SCREENING FABRY DISEASE IN PATIENTS WITH CHRONIC KIDNEY DISEASE WITHOUT RENAL REPLACEMENT THERAPY: PRELIMINARY RESULTS OF A MULTICENTER STUDY

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INTRODUCTION AND AIMS

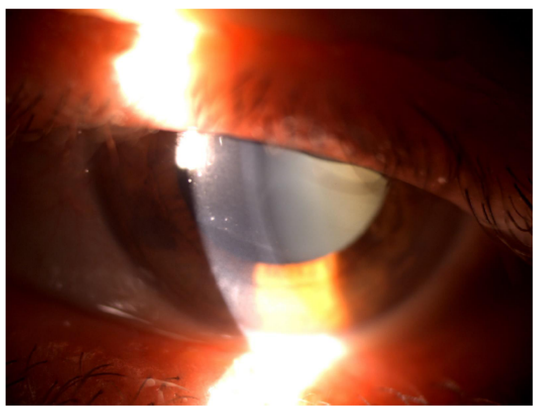
Fabry's disease (FD) is an X-linked inherited, rare, progressive, multisystem disorder of glycosphingolipid metabolism affecting multiple organs and causing varying degrees of dysfunction. Its prevalance ranges between 1/17,000-1/117,000 in white caucasian men. Fabry disease may cause premature stroke, acroparesthesia, angiokeratoma, hypohydrosis and left ventricular hypertrophy. Initial finding in renal involvement is usually proteinuria and sometimes it presents with chronic renal failure with unknown etiology. End stage renal disease generally ensues before the age of 55 years. Accumulation of glycosphingolipids particularly globotriaosylceramide due to deficient activity of α-galactosidase A enzyme is the hallmark of the disease. The diagnosis of the disease is established on clinical grounds by low levels of enzyme activity and determination of genetic mutations. Possibilty of prevention of further globotriaosylceramide accumulation by means of enzyme replacement theraphy makes early diagnosis attractive. The data concerning the prevalance of the disesase in chronic kidney disease other than ESRD is lacking. In this study we aimed to determine the prevalence of Fabry disease in this population.

METHODS

The present study is a cross-sectional, analytic, multicenter study. The patients older than 18 years, enclosing KDIGO 2012 chronic kidney disease definitions, other than end stage renal disease, were enrolled into the study. Patients, transfused within last 6 months period, were excluded. Eligible patients were screened for α-galactosidase A deficiency in five seperate nephrology clinics in Turkey namely: Adnan Menderes University, School of Medicine-Aydın, Pamukkale University, School of Medicine-Denizli, Sıtkı Koçman University, School of Medicine-Muğla, Aydın Devlet Hastanesi-Aydın, Denizli Devlet Hastanesi-Denizli. All patients were signed informed consent. Demographic data, patients' history and physical examination findings, and basic laboratory results(serum creatinine, urinanalysis, daily urinary protein loss) are recorded. Peripheral venous blood dried blood samples on guthrie papers were used to analyse enzyme activity and genetic testing when required. All tests performed by ARCHIMED Life Science GmbH Laboratories Vienna,Austria. The patients diagnosed as Fabry Disease are invited to Adnan Menderes University, School of Medicine. Hospitalised patients were examined by the same physician in Genetics, Opthalmology, Radiodiagnositcs, Neurology, Endocrinology, Hematology, Cardiology, Ear Nose Throat and Dermatology departments. The study is approved by Local Ethical Committe of Adnan Menderes University School of Medicine (14/02/2014, 56989545/050,04-26). All data were collected in Adnan Menderes University and proccessed. SPSS program was used for data analysis.

RESULTS

A total of 736 patients were screened in 5 centers. Patients were enrolled into the study because of decreased GFR(90,5%), proteinuria(18,5%), isolated microscopic hematuria(0,9%) Basic demographic, clinical and laboratory data of the pateints were presented in tables 1 and 2. 80 patients had low levels of α-galactosidase enzyme activity (<1.2 µmol/L/min). Mutations in the α-galactosidase A gene specific for Fabry disease were observed in three patients with low enzyme activity. In Mutaion analysis by means of sequential DNA analysis technique in exons and introns, A143T and D313Y variants were disclosed. The prevalance of Fabry disease mutations in CKD other than ESRD was 0.4%. Mutation detected patients were clinically evaluated in our nephrology department. The datas of the two patients were described in the table (Table 4). In Figure I, cornea vercilata in patient 2 was presented. The 3rd patient rejected further evaluation.



Age (years)	61.7±14.3
BMI (kg/m2)	28.3±5.4
Urea (mg/dL)	65,3±37,1
Serum creatinine (mg/dL)	2.0±1.0
Proteinuria (g/day)	1.4±2.6
Hemoglobin (g/dL)	12,3±1,8
Hemotocrit (%)	37,8±5,4
α-galactosidase A activity (µmol/L/min)	2.31±2.42

	Patient 1	Patient 2
Age	70	83
Gender	M	M
Etiology	Diabetic nephropathy	Hypertensive nephropathy
Clinical manifestations	Cornea verticillata* Cataract Type 2 DM Coronary artery disease LVH (IVS:13mm,PW 12 mm) Sensorineural hearing loss Carpal tunnel syndrome Osteoporosis (Total T score -3,3) Chronic lacunar infarcts Renal cortical exophytic cysts	Cornea verticillata* Hypertension Coronary artery disease LVH (IVS:16 mm,PW:15 mm) Sympathetic autonomic dysfunction
Symptoms	Hearing loss	Intolerance to heat Sweating disorder
Family history	Premature coronary heart dis.	Non-significant
Creatinine on admission	1,95 mg/dl	1.81 mg/dl
24 h protein excretion	50 mg/d	58,75 mg/d
Enzyme activity	0,5 µmol/l/h	0,3 µmol/l/h
Mutations	c.[937G>T] (p.[D313Y])	c.[427G>A] p.[A143T]
Renal biopsy	FSGS	Not accepted the procedure

Table 1: Co-morbidities and symptoms(n: 736)			
Hypertension	80,3%	Sweating disorders	16,3%
D. Mellitus	39,8%	History of stroke/TIA	7,6%
Cardiac dis.*	32,3%	Corneal opasity	2,3%
Paresthesia	11,8%	Epilepsy	2,2%
*: Coronary artery disease, left ventricular hypertrophy, congestive heart failure, valvular diseases. TIA Transient ischemic attack			

DISCUSSION

In the literature, D313Y variant, taking into consideration, its prevalans in healthy people, in vitro expression studies, plasma lysoGb3 and Gb3 concentrations in affected patients and tissue biopsises, is considered to be non-pathogenic. On the other hand, one other author reported that D313Y variant in seven people from the same pedigree could be pathogenic because of depressed enzyme activity and multifocal central nervıus system lesions.

Although A143T variant was reported to cause left ventricular hypertrophy and renal type Fabry disease initially, the following studies were failed to document accumulation of Gb3 ande lysoGb3 in target organs thereof it is considered to be non-pathogenic. In contrast, a case with aforementioned mutation was diagnosed as classical Fabry disease, because of presence of angiokeratomas.

In the literature, mutations with conflicting pathogenicity were defined as "genetic variants with unknown pathogenecity" and considered as necessity for the diagnosis. Therefore, our cases are considered to be classical Fabry disease because of low enzyme activity, presence of acroprethesia, cornea vercilata. However in the case with D313Y variant, inspite of history of facial paralysis, presence of hearing problems, tinnitus, vertigo, gastrointestinal symptoms proteinuria and plasma alpha galactosidase levels decreased to 9% of normal, measurement of plasma lysoGb3 levels, electron microscopic examination of the target organs were required for he diagnosis

CONCLUSIONS

In our study the prevalence of Fabry disease was 0,4%. Fabry disease is speculated to cause end stage renal disease requiring renal replacement therapy near 4th or 5th decades. However; it is notable that our patients had a better renal function than expected although they were older (70 yo;83 yo). It is not clear whether this difference should be attributed to the racial, ethnic or regional differences, or genetic variations.

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