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ORIGINAL ARTICLE

Anderson–Fabry disease: a case-finding study among male kidney transplant recipients in Austria

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Summary

The diagnosis of Anderson–Fabry disease is often delayed or even missed. As severe renal manifestations are a hallmark of alfa-galactosidase A (AGAL) deficiency, we tested the hypothesis that Anderson–Fabry disease is under-recognized among male kidney transplant recipients. This nation-wide study in Austria enrolled 1306 patients (ca 65% of all kidney transplanted males) from 30 kidney centers. AGAL activity was determined from filter paper dried blood spots by a fluorescence assay. A positive screening test was defined by an AGAL activity below 1.5 nmol/h/ml. In patients with a positive blood spot-screening test, AGAL activity was re-examined in peripheral blood leukocytes. Genetic testing for mutations in the *GLA* gene was performed by sequencing to confirm the diagnosis of Anderson–Fabry disease. Two previously not recognized cases with Anderson–Fabry disease were identified. Our study is the first showing that a diagnosis of Anderson–Fabry disease can be missed even in patients who undergo kidney transplantation. Case-finding strategies may be considered a useful tool for diagnosis of this rare disease that may be somewhat more prevalent among kidney transplant recipients compared with dialysis populations.

Introduction

Anderson–Fabry disease is a rare X-linked lysosomal storage disorder caused by the deficiency of alfa-galactosidase A (AGAL), resulting in cellular accumulation of glycosphingolipids [1]. Typical early symptoms include pain in the legs, cold intolerance, hypohidrosis and gastrointestinal complaints during childhood. The progression of the disease leads to cardiac, renal, and central nervous system complications, as well as premature demise [2–5].

The incidence of Anderson–Fabry disease is reported between 1 in 117 000 [6] and 1 in 240 000 [7] live births. However, recent studies suggest a much higher incidence among male newborns [8]. Although the awareness of this rare disease has increased recently, the diagnosis is often delayed for many years or even missed [3,9]. In this

context, studies among patients with cardiomyopathy [10], juvenile stroke [11], or chronic kidney disease on dialysis [12] revealed a surprisingly high prevalence of Anderson–Fabry disease among these high risk groups. For example, case-finding studies of dialysis patients revealed a 10-times higher prevalence of Anderson–Fabry disease compared with European dialysis registry data [12,13].

We therefore hypothesized that Anderson–Fabry disease is under-recognized in prevalent male kidney transplant recipients. To test this hypothesis, we initiated a nationwide case-finding study for Anderson–Fabry disease in Austria.

Methods

Study design

Prevalent male kidney transplant recipients followed up at the 30 major nephrology centers in Austria were invited to participate in this study. Details of participating centers and involved physicians are given in the acknowledgement section. Blood spots dried on a filter paper were collected locally at routine follow-up visits and shipped to a laboratory in Italy (Department of Pediatrics, University of Torino) for high throughput determination of AGAL activity. In patients with blood spot test results suggestive of Anderson–Fabry disease, AGAL activity was measured in leukocytes at the Institute of Neurology at the Medical University Vienna. In one large center (Medical University Graz) screening for AGAL deficiency was performed directly by measuring leukocyte enzyme activity in the Laboratory for Metabolic Diseases at the Department of Pediatrics. In patients with decreased leukocyte enzyme activity, the diagnosis of Anderson–Fabry disease was confirmed by genetic testing for mutations in the *GLA* gene. The Institutional Review Board of the Medical University Vienna waived the requirement for a written and signed consent form for case-finding studies of Anderson–Fabry disease. Patients who underwent genetic testing gave prior written informed consent as required by the Austrian Law on Gene Technology. The study was conducted under the auspices of the Austrian Society of Nephrology, and the Austrian Dialysis and Transplant Registry.

Laboratory analyses

Alfa-galactosidase A activity was determined from filter paper dried blood spots by a fluorescence assay using a high throughput microplate method [14] at the University of Torino, Italy. A positive screening test was defined by an AGAL activity below 1.5 nmol/h/ml. This threshold represents 35% of control AGAL activity (controls: 4.5 ± 1.8 nmol/h/ml) [14].

In patients with a positive blood spot-screening test, AGAL activity was re-examined in peripheral blood leukocytes (normal: >40 nmol/h/mg protein) at the Institute of Neurology of the Medical University Vienna. For the isolation of leukocytes, 1 ml of 5% dextran in saline containing 0.504 mg of sodium heparin was combined with 5 ml of EDTA blood and gently mixed by turning the reaction tube three times up and down. Erythrocytes were allowed to sediment at room temperature; subsequently, the upper phase was centrifuged at 600 *g* at 5 °C for 15 min. The pellet was washed with 1 ml of cold 0.85% saline and was stored at −20 °C. Prior to analysis, the pellet was sonicated for 30 s at 4 °C and the homogenate was centrifuged at 3000 *g* at 4 °C for 30 min. Leukocyte AGAL activity was measured with a modification of the method described by Desnick *et al.* [15]. In brief, a reaction mixture containing 30 μmol of citrate-phosphate buffer (pH 4.8), 10–12 μg of protein from the supernatant and 1 μmol of 4-methylumbelliferyl-alfa-D-galactopyranoside was prepared on ice in a total volume of 250 μl. Reaction mixtures were incubated at 37 °C for 2 h. Results were expressed as nmoles of substrate hydrolyzed per hour per mg of protein.

In the Laboratory for Metabolic Diseases of the Department of Pediatrics at the Medical University of Graz, leukocytes were prepared by mixing 10 ml of EDTA blood with 10 ml of a mixture containing Dextran T 500 (3 g/100 ml), 0.25 mol/l Na-citrate, 0.1 mol/l citric acid, 0.2 mol/l glucose and 0.15 mol/l NaCl. Blood cells were sedimented for 30–45 min and the supernatant centrifuged for 15 min at 4 °C at 800 *g*. The pellet was suspended in 0.8 ml 0.15 mol/l NaCl and residual erythrocytes lysed by additon of 2.4 ml water. After 10 s, 0.8 ml of 0.6 mol/l NaCl were added and the leucocytes collected by centrifugation. This procedure was once repeated and the purified leukocytes stored at −80 °C. For assay, the pellet was homogenized by sonication in 1 ml of 0.45% NaCl and centrifuged (5 min, 10 000 *g*). 12.5 μl of supernatant (1 mg cell protein/ml) were used to measure AGAL activity in a total reaction volume of 125 μl containing 100 mmol/l *N*-acetylgalactosamine, 4 mmol/l 4-methylumbelliferyl-a-galactoside, 60 mmol/l citrate and 120 mmol/l Na_2HPO_4 at pH 4.5, incubation time 20 min. Values were expressed as nmoles of substrate degraded per hour and mg of cell protein.

Genetic testing for mutations in GLA was performed at the Clinical Institute of Medical and Chemical Laboratory Diagnostics of the Medical University of Vienna (sequencing of all seven exons and of exon–intron boundaries) or in Graz (complete sequencing of all seven exons as well as ca 100 bp of the flanking introns; confirmation of mutations by digestion of replicons with site-specific restriction enzymes).

The prevalence of Anderson–Fabry disease was expressed as percent of total study population.

Results

Case-finding study

Between September 2003 and November 2004 in a total of 1306 male kidney transplant recipients from 30 Austrian nephrology centers, AGAL activity was examined. As of December 31, 2004, 3372 kidney transplant patients were registered in Austria [R. Kramar, H. K. Stummvoll, Austrian Dialysis and Transplantation Registry (OEDTR), Annual Report 2004, Austrian Society of Nephrology; page 20; http://www.nephro.at/oedr2004/JB_2004ger.pdf]; among them 2056 males (R. Kramar; personal communication). Thus, roughly 65% of the male kidney transplant population of Austria was enrolled in this study.

Among these patients, the diagnosis of Anderson–Fabry disease was already established prior to the present case-finding study in three cases. One of these patients was identified through our previous study among dialysis patients in 2002; he received a kidney graft in 2003 at the age of 25 years [12]. The second known case, born in 1960, was diagnosed at the age of 29 years by kidney biopsy and received a kidney graft at the age of 40 years after 4 years of dialysis treatment [16]. Both patients are currently receiving enzyme replacement therapy. The third patient, born in 1963, was diagnosed while he was on dialysis, because of the remarkable history of stroke, extensive left ventricular hypertrophy, and renal failure. Clinical suspicion was probably raised by the Austrian Anderson–Fabry screening study in dialysis patients in 2002. This patient received a kidney graft in the year 2002 at the age of 39 years (leukocyte AGAL activity: 0.18 and 0.49 nmol/h/mg protein at two different occasions, respectively; mutational analysis of *GLA*: g.1262ins6bp, 3′-TCgacttcAAGG-5′). Interestingly, the mutation in this patient was similar to that of the already known second case reported here; although the families of both zpatients live in the county of Styria, their family histories revealed no known common ancestors.

Patients identified by case-finding study

One hundred fifty-eight out of 1099 patients from 29 centers tested by means of blood spot tests showed a decreased AGAL activity. Leukocyte AGAL activity was measured in 151 patients (one patient died in the meantime, in six no further follow-up was done by the respective centre). In one of those patients, a reduced enzyme activity was confirmed. In one centre (Medical University Graz), leukocyte AGAL activity was determined in all 207 kidney transplant patients; one of them showed a decreased AGAL enzyme activity. Taken together, in the 1306 patients tested for the presence of Anderson–Fabry disease, two previously not recognized cases were identified (the patient flow is shown in Fig. 1). Together with three previously diagnosed patients, five out of 1306 kidney transplant recipients enrolled in this study suffered from Anderson–Fabry disease, resulting in a prevalence of 0.383% (one in 262 patients) among male kidney transplant recipients.

Case 1

This patient was born in 1941 and presented with end-stage renal disease at the age of 40 years. The cause of chronic kidney disease was unknown at the time he commenced dialysis. He received three kidney transplants (in 1984, 1995, and 1996). His graft function is currently stable (serum-creatinine 1.7 mg/dl, proteinuria in the range of 1 g/24 h, microhematuria). Comorbidities and symptoms including arterial hypertension, peripheral artery disease, polyps of the colon, occasional diarrhea, diabetes mellitus, and hepatitis C. Retinal, corneal, or cutaneous signs compatible with Anderson–Fabry disease are not present. He suffers from hypertrophic cardiomyopathy, grade III atrioventricular block (pacemaker implanted in 1994) and survived two cardio-pulmonary resuscitations. His mother died from kidney failure at the age of 80 years; the patient has neither siblings nor children. AGAL activity in leukocytes was less than 10% of normal (2 nmol/h/mg protein). Genetic testing of *GLA* showed a missense mutation [g.5234G>A, p.R112H(Y)] that was previously described in another patient with Anderson–Fabry disease [17]. Until now, he is not scheduled for enzyme replacement therapy.

Case 2

This patient was born in 1942 and received a kidney graft in 1998 at the age of 56 years. Renal function is stable with a serum creatinine of 1.15 mg/dl. He has no retinal, corneal, or cutaneous signs of Anderson–Fabry disease and no history of stroke or transient ischemic attack. Echocardiography revealed left ventricular hypertrophy. The family history was negative with both parents having died in their ninth decade of life. He has no siblings; his 44-year-old daughter is healthy without signs or symptoms of Anderson–Fabry disease. Patient's leukocyte AGAL activity was 21, 7, and 18 nmol/h/mg protein at three different time points (47, 13, 32%, respectively, of the mean AGAL activity of the kidney transplant recipients tested in Graz). Genetic testing confirmed the diagnosis of Anderson–Fabry disease and revealed a missense mutation in *GLA* (c.70T>G, p.W24G) that was previously

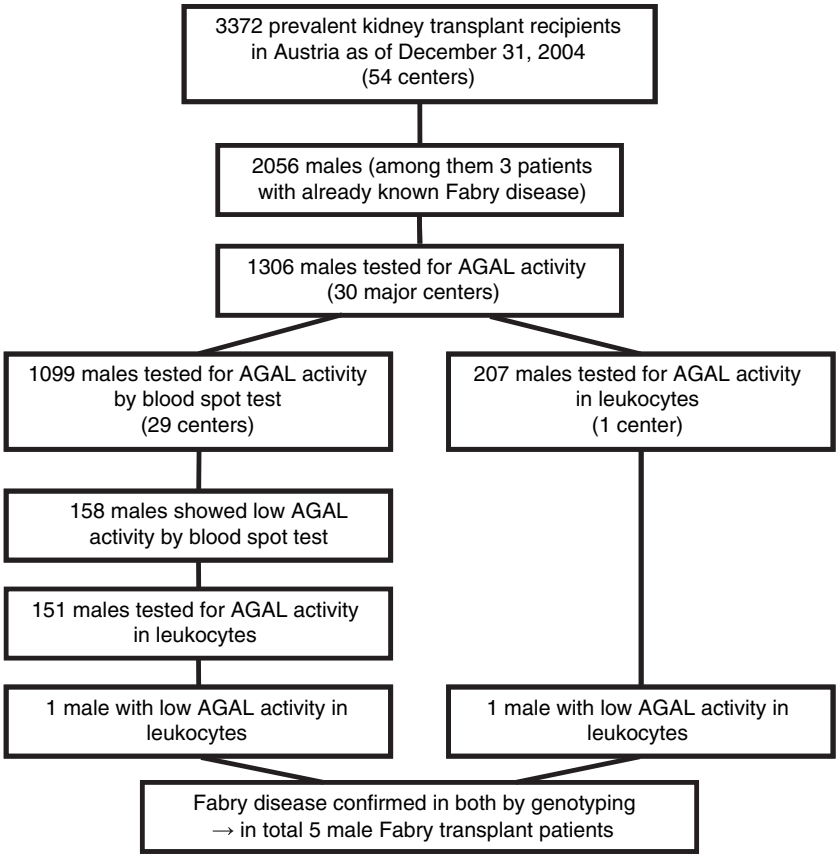

Figure 1 Flow of participants in the case-finding study for Anderson–Fabry disease in Austria.

not described. He does not receive enzyme replacement therapy.

Discussion

The present study shows that case-finding studies for Anderson–Fabry disease among male kidney transplant recipients have the potential to identify families with a hitherto unknown hereditary disease. The importance of our findings is also underlined by the recent observation of accidental transplantations of kidneys with Anderson–Fabry disease in a living related donor and a deceased donor scenario [18,19].

Recent case-finding studies of end-stage renal disease patients have revealed a much higher prevalence of Anderson–Fabry disease among dialysis patients [12,13] compared with more historical registry data. In 1996, an analysis of 440 665 patients who began renal replacement therapy in Europe between 1987 and 1993 revealed 83 patients with Anderson–Fabry disease [European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) registry, one case per 5309 patients; 0.0188%] [20]. Among 250 352 US patients who began renal replacement therapy between April 1995 and July 1998, 42 patients with Anderson–Fabry disease were identified (United States Renal Data System; one case per 5961 patients; 0.0168%) [21]. Eighty-eight percent of all dialysis patients with Anderson–Fabry disease were males with a prevalence of 0.027% in both registries. These figures are consistent with historical data from Austria that suggested a prevalence of 0.027% since 1965 until 2001 [22]. More recently, a nation wide screening study showed that the prevalence of Anderson–Fabry disease among male dialysis patients in Austria was 0.264 [12], a finding that compares well with a large study in the Czech Republic that revealed a very similar result [13]. Both studies clearly showed that Anderson–Fabry disease is under-recognized among dialysis patients in the Western world.

In this study of male kidney transplant recipients, the prevalence of Anderson–Fabry disease is 1.45 times higher compared with that delineated in male Austrian dialysis patients in the course of a 2002–2003 case-finding study, which revealed a prevalence of four cases in 1516 male dialysis patients (0.264%; one per 379). Thus, our study stresses the importance of proper medical work up in patients who present with chronic kidney disease and other potential manifestations of AGAL deficiency [23].

In general, the prognosis in transplanted Anderson–Fabry patients does not differ from that in non-Anderson–Fabry patients. In a study from the ERA-EDTA Registry, graft survival after 3 years and patient survival after transplantation in patients with Anderson–Fabry disease were comparable to that of patients with other nephropathies [20]. This finding was corroborated by a review of the US Renal Data System Registry [24]. Obrador *et al.* [25] showed that the mortality in Anderson–Fabry patients on dialysis was significantly higher compared with that in their non-Anderson–Fabry fellow patients; in contrast, mortality did not differ in transplanted patients.

Enzyme replacement therapy for Anderson–Fabry disease is available since 7 years [26,27] and several groups offer this treatment to kidney transplant recipients [28–30]. Although it is currently unclear whether or not enzyme replacement therapy improves outcomes in kidney transplant patients, we suggest testing for Anderson–Fabry disease in patients with end stage renal disease of unknown genesis.

A potential limitation of our study is that one third of the male Austrian renal transplant patients were not enrolled. Many transplant patients are looked after by local nephrologists or in small centers and despite major efforts, it was logistically impossible to reach out to that segment. Furthermore, Anderson–Fabry disease as the specific cause of end-stage renal disease in both cases identified by this study was not confirmed by kidney biopsy.

Andrade *et al.* [31] recently reported the results of a study of CKD patients including kidney transplants that failed to identify patients with Fabry disease. The authors speculated that the negative findings of their study may have been related to the high throughput screening test, which was based on measurement of plasma enzyme activity. In our study, however, screening was performed in dried full blood samples. The cut-off of enzyme activity of this test was set to identify all positive controls, as shown in our previous study and therefore resulted in a high false positive rate [12].

In conclusion, our study is the first to show that Anderson–Fabry disease is missed in patients undergoing kidney transplantation. Case-finding strategies aid the diagnosis of this rare disease, which may be somewhat more prevalent among kidney transplant recipients compared with male dialysis populations.

Authorship

GS-P, PK: designed the study. JK, GS-P: performed the study. MW, RK, CS, HKS, SH, HH: collected data. MF, SP, EP, KP, MS, TV: did laboratory analyses including genetic testing and/or measurement of AGAL activity. PK, GS-P: analyzed data. JK, GS-P: wrote the paper. MF, PK, EP, GS-P: proof read the paper.

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