Fabry disease: the many faces of a single disorder

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In 1898, two dermatologists, William Anderson in England and Johannes Fabry in Germany, separately described a disease characterized by skin lesions, known as angiokeratomas. This issue contains two reports of Fabry disease (FD) patients presenting with proteinuric chronic kidney disease (CKD) but lacking angiokeratomas [1, 2]. These cases illustrate the phenotypic heterogeneity of the disease in females [1] and FD variants [2], the role of genetic diagnosis [1] and renal biopsy [2] and recent advances in pathophysiology [1]. FD is caused by deficient activity of alpha-galactosidase A (α-GalA) due to mutations in the X-chromosome GLA gene, leading to accumulation of neutral glycolipids and eventual tissue injury and organ dysfunction [3]. In classical FD males, α-GalA activity is absent or nearly absent and there is an early onset of acroparesthesias, angiokeratoma and hypohidrosis followed by life-threatening cardiac, central nervous system and kidney disease leading to end-stage renal disease (ESRD) at a mean age of 40 years [3, 4].

FD in females

Although FD is an X-linked disorder, women should not be considered as just carriers of the disease. The term X-linked recessive, which used to be applied to this disorder, should probably be discontinued and FD should simply be described as following an ‘X-linked inheritance’. The same is true for another well-known X-linked renal disorder: Alport's syndrome. FD females may show a milder form of the disease with signs and symptoms starting later as reported by Lukas et al. in this issue of CKJ [1]. Although this milder form is true for most cases, some women with FD show a severe and aggressive presentation indistinguishable from that seen in males [5]. The explanation for the wide variability in clinical presentation may be partly due to lyonization [6], a process where one copy of the X-chromosome is randomly inactivated in all cells of the female embryo. Therefore, females are essentially a ‘mosaic’ of normal and mutant cells in varying proportions. In X-linked diseases, females may show a severe phenotype as a consequence of skewed X-chromosome inactivation, resulting in a higher percentage of the wild-type X-chromosome being inactivated in a specific tissue. A high percentage of women with FD show vital organ damage as shown by Lukas et al. [1]. Although most females present scarce renal signs, some may show proteinuria as stated by Lukas et al. [1, 7, 8] and even ESRD. In a retrospective study of 279 affected males and 168 females with FD, the mean rate of estimated glomerular filtration rate decline was −1.02 mL/min/1.73 m² per year for females compared with −2.93 mL/min/1.73 m² per year for males [9]. While this is the expected rate of renal function decline in correlation with age in female patients, it is twice the expected rate in males. ESRD was less prevalent in females, who account for around 10% of FD patients on renal replacement therapy [4]. However, those females who reach ESRD do so at the same mean age as males [4, 8].

Renal variant

Late-onset FD variants are generally caused by less severe mutations, resulting in a residual enzymatic activity of 1–15% of normal, and phenotypically may not display many of the multisystem symptoms of classical FD. Cardiac and renal variants have been recognized based on predominant or exclusive symptoms related to these organs [10, 11]. In this issue, Al-Salam et al. report a case of renal variant FD [2]. Although the clinical variability of FD had been recognized previously, the term ‘renal variant’ was coined in 2003 [11]. Haemodialysis patients in Japan were previously screened and five male FD patients who had initiated haemodialysis at 25–56 years of age with a clinical diagnosis of chronic glomerulonephritis were found, a diagnosis also entertained in the case by Al-Salam et al. [2]. Angiokeratoma, corneal opacities, acroparesthesias and hypohidrosis were not observed, but most had left ventricular hypertrophy, a common finding in CKD. In an additional patient with acroparesthesias, the FD diagnosis had been missed in a renal biopsy where, in retrospect, deposits were observed [11]. Thus, the renal variant may display severe and early renal disease, despite relatively high residual enzymatic activity [11]. A correct understanding of the pathogenesis of FD is required to fully understand this phenotypic variability.

Pathogenesis of kidney injury in FD

The enzymatic defect in FD causes intracellular accumulation of neutral glycosphingolipids, mainly globotriaosylceramide (GL-3; GB-3, ceramide trihexoside (CTH)) and, as
observed in the report by Lukas et al. [1], increased circulating and even urinary levels of Gb3 and globotriaosylsphingosine (Lyso-Gb3) [12]. These lipids have been confused in the literature [13]. Lyso-Gb3 is a deacylated metabolite of Gb3. The loss of a fatty acid makes lyso-Gb3 more soluble than Gb3. How the accumulation of these glycolipids contributes to Fabry nephropathy is unclear (Figure 1). It was initially suggested that glycolipid accumulation in endothelial cells led to endothelial dysfunction or physical obstruction of small vessels and resultant ischemic tissue injury. The lack of endothelial deposits in a non-dialysis septuagenarian with a cardiac variant and extensive podocyte deposits was interpreted as supporting the key role of the endothelium in promoting early ESRD. However, this patient had proteinuria and Stage 3 CKD [14]. Younger patients with proteinuria and Stage 3 CKD have been described that had podocyte but not endothelial deposits [15]. Endothelial deposits may be a surrogate marker for extensive glycolipid deposition rather than a cause of ESRD. Indeed, severe cardiac fibrosis was observed in lethal cardiac variants characterized by cardiomyocyte deposits in the absence of endothelial deposits [16]. In this regard, FD nephropathy is a progressive proteinuric nephropathy of metabolic origin [8], features shared by diabetic nephropathy. Podocyte injury is considered central to proteinuric nephropathies. Podocyte apoptosis, podocytopenia and increased synthesis of extracellular matrix are early features of diabetic nephropathy. Evidence is accumulating supporting a central role of podocyte injury in FD. Thus, in FD children podocyte, but not endothelial, inclusion volume density increases progressively with age, along with the foot process width, which correlates with proteinuria [17]. Furthermore, similar to the effects of high glucose, lyso-Gb3 elicits in cultured human podocytes a pro-fibrotic, proapoptotic response characterized by increased TGFβ1-mediated extracellular matrix production and increased CD74 [18]. Increased CD74 is found in human podocytes in diabetic nephropathy [19]. Both in FD males and in females, proteinuria is a key determinant of CKD progression, either in natural history or in enzyme-treated populations [20, 21]. Proteinuria, contrary to other features of FD, hardly improves with enzyme replacement therapy (ERT) [22, 23]. Since podocyte deposits are difficult to clear by ERT,
contrary to endothelial deposits, this further supports a key role of podocyte injury in FD [24]. The definite unraveling of the mechanisms and role of podocyte injury in the pathogenesis of Fabry nephropathy awaits the availability of adequate FD animal models.

Diagnosis of FD

Diagnosis of FD is usually first suspected on clinical basis. However, in this issue, two reports show how difficult it can be to diagnose FD due to the phenotypic variability in females [1] or unusual clinical features [2]. The latter case also illustrates both the power of renal biopsy in suspected cases of FD in the context of absent or overlooked classical systemic symptoms or family history, and the limitations of renal biopsy when electron microscopy or an expert pathologist is not available. Even in typical cases, recognizing the early manifestations in clinical practice may be challenging. When these signs or symptoms raise the suspicion of FD, appropriate biochemical and/or genetic confirmation is needed. The demonstration of a deficient activity of α-galactosidase in plasma, leukocytes or whole blood is the reference laboratory method, which should be used to screen males for FD. A plasma assay may occasionally lead to false diagnosis and should be confirmed by a leucocyte assay or genetic analysis [25]. However, as reported by Lukas et al. in this issue, the α-galactosidase levels are normal in ~50% of females [1]. Therefore, in females the definitive diagnostic confirmation should be made by genetic analysis. Direct sequencing is easy because of the small size of the gene (7 exons) and has become widely available. It should be carried out to confirm any suspected case of FD. A method that uses filter paper cards containing dried blood spots has been set up for both α-galactosidase levels determination and genetic screening. All kinds of mutations have been described in the α-galactosidase gene: missense or nonsense point mutations, splicing mutations, small deletions or insertions and large deletions. There is neither a hot spot for mutations or a common mutation in this gene. Most mutations are isolated and >600 mutations have been described to date [26]. The majority of these mutations render a nonfunctional enzyme. Two issues may complicate genetic studies. First, direct sequencing of the gene may miss some cases as reported by Lukas et al. [1]. The use of multiplex ligation-dependent probe amplification (MLPA) is recommended in cases where a decreased enzyme activity is not associated with the identification of a pathogenic mutation [27]. The second issue is assessing the pathogenicity of base pair changes. R118C was described in newborn screening as a late-onset mutation based on cell culture activity data, but, at the time, not a single patient with FD symptoms carrying this mutation had been described [28]. Renal variant FD was diagnosed by electron microscopy in a renal biopsy in a male hemizygote for the C174G mutation [15]. However, the single nucleotide polymorphism database of functional effects had considered C174G a non-pathogenic polymorphism based on predicted functional effects assessed by screening for non-acceptable polymorphisms and sorting intolerant from tolerant scores [29]. MLPA should be considered in these cases to search for additional genetic defects. Finally, as indicated by Lukas et al., there is an active field of research on the role of assessment of different glycolipid metabolites in body fluids in the diagnosis and monitoring of FD [1].

Summary

In summary, the articles presented in the current issue of CKJ focus our attention towards ‘non-typical’ forms of the disease. Patients with unusual clinical or genetic features contribute to unravelling the pathogenesis of FD nephropathy. Considering the different diagnosis approaches we have nowadays and, above all, the availability of ERT, it is important to raise the suspicion of FD when we face unexplained proteinuric CKD in either males or females.

Acknowledgements. Funding. A.O. is supported by FIS PS09/00447, Comunidad de Madrid/CIFRA/S2010/BMD-2378, Sociedad Española de Nefrología, Fundacion Renal Inigo Alvarez de Toledo-IRSN, ISCIII-RETIC REDinREN/RD06/0016 and Programa Intensificación Actividad Investigadora (ISCIII/Agencia Lain-Entralgo/CM). R.T. is supported by FIS 09/01506, Programa Intensificación Actividad Investigadora ISCIII/Generalitat de Catalunya, ISCIII-RETIC REDinREN, Consolidated Research Catalan Group (AGAUR 2009/SGR-1116), Fundacion Renal Inigo Alvarez de Toledo-IRSN.

Conflict of interest statement. None declared.

(See related articles by Lukas et al. Broad spectrum of Fabry disease manifestation in an extended Spanish family with a new deletion in the GLA gene. Clin Kidney J 2012; 5: 395–400; and Al-Salam et al. Renal variant of Fabry disease with sporadic GLA gene mutation: role of early renal biopsy. Clin Kidney J 2012; 5: 416–419)

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Received for publication: 7.8.12; Accepted in revised form: 7.8.12