Early Biomarkers of Fabry Nephropathy: A Review of the Literature

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Keywords

Fabry nephropathy · Biomarkers · Early marker · Early diagnosis

Abstract

Progressive nephropathy is one of the main features of Fabry disease. Although some clinical signs of Fabry nephropathy are already present in childhood, patients are often diagnosed relatively late in the course of the disease due to the absence of specific clinical markers, while a timely diagnosis and the prompt start of enzyme replacement therapy may be beneficial in stabilizing renal function or slowing its decline. Proteinuria/albuminuria has been accepted as the most important marker for Fabry nephropathy; however, a large proportion of renal impairment occurs in nonalbuminuric state. Therefore, early biomarkers may be useful for early identification of kidney involvement. The aim of this article is to review the current available literature on all biomarkers of Fabry nephropathy, with a comprehensive and critical description of their utilization in early recognition of renal damage.

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Introduction

Fabry disease (FD) is an X-linked disorder caused by lysosomal α -galactosidase A (α Gal-A) deficiency, with subsequent deposition of undegraded glycosphingolipid

products, mainly globotriaosylceramide (Gb3), in multiple organs, that, together with other pathophysiological triggers (such as cellular death, compromised energy metabolism, small vessel injury, and tissue ischemia) are responsible of significant morbidity and premature death [1].

Nephropathy is one of the main features of FD: kidney involvement follows Gb3 deposition in all types of renal cells and is characterized by a progressive disease that usually leads, in untreated patients with classical mutations, to end-stage renal disease from the third to the fifth decade of life [2–5].

Although some clinical signs of Fabry nephropathy are already present in childhood, its heterogeneous and non-specific presentation is associated with a delay in diagnosis of approximately 15 years, also due to the absence of specific clinical markers [6].

The availability of a disease-specific treatment with enzyme replacement therapy (ERT) and chaperone therapy, and the evidence that a severe renal dysfunction may compromise its effectiveness, stress the need for a prompt recognition of the early markers of organ involvement [5, 7–9].

To date, albuminuria and reduction of glomerular filtration rate (GFR) are the only markers of renal dysfunction in FD and the most important predictors of renal disease progression in adult Fabry patients [5, 7, 8]. Even Canadian Guidelines for treatment of FD (October 2018) report, as major criteria to satisfy the start of ERT, besides the findings of high-risk pathology on renal biopsy in

males, only the reduction of GFR or persisting proteinuria of 500 mg/day/1.73 m² or greater [10]. Therefore, unfortunately, the treatment with ERT is commonly delayed until proteinuria or even overt organ involvement occurs, when the reversibility of renal damage is difficult to achieve, and the prognosis is poor [8, 11–13].

Based on the 2 assumptions that early kidney involvement is clinically silent and early treatment is more likely to prevent progressive kidney injury, alternative markers of kidney dysfunction are mandated. So, the identification of biomarkers correlated to the earliest pathological findings is paramount, as these biomarkers may become a noninvasive, diagnostic method of preclinical renal involvement by FD.

We performed a review of the literature with PubMed, US National Library of Medicine, Google Scholar, and Cochrane Library databases to describe the “state of the art” in the knowledge on biomarkers in Fabry nephropathy, with a comprehensive and critical description of their utilization in early recognition of renal damage.

Urine Microscopy

Targeted urinary microscopy has been widely described as a noninvasive, inexpensive, accessible, and rapid diagnostic technique, especially applicable where plasma and/or leucocyte α Gal-A activity and genotyping are not affordable or available. Different reports suggest that urine microscopy may be a useful tool for the noninvasive diagnosis of FD and for the assessment of disease progression [14–31]; however, it presents some limitations because its diagnostic value is not well established in patients with attenuated phenotypes (mainly in females), most of the findings are not pathognomonic of FD, and its prognostic value needs further evidence.

Desnick et al. [14] and Nagao et al. [15] described the common variety of birefringent Maltese cross (MC) pattern (oval fat bodies) in the urine sediment of FD patients when viewed under a polarized microscope; Birch et al. [16] and later Branton et al. [3] further described characteristic internal lamellation and irregular surface protrusions of MC particles in FD. More recently, Selvarajah et al. [17] identified a specific morphological population of MC particles (MC 2), characterized by lamellated appearance with protrusions, likely due to Gb3, and resembled “mosquito coils,” that probably represents fragmentation of shed nephronal epithelial cells containing lysosomal Gb3. The authors demonstrated that albuminuria correlated with quantitative particle excretion, and that MC 2

particles were highly specific (100%) and sensitive (100%) for FD.

The deficiency in α Gal-A in FD leads to the progressive accumulation of Gb3, which is identical to the CD77 membrane antigen. The same authors showed that characteristic CD77/Gb3-positive cells (GL3 cell) detection in urine of Fabry patients is also highly sensitive (97%) and specific (100%). Like MC 2 particles, GL3 cells were seen even in patients without clinical nephropathy [17].

Mulberry cells are frequently observed in the urinary sediment and are strongly suggestive of renal FD [18]. Nakamichi et al. [19] reported mulberry cells as distal tubular epithelial cells, in which Gb3 has accumulated, but no proof about their origin is reported in the literature; they are similar to oval fat bodies, but can be distinguished by the difference in refractivity, size, and inner lamellar appearance [19]. Some reports have suggested that the detection of urinary mulberry cells may be a useful tool to identify incipient FD nephropathy [20, 21]; however, screening for urinary mulberry cells has several limitations. First, the incidence of these cells in renal FD patients is unknown; second, a diagnosis can depend on the experience of the technician or physician performing the exam.

Another important finding in FD patients is the urinary loss of podocytes, a phenomenon known as podocyturia. Podocytes, which are a major target cell in Fabry nephropathy, do not proliferate and therefore continue accumulating α Gal substrates throughout their whole lifespan, with morphologic and functional alterations, which may occur before the clinical evidence of proteinuria [22, 23]. In particular, despite the exact mechanisms of podocyte detachment and podocyturia in FD are not fully understood, some authors reported that they are likely caused by the accumulation of Gb3, which interacts with actin causing cell contraction, slit diaphragm widening, and the coupling with integrins [24–28]. Trimarchi et al. [27, 29] showed that Fabry patients displayed higher levels of podocyturia compared to the normal population, suggesting that podocyturia could be an ideal biomarker to assess early glomerular involvement in FD. Moreover, Fall et al. [30] found a direct association between podocyturia and proteinuria and an inverse association between podocyturia and eGFR in male Fabry patients, concluding that there are important correlations between podocyturia and severity of Fabry nephropathy. In contrast, the finding of the study by Selvarajah et al. [17], of a relatively low-grade podocyte excretion (54%) in urine from Fabry patients, is consistent with a glomerular injury which is slowly progressive, but does not endorse the

use of podocyturia as a diagnostic or monitoring tool in FD. However, different limitations in the use of podocyturia as early marker of Fabry nephropathy have been reported: the main is that the diverse techniques used to assess podocyturia (microscopy of stained cells, proteomics-based assays, or mRNA quantification) have not yet been standardized to the point that they may enter/be used in clinical practice. Moreover, the available methods are time-consuming, expensive, and laborious, and the best urinary podocyte-specific markers have not been established [27–29]. Finally, podocytes are frequently lost in clusters and erratic; therefore, their intermittent loss in the urine may oblige physician to perform serial analyses of repeated urine samples to correctly evaluate the case [31]. In addition, since glomerular podocyte loss is thought to be irreversible, amelioration or halting of podocyturia may be a reasonable indicator of treatment efficacy on renal damage. Some authors have shown that patients on ERT had lower podocyturia, suggesting that treatment may stabilize podocytes attachment and reduce their irreversible loss, and concluding that podocyturia may also be used during the follow-up of patients on ERT in order to assess the response to treatment [27, 30]. Trimarchi et al. [27] reported higher podocyturia and lower proteinuria in untreated patients compared to patients on ERT, suggesting that clinically covert podocyturia may antedate proteinuria; moreover, individuals on ERT presented worse renal function, which may indicate that enzyme therapy is currently started at advanced stages of FD. In contrast, in other studies [17, 30], authors did not find differences in podocyturia between treated and untreated patients; however, proper assessment of ERT effect on podocyturia would require longitudinal studies to be done in the future.

Proteinuria

Albuminuria/proteinuria is usually considered to be the current gold standard and a sensitive biomarker for the Fabry nephropathy [4, 32]. In classically affected patients, it usually emerges in the second or third decade of life and contributes to the progression of the FD nephropathy; in fact, it is one of the most important indicator of renal disease progression in both treated and untreated patients [5, 33]. Nevertheless, significant histological changes may occur without pathological albuminuria/proteinuria [23, 34], thus its sensitivity to identify incipient FD nephropathy is questionable [6, 35]. Moreover, some authors reported that proteinuria may not be overt

in patients with advanced kidney disease, and not correlates with GFR decline [3, 4]: in particular, Ortiz et al. [4] showed that the prevalence of proteinuria and its magnitude increased with decreasing renal function in both sexes, but several patients with eGFR <60 mL/min/1.73 m² had proteinuria <300 mg/24 h.

Hyperfiltration

It is reported that glomerular hyperfiltration (HF) may represent an early feature of Fabry nephropathy [36–38]. In particular, a recent study reported, in a cohort of 87 patients with classical FD, a prevalence of HF (estimated GFR >130 mL/min/1.73 m² corrected for age) of 24%, which increased to 50% when only young-adult patients (age ≤40 years) were considered. Moreover, the authors showed a negative correlation between estimated GFR and age, and with proteinuria levels and the presence of cardiovascular and other manifestations of FD, suggesting that HF in Fabry patients could be related predominantly to a predisease state [39]. An important limitation of this study, however, is the use of an equation-based GFR that, although is the one which better correlates with true GFR, needs to be confirmed by a nuclear medicine technique. Therefore, the authors concluded that HF may be considered a relatively frequent feature in young Fabry patients, in comparison to other diseases classically related to an early HF status [40–42], and, once suspected on the basis of an elevated eGFR, must be confirmed with a nuclear medicine technique, since its recognition represents a relevant feature to start nephroprotective treatments in the very early stages of the disease [39].

In line with these evidences, the Canadian Guidelines for treatment of FD (September 2017) report, among the minor criteria to satisfy the start of ERT, the finding of HF (GFR >135 mL/min/1.73 m²) in at least 2 measurements of GFR by nuclear medicine techniques [10].

Cystatin-C

To overcome the limitations of creatinine as a marker of GFR [43, 44] and the difficulties linked to the feasibility of nuclear medicine techniques (Cr51-EDTA, ioehxol, or iothalamate clearance) that are expensive, time consuming, cumbersome, and difficult to repeat on a serial basis, Cystatin-C has been proposed as a marker of early changes of renal function in Fabry nephropathy.

Cystatin C is a small (13 kDa) monoglycosylate protease inhibitor, which is produced at a constant rate, is freely filtered by the glomeruli, and is completely reabsorbed and catabolized by proximal tubules. Its serum concentration is very sensitive to changes in GFR in the early phases of renal function impairment [45]. Different studies have demonstrated that the Cystatin C concentration is a superior and more sensitive marker than serum creatinine to detect early renal involvement or small decreases in the glomerular filtration rate in FD patients of both genders [46, 47]. In particular, Feriozzi et al. [48] showed that the accuracy of Cystatin C in highlighting early changes in renal function is likely to be for several reasons: in particular, its serum levels do not depend on age, sex, and muscle mass, and creatinine has a tubular secretion that increases with the reduction of renal function [49, 50].

Urinary Gb3 and Globotriaosylsphingosine

Molecules such as Gb3, the main substrate of the enzyme α Gal-A [51], and its deacylation product globotriaosylsphingosine (Lyso-Gb3), accumulate due to the enzymatic defect and have been extensively considered as a possible biomarker of FD [6]. Their urinary excretion has been identified as the gold standard with better sensitivity to identify FD patients than the plasma levels [52–54]. However, there was no apparent correlation between their values and renal involvement, so there is no evidence of their utilization in assessing renal prognosis [55]. Moreover, different studies showed the importance of serum lyso-Gb3 levels as markers of Fabry nephropathy in both genders [52, 56–58]; in particular, Nowak et al. [57] reported that lyso-Gb3 was a useful marker along with the leukocyte α Gal-A activity for the diagnosis of females with FD and may be useful to assess which heterozygotes should be considered for treatment, even though they have normal α Gal-A activities; the same authors, showed, in a following paper, an important relation between lyso-Gb3 serum levels and disease severity, enzyme replacement response, metabolic phenotyping, and genotype severity in males [58].

Tubular and Glomerular Proteins

Abnormal urinary excretion of some proteins may indicate impairment in the glomerular and tubular functions. In FD, changes in the excretion of the markers of glomeru-

lar protein leakage transferrin, type IV collagen, and IgG, as well as proximal tubule reabsorptive dysfunction uromodulin, α 1-microglobulin, retinol-binding protein, N-acetyl- β -D-glucosaminidase, and β -2-microglobulin have been reported.

In a study by Aguiar et al. [35], aimed to identify biomarkers of incipient nephropathy in FD, the authors have reported that analyzed biomarkers of glomerular (transferrin and type IV collagen) and tubular (α 1-microglobulin, N-acetyl- β -glucosaminidase, and alanine aminopeptidase) dysfunction were increased even in Fabry patients without evidence of nephropathy. Moreover, the correlation with estimated GFR was even stronger for type IV collagen and N-acetyl- β -glucosaminidase than for albuminuria, indicating that such biomarkers seem more accurate than albuminuria in the identification of the FD nephropathy [30].

Association of uromodulin changes with the degree of the storage process in FD, and its reversibility by ERT suggests that uromodulin excretion monitoring may be a useful marker, particularly of response to treatment: in fact, a study by Vylet'et al. [59] showed that urinary excretion of uromodulin was reduced in untreated Fabry patients and normalized in all patients on ERT.

Prabakaran et al. [60] showed a significant increase in the excretion of tubular urine protein markers α 1-microglobulin and retinol-binding protein and of glomerular urine protein marker IgG in a population of 13 females with FD, with a correlation between changes in their excretion and albuminuria; moreover, the authors reported a decrease in the excretion of these proteins with ERT.

Bikunin

A study by Lapedda et al. [61] showed that urine levels of bikunin, also known as urinary trypsin inhibitor, are significantly higher in Fabry patients with renal impairment than in controls. This finding suggests that the amount of this proteoglycan in urine could represent a biomarker of renal impairment in Fabry patients, useful in monitoring renal functionality also in those patients without overt renal damage. Moreover, the authors showed that the origin of higher urine bikunin levels may imply a direct kidney involvement, and the secondary activation, in response to glycosphingolipids storage, of biochemical pathways related to inflammation [61]. Nevertheless, the mechanisms by which urine levels are elevated in Fabry patients remain unclear and need further evaluation.

Proteomics

The proteomics approach has been applied in FD to find biomarkers that might allow the measurement of the disease severity, the prognosis and the evaluation of the therapy effects, in addition to the possibility to give some insights on the pathophysiology of the disease [62–69]. A study by Matafora et al. [70] showed that the urinary proteome of FD patients is different from normal subjects and allowed the identification of several proteins with an altered expression (among them uromodulin, prostaglandin H2 D-isomerase, and prosaposin) that are known to play a role in the processes that might be involved in the disease pathophysiology, as inflammation, immune response, and glycosphingolipid metabolism. In particular, unlike to that reported in literature, the authors found the upregulation of uromodulin in the urine of Fabry patients; usually, kidney disease results in a marked decrease in the synthesis of uromodulin, as well as in the accumulation of abnormal uromodulin in tubular cells, leading to tubular cell death [71]. However, all the patients of the study by Matafora et al. [70] showed almost normal values for both creatinine and GFR, and therefore uromodulin upregulation could be considered as a very early marker of kidney damage at the tubular level. These findings confirm the possible role of the urinary concentration of uromodulin as a valuable biomarker for the development of chronic kidney disease [72].

An important limitation of these studies is the small number of analyzed patients and a lack of follow-up data; therefore, further studies are needed to confirm these data.

Parapelvic Cysts

The presence of parapelvic cysts has been linked to FD and reported in the literature as a possible feature of its renal involvement [73–77]. A recent study showed that the prevalence of parapelvic cysts, observed during a routine ultrasonography study, is significantly higher in FD patients (29%) compared with patients with kidney disease of similar age and level of renal function (1.1%) and that such prevalence becomes even higher (43%) when the specific ultrasonography was performed [11]. Moreover, the authors did not report any statistical associations between parapelvic cysts and demographic, clinical or laboratory data of their Fabry patients.

The pathogenesis of parapelvic cysts in FD is unknown, but a possible role of glycosphingolipids has been postulated. In fact, it has been demonstrated that intrare-

nal levels of 2 glycosphingolipids, such as glucosylceramide and ganglioside, were significantly higher in 2 mouse knockout models of polycystic kidney disease and of nephronophthisis [78–80]. It has also been shown that the glucosylceramide synthase inhibitor Genz-123346 effectively inhibited the cystogenesis in these models orthologous to human polycystic kidney disease [81]. This evidence allows us to hypothesize an indirect role of Gb3 storage also in the pathogenesis of parapelvic cysts formation in FD, potentially associated with altered local metabolism or peculiar genetic regulatory processes.

These data suggest that although to date parapelvic cysts cannot be considered a pathognomonic sign of FD, their presence should alert both nephrologists and radiologists to consider the diagnosis of FD, especially in subjects with an unclear family history of renal disease and when other stigmata of the disease are evident.

Conclusions

Proteinuria/albuminuria has been considered as the most important marker for Fabry nephropathy; however, a large proportion of renal impairment occurs in nonalbuminuric state. It is important to implement different strategies for earlier detection of Fabry nephropathy, aiming to prevent the long-term devastating outcomes of renal loss in FD. In this review, we have reported that limitations of albuminuria as a sensitive marker of early renal dysfunction in FD may be overcome by the newly identified biomarkers. Some of them, in fact, are impaired also in normoalbuminuric patients and showed better correlation with eGFR than albuminuria. However, direct comparisons of these biomarkers with albuminuria are needed to confirm their superiority in early detection of Fabry nephropathy.

Statement of Ethics

This article does not contain any studies with human participants or animals performed by any of the authors.

Disclosure Statement

The authors declare that they have no conflict of interest.

Informed Consent

Not applicable.

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