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Globotriaosylceramide (GL-3) Accumulation in the Renal Biopsy of a 1-year-old Patient with Fabry Disease and Ureteropelvic Junction Obstruction

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Authors' contributions

This work was carried out in collaboration between all authors. Authors DR, FM and HA were directly involved in the patient management. Author DR designed the study, managed the literature search and wrote the first draft of the manuscript. Author JIB performed the surgery. Author FM performed the genetic studies. Author NL performed the pathology study. Author HAR participated in the design and review the findings and the final manuscript. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Introduction: Fabry disease is a x-chromosome hereditary disease with an incidence of 1/40000 newborns. Nowadays it presents as much in males as in females and its first clinical symptoms are seen in pediatric patients. Patients have reduced or no activity of alpha-galactosidase which leads to progressive accumulation of GL-3 in lysosomes of all types of cells. This early deposition disrupts lysosomal function, leading to cell death, metabolic problems, vascular lesions, endothelial dysfunction, oxidative stress, alterations in autophagy tissue ischemia, and finally producing fibrosis

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in different tissues. On the other hand, ureteropelvic junction obstruction (UPJO) is the most frequent congenital anomaly of the urinary tract; with an incidence of 1 in 1000-2000 newborns.
A patient with antenatal diagnosis of Fabry disease and pre-natal diagnosis of UPJ is described. GL-3 deposits were found in all progeny of renal cells in the surgical biopsy.
Patient Report: Prenatal diagnosis of FD and severe left hydronephrosis (left renal pelvis 23 mm) He was born at term with adequate weight. Enzymatic activity of Alpha-Gal A was low and the molecular analysis confirmed the family's mutation. Pyeloplasty was performed when he was 17 months old and, having obtained informed consent, a small piece of kidney was studied, showing evidence of characteristic GL-3 deposits in all cell types and showed podocyte "effacement", a marker of injury and stress.
Conclusion: We demonstrate in this report that the deposits that lead to the sequence of a series of inflammation and fibrosis are present at a very early age. Based upon this finding, one can speculate about the prevention of late lesions with an early start of enzyme replacement therapy (ERT). Long term follow-up studies will be necessary to confirm this hypothesis.

Keywords: Fabry diseases; kidney biopsy; fabry nephropathy; pediatric.

1. INTRODUCTION

Fabry disease (FD) is an X-linked inherited disorder with an incidence of 1 in 40,000 live newborns. It is currently known that it affects both men and women and that the early signs and symptoms usually appear in childhood.

The deficient or absent activity of lysosomal alpha-galactosidase (α-GalA), results in the progressive deposition of its substrate, predominantly GL-3 in the various cell strains of different organs. The cardiovascular, neurological, and renal systems are severely affected, causing the main complications and the morbidity and mortality of the disease [1].

The accumulation of GL-3 triggers a cascade of events, including cell death, metabolic involvement, vascular injuries, endothelial dysfunction, oxidative stress, autophagic involvement, tissue ischemia, and eventually tissue fibrosis [2]. These signs and symptoms start early in patients with FD, and they are even described in the biopsies of affected fetuses, [3] in the placental tissue, [4] and in the renal biopsies of pediatric patients with normal glomerular filtration (GF) rate and without pathological proteinuria or albuminuria [5].

Since the advent of the ERT in 2001, the optimal time for initiation of treatment has been under discussion. Even though from the renal perspective, this disease remains silent during childhood, it usually progresses to renal failure once proteinuria becomes evident. In addition, patients generally do not benefit from ERT when proteinuria is overt or when the glomerular filtration rate has started to decline. As a result, early diagnosis and treatment of Fabry nephropathy in pediatric patients may be critical for the preservation of renal function.

On the other hand, UPJO is the most common congenital obstruction of the urinary tract and it is the leading cause of antenatal hydronephrosis. The incidence described in the literature is around 1 in 500 live newborns diagnosed by prenatal ultrasound screening [6].

This paper describes a patient with a prenatal diagnosis of UPJO and FD with evidence of early GL-3 deposition in different renal cell strains. The importance of this description lies in the fact that this is the youngest FD patient in the literature who has undergone a renal biopsy and is helping to improve our understanding of the pathophysiology of the disease.

2. CASE REPORT

The mother of our patient, was referred to our center in her fifth month of pregnancy with a diagnosis of FD. Her mother's grandmother and her uncle had died at the age of 65 and 27 respectively, both diagnosed with FD and end-stage renal failure. Two aunts and 4 first cousins are currently receiving ERT.

During the third trimester of pregnancy the fetus was diagnosed with antenatal hydronephrosis (AHN), with a 23-mm dilation of the left renal pelvis and cortical thinning, invisible urethra, and normal bladder.

The baby was born at Week 39, with a weight of 3,365 Kg. Decreased α-GalA enzyme activity (0.82 µmol/h, reference value 2.10-10.51) and

molecular analysis revealed the presence of the hemizygous c.647A>G mutation in exon 5 of the GLA gene.

Due to the history of AHN, an ultrasound of the kidneys and the bladder (25-mm left pyelocalyceal dilation) and a voiding cystourethrogram were performed, ruling out the presence of vesicoureteral reflux. A renal scan with dimercaptosuccinic acid (DMSA) (right kidney's relative function: 66% with normal distribution of the radiopharmaceutical; left kidney: 34%, with little avidity for the tracer, and cortical thinning) and a radiorenogram with diethylenetriaminepentaacetic acid (DTPA) (left kidney's obstructive curve without response to furosemide) were performed.

No urinary tract infections were registered. The estimated glomerular filtration (Schwartz 09) was normal (110 mL/min/1.73 m^2), with a proteinuria/creatininuria index of 0.58 mg/mg (normal value < 0.5 mg/mg) and albuminuria/creatininuria of 318 mg/g (NV<30 mg/g), both within the pathological range.

Following the diagnosis of UPJO, a surgical intervention (pyeloplasty) is scheduled at 1.5 years of age. After the *ethics committee approval*, the mother signed the informed consent and renal biopsy samples were obtained during the procedure to determine the involvement of FD.

A high-resolution optical microscopy (HROM) and an electronic microscopy (EM) were performed. The HROM (Fig. 1A, B) shows 18 complete glomeruli, one of them with extracapillary fibrocellular proliferation and pericapsular fibrosis. The remaining ones show mild and variable matrix proliferation and mesangial hypercellularity. Small lipid vacuoles were observed in these areas, as well as in some endothelial cells, in most podocytes and parietal cells of the Bowman's capsule, and in tubular cells. Mild focal fibrosis and edema were observed in the interstitium. Vessels showed endothelial tumefaction and cytoplasmic vacuolization. The EM (Fig. 1C) describes segmental fused podocyte foot processes with podocyte vacuolization, lost of attachment to the basal membrane and presence of intralysosomal lamellar bodies, which also appear in endothelial, mesangial, and tubular cells. Variably enlarged mesangial matrix and segmental collapse of one glomerulus together with extracapillary fibrocellular proliferation were observed.

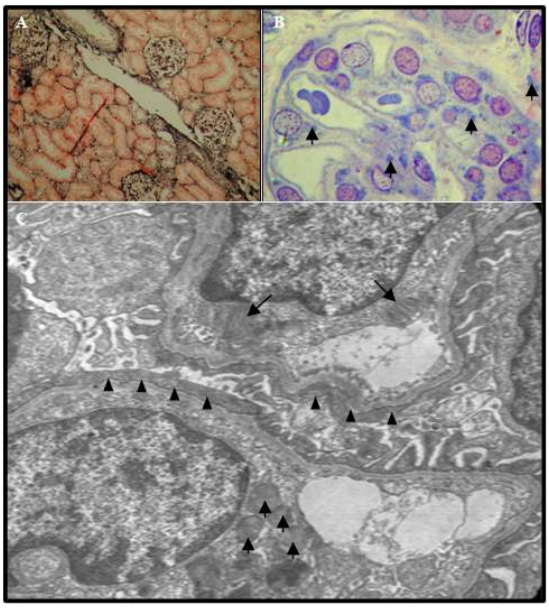

Fig. 1. A y B: High-resolution optical microscopy

A Scarce tubular-interstitial component. B GL-3 deposits in all glomerular cell compartments (Arrows). C: Electronic Microscopy: Intra-capillary lamellar bodies in endothelial and mesangial cells (arrows). Segmental fused podocyte foot processes ("effacement", arrow heads). Uranyl acetate/ Reynolds 7,000x

3. DISCUSSION

The classical pathophysiological concept which associated ultimate FD damage –fibrosis- to the ischemic injury underlying the buildup of glycosphingolipids in the endothelial cell lysosomes of the microvasculature is increasingly being left behind. Current reviews involve a series of secondary mediators which result in injury, affecting the parenchymal cells.[2] Consequently, fibrosis would only be the end product of all of these inflammatory processes, apoptosis and tissue injury, thus being irreversible and having only a few or no treatment options at all.

Additional information regarding the pathophysiological relation between glycosphingolipid deposition and tissue damage is constantly reported. The activation of multiple inflammatory mediators is described as responsible for the progressive fibrosis. Globotriaosylsphingosine (Lyso-GL-3) has been recently described as one of many other molecules which are accumulated in FD and has been associated with the expression of TGF-β1,

a critical mediator of extracellular matrix production, fibrosis, and injury of podocytes, extracellular matrix proteins (fibronectin and type IV collagen) and CD74, the inflammatory cytokine receptor [7].

FD nephropathy results in protein losses and this in itself is a marker of renal disease progression [8].

With regard to the understanding of renal histology in FD, the publications only date from 50 years ago, when Pompen et al. [9] first described the autopsies of two siblings. More extensive papers were published later on, including that of Gubler et al. [10] and Desbois et al. [11]. The latter includes pediatric biopsies. Tøndel *et al* describe the involvement of several renal strains, including podocytes, in 9 FD pediatric patients with normal-for-age glomerular filtration rate and even some of them with physiological albuminuria [5]. This has led to put albuminuria under discussion as a sufficiently sensitive glomerular damage marker.

Once again, in their last publication, Tøndel et al. [12] quote the finding of fused podocyte foot processes in pediatric patients with normal albuminuria and glomerular filtration. Our patient showed podocyte “effacement” at 1 year of age. We know that this phenomenon is a marker of podocyte injury and stress, as intact podocytes are necessary to preserve the glomerular filtration barrier and its damage is generally associated with glomerular diseases involving protein loss.

Najafian et al. [13] describe the relation between proteinuria and early glomerular lesions in young patients with Fabry nephropathy. Once proteinuria is established, glomerular filtration is also known to unavoidably decrease and lead to end-stage renal failure, usually between the third and the fifth decade of life in men, [14] although cases of patients as young as 16 years old have been reported [15].

Laney et al. [16] have conducted a recent review on FD in patients under the age of 5 with early signs and symptoms. From the perspective of renal involvement, even though publications are limited, the presence of pathological albuminuria, proteinuria, and even decreased glomerular filtration are described in this age group, showing deposits in all renal cell strains [5,17].

The right time to start the ERT is still controversial. It should be as early as possible so as to avoid the cascade of inflammatory mediators, and before irreversible damages occur. Just as other authors, we have previously documented deposits clearance in the various cell strains, as well as the limitation of the ERT activity in podocytes [18].

In the patient we described, the lesion of podocyte effacement is clearly observed. On the other hand pathological changes related to obstructive nephropathy are tubulointersticial fibrosis and only on late stages, involvement like atubular glomeruli injury can be found [19]. In this patient there are only mild tubulointersticial fibrosis, and he has normal glomerular filtration.

Our patient may be eligible for early treatment, not only because of the histological findings we have, but also because of proteinuria/albuminuria, which is one of the earliest markers of FD renal involvement. Despite the fact that we cannot distinguish whether proteinuria derives from the early involvement of FD or prenatal damage resulting from uropathy, this cannot be considered for longitudinal follow-up. Also, as a result of prenatal uropathy, the patient shows reduced renal mass, and so FD renal damage could be expected to develop much earlier. Finally, the extensive family history of progression could be predictive of some kind of geno-phenotype correlation.

Clinical trials have shown the effectiveness of ERT in reducing GL-3 concentrations in plasma, the renal vascular endothelium, the skin, and the heart. They have also proven the benefits in the management of pain and digestive symptoms, as well as the safety and efficacy of both ERTs [20]. In view of the findings of this study, our patient could be eligible for early treatment initiation.

4. CONCLUSIONS

FD is a variable condition of insidious progression whose manifestations arise early in the fetus. We believe that descriptions similar to that of our patient may contribute to the challenge of understanding the pathophysiology of renal involvement.

We are aware that in many publications showing irreversible renal damage ERT has been started in late stages. Although based on current data, the optimal time to start ERT remains unclear, the trend is set towards early initiation, in order to prevent damage as stated in our discussion. The

available evidence may lead to conjectures on the ability of the ERT to halt this cascade of inflammatory mediators and cytokines before abnormalities become irreversible.

Yet, long-term publications on patients treated early will be necessary to support this recommendation.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: Clinical manifestations and impact of disease in a cohort of 98 hemizygous males. J Med Genet. 2001;38:750–760.
2. Weidemann F, Sanchez-Niño MD, Politei J, Oliveira JP, Wanner C, Warnock DG, Ortiz A. Fibrosis: A key feature of Fabry disease with potential therapeutic implications. Orphanet J Rare Dis. 2013;8: 116.
3. Tsutsumi O, Sato M, Sato K, Mizuno M, Sakamoto S. Early prenatal diagnosis of inborn error of metabolism: A case report of a fetus affected with Fabry's disease. Asia Oceania J Obstet Gynaecol. 1985; 11:39–45.
4. Thurberg BL, Politei JM. Histologic abnormalities of placental tissues in Fabry disease: A case report and review of the literature. Hum Pathol. 2012;43(4):610-4.
5. Tøndel C, Bostad L, Hirth A, Svarstad E. Renal biopsy findings in children and adolescents with Fabry disease and minimal albuminuria. Am J Kidney Dis. 2008;51:767–776.
6. Morin L, Cendron M, Crombleholme TM, Garmel SH, Klauber GT, D'Alton ME. Minimal hydronephrosis in the fetus: Clinical significance and implications for management. J Urol. 1996;155:2047.
7. Sanchez-Niño MD, Sanz AB, Carrasco S, Saleem MA, Mathieson PW, Valdivielso JM, Ruiz-Ortega M, Egido J, Ortiz A. Globotriaosylsphingosine actions on human glomerular podocytes: Implications for Fabry nephropathy. Nephrol Dial Transplant. 2001;26(6):1797-802.
8. Gorriz JL, Martinez Castelao A. Proteinuria: Detection and role in native renal disease progression. Transplantation. Reviews. 2012;26:3–13.
9. Pompen AW, Ruiter M, Wyers HJ. Angiokeratoma corporis diffusum (universale) Fabry, as a sign of an unknown internal disease; two autopsy reports. Acta Med Scand. 1947;128:234–255.
10. Gubler MC, Lenoir G, Grunfeld JP, Ulmann A, Droz D, Habib R. Early renal changes in hemizygous and heterozygous patients with Fabry's disease. Kidney Int. 1978; 13:223–235.
11. Desbois JC, Maziere JC, Gubler MC, Allaneau C, Verhaeghe MP, Herrault A. Fabry's disease in children. Clinical and biological study of one family. Structure and ultrastructure of the kidney in a hemizygote and a heterozygote. Ann Pediatr. 1977;24:575–586.
12. Tøndel C, Kanai T, Larsen KK, Ito S, Politei JM, Warnock DG, Svarstad E. Foot process effacement is an early marker of nephropathy in young classic Fabry patients without albuminuria. Nephron. 2015;129(1):16-21.
13. Najafian B, Svarstad E, Bostad L, Gubler MC, Tøndel C, Whitley C, Mauer M. Progressive podocyte injury and globotriao sylceramide (GL-3) accumulation in young patients with Fabry disease. Kidney Int. 2011;79(6):663-70.
14. Branton MH, Schiffmann R, Sabnis SG, Murray GJ, Quirk JM, Altarescu G, Goldfarb L, et al. Natural history of Fabry renal disease: Influence of alpha-galactosidase A activity and genetic mutations on clinical course. Medicine (Baltimore). 2011;81:122–138.
15. Sheth KJ, Roth DA, Adams MB. Early renal failure in Fabry's disease. Am J Kidney Dis. 1983;2:651–654.
16. Laney DA, Peck DS, Atherton AM, Manwaring LP, Christensen KM, Shankar SP, Grange DK, et al. Fabry disease in infancy and early childhood: A systematic literature review. Genet Med. 2015;17(5): 323-30.
17. Hopkin RJ, Bissler J, Banikazemi M, Clarke L, Eng CM, Germain DP, et al. Characterization of Fabry disease in 352 pediatric patients in the Fabry Registry. Pediatr Res. 2008;64:550–555.

18. Ripeau D, Masllorens F, Repetto HA. Enfermedad de Fabry y riñón en pediatría. Arch Latin NefrPed. 2011;11(2): 50-64.
19. Chevalier RL, Forbes MS, Thornhill BA. Formation of atubular glomeruli in the developing kidney following chronic urinary tract obstruction. Pediatr Nephrol. 2011; 26(9):1381-5
20. Desnick RJ, Brady RO. Fabry disease in childhood. J Pediatr. 2004;144(suppl5): S20–S26.

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