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Original Article

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Screening for Fabry Disease in Patients Who Underwent Renal Biopsy and Identification of a Novel Mutation

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ABSTRACT

Background: The X-linked Fabry disease (FD) with lysosomal storage of globotriaosylceramide (Gb3) due to α-galactosidase deficiency contributes to nephropathy consisting of proteinuria and renal failure eventually. Early initiation of the enzyme replacement therapy promises favorable renal outcomes. With the importance of early diagnosis, we screened FD among proteinuric patients in whom biopsy findings revealed Fabry nephropathy.

Methods: Patients with light microscopic biopsy findings of vacuolated cells, focal and/or segmental glomerular sclerosis, tubular atrophy, and interstitial fibrosis were not associated with particular etiology, the presence of acro-paresthesia, angiokeratomas, and cornea verticillata, stroke history younger than 50 years, family history of renal failure with no cardiovascular risk factors were screened. Fifty-three of 308 consecutive adult patients (45.34 ± 15.23 years old, 60.1% male) who underwent renal biopsy because of proteinuria were enrolled in the study. Screening for FD was performed by assessing α-Gal A activity in dried blood spots (DBS) for males and by genetic testing for females.

Results: Fifty-three patients (39.94 ± 11.97 years, 69.8% male) who underwent renal biopsy were screened. Laboratory findings revealed mean serum creatinine of 1.44 ± 1.06 mg/dL, mean estimated glomerular filtration rate of 78.31 ± 39.89 mL/min/1.73 m^2, and mean proteinuria of 4.32 ± 3 g/day, whereas the females genetic screening was negative. Two of 37 males had low enzyme activity (<0.1 micmol/L/h) and confirmed FD by genetic analysis in whom one had a novel mutation of GLA gene (c.(1047G>A) p.(Trp349*)).

Conclusion: It is worth noting that FD screening in patients with proteinuria, in whom vacuolated cells, mesangial expansion, glomerulosclerosis, interstitial fibrosis, and tubular atrophy of unknown etiology, are present in the renal biopsy either with or without a family history of kidney disease.

Keywords: α-Galactosidase, Fabry disease, Fabry nephropathy, renal biopsy

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INTRODUCTION

Fabry disease (FD) is an X-linked lysosomal storage disease due to α-galactosidase deficiency that leads accumulation of globotriaosylceramide (Gb3) in several cells.[1] Glycosphingolipid deposition of lysosomes has cytotoxic, proinflammatory, and profibrotic effects that reveal tissue damage and organ failure.[2] FD prevalence is reported in 0.85-2.5 cases per 100 000 individuals worldwide.[3]

The enzyme activity is a predictor of the disease symptoms and complications.[4,5] Clinical variants of FD are described according to varying degrees of residual α-galactosidase activity.[5] In a classical variant, clinical signs of neuropathic pain, angiokeratoma, hypohydrosis, and gastrointestinal symptoms are the main features in the first 2 decades. In adults, left ventricular hypertrophy (LVH), proteinuria, renal failure, and neurovascular ischemic disease are concomitant

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findings.[6] Furthermore, FD phenotype differs between genders. Clinic in females is variable due to random X-chromosome inactivation and ranges from asymptomatic to severe organ involvement.[1]

Renal involvement is an important cause of morbidity and mortality with a mean age of diagnosis of 35-40 years. Untreated all the classical FD patients and 32% of other variants progress to end-stage renal disease.[4,7] Accumulation of Gb3 in glomerular, tubular, and vascular smooth muscle cells causes ischemia, inflammation, and oxidative stress which leads to renal disease.[2] Accumulation in podocytes can be the initial event that reveals proteinuria which is an early sign of renal involvement.[8] Furthermore, renal disease with low glomerular filtration rate (GFR) and proteinuria, unexplained renal insufficiency are late findings in FD patients.[9]

The prevalence of FD in screening studies is 0.11-0.17% in dialysis and 0.2-0.95% in chronic kidney disease (CKD) patients.[10-15] Clinical signs usually begin in childhood but diagnosis can be delayed until 13.7-16.3 years once the initial symptoms such as organ failure noticed in the adulthood.[3] Proteinuria is an early and common finding of renal involvement in FD. In the literature, there are several cases who had undergone renal biopsy due to proteinuria, in whom FD was diagnosed subsequently.[16-21]

In the era of novel enzyme replacement treatments (ERT), early diagnosis of FD is essential before organ failure. Recent data indicate that applying ERT at a younger age and early period provides favorable renal outcomes.[22-24]

Although FD is rare, early diagnosis and preventive ERT are essential and effort for this purpose should be encouraged. With this regard, we aimed to screen FD among proteinuric patients in whom biopsy findings revealed Fabry nephropathy.

MAIN POINTS

- Fabry disease is a rare X-linked disease that contributes to nephropathy consisting of proteinuria and renal failure eventually. Early initiation of the enzyme replacement therapy promises favorable renal outcomes.
- Light microscopic findings of glomerulosclerosis, vacuolated cells, tubular atrophy, and interstitial fibrosis are not associated with particular etiology can be a feature of Fabry nephropathy and these findings should be cared for Fabry disease screening.
- It is worth screening patients with proteinuria, in whom vacuolated cells, mesangial expansion, glomerulosclerosis, interstitial fibrosis, and tubular atrophy of unknown etiology, are present in the renal biopsy either with or without a family history of kidney disease.

MATERIALS AND METHODS

Patients and Study Design

Fifty-three of 308 consecutive adults (45.34 ± 15.23 years old, 60.1% male), who underwent renal biopsy between January 2016 and December 2018 with inclusion criteria were enrolled in the study. Patients who had at least one of the inclusion criteria were screened for FD and informed consent was obtained from all individual participants. Inclusion criteria were light microscopic biopsy findings of vacuolated cells, focal and/or segmental glomerular sclerosis, tubular atrophy and interstitial fibrosis not associated with particular etiology, the presence of acro-paresthesia, angiokeratomas, and cornea verticillata, stroke history younger than 50 years, family history of renal failure with no cardiovascular risk factors. The patients who had systemic lupus erythematosus and crescentic glomerulonephritis were excluded from the study. Furthermore, biopsy diagnosis of membranous nephropathy with positive anti-PLA2r, typical diabetic, and hypertensive nephropathies with retinopathy were also excluded. Although retinopathy might not accompany diabetic and hypertensive nephropathies, and anti-PLA2r might be negative in membranous nephropathy; thus we aimed to exclude typical glomerulopathies. Also, primary FSGS is usually presented with nephrotic proteinuria. So, we excluded the patients with FSGS with nephrotic range proteinuria.

Demographic and laboratory findings were obtained from outpatient charts.

All procedures performed in the study involve human participants in accordance with the ethical standards of the institutional research committee at which the studies were conducted (IRB approval number 2015-11/18) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

FD Screening

Screening for FD was performed by assessing α-Gal A activity in dried blood spots (DBS) for males and by genetic testing for females. The males who had a low α-Gal A enzyme activity were screened subsequently for mutation analysis of the GLA gene by genetic testing.

DBS

The α-Gal A enzyme activity was determined by the method described in the study of Chamoles et al.[25] The enzyme activities were calculated in micmol/mL/h. The activity of below 0.6 micmol/mL/h was considered as low and higher than 2.5 micmol/mL/h as normal.

Genetic Analysis

Genetic analysis was performed using DNA Sanger sequence analysis and the genomic DNA was isolated from DBS.

Statistics

Statistical analyses were performed with Statistical Package for the Social Sciences (SPSS) software (SPSS: An IBM Company, version 23.0, IBM Corporation, Armonk, NY, USA). The numerical and categorical variables were expressed as the mean ± standard deviation and ratios, respectively.

RESULTS

Fifty-three patients (39.94 ± 11.97 years, 69.8% male) who underwent renal biopsy were enrolled in the study. The presence of biopsy findings were described in Table 1. The pathologic diagnosis were FSGS ($n=26$, 49.1%), IgA nephropathy ($n=8$, 15.1%), minimal change disease ($n=4$, 7.5%), chronic changings ($n=4$, 7.5%), membranous nephropathy ($n=3$, 5.6%), membranoproliferative glomerulonephritis ($n=3$, 5.6%), and not-specified ($n=5$, 9.4%). Twenty-seven (50.9%) participants were hypertensive and 1 was diabetic and 28.3% had a family history of renal disease. Laboratory findings revealed that mean serum creatinine as 1.44 ± 1.06 mg/dL, mean estimated GFR (eGFR) as 78.31 ± 39.89 mL/min/1.73 m^2, and mean proteinuria as 4.32 ± 3 g/day.

Enzyme activity was normal in 35 of 37 males and genetic screening of GLA gene were negative in the females. Two of 37 males had low enzyme activity (<0.1 micmol/L/h). In the first patient, a previously unreported hemizygous variant in exon 7 of the GLA gene, c.(1047G>A) p.(Trp349*) and in the second a heterozygous mutation in exon 3 of the GLA gene, c.(422C>T) p.(Thr141Ile), was detected.

First patient was a 32-year-old male who biopsied because of non-nephrotic range proteinuria. His elderly brother had deceased renal transplantation for unknown etiology and history of cerebrovascular event. Other biochemical, serologic, and radiologic evaluations of the first patient were normal. The renal biopsy revealed FSGS with segmental sclerosis in 3 of 13 glomeruli and mild interstitial fibrosis (Table 2). He had the complaints of fatigue, arthralgia, non-productive cough, paresthesia, occasionally abdominal pain, and hypohydrosis. In the DBS the enzyme activity was undetectable (<0.1 micmol/L/h) and the FD was confirmed subsequently with the novel mutation of GLA gene. In the family screening, enzyme activity was normal in the younger brother. The same mutation was detected in his mother and elderly brother. The elderly brother had deceased renal transplantation and his enzyme activity was undetectable (<0.1 micmol/L/h).

Table 1. Light Microscopic Findings of Study Population

Number of total glomeruli	**12.46 ± 7.2**
Presence of glomerulosclerosis	31 (58.5%)
Number of sclerotic glomeruli (segmental/global)	1 ± 1.26/4.49 ± 4.9
Presence of vacuolated cells	17 (32.1%)
Presence of interstitial fibrosis	29 (54.7%)
Presence of tubular atrophy	26 (49.1%)
Presence of inflammatory infiltration	25 (47.2%)

The second case was a 28-year-old male who was admitted to the hospital because of not gaining weight and underwent renal biopsy due to 2.3 g/day proteinuria. There were no pathological findings in the physical examination and laboratory evaluation before the biopsy. His family history of kidney, cardiovascular, and cerebrovascular diseases were all negative. The biopsy was reported as FSGS with 4 segmental and 4 global sclerotic of 13 glomeruli, mild mesangial expansion, and tubular epithelial cell vacuolization. He was complaining of burning in the hands and feet sometimes in the questioning for FD. His enzyme activity was undetectable (<0.1 micmol/L/h) and FD was confirmed with a heterozygous mutation in exon 3 of the GLA gene. The lyso-Gb3 level was 113.6 ng/mL (≤1.8 ng/mL). Further evaluations revealed cornea verticillata and LVH (Table 2). In the family screening, his mother had the same mutation and LVH was detected with no other particular etiologies.

ERT for the 2 index patients, the elder brother of the first case and the mother of second patient, was started. The second patient and his mother continue their treatment at another center. The elder brother of the first case withdrew the ERT because of immobility and recurrent cerebrovascular events. The first case continues his treatment and his complaints of abdominal pain and paresthesia declined. His renal functions are stable with an eGFR of 118 mL/min/1.73 m^2 and proteinuria of 1.1 g/day at 30 months under the ERT. And the lyso-Gb3 level was decreased from 152 ng/mL to 71.6 ng/mL (≤1.8 ng/mL).

DISCUSSION

Fabry disease is an orphan disease with a low prevalence which has detrimental outcomes of end-stage renal disease, cardiovascular, and neurovascular diseases. The majority of the studies and updated recommendations focused on the importance of early treatment initiation in both genders.[6] So the issue must be early diagnosis and initiating ERT at the early stages of the disease to prevent organ failures. With this purpose, we diagnosed 2 FD, of 1 had a novel mutation, by screening renal biopsied patients with signs of renal involvement. Although our cohort was small, a prevalence of 3.7% among carefully selected patients who underwent renal biopsy is a remarkable finding.

Proteinuria and podocyte injury are the initial clinical and histopathological markers of renal involvement, respectively. However, histopathological findings of involvement was also observed in the absence of overt proteinuria.[26] Renal histological findings of FD are well known with biopsy studies in FD patients which are primarily due to glycosphingolipid accumulation.

Light microscopic (LM) of FD are foamy podocytes, and vacuolation of the renal cells are due to accumulation. During the tissue

Table 2. Characteristics of FD Cases

	Case 1	Case 2
Age (years)/gender	32/M	28/M
Clinical findings	Fatigue Arthralgia Acro-paresthesia Abdominal pain Hypohydrosis Non-productive cough Proteinuria	Fatigue Acro-paresthesia Proteinuria LVH
Physical examination	Periorbital edema, hemangiomas on the back	Cornea verticillata
Family history of CKD	Yes	No
eGFR	116 mL/min/1.73 m^2	102 mL/min/1.73 m^2
Proteinuria (g/day)	2	2.3
Biopsy diagnosis	FSGS	FSGS
Biopsy findings	LM: 3/13 SS, mild interstitial fibrosis, vascular intimal fibrosis IF 1+ meningeal IgM	LM: 4/13 SS, 4/13 GS mild meningeal expansion, tubular epithelial cell vacuolization, vascular intimal fibrosis IF negative
Enzyme activity	< 0.1 micmol/L/h	< 0.1 micmol/L/h
Genetic analysis	c.(1047G>A) p.(Trp349*)	c.(422C>T) (p.(Thr141Ile))

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomeruloscrelosis; GS, global sclerosis; IF, immunofluorescence; LM, light microscopy; LVH, left ventricular hypertrophy; M, male; SS, segmental sclerosis.

processing for paraffin embedding the accumulated glycosphingolipids are removed and consequently vacuolated appearance is formed. The most and early affected group of cells are the podocytes. Besides, parietal epithelial cells and distal tubular epithelial cells are involved too. With the progression glomerular mesangial widening becomes evident and proceeds to segmental and/or global glomerulosclerosis. Vascular involvement includes vacuolation of capillary, arterial and arteriolar endothelium, pericytes, and smooth muscle cells. Through the disease progress, tubular atrophy and interstitial fibrosis are the concomitant findings with glomerulosclerosis.[27,28]

Immunofluorescence microscopy is generally negative. Electron-dense multilamellar inclusions of glycosphingolipids in almost all the cell types, which are described as myeloid or zebra bodies, are characteristic findings of electron microscopic (EM) evaluation. Also, these inclusions stain darkly by toluidine blue.[27] Fusion of podocyte foot processes, focal glomerular and tubular epithelial necrosis and thickening of glomerular and tubular basement membranes are other late EM findings of advanced disease.[28]

The international study group of Fabry nephropathy investigated and scored the LM and toluidine blue-stained semi-thin sections of renal biopsies of 59 Fabry cases. The major histopathologic findings were segmental sclerosis, global sclerosis, interstitial fibrosis, arteriosclerosis, vacuolization in LM sections, and inclusions in semi-thin sections. Although the inclusions were prominent in podocytes, they were observed in almost all renal cells as tubular epithelium, peritubular capillary, and vascular endothelium. These changings which some are associated with advanced involvement were presented even in the patients with mild or no proteinuria and preserved eGFR. Concomitant with other studies their findings endorsed that significant renal histopathological influences develop early in FD.[29]

In the literature screening studies are generally among CKD on dialysis and pre-dialysis stages. There are several cases of FSGS, IgA nephropathy, and membranous nephropathy in whom FD diagnosed subsequently.[16,21] The most frequent histopathologic findings of injury to podocytes are minimal change disease and FSGS. And glomerulosclerosis is a common morphologic finding of a wide range of etiology and a consequence of chronic damage.[30] The podocyte involvement is an early and the leading factor in the pathogenesis of Fabry nephropathy even without overt proteinuria.[26,29] So a biopsy of a Fabry patient can be easily reported as FSGS in the absence of EM. In our screening population, the 2 cases of biopsy were also reported as FSGS. Concomitant with the literature presentation and laboratory findings of our cases differed from the primary FSGS. The most considerable difference was non-nephrotic range proteinuria. The proteinuria of all of the previously presented cases with FSGS[16,18,19] and our 2 cases was under 3.5 g/day. Other presented cases were diagnosed with variable glomerulopathies of IgA nephropathy and membranous nephropathy. The common feature of all the presented cases was the specific EM findings of FD accompanying LM findings of vacuolated cells, mesangial

expansion, glomerulosclerosis, and tubulointerstitial changings. The EM evaluation was the crucial instrument for FD diagnosis in of all.[16-21]

In the present study, we screened the patients with histopathological findings that point out FD involvement like vacuolated renal cells, glomerulosclerosis, tubular atrophy, and interstitial fibrosis unrelated to specific glomerulopathies (Table 1). In our study cohort, there were different pathologic diagnoses, however, we screened the patients according to the LM findings independent of the pathologic diagnosis. Although EM findings are more specific for screening, in our center we do not perform EM evaluation. With this obstacle, we decided to screen the patients with the aforementioned LM findings. Eventually, we conclude that in the centers that have no chance to perform EM, the patients with vacuolated renal cells, glomerulosclerosis, tubular atrophy, and interstitial fibrosis of unknown etiology can be screened for FD.

The GLA gene is located on the long arm of the X chromosome.[1] Recently numerous mutations over 1000 are reported in gene databases. However, the mutations causing enzyme deficiency are associated with the clinical variants.[31] Furthermore, most of the pathogenic GLA mutations are private which are occurring in a single or few families.[1] In our first case a previously unreported, hemizygous variant in exon 7 of the GLA gene, c.1047G>A p.(Trp349*) was detected. This novel variant creates an interruption of the reading frame leading to a premature stop codon. To date, this variant is not described in the databases. In CentoMD® 3.3 it has been previously detected in 6 affected patients; 3 of them in a heterozygous state, further 2 in a hemizygous and one patient in a homozygous state, all of them with a pathologically increased lyso-Gb3. Centogene's internal allele frequency for this variant accounts for 0,000062. It is classified as pathogenic, class 1 according to the recommendations of Centogene and ACMG. And the mutation of the second case was a heterozygous mutation in exon 3 of the GLA gene, c.(422C>T) p.(Thr141Ile), which was previously reported as pathogenic missense type mutation for a classical phenotype of FD (http://fabry-database.org/mutants/).

Management of FD is composed of ERT and concomitant therapy for symptoms and organ involvements. It is essential to start the ERT as early as possible to prevent organ failure. There are promising results for renal outcomes with short- and long-term ERT use.[32-37] More importantly early initiation of ERT is the major issue for favorable renal and extrarenal outcomes. Furthermore, these studies demonstrated that decline in GFR continues in a patient with advanced kidney disease or with more than 50% glomerulosclerosis or with proteinuria >1 g/g creatinine under ERT.[23,37]

We planned our study with the purpose of early diagnosis and early ERT initiation. Although we do not perform EM evaluation, by attentive determination of screening cohort of biopsied patients according to LM findings we succeeded to diagnose 2 FD patients. Additionally, stable renal function was obtained in our first case under ERT at the end of 30 months with an eGFR of 118 mL/min/1.73 m^2 and proteinuria of 1.1 g/day. Although the second case and his mother continued their treatment at another center we learned that they are free of renal, cardiovascular, and neurologic events.

A small number of participants is the major limitation of the present study. Because of a biopsy number of 100 per year at our center. According to our inclusion criteria 53 patients, is an acceptable study population number for one center. Additionally, it would be better to determine the biopsies for screening in cooperation with the pathologist. We determined the screening population according to pathology reports. The cooperation will be more appropriate to specify possible case and to exclude the ones that have the aforementioned histopathologic findings of specific etiologies. Another point that has to be discussed is questioning the patients for FD. In practice, FD might be questioned in the proteinuric patients before the biopsy.

In conclusion, we conclude that its worth screening patients who had microscopic findings of vacuolated cells, mesangial expansion, glomerulosclerosis, interstitial fibrosis, and tubular atrophy of unknown etiology in the renal biopsy, either with or without CKD family history. Large-scale screening studies among proteinuric patients who underwent renal biopsy can strengthen our results.

Ethics Committee Approval: Ethics Committee Approval was received from the Institutional Research Committee of Uludağ University School of Medicine (2015-11/18).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Writing - A.O., Materials - A.O., A.Y., S.A., O.U., M.F.A., A.E., M.Y., K.D., M.G.; Critical Reviews - A.E., Supervision - M.G.

Conflict of Interest: The authors have no conflicts of interest to declare.

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