FAMILY SCREENING FOR FABRY DISEASE BASED ON MALE INDEX CASES WITH END-STAGE RENAL DISEASE

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INTRODUCTION

- Fabry disease (FD) is a lysosomal storage disorder with X-linked inheritance pattern caused by enzyme α galactosidase A (α-Gal A) deficiency due to mutations in the galactosidase alpha (GLA) gene.
- There is a complete or partial inability to catabolize lipids with terminal alpha-galactosyl residues, mainly globotriaosylceramide (GL-3), which systemically accumulates in the lysosomes of the vascular endothelium.
- The progressive glycolipid accumulation leads to damage in the kidney and other organs often presenting in the 3rd and 4th decade of life.[1,2]
- Prevalence rates of FD in hemodialysis (HD) patients in other Brazilian regions was 0.36%, 0.52% and 0.57%[4-6]; and in other countries ranged from 0.04 to 1.16%.[7-10]

OBJECTIVES

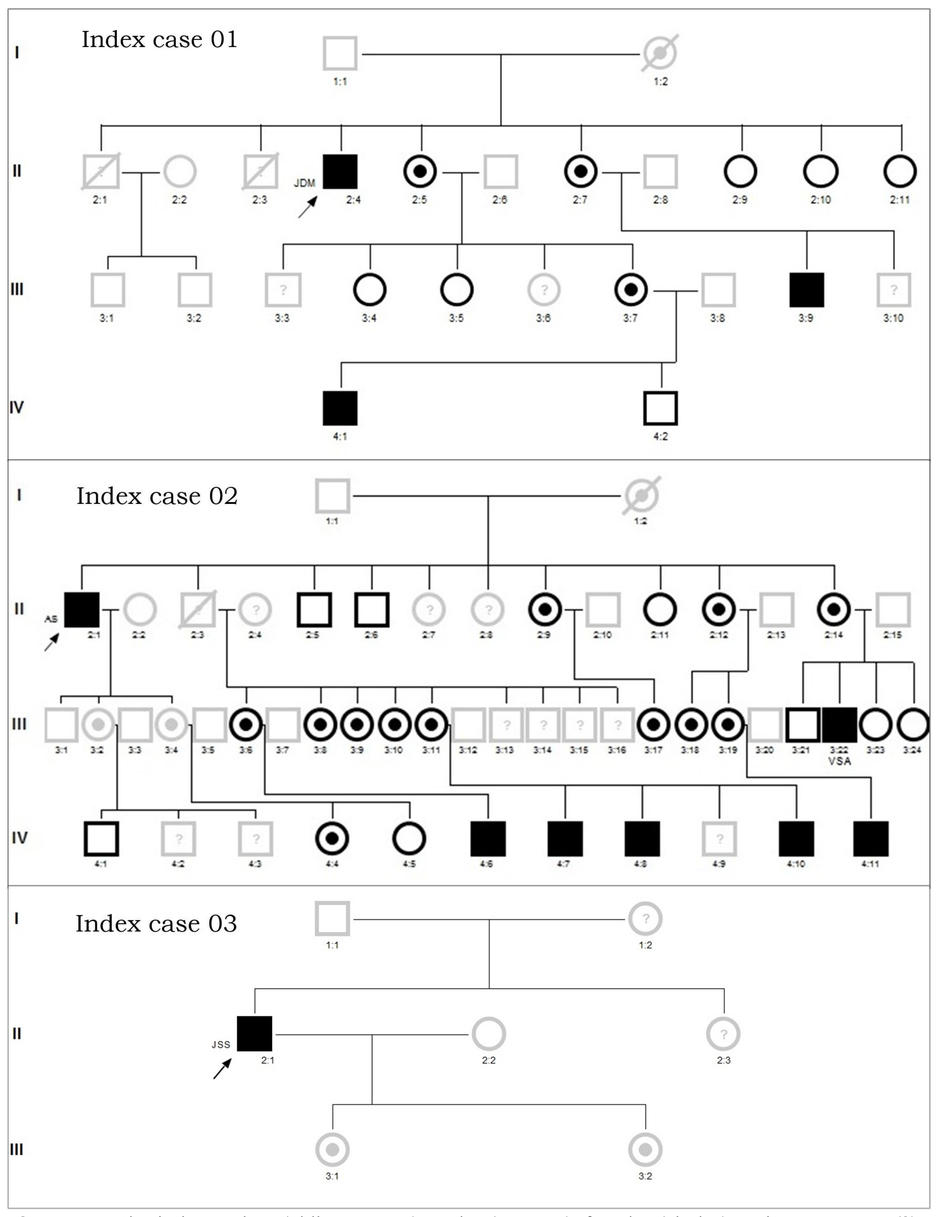
- To estimate the prevalence of FD among male patients in 23 HD centers in a northeastern state of Bahia in Brazil.
- To facilitate the early identification of family members that may present asymptomatic or are misdiagnosed.

METHODS

- Screening was performed using a dried blood spot on filter paper α-Gal A assay.[3]
- Patients with low enzyme activity (≤ 2.2 µmol/L/h) underwent a clinical evaluation and genetic analysis of the GLA gene to confirm the diagnosis of FD.
- A family screening was conducted in those patients with FD.

RESULTS

- 2724 patients were invited to participate in the study, of which 141 (5.17%) chose not to participate.
- 2583 male HD patients participated.
- Median age of 52 (18 – 91) years.
- α-Gal A assay identified 72 males (2.78%) with low enzyme activity.
- Genotyping identified 3 with GLA mutations.
  - two previously reported (W204X, A368T) and a novel missense mutation (C52F).
- Only the patient with W204X mutation demonstrated classical signs of FD.
- Prevalence rate of FD was 0.12% (CI 95% 0.02 – 0.28).
- Family screening of these 3 index cases identified 23 family members who were affected or heterozygotes of the disease.



Genogram: the index patient (oblique arrow), males (squares), females (circles), unknown status (?), diagonal lines (dead subjects), male FD (square black), female FD (overlapping circles), unrelated or not genetically evaluated individuals (gray), individuals without FD after genetic evaluation (black circle or black square, not filled).

Flow chart of screening results

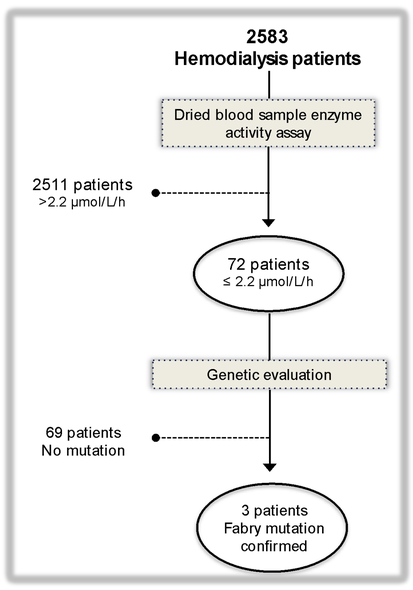


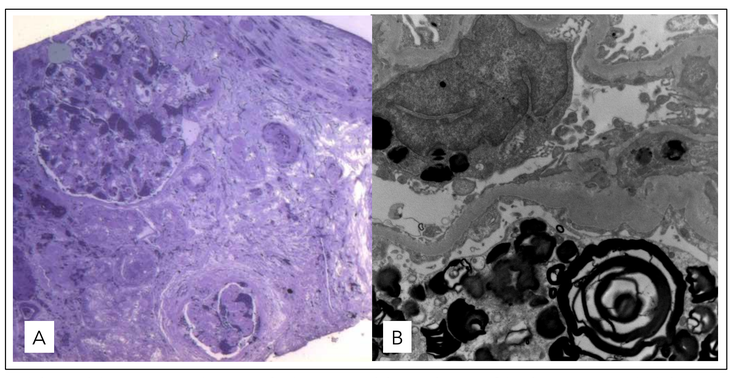
Table 1: Characteristics of the detected index patients.

	Index Case 1	Index Case 2	Index Case 3
Age (years)	44	61	73
Ethnic group	Mixed Brazilian	African Brazilian	African Brazilian
Previous CKD diagnosis	indeterminate	CGN	indeterminate
Comorbidities	-	hypertension	hypertension
Age at start of dialysis	40 years	46 years	68 years
Time on HD till FD diagnosis	4 years	15 years	5 years
Enzyme activity on DBS (µmol/l/h)	0.7	0.07	1.69
Mutation in GLA	exon 4:p.W204X	exon 1:p.C52F	exon 7:p.A368T
• Base substitution	tryptophan → stop-codon	cysteine → phenylalanine	alanine → threonine
Affected relatives	5	18	2
Enzyme replacement therapy	yes	yes	no

Abbreviations and units: CKD – chronic kidney disease; CGN – chronic glomerulonephritis; HD – hemodialysis; FD – Fabry disease; DBS – dried blood spot; GLA – galactosidase alpha; µmol/l/h – micromoles per liter per hour

Table 2: Clinical manifestations of Fabry in index cases and relatives

	Cornea verticillata	Hypohidrosis	Acroparesthesia	Angiokeratomas lymphedema	Joint or generalized pain	Fatigue	Fabry nephropathy	Left ventricular hypertrophy	Early death	Asymptomatic
Index Case 1	✔			✔			✔	✔		
Sister 1					✔					
Son of Sister 1		✔	✔	✔						
Sister 2					✔					
Daughter of Sister 2										✔
Grandson of Sister 2										✔
Index Case 2	✔						✔	✔		
Sister 1					✔	✔				
Daughter of Sister 1										✔
Sister 2					✔	✔				
Daughter 1 of Sister 2										✔
Daughter 2 of Sister 2										✔
Sister 3					✔	✔				
Son of Sister 3		✔	✔	✔			✔			
Brother									✔	
Daughter 1 of Brother										✔
Grandson of Brother		✔	✔							
Daughter 2 of Brother										✔
Grandson of Brother			✔	✔						
Grandson of Brother			✔	✔						
Grandson of Brother			✔	✔						
Daughter 3 of Brother										✔
Daughter 4 of Brother										✔
Daughter 5 of Brother										✔
Index Case 3	✔						✔	✔		
2 Daughters - unknown										



Kidney biopsy specimen of 27 year-old nephew of index case 2 (with novel mutation) shows full score of GL3 deposits. (A) Images of toluidine blue stain (X 1040) and (B) Electron microscopy (X 7000)

CONCLUSIONS

- The 0.12% prevalence of FD amongst male hemodialysis patients in Brazil was low, however in conjunction with family screening of the 3 index cases identified, 23 family members were identified who might benefit from earlier treatment.
- Nephrologists should consider FD in patients who are receiving renal replacement therapy - in HD, peritoneal dialysis or renal transplantation, even if older than 50 years of age.

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