Results of a Nationwide Screening for Anderson-Fabry Disease among Dialysis Patients

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Abstract. Anderson-Fabry disease is possibly underdiagnosed in patients with end-stage renal disease. Nationwide screening was therefore undertaken for Anderson-Fabry disease among dialysis patients in Austria. Screening for α-galactosidase A (AGAL) deficiency was performed by a blood spot test. In patients with a positive screening test, AGAL activity in leukocytes was determined. Individuals with decreased leukocyte AGAL activity were subjected to mutation testing in the *GLA* gene. Fifty (90.9%) of 55 Austrian hemodialysis centers participated in this study; 2480 dialysis patients (80.1% of the Austrian dialysis population) were screened. In 85 patients, the screening test was positive (85 of 2480, 3.42%; women, 3.32%; men, 3.50%). Among these 85 patients, 4 men (in 3 of whom Anderson-Fabry disease was already known before screening) had a severely decreased and 11 subjects had a borderline low AGAL activity. Genetic testing revealed mutations associated with Fabry disease in all four men with severely decreased AGAL activity resulting in a prevalence of 0.161% for the entire study population. A nationwide screening of dialysis patients permitted detection of a hitherto unknown man with Anderson-Fabry disease. The overall prevalence among dialysis patients was at least ten times higher as compared with recent registry data. Screening programs among patients with end-stage renal disease, especially men, should be put in place to identify families with Anderson-Fabry disease who probably may benefit from specific clinical care, and perhaps from enzyme replacement therapy. In dialysis patients, however, there is no evidence to support enzyme replacement therapy at present.

Anderson-Fabry disease is a rare X-linked storage disease resulting from the deficient activity of the lysosomal hydrolase α-galactosidase A (AGAL) (1,2). As a consequence, glycosphingolipids (predominantly globotriaosylceramide [GL-3]) accumulate progressively, particularly in blood vessels, kidneys, and the heart (3,4). Affected men who have little, if any, AGAL activity (classic Anderson-Fabry disease) present with acroparesthesia, angiokeratoma, hypohidrosis, and corneal and lenticular opacities during childhood or adolescence. In the course of the disease, the lysosomal GL-3 accumulation, particularly in the vascular endothelium, leads to end-stage renal disease, cardiac and cerebrovascular disease, and premature death. Recently, cardiac variants of Anderson-Fabry disease with a milder clinical phenotype have been described in patients with residual AGAL activity (5,6). In contrast to some other diseases with X-linked inheritance, most female heterozygotes are also affected but do not always present with the classic phenotype. Presumably as a result of random X-inactivation, women show a broad spectrum of clinical symptoms, ranging from completely asymptomatic individuals to those with full-blown disease.

The renal manifestation results from GL-3 deposition in podocytes, mesangium, glomerular endothelium, epithelium of

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the loop of Henle and the distal tubule, arterial and arteriolar endothelial and smooth muscle cells, and interstitial cells (7). Deposition in the renal vascular endothelium is progressive and associated with interstitial fibrosis and glomerulosclerosis (8). End-stage renal disease usually occurs in the third to fifth decade of life (9).

Anderson-Fabry disease occurs in subjects of all ethnicities, and estimates of incidence range from 1 in 40,000 to 60,000 male individuals (10). Among patients treated with renal replacement therapy, the prevalence seems to be higher. However, the precise prevalence is unknown. 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 registry, 1 case per 5309 patients, 0.0188%) (11). Among 250,352 U.S. 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; 1 case per 5961 patients, 0.0168%) (9).

Because not all patients undergo renal biopsy before commencing renal replacement therapy, the observed prevalences mentioned above may be underestimated. It is therefore possible that undiagnosed cases of Anderson-Fabry disease can be found among patients with end-stage renal disease. This notion is supported by results obtained from small studies from Italy (12) and Japan (13,14), suggesting a prevalence among hemodialysis patients of up to 1.2%. Because a specific enzyme replacement therapy is now available for patients with Anderson-Fabry disease (15,16), identification of affected patients is important. We therefore initiated a screening program for Anderson-Fabry disease among dialysis patients in all nine provinces of Austria.

Materials and Methods

Study Design

A nationwide screening for Anderson-Fabry disease among dialysis patients was performed in all nine provinces of Austria in 2002 and 2003. The study was conducted under the auspices of the Austrian Society of Nephrology, and the Austrian Dialysis and Transplant Registry. Local study coordinators approached 55 Austrian dialysis centers. Centers that agreed to participate received the study material. The Institutional Review Board of the Medical Faculty at the University of Vienna waived the requirement for a written and signed consent form for the screening test. Patients who underwent genetic testing had previously provided informed consent, as required according to the Austrian Law on Gene Technology.

Biochemical Methods

AGAL Blood Spot Test. AGAL activity was determined from filter paper dried blood spots by a fluorescence assay that used a high-throughput microplate method (12). A positive screening test was defined by an AGAL activity below 1.5 nmol/h/ml, the cutoff level according to the manufacturer's instructions. This threshold represents 35% of control AGAL activity (controls, 4.5 ± 1.8 nmol/h/mL) (12). Five hemizygote patients with known Anderson-Fabry disease, among them three dialysis patients, were included as positive controls.

AGAL Activity in Leukocytes. In patients with a positive blood spot screening test, two independent laboratories at the Pediatric University Hospital Graz, and at the Vienna University, Institute of Neuropathology, determined AGAL activity in leukocytes.

In one laboratory (Graz), 4.5 ml EDTA blood was mixed at 4°C with 40 ml of buffer containing 155 mM NH_4Cl, 10 mM $NaHCO_3$, and 0.1 mM EDTA (pH 7.4). After lyses of erythrocytes, the sample was centrifuged at 600 × *g*, washed with saline, suspended in 500 μl of 0.45% NaCl, and sonicated for 1 × 10 s at 4°C. Homogenates were centrifuged at 10.000 × *g* for 1 min, and the supernatant was stored until use at −80°C. A total of 12.5 μl of leukocyte supernatant (1 mg cell protein/mL) was used to measure AGAL activity in a total reaction volume of 125 μl of an assay mixture containing 100 mM N-acetylgalactosamine, 4 mM 4-methylumbelliferyl-α-galactoside, 60 mM citrate, and 120 mM Na_2HPO_4 (20 min, pH 4.5). Values were expressed as nanomoles of substrate degraded per hour and milligram of cell protein.

In the second laboratory (Vienna), 1 ml 5% dextran in saline containing 0.504 mg sodium heparin was combined with 5 ml of EDTA blood and gently mixed by turning the reaction tube up and down three times. Erythrocytes were allowed to sediment at room temperature, and 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 stored at −20°C. After sonication for 30 s at 4°C, the homogenates were 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.* (2). In brief, a reaction mixture contained 30 μmol of citrate-phosphate buffer (pH 4.8), 10 to 12 μg of protein, and 1 μmol of 4-methylumbelliferyl-α-D-galactopyranose was prepared on ice in a total volume of 250 μl. Reaction mixtures were incubated at 37°C for 2 h. Values were calculated as nanomoles of substrate hydrolyzed per milligram of protein per hour.

Mutation Detection in *GLA*. Genetic testing was performed in male patients with decreased AGAL activity and in female patients with decreased or borderline AGAL activity (leukocyte AGAL activities <40 nmol/h/mg protein and/or <2.3 nmol/h/mU β-hexosaminidase) in leukocytes. Screening for mutations was performed by melting point analysis. Exons of the *GLA* gene showing unusual melting characteristics were selected for bidirectional sequencing. The presence of a mutation was confirmed by RFLP.

Statistical Analyses

Continuous data are shown as mean ± SD. Categorical data are given as absolute counts and as proportions. A true-positive (TP) screening test result is defined as a diagnosis of Anderson-Fabry disease in a subject with a positive screening test; a false-positive (FP) screening test is defined as a positive screening test in a patient without Anderson-Fabry disease. A true-negative (TN) result of the screening test is defined as negative test result in a subject without Anderson-Fabry disease; a false-negative (FN) result is defined as negative screening test in a patient with Anderson-Fabry disease. The sensitivity and specificity of the test are defined as sensitivity = TP/(TP + FN), and specificity = TN/(TN + FP). The prevalence describes the proportion of the study population affected with the disease; it is defined as prevalence = (TP + FN)/(TP + FN + TN + FP). The positive predictive value (PPV) of the screening test is defined as PPV = (prevalence × sensitivity)/[(prevalence × sensitivity) + (1 − prevalence) × (1 − specificity)] (17).

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Results

Patients

Fifty (90.1%) of 55 dialysis centers in Austria participated in this study. A total of 2480 dialysis patients (964 women and 1516 men; mean age, 61.8 ± 14.5 yr), representing 80.1% of the total Austrian dialysis population, were screened for the presence or absence of AGAL deficiency by the blood spot test (Figure 1).

Screening for AGAL Deficiency

In 85 (3.34%) of 2480 patients, the blood spot screening test was positive. The frequency of a positive screening test among women was 32 (3.32%) of 964 and 53 (3.50%) of 1516 in men, raising the possibility of AGAL deficiency. Of 85 patients with a positive screening test, blood of 79 individuals was available for determination of leukocyte AGAL activity (6 of 85 patients died after blood spot screening). A severely decreased activity of AGAL was observed in four men. A borderline low enzyme activity in at least one of the two laboratories was observed in six male and five female dialysis patients.

Mutation Analysis of the GLA Gene

Genetic testing revealed the presence of missense mutations in all four men with severely decreased AGAL activity. Patient 1 showed an exchange of proline for alanine in exon 2 (A121P). Patient 2 showed an exchange of tryptophan by arginine in exon 3 (W162R), and in patient 3, an exchange of isoleucine by threonine in exon 5 (I239T) was identified. This mutation was also present in his mother and his two daughters. Furthermore, we identified a mutation in exon 2 in patient 4, which resulted in an exchange of arginine for histidine (R112H). In individuals with borderline low AGAL activity (five women, six men), no *GLA* mutations were present.

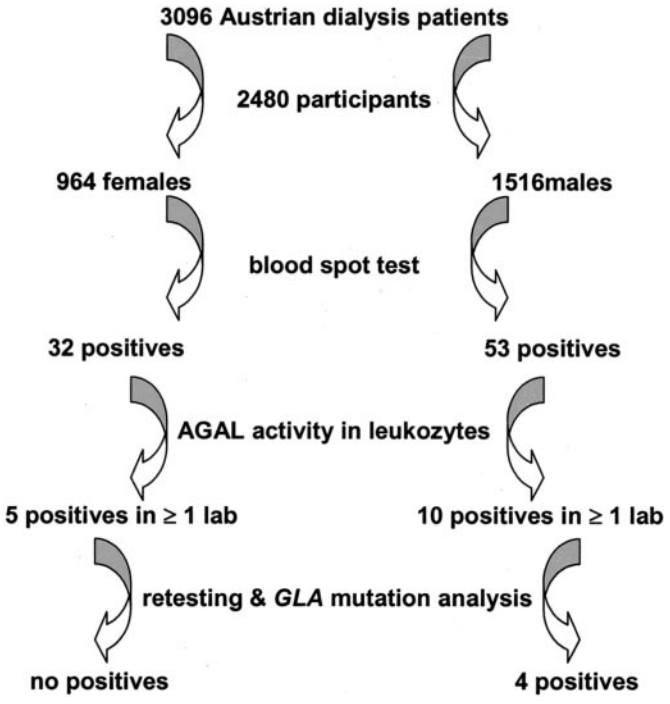

Figure 1. Flow chart illustrating the patients.

Patients with Anderson-Fabry Disease

In the study presented here, a new case of Anderson-Fabry disease (patient 3) was identified, as well as three additional family members with previously unknown disease. In the three other cases of Anderson-Fabry disease (patients 1, 2, and 4), the diagnosis was already known before the screening study. Important characteristics of these patients are indicated in Table 1. Thus, on the basis of enzymatic and genetic data, and assuming that the six patients who had died after the screening test did not have Anderson-Fabry disease, the prevalence of Anderson-Fabry disease in the entire cohort studied was 4 in 2480 (1 case per 620 patients, 0.161%). The prevalence in male subjects was 4 in 1516 (1 case per 379 male patients, 0.264%). It is of note that the blood spot screening test was positive in all five subjects included as positive control patients. In male dialysis patients, 4 TP, 49 FP, 1463 TN, and no FN screening test results were obtained. Therefore, the sensitivity of the screening test can be estimated to be $4/(4 + 0) = 1.0$, and the specificity to be $1463/(1463 + 49) = 0.968$ for male individuals. Given a prevalence of Anderson-Fabry disease of 0.00264 in male dialysis patients, the PPV of the screening test in that particular group is 0.0755.

Patient 1

Patient 1 had experienced attacks of pain since childhood. Renal biopsy performed when the patient was 44 resulted in the diagnosis of Anderson-Fabry disease, which was confirmed biochemically. Since the age of 49, the patient had been receiving peritoneal and hemodialysis to treat end-stage renal disease. Additional symptoms of Anderson-Fabry disease included left ventricular hypertrophy, cornea verticillata, cataract, hypohidrosis, angiokeratoma, and lymphedema of the legs. None of his relatives was known to have Anderson-Fabry disease. He was included in the screening study as positive control.

Patient 2

In patient 2, acroparesthesia and hypohidrosis began at the age of approximately 7 yr. At the age of 47 yr, he was referred to a nephrologist because of end-stage renal disease. At this time, he received a diagnosis of Anderson-Fabry disease on the basis of clinical suspicion, and it was confirmed by low AGAL activity. He had angiokeratoma, tortuositas vasorum, hypertrophic cardiomyopathy, and ventricular arrhythmia. He received a kidney graft within 2 yr and had to start dialysis again because of graft failure 15 yr later. He died from severe sepsis at the age of 64 yr. No other family members with Anderson-Fabry disease were known. He was also included in the screening study as positive control.

Patient 3

From early childhood on, patient 3 experienced recurrent fever and acroparesthesia. At the age of 12 yr, fever, pain, and lymphadenopathy responded to corticosteroid treatment. Seven

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Table 1. Characteristics of four male dialysis patients with Anderson-Fabry disease

Case	Age at Start of Dialysis (yr)	Leukocyte AGAL Activity (nmol/ml/h)	Mutation in *GLA*	Enzyme Replacement Therapy
1	49	1.38	g.5260G>C p.A121P	Yes
2	47	Not detectable	g.7383T>C p.W162R	No
3[a]	27	Not detectable	g.10207T>C p.I239T	Yes
4	53	1.23	g.5234G>A p.R112H	Yes

[a] This case was identified by the screening study.

years later, a shrunken right kidney was found. At the age of 27 yr, he was admitted to another hospital to treat acute hearing loss, dizziness, and headache. At this time, stage 4 chronic kidney disease was diagnosed. Angiography ruled out renal artery stenosis, and several serologic tests (anti-neutrophil cytoplasmic antibodies, anti-glomerular basement membrane antibodies, anti-nuclear antibodies, complement factors C3 and C4, cryoglobulins, hepatitis B and C antibodies, HIV antibodies) were negative. A kidney biopsy revealed end-stage renal disease. Dialysis therapy was initiated 6 mo later. In the same year, the patient presented with recurrent fever, headache, dysphagia, and dysarthria. Multiple cerebral lesions detected by magnetic resonance imaging were related to stage 3 hypertension.

Two months later, the patient presented with a central paresis of the facial nerve, dizziness, vomiting, and worsening of dysarthria. Magnetic resonance imaging of the brain revealed a deterioration of cerebral lesions. The patient received a diagnosis of cerebral vasculitis, and he responded well to corticosteroid therapy. Anderson-Fabry disease was diagnosed 2 yr later during the course of the present screening study. Reexamination of the kidney biopsy material by electron microscopy showed typical signs of Anderson-Fabry disease that were previously not identified by light microscopy. The patient also had cornea verticillata and mild left ventricular hypertrophy. In the meantime, he received a kidney graft and is scheduled for enzyme replacement therapy. His 48-yr-old mother (normal AGAL activity) and his two daughters (ages 3 and 8 yr; decreased AGAL activity in both) exhibited the same mutation. At present, these three female relatives do not show clinical signs and symptoms of Anderson-Fabry disease.

Patient 4

This patient presented with mild renal insufficiency at the age of 45 yr. The diagnosis of Anderson-Fabry disease was established by renal biopsy. At the age of 53 yr, he developed end-stage renal disease. There was no history of pain attacks. Besides renal insufficiency, he presented with tortuositas vasorum, left ventricular hypertrophy, and cerebral lesions confirmed by magnetic resonance imaging. A comorbidity of Crohn's disease was verified histologically and by endoscopy. He was included in the screening study as a positive control. No other family members with Anderson-Fabry disease were known.

Discussion

The study presented here aimed to determine the prevalence of Anderson-Fabry disease among dialysis patients. A cohort of 2480 patients (80.1% of the Austrian dialysis population) was screened for the presence or absence of low AGAL activity by means of a blood spot test. Further workup included measurement of AGAL activity in leukocytes, followed by mutation testing of the *GLA* gene in subjects with low enzyme activity. The diagnosis of Anderson-Fabry disease was finally confirmed in four patients, resulting in a prevalence of 0.161% among dialysis patients.

The prevalence of 0.161% of the study presented here differs significantly from the prevalence of 0.0181% obtained from American and European registries (125 cases among 691,017 end-stage renal disease patients; 1 case per 5528 subjects). In these registries, a prevalence of 0.0167% was reported in Europe and of 0.0188% in the United States (9,11). Eighty-eight percent of all dialysis patients with Anderson-Fabry disease were men, with a prevalence of 0.027% in both registries. These figures are in line with historical data from Austria, suggesting a prevalence of 0.027% in the years 1965 to 2001 (18). In the study presented here, the prevalence of Anderson-Fabry disease was 0.264% among male individuals. Thus, our study demonstrates that there are undiagnosed men with Anderson-Fabry disease who have end-stage renal disease.

Recently, three small studies of 440, 514, and 508 dialysis patients revealed a higher proportion of Anderson-Fabry disease in patients from Japan (13,14) and from the Netherlands (19). Among male patients, the prevalence of Anderson-Fabry disease in these studies was 0.49%, 1.17%, and 0.22%, respectively, suggesting that the frequency of Anderson-Fabry disease among male dialysis patients is much higher (10 to 50 times) than previously reported. The divergence among reported prevalences may be related to the small patient populations and/or a selection bias of the patients screened. Importantly, there may be individuals who have renal failure from

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other causes who also can have Anderson-Fabry disease (20,21).

Recently, Nakao *et al.* (14) described a renal variant of Anderson-Fabry disease in Japanese hemodialysis patients. Five of six male patients received a diagnosis of Anderson-Fabry disease limited to the kidney and without pain attacks, cutaneous and ophthalmologic signs, and symptoms of the disease. This observation is in contrast to the findings of the study presented here and to reports from Italy (12), the Netherlands (19), and Japan (13), suggesting that the renal variant of Anderson-Fabry disease is a rare phenotype.

Admittedly, a shortcoming of the study presented here is the fact that AGAL activities in leukocytes have only been determined in patients who exhibited an AGAL activity less than 35% of control activity in the blood spot test. Although it is unlikely that this cutoff influences the identification rate of hemizygotes, it may be of relevance for identification of heterozygous women (12) with AGAL activity measured in blood and leukocytes within the normal range (22). We think that screening for AGAL activity in women with renal disease but without a positive family history, and without clinical signs and symptoms of Anderson-Fabry disease is not sensible. In the presence of clinical findings compatible with the presence of Anderson-Fabry disease, further biochemical and genetic investigations are mandatory.

Another potential limitation to our study relies on the mutation screening method used, because melting point analysis of the selected exons may miss some *GLA* mutations. Because rapid large-scale genetic testing is currently not available, measurement of GL-3 in the urine may be worthwhile (23). However, because the vast majority of dialysis patients are anuric or oliguric, this approach is not feasible in that population. Thus, we cannot exclude the notion that female carriers may have escaped diagnosis in our study and that the true prevalence of Anderson-Fabry disease among end-stage renal disease patients is even higher.

We have identified a novel case with Anderson-Fabry disease among 2480 dialysis patients screened; three of four patients had been previously diagnosed with Anderson-Fabry disease. These three known cases were included in the screening study with their samples blinded to the laboratory performing the screening test. Therefore, the conclusion that this screening method enables the detection of male patients with Anderson-Fabry disease among dialysis patients seems to be reasonable. The prevalence of disease in a population affects screening test performance. In low-prevalence settings, even very good tests have poor PPV (24). PPV estimates should also account for the prevalence of the disease in the population studied. In the study presented here, the sensitivity of the screening test was 1.0 and the specificity 0.968. In the male cohort studied by us, the prevalence of Anderson-Fabry disease was 0.264%, resulting in a PPV of the screening test of 0.0755. Because of the potent effect of disease prevalence on predictive values, the PPV will be greatly reduced in a population with low disease prevalence. Assuming a prevalence of Anderson-Fabry disease of 1 in 117.000 (10) in the general population, the PPV (calculated according to the formula given above) will be as low as 0.000009.

To avoid a high number of FP test results, that screening test should not be used in the general population. It should be applied preferentially in patients without a known cause of renal disease. This approach will help to increase the pretest likelihood of Anderson-Fabry disease and the PPV of the test. Some patients with Anderson-Fabry disease may have additional other renal diseases. Therefore, in the rare patient with a known renal disease and a clinical presentation suggestive of Anderson Fabry disease, specific testing is recommended.

Retrospectively, the new patient diagnosed in the present screening study resembles the classic phenotype. Therefore, it is particularly important to appreciate the broad clinical spectrum of Anderson-Fabry disease and to have a high level of suspicion especially in male patients with end-stage renal disease.

Recently, enzyme replacement therapy has become available for patients with Anderson-Fabry disease, and expert recommendations have been issued for the treatment of the disease (25). Treatment of patients with Anderson-Fabry disease stresses the importance of diagnosing the disorder and offering specific investigations to family members.

In summary, this nationwide study of Anderson-Fabry disease clearly demonstrates that the prevalence of the disease among dialysis patients is at least ten times higher than previously anticipated. We therefore strongly encourage screening programs among patients with end-stage renal disease, especially males who have the potential to identify new cases with Anderson-Fabry disease and also provide the possibility for early diagnosis, specific clinical care, and eventually for enzyme replacement therapy in affected family members. In dialysis patients, however, no data are currently available supporting enzyme replacement therapy.

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ERRATA

Anders H-J, Belemezova E, Eis V, Segerer S, Vielhauer V, Perez De Lema G, Kretzler M, Cohen CD, Frink M, Horuk R, Hudkins KL, Alpers CE, Mampaso F, Schlöndorff D: Late onset of treatment with a chemokine receptor CCR1 antagonist prevents progression of lupus nephritis in MRL-Fas(lpr) mice. *J Am Soc Nephrol* 15: 1504–1513, 2004

In the Abstract and the Methods section the treatment of mice is noted to be:

"subcutaneous injections three times a week. . . "

The correct information is: "subcutanous injections three times a day. . . . "

Kotanko *et al.*: Results of a Nationwide Screening for Anderson-Fabry Disease among Dialysis Patients. *J Am Soc Nephrol* 15: 1323–1329, 2004

Due to a miscommunication, the above article from the May issue of JASN was published omitting the names of two important authors and one institution involved in the work. The corrected citation reads:

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