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EDITORIAL

How to improve the early diagnosis of Fabry's disease?

Fabry's disease is an X-linked recessive lysosomal disorder due to α-galactosidase A (α-Gal A) deficiency. This defect is responsible for the gradual accumulation of glycosphingolipids, mainly globotriaosylceramide (GL3), in many organs, predominantly in vascular cells, and which leads to ischemic organ damage. In a recent study performed in Australia, the median age at diagnosis was 28.6 years [1], and similar findings have been documented in the United States and Europe. Because enzyme replacement therapy (ERT) by human α-Gal A has emerged as a promising means to prevent and remove GL3 deposition, it is now necessary to make this diagnosis earlier.

Why is an early diagnosis of Fabry's disease so difficult? A diagnosis of rare diseases, in general, is not easy [2]. Acroparesthesias and pain crises, triggered by heat or fever and often misdiagnosed, are the first symptoms arising in childhood. The disease was first described in 1898 by two dermatologists, W.A. Anderson and J. Fabry. Skin angiokeratomas may be profuse, but are sometimes limited to rare and small lesions, or even absent [3, 4]. Later in life, the diagnosis can be made by ophthalmologists who discover typical corneal deposits, known as cornea verticillata, or by neurologists who are confronted with young male patients with transient ischemic attacks or cochleovestibular abnormalities, or finally by nephrologists. Indeed, nephrologists are well placed among those capable of diagnosing Fabry's disease. In a man presenting with proteinuria during the 3rd or 4th decade, a renal biopsy examined by an experienced renal pathologist should be diagnostic by showing typical diffuse vacuolation of glomerular cells, predominantly in podocytes. Similar changes are found in vascular and tubular cells. Adequate staining demonstrates that renal cells contain massive lipid deposits [5, 6]. Electron microscopy confirms the diagnosis by showing typical lamellar inclusions located in lysosomes, but this is not absolutely required for diagnosis in clinical practice.

Nephrologists are well aware of the clinical heterogeneity of genetic diseases: this is true in autosomal-dominant polycystic kidney disease; Alport syndrome may present without sensorineural hearing loss; and tuberous sclerosis, without skin lesions, epilepsy, or mental retardation. Renal disease may be the only or prominent manifestation of Fabry's disease, as shown by the Japanese study carried out by Nakao et al [7] and published in this issue of *Kidney International*. Indeed, these authors consecutively screened 514 male hemodialysis patients for α-Gal A deficiency and found 6 patients with low enzyme activity. These 6 patients had mutations in the α-Gal A gene, confirming the diagnosis of Fabry's disease. This cohort, however, is different from American and European dialysis patients: 366 screened patients (71%) were classified as having chronic glomerulonephritis, albeit based on rather weak criteria, and only 16 of them (4%) had a renal biopsy.

Two groups of patients should be differentiated: misdiagnosed patients with classic Fabry's disease (as patient 6, in whom the renal biopsy was initially misinterpreted), and patients with Fabry's disease clinically limited to the kidney, also called "renal variant" (although all had left ventricular hypertrophy, the mechanism of which can be questioned in the absence of endomyocardial biopsy). Conflicting results regarding the prevalence of this renal variant have been reported. The prevalence rate in three studies performed in dialysis patients was 0% in The Netherlands [8], 0.47% in the United States [abstract; Desnick et al, European Symposium on Fabry's Disease, Athens, Greece, November 2002], and 0.97% in Japan [7]. In two other studies, the prevalence rate of Fabry's disease in dialysis patients was 0.22% in Italy [abstract; Pagliardini et al, European Symposium of Fabry's Disease, Athens, Greece, November 2002] and 0.49% (2 of 440 males) in Japan [9]; in the latter study, at least one patient had classical Fabry's disease.

These figures are much higher than those reported in European and American registries (i.e., approximately 0.02%) [10, 11]. Data from large registries and those from small epidemiologic studies should be cautiously compared. In addition, the prevalence rate of the renal variant critically depends on early referral to nephrologists and to the renal biopsy policies for proteinuric patients, which may differ from one country to another.

Is it clinically relevant to screen male dialysis patients for α-Gal A deficiency? It should be stressed that the aim, obviously, is not to perform diagnosis of Fabry's renal variant in end-stage renal disease (ESRD), but to make the diagnosis much earlier in the course of the renal disease. To achieve this goal, we should improve nephrologists' training in rare metabolic and genetic diseases, pay particular attention to patients with a positive family history of kidney disease (such as in patient 5 in the Japanese series) [7], and improve the process of early referral of renal patients to nephrologists. On the other

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hand, nephrologists should be aware that it is possible to miss or delay diagnosing Fabry's disease, particularly in patients without a previously identified family member and who have only subtle or no systemic symptoms. In some patients, these abnormalities may be limited to tortuous conjunctival and retinal vessels [4]. We should not hesitate to measure α-Gal A activity in male renal patients with no etiologic diagnosis and who have not undergone renal biopsy. This may also extend to women with unexplained renal disease. Systemic symptoms are milder in Fabry's females than in males, and although renal failure in women is very rare, 12% of Fabry's dialysis patients are females [10, 11]. However, in heterozygous women, α-Gal A activity may be in the normal range.

There is no evidence that ESRD patients with Fabry's renal variant will benefit from screening and ERT. Obviously it is too late to expect beneficial renal effects. In addition, we have no clinical or histopathologic information on the diffusion of vascular GL3 deposits. Do these patients run a high risk of developing cerebrovascular and cardiac complications related to GL3 extrarenal deposits? On the contrary, ERT should be considered in dialysis patients with classic Fabry's disease since two studies have shown a higher mortality rate in these patients compared to non-Fabry's patients [10, 11]. Effectively, ERT could correct this.

Finally, the detection of Fabry's disease, even in ESRD patients, may have important consequences for their families. Indeed, an investigation should be proposed to these families to screen members who are at risk after their informed consent. Hemizygous males and carrier females can be identified by clinical examination and by using α-Gal A measurement and DNA analysis. Heterozygous women may receive genetic counseling. Symptomatic management and ERT should be proposed to affected males to prevent progression of the kidney disease. This should be carefully explained to these men who may have no symptoms and only minimal proteinuria. This strategy is probably the best way to improve the diagnosis in Fabry's disease. Whatever the mode of presentation of the disease in the propositus (classic versus renal variant), information should be given to affected families and "active" investigation should be offered.

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