Editorial

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Pathologic findings of Fabry nephropathy: the pivotal role of kidney biopsy

Jung-ho Shin, Su Hyun Kim

Division of Nephrology, Department of Internal Medicine, Chung-Ang University Hospital, Seoul, Republic of Korea

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Fabry disease is a rare lysosomal storage disorder caused by absent or reduced activity of α-galactosidase A, and the subsequent systemic accumulation of predominantly globotriaosylceramide (GL3, also called GB3) is caused by mutations in the α-gal A-encoding gene on the X chromosome (Xq22.1). This deposition within the lysosomes triggers pathogenic pathways in the vascular endothelium and activities of cells of different tissues in vital organs (renal, cardiac, and nervous systems) that lead to cell death and irreversible organ damage.

The severity of clinical expression in hemizygous males correlates with α-gal residual activity, and the classical phenotype develops in individuals with <1% of residual enzyme activity. At a young age, classic male patients show severe general symptoms (neuropathic pain, angiokeratoma, hypohidrosis, and corneal opacity). Kidney involvement is a significant feature of Fabry disease, and untreated classical male patients develop end-stage renal disease in the third to fifth decade of life. On the other hand, manifestations of heterozygous females can range from asymptomatic, mild, or severe due to skewed X inactivation [1].

Fabry disease can be divided into a classic phenotype and a late-onset variant (nonclassical or atypical). This clinical phenotype is usually considered to be defined (at least partially) by the genotype. Classic Fabry disease manifests with typical symptoms of absent or low enzyme activity levels that begin in childhood. Late-onset Fabry disease is characterized by a more variable disease course (adulthood onset) with residual enzyme activity. In this issue of *Kidney Research and Clinical Practice*, Kim et al. [2] report the clinical and pathologic findings of patients with Fabry disease who underwent kidney biopsy before or after enzyme replacement therapy [ERT]. In particular, the before-treatment group showed pathologic GL3 accumulation in kidney tissues, even in those without microalbuminuria. Apparent nephropathy, including GL3 accumulation, can occur in patients with normal glomerular filtration rate and no or minimal microalbuminuria.

In a recent study in 14 patients with Fabry disease between 4 and 19 years of age with normal glomerular filtration rates, the amount of GL3 accumulation in the podocytes correlated with age [3]. In a study by Tøndel et al. [4], loss of segmental foot processes was observed in patients

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Editor: Tae-Hyun Yoo, Yonsei University, Seoul, Republic of Korea
Correspondence: Su Hyun Kim
Division of Nephrology, Department of Internal Medicine, Chung-Ang University Hospital, 102 Heukseok-ro, Dongjak-gu, Seoul 06973, Republic of Korea. E-mail: sh76so@cau.ac.kr
ORCID: https://orcid.org/0000-0003-3382-528X

Table 1. Renal pathologic changes after enzyme replacement therapy (ERT)

Study	Year	Pathologic changes after ERT			Patients achieving zero scores (%)				Major finding
		No. of patients (male)	Age (yr)	ERT duration (yr)	Podocytes	Mesangium	Endothelium	Interstitium	
Kim et al. [2]	2021	9	19–58	1.2–8	22	67	78	33	Segmental FPE and GL3 deposits can be persistent in Fabry nephropathy despite ERT
Skrune et al. [6]	2017	20 (12)	21 (7–62)	9.4 (4.4–11.7)	-	-	-	-	Adult male patient who started ERT at 18 years of age showed clearance of GL3 deposits from podocytes, yet a pediatric male patient who started ERT at 7 years of age showed better clearance
Najafian et al. [4]	2016	5 (5)	31 (18–46)	1 (11–12 mo)	-	-	-	-	73% decline in podocyte GL3 content and 63% reduction in podocyte volume after 11–12 months of agalsidase beta
Tøndel et al. [4]	2013	12 (11)	16.5 (7–33)	5 (4.2–5.8)	-	100	100	-	Significant correlation between reduction in podocyte GL3 inclusions and cumulative dose of agalsidase alfa or beta
Lubanda et al. [8]	2009	21	35.7 (19–55)	8	0	100	100	90	Lower dosage than 0.3 mg/kg can maintain GL3 clearance in some patients with Fabry disease, but other patients seem to require a dosage higher to prevent recurrence of GL3 accumulation in cells
Thurberg et al. [5]	2002	58 (56)	28.4 ± 11.4	1 (11 mo)	0[a]	100	96	100	Significantly more patients treated with agalsidase beta achieved GL3 clearance from glomerular capillary endothelial cells, arterial/arteriolar endothelial cells, mesangial cells, and interstitial cells compared to placebo

FPE, foot process effacement. GL3, globotriaosylceramide.
[a]Some patients (18%) showed reduction of GL3.

Table 2. Proposed assessments in Fabry disease

Organ system	Diagnostic tool
Kidney	eGFR (MDRD, CKD-EPI), ACR/PCR, kidney ultrasound, kidney biopsy
Cardiac	EKG, echocardiography, 24 hr Holter, cardiac MRI, troponin, BNP
Neurologic	Neurologic status, carotid/vertebral Doppler, nerve conduction studies, brain MRI
Others	Genetic counseling, Lyso GL3
	Ophthalmologic diagnosis, ENT
	Pulmonology (spirometry including response to bronchodilators and chest X-ray)
	Gastrointestinal (endoscopy or radiographic findings)
	Skeletal (bone mineral density)

ACR, albumin-creatinine-ratio; BNP, brain natriuretic peptide; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; ENT, ear, nose, and throat; GL3, globotriaosylceramide; MDRD, modification of diet in renal disease; MRI, magnetic resonance imaging; PCR, protein-creatinine-ratio.

with Fabry disease with albuminuria in the normal range of less than 30 mg/day. Similarly, the present study showed that podocyte foot process effacement (FPE) is one of the earliest signs of renal damage in Fabry disease.

Thurberg et al. [5] reported that patients receiving 11 months of ERT demonstrated a 100% reduction (complete clearance) in GL3 in peritubular capillary endothelial, mesangial, and interstitial cells. In contrast, only 18% of patients showed a reduction of GL3 in podocytes that responded after 11 months of ERT. This result might reflect the rate at which these cells turn over. In contrast to endothelial and mesangial cells, podocytes are differentiated terminally and proliferate poorly in response to injury or loss. We summarized several studies of renal pathologic changes after ERT for patients with Fabry disease (Table 1) [2,4–8]. Higher dose and early initiation of ERT might be positively associated with clearance of GL3 deposits from podocytes [4,6,8].

For assessment of disease severity and renal effect of ERT, we recommend histopathologic examination of the glomerular, tubulointerstitial, and vascular compartments. Therefore, kidney biopsy is pivotal. Because it can serve as a standard for treatment, kidney biopsy is a crucial screening test for women who suffer from classical complications. Therefore, kidney biopsy can be performed in a Fabry disease patient group to assess the degree of damage to the underlying tissues before enzymatic treatment and for clinical judgment of Fabry disease with atypical expression. ERT leads to a rapid and marked decrease in mesangial and endothelial cell GL3 inclusions, whereas podocyte inclusions and proteinuria persist despite treatment. Early intervention is crucial because ERT is less effective in more advanced diseases and results in irreversible damage.

Since Fabry disease is a progressive multisystem disease, various organs should be tested upon diagnosis (Table 2) [9,10]. A renal examination can be performed by a nephrologist (including estimated glomerular filtration rate and albuminuria), but involvement of other vital organs (especially the cardiac and neurologic) must be determined by an appropriate specialist.

In summary, Kim et al. [2] suggest the pivotal role of kidney biopsy in patients with Fabry disease as a screening tool for kidney damage and as an ERT response evaluation tool. In addition, they demonstrate segmental FPE and GL3 accumulation in renal pathologic findings even in patients with normoalbuminuria. Kidney biopsy is a vital tool in assessing renal involvement and can lead to early initiation of ERT, which can change the course of Fabry disease.

Conflicts of interest

All authors have no conflicts of interest to declare.

Authors' contributions

Writing–original draft: All authors
All authors read and approved the final manuscript.

ORCID

Jung-ho Shin, https://orcid.org/0000-0001-9755-3100
Su Hyun Kim, https://orcid.org/0000-0003-3382-528X

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