105 (93.8)	
Abdominal pain and diarrhea				
Yes	0	1 (1.1)	1 (0.9)	1.0
No	19 (100.0)	92 (98.9)	111 (99.1)	
History of CVA				
Yes	2 (10.5)	8 (8.6)	10 (8.9)	0.677
No	17 (89.5)	85 (91.4)	102 (91.1)	
LVH on ECG				
Yes	8 (42.1)	21 (22.6)	29 (25.9)	0.077
No	11 (57.9)	72 (77.4)	83 (74.1)	
Total	19 (100.0)	93 (100.0)	112 (100.0)	

*Chi-square test/Fisher's exact test was applied. CVA: Cerebrovascular accident; LVH: Left ventricular hypertrophy; ECG: Electrocardiogram; DBS: Dried blood spot

Table 4: Important worldwide studies on Fabry's disease

Country/centers	Number of patients screened (*n*)	Subject population	Type of assay used	Fabry's disease confirmed - prevalence, *n* (%)	Reference
Argentina Multicentric	9604	Males on HD	DBS	22 (0.23)	Frabasil *et al*. (2019)[8]
Czech Republic Multicentric	3370	All patients on HD	DBS	4 (0.26)	Merta *et al*. (2007)[9]
Austria Nation Wide	2480	All patients on HD	DBS	4 (0.16)	Kotanko *et al*. (2004)[10]
Russia Multicentric	5572	All patients on HD	DBS	20 (0.58)	Moiseev *et al*. (2019)[25]
Saudi Arabia	619	All patients on HD	DBS	3 (0.48)	Alhemyadi *et al*. (2020)[26]
Japan	722	All patients on HD	Plasma	2 (0.28)	Utsumi *et al*. (2000)[27]

DBS: Dried blood spot; HD: Hemodialysis

in males; however, it should be supplemented with Lyso Gb3 levels and mutation analysis in suspected patients.[29]

The mutation that was found in this study was heterozygous missense variation in exon 7 of the GLA gene (p.Arg363His). This particular mutation has earlier been reported from India[30] and Argentina[31] where it was seen in late-onset renal variants suggesting genotype phenotype correlation.

Description of the Fabry disease patient and her family

In this study, a confirmed case of Fabry disease was a female aged 82 years. She led an almost healthy life till 70 years, and then, she was found to have diabetes and put on regular antidiabetic medication. At the onset of diabetes, the subject patient did not show any complications as a consequence of diabetes. In fact, she developed renal dysfunction at the age of 75 years, which was attributed to diabetic kidney disease, and the disease progressed to ESRD over 2 years. She was put on regular maintenance dialysis. On DBS screening, she was found to have low enzyme activity and the mutation analysis confirmed her for Fabry disease. It is important to note that she lived a normal and healthy life for almost seven decades without any clinical manifestation of Fabry disease. All the available family members of the subject patient were screened. Her father died at young age of 25 years due to some unknown illness details of which are not available. Her mother died at 65 years of age due to CVA ischemic stroke and hypertension. Her elder brother died, natural death, at the age of 80 years. She has three children, the eldest is a daughter aged 54 years, second is son aged 40 years and the youngest son died of some cardiac cause at the age of 35 years. On screening her son aged 40 is asymptomatic and has the same genotypic mutation as his mother for Fabry disease.

Conclusions

Out of 112 patients on dialysis, this study found one confirmed patient of Fabry disease. From this important

precision medicine study, we have made some conclusions and recommendations, which are as follows:

- Fabry disease is underrepresented as a cause of ESRD and it is suggested that all nephrologists should be familiar with genomics of kidney disease.
- DBS is an easily transportable and effective screening method, especially in developing countries like India, where few genetic labs are available.
- It is suggested that likewise further screening studies for Fabry disease in high-risk populations should be carried out.

Ethical statement

The study was approved by the institutional Ethics Committee of Command Hospital Chandimandir with approval no. 04/07/Feb/CHWC/2023.

Financial support and sponsorship

The DBS kits were supplied free of cost by Sanofi Genzyme as part of Disha Program.

Conflicts of interest

There are no conflicts of interest.

References

1. Kramer A, Boenink R, Stel VS, Santiuste de Pablos C, Tomović F, Golan E, *et al.* The ERA-EDTA registry annual report 2018: A summary. Clin Kidney J 2021;14:107-23.
2. Johansen KL, Chertow GM, Gilbertson DT, Herzog CA, Ishani A, Israni AK, *et al.* US renal data system 2021 annual data report: Epidemiology of kidney disease in the United States. Am J Kidney Dis 2022;79:A8-12.
3. Torra R, Furlano M, Ortiz A, Ars E. Genetic kidney diseases as an underrecognized cause of chronic kidney disease: The key role of international registry reports. Clin Kidney J 2021;14:1879-85.
4. Devuyst O, Knoers NV, Remuzzi G, Schaefer F, Board of the Working Group for Inherited Kidney Diseases of the European Renal Association and European Dialysis and Transplant Association. Rare inherited kidney diseases: Challenges, opportunities, and perspectives. Lancet 2014;383:1844-59.
5. Fabry F. Purpura papulosa haemorrhagica Hebrae. Arch. f. Dermat. 1898;43:187–200.
6. Anderson W. A case of angiokeratoma. Br J Dermat 1898;1:113-7.
7. Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. JAMA 1999;281:249-54.
8. Frabasil J, Durand C, Sokn S, Gaggioli D, Carozza P, Carabajal R, *et al.* Prevalence of Fabry disease in male dialysis patients: Argentinean screening study. JIMD Rep 2019;48:45-52.
9. Merta M, Reiterova J, Ledvinova J, Poupetová H, Dobrovolny R, Rysavá R, *et al*.. A nationwide blood spot screening study for Fabry disease in the Czech Republic haemodialysis patient population. Nephrol Dial Transplant 2007;22:179-86.
10. Kotanko P, Kramar R, Devrnja D, Paschke E, Voigtländer T, Auinger M, *et al.* Results of a nationwide screening for Anderson-Fabry disease among dialysis patients. J Am Soc Nephrol 2004;15:1323-9.
11. Rolfs A, Böttcher T, Zschiesche M, Morris P, Winchester B, Bauer P, *et al.* Prevalence of Fabry disease in patients with cryptogenic stroke: A prospective study. Lancet 2005;366:1794-6.
12. Linhart A, Elliott PM. The heart in Anderson-Fabry disease and other lysosomal storage disorders. Heart Br Card Soc 2007;93:528-35.
13. Zarate YA, Hopkin RJ. Fabry's disease. Lancet 2008;372:1427-35.
14. Hoffmann B, Mayatepek E. Fabry disease-often seen, rarely diagnosed. Dtsch Arztebl Int 2009;106:440-7.
15. Branton M, Schiffmann R, Kopp JB. Natural history and treatment of renal involvement in Fabry disease. J Am Soc Nephrol 2002;13 Suppl 2:S139-43.
16. Bishop DF, Calhoun DH, Bernstein HS, Hantzopoulos P, Quinn M, Desnick RJ. Human alpha-galactosidase A: nucleotide sequence of a cDNA clone encoding the mature enzyme. Proc Natl Acad Sci U S A 1986;83:4859-63.
17. Germain DP, Levade T, Hachulla E, Knebelmann B, Lacombe D, Seguin VL, *et al.* Challenging the traditional approach for interpreting genetic variants: Lessons from Fabry disease. Clin Genet 2022;101:390-402.
18. Caudron E, Prognon P, Germain DP. Enzymatic diagnosis of Fabry disease using a fluorometric assay on dried blood spots: An alternative methodology. Eur J Med Genet 2015;58:681-4.
19. Linthorst GE, Vedder AC, Aerts JM, Hollak CE. Screening for Fabry disease using whole blood spots fails to identify one-third of female carriers. Clin Chim Acta Int J Clin Chem 2005;353:201-3.
20. van der Veen SJ, Hollak CE, van Kuilenburg AB, Langeveld M. Developments in the treatment of Fabry disease. J Inherit Metab Dis 2020;43:908-21.
21. Terryn W, Cochat P, Froissart R, Ortiz A, Pirson Y, Poppe B, *et al.* Fabry nephropathy: Indications for screening and guidance for diagnosis and treatment by the European renal best practice. Nephrol Dial Transplant 2013;28:505-17.
22. Kumar V, Yadav AK, Sethi J, Ghosh A, Sahay M, Prasad N, *et al.* The Indian Chronic Kidney Disease (ICKD) study: Baseline characteristics. Clin Kidney J 2022;15:60-9.
23. Dattu MS, Kumar EK, Krishnamurthy S, Reddy YJV. Aetiology of chronic kidney disease in rural patients. J Clin Sci Res 2016;5:221-4.
24. Modi GK, Jha V. The incidence of end-stage renal disease in India: A population-based study. Kidney Int 2006;70:2131-3.
25. Moiseev S, Fomin V, Savostyanov K, Pushkov A, Moiseev A, Svistunov A, *et al.* The prevalence and clinical features of Fabry disease in hemodialysis patients: Russian nationwide Fabry dialysis screening program. Nephron 2019;141:249-55.
26. Alhemyadi SA, Elawad M, Fourtounas K, Abdrabbou Z, Alaraki B, Younis S, *et al.* Screening for Fabry disease among 619 hemodialysis patients in Saudi Arabia. Saudi Med J 2020;41:813-8.
27. Utsumi K, Kase R, Takata T, Sakuraba H, Matsui N, Saito H, *et al*. Fabry disease in patients receiving maintenance dialysis. Clin Exp Nephrol 2000;4:49-51.
28. Linthorst GE, Hollak CE, Korevaar JC, Van Manen JG, Aerts JM, Boeschoten EW. Alpha-galactosidase a deficiency in Dutch patients on dialysis: A critical appraisal of screening for Fabry disease. Nephrol Dial Transplant 2003;18:1581-4.
29. Delarosa-Rodríguez R, Santotoribio JD, Paula HA, González-Meneses A, García-Morillo S, Jiménez-Arriscado P, *et al.* Accuracy diagnosis improvement of Fabry disease from dried blood spots: Enzyme activity, lyso-Gb3 accumulation and GLA gene sequencing. Clin Genet 2021;99:761-71.
30. Nampoothiri S, Yesodharan D, Bhattacherjee A, Ahamed H, Puri RD, Gupta N, *et al.* Fabry disease in India: A multicenter study of the clinical and mutation spectrum in 54 patients. JIMD Rep 2020;56:82-94.
31. Serebrinsky G, Calvo M, Fernandez S, Saito S, Ohno K, Wallace E, *et al.* Late onset variants in Fabry disease: Results in high risk population screenings in Argentina. Mol Genet Metab Rep 2015;4:19-24.