ORIGINS OF RENAL DISEASES

# The Renal History of Fabry Disease

Martina Gaggl, Sarah El-Hadi, Christof Aigner, **Gere Sunder-Plassmann**

Division of Nephrology and Dialysis Department of Medicine III Medical University of Vienna Vienna, Austria

Address correspondence to: Gere Sunder-Plassmann; Division of Nephrology and Dialysis Department of Medicine III Medical University of Vienna Währinger Gürtel 18-20 A-1090 Vienna, Austria; Tel:+43-1-40400-42170 Fax:+43-1-40400-43470 e-mail: gere.sunder-plassmann@meduniwien.ac.at

## Abstract

*In 1898 William Anderson and Johannes Fabry described the red-purple maculopapular skin lesions characteristic for Fabry disease and also mentioned the presence of proteinuria. Four decades later Maximiliaan Ruiter concluded that angiokeratoma corporis diffusum is the cutaneous manifestation of an inherited systemic internal disease. In 1947 autopsy findings of two cases who died from uraemia revealed sclerosis of glomeruli. At this time the presence of a thesaurismosis was also considered. The first renal needle biopsy in 1958 showed vacuolation and distension of the cells of the glomerular tufts and distal tubules suggestive of a storage disorder. The ability to concentrate the urine was also impaired in these patients. Sweely und Klionsky in 1963 demonstrated that the major storage component is a trihexoside. As of 1967 Roscoe Brady finally described the deficiency of the enzyme ceramidetrihexosidase/α-galactosidase A characteristic in patients with Fabry disease.*

**Key words:** Fabry disease, angiokeratoma, chronic kidney disease, heart failure, history, stroke

## Introduction

Fabry disease is an X-linked lysosomal storage disorder caused by accumulation of glycosphingolipids due to a deficiency of the lysosomal enzyme α-galactosidase A. Deposition of substrate results in renal failure, stroke and cardiac death. Other symptoms include angiokeratoma or corneal opacities, amongst others. Life expectancy is reduced by an average of 15 and 20 years in female and male patients, respectively [1].

In 1898 first reports of Fabry disease were published by William Anderson and Johannes Fabry, who described patients with 'angiokeratoma corporis diffusum', the red–purple maculopapular skin lesion that represents a characteristic feature of this disease [2] [3]. Although the disorder is now simply known as Fabry disease, it is also referred to as Anderson-Fabry disease in recognition of the original descriptions made by both, Anderson and Fabry [4].

After the initial reports of angiokeratoma corporis diffusum, several other disease manifestations were described, (Table 1) until in 1939 Ruiter concluded that angiokeratoma corporis diffusum is the cutaneous manifestation of a systemic disease [5], which in the following years was classified to be a storage disorder [6].

In 1951 Scriba confirmed the lipid character of the storage material [7] and in 1959 Nobel laureate Christian de Duve described the lysosome as an important cellular organelle. Thus, he provided the basis for the concept of lysosomal storage disorders and even at this time suggested enzyme replacement as a therapeutic opportunity [8].

In 1962 Wise and colleagues reported on several families with Fabry disease, including the offspring of the first patient of William Anderson. They also examined the first living female patients with Fabry disease and clearly demonstrated X-linked inheritance, which was confirmed by further pedigree analyses within the next years [9]. Later, Sweely und Klionsky characterised the disease as sphingolipidosis [10].

**Table 1.** First description of symptoms and organ manifestations other than skin

| Year | Author | Journal | Symptoms |
|---|---|---|---|
| 1898 | Anderson, W | British Journal of Dermatology | Proteinuria |
| 1909 | Steiner, L | Deutsches Archiv für klinische Medizin | Acroparesthesia, gastrointestinal symptoms, anhydrosis, dizziness, impaired vision |
| 1910 | Fleischer, B | Archiv für Dermatologie | Corneal opacity, multiple sclerosis* |
| 1913 | Guenther, H | Zeitschrift für Klinische Medizin | Diabetes insipidus, cardiac hypertrophy |
| 1917 | Head, GD | Archives of Internal Medicine | Hypertension |
| 1918 | Sibley, K | British Journal of Dermatology | Rheumatism* |
| 1925 | Weicksel, J | Deutsche Medizinische Wochenschrift | Tortuositas vasorum |
| 1927 | Archer, BWC | Lancet | Stroke |
| 1939 | Ruiter, M | Archiv für Dermatologie und Syphilis | Cardio/vascular/renal symptoms |

*: frequent misdiagnosis in patients with Fabry disease

**Table 2.** The renal lesion in Fabry disease - case reports in the early years

| Year | Author | Journal | Kidney involvement |
|---|---|---|---|
| 1898 | Anderson, W | British Journal of Dermatology | Proteinuria* |
| 1909 | Steiner, L | Deutsches Archiv für Klinische Medizin | Proteinuria, casts * |
| 1912 | Madden, FC | British Medical Journal | Proteinuria |
| 1916 | Fabry, J | Archiv für Dermatologie und Syphilis | Proteinuria |
| 1917 | Head, GD | Archives of Internal Medicine | Proteinuria (2 brothers) |
| 1918 | Sibley, WK | Proceedings of the Royal Society of Medicine | Proteinuria |
| 1931 | Vogels, A | Klinisches Monatsblatt für Augenheilkunde | Proteinuria |
| 1936 | Robba, G | Dermatologische Wochenschrift | Nephritis* |
| 1939 | Ruiter, M | Archiv für Dermatologie und Syphilis | Proteinuria, cells and casts in the urine*(3 brothers) |

*: association of angiokeratoma corporis diffusum with kidney disease suggested

In 1965, an electron microscopy study by Hashimoto et al. revealed the presence of bodies in endothelial cells, smooth muscle cells, fibrocytes and perivascular cells of patients with Fabry disease. Referring to these structures as "extremely overcrowded lysosomes", he concluded that malfunctioning lysosomal enzymes had to be the result of a genetic abnormality [11].

In 1967 Roscoe Brady finally elucidated in detail the underlying cause of Fabry disease, the deficient activity of the enzyme catalyzing the hydrolysis of the terminal galactose molecule of ceramidetrihexoside, ultimately leading to multiorgan symptoms and manifestations [12]. Thereafter they purified the enzyme from human placenta cells and demonstrated biochemical effects of the enzyme in patients with Fabry disease [13]. In the meantime the enzyme was identified as α-galactosidase A [14]. Cloning of the *GLA* gene by Robert Desnick's group in 1985 provided the basis for molecular genetic diagnosis and specific therapy [15]. Following the introduction of enzyme replacement therapy at the begin of this century by Raphael Schiffmann et al. [16] and Christine Eng et al. [17], molecular chaperone therapy represents the next step forward to provide cure for this devastating disease [18].

## The renal lesion of Fabry disease - case reports in the early years

Notably, even the first two cases reported in the literature presented with proteinuria, aside from the back then central manifestation of the disease, the angikeratoma corporis diffusum. William Anderson described the obvious cutaneous lesions of a 39 year-old man, but did not overlook the elevated albumin content of his urine. Even at this time he suggested that the proteinuria may possibly be related to the "diseased condition of the vessels" [2]. In contrast, the first report of Johannes Fabry on a 13 year-old boy highlighted the progressive nature of the cutaneous lesions, while at this point of time, however, the urine of the boy was unremarkable. Following his initial report, Johannes Fabry published two further papers on his patient in 1916 and 1930 [19] [20]. Finally, in 1916 he observed proteinuria in this case, whom he followed until his death in 1928 at the age of 43 years. A pedigree of this family was published in 2001 by Hermann Fabry, a dermatologist and a nephew of Johannes Fabry [21].

In the first decades following the initial description of what is known today as Fabry disease, several authors mentioned the presence of proteinuria or abnormal urinary sediment in patients with angiokeratoma (Table 2). In 1939 Maximiliaan Ruiter reported on three brothers, who presented with angiokeratoma, acroparesthesia, arterial hypertension, left ventricular hypertrophy, edema, and proteinuria with cells and casts in the urinary sediment. He summarized these findings as a cardiac-vascular-renal complex of symptoms and concluded that angiokeratoma corporis diffusum is the cutaneous manifestation of an inherited systemic internal disease [5].

## Autopsy reports, kidney biopsies, and electron microscopy

In 1944 one of the three brothers described by Ruiter in 1939, died and in 1947 Pompen, Ruiter, and Wyers reported on autopsy findings of this and a second case, who died the same year from uraemia: "In the kidneys of both cases sclerosis of many glomeruli was found with, probably secondary to this, alterations in the tubule structure, leading to renal failure. Moreover, unexplained pathological changes in many of the glomeruli were found in the first case." and " As regards the pathogenesis of this disease, the authors suggest as a hypothesis the existence of a primary congenital disease of the entire vascular system, in which some form of metabolic disturbance occurs in the muscle cells of the heart and vessels. A thesaurismosis, whereby some substance is deposited in these muscle fibres, could also be considered" [6].

The first renal needle biopsy was performed by Colley and colleagues in 1958: "Renal needle biopsy was performed on two men suffering from angiokeratoma. The distinguishing feature was a vacuolation and distension of the cells of the glomerular tufts and distal tubules. In both cases the ability to concentrate the urine was grossly impaired; in one case the glomerular filtration rate was normal and in the other it was moderately impaired. A retrospective

re-examination of the kidney of a female relative of these two patients, who had died some years before, showed identical lesions. Her relatives state that she did not suffer from the characteristic skin lesions. It is possible, therefore, that the metabolic disturbance associated with angiokeratoma can also occur in women, perhaps without the typical skin manifestations" [22].

Sweely und Klionsky in 1963 examined kidney lipids from a patient, who died at the age of 28 years of renal failure and whose clinical symptoms were classic ones for Fabry disease [10]. They provided convincing evidence that the major component of the glycolipid fraction is a trihexoside composed of sphingosine, glucose, and galactose at a molar ratio of 1:1:2.

In the same year an electron microscopy study of a kidney biopsy by Henry revealed further resolution of the lipid material, „which has an interesting "lamellar" pattern" [23]. "Despite the inability to concentrate urine above a specific gravity of 1.012, this patient showed preserved ability to acidify and alkalinize urine after oral ammoniumchloride (150 mEq./day) and sodium bicarbonate (158 mEq./day) loading, respectively, over several days. This observation stands in contrast to previous reports and suggests that the regularly observed hyposthenuria in this disease is independent of defects in ion transfer in the distal tubule system".

## A Fabry disease pedigree spanning some 150 years

This family includes the first case described by Anderson in 1898 [2]. Sixty years later Colley and colleagues performed the first kidney biopsies in patients with Fabry disease in affected offspring from Anderson's original patient and also mentioned the first female suffering from Fabry disease [22]. Further details of this family were described in the same year by Wallace [24]. In 1962 Wise and colleagues reported on eight British families, including Anderson's family, with a total of 21 affected patients. They showed an X-linked inheritance pattern and also reported the first living woman with a confirmed diagnosis of Fabry disease [9].

Most recently, Rohman and colleagues from the Royal Free Hospital in London described 5 further patients of this family, including one of the first men to start enzyme replacement therapy in 1999 and who died in 2014 from cardiac complications [25]. The sister of this patient, suffering from renal and cardiac disease, has four sons, of which two are affected by Fabry disease. One of her sons started enzyme replacement therapy at the age of three years because of severe acroparesthesia and gastrointestinal symptoms, being the youngest Fabry patient in the UK to start enzyme replacement therapy (personal communication, Figure 1).

Interestingly, this family harbors the *GLA* mutation p.A143T, the disease-causing role of which was recently challenged by some experts. However, the kindred summarized here, clearly demonstrate that this mutation can result in significant disease burden in hemizygous and heterozygous patients.

## Conclusion

In 1898 the cutaneous lesions of Fabry disease, angiokeratoma corporis diffusum, were initially described by two independent dermatologists. The renal involvement of the disease was documented by the presence of proteinuria in these two cases. In 1939 the full-blown picture of the disease was described, suggesting that angiokeratoma corporis diffusum is the cutaneous manifestation of an inherited internal disease. Autopsies and kidney biopsies between 1947 and 1963 elucidated the renal pathology of Fabry disease and indicated that Fabry disease is a metabolic storage disorder. Biochemical studies in 1963 and 1967 explained the characteristics of the accumulated material and the enzyme deficiency in Fabry disease.

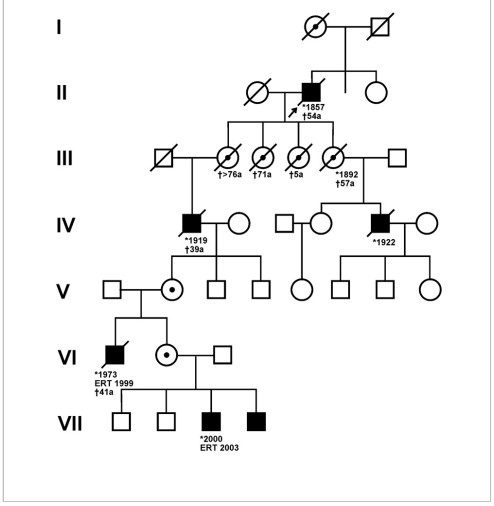


***Figure 1.***
*The pedigree of the patient with Fabry disease described in1898 by William Anderson (ERT; enzyme replacement therapy).*

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