Anderson-Fabry disease (AFd) is a rare, inherited, x-linked disease characterized by the deficiency of the lysosomal enzymatic \( \alpha \)-galactosidase A activity (\( \alpha \)-Gal-A). The enzyme defect leads to progressive accumulation of glycosphingolipids (GL) in all kinds of cells, tissues, organs, and body fluids. The clinical manifestations are very protean, the residual activity of \( \alpha \)-Gal-A and/or different gene mutations might explain different phenotypes, but as yet these concepts have not been proven. Usually, patients with AFd show 3 clinical phases, more evident in men than in heterozygous women. The first phase (childhood and adolescence) is characterized by myalgia, arthralgia, acroparesthesia, fever, cutaneous angiokeratomas, and corneal opacities. The second phase is characterized mainly by renal involvement. In the third phase, severe renal impairment and involvement of cerebrovascular and cardiovascular systems are present. The progression to end-stage renal disease (ESRD) is common in hemizygous males (3rd-5th decade of life); usually, death occurs because of cerebral and/or cardiovascular complications in patients undergoing chronic dialysis therapies. The survival of patients with AFd in dialysis is better than in diabetic patients, but it clearly is decreased compared with uremic patients with other nephropathies, despite a lower mean age of uremia (50 versus 60 y). The outcome of kidney transplantation is similar to that found in other patients with ESRD, despite controversial issues published in the past. The use of a kidney donor with normal \( \alpha \)-Gal-A activity in the control of the metabolic systemic disease is unproven. The recurrence of GL deposits in the kidney graft has been documented rarely. The definitive treatment for AFd is enzyme replacement therapy with purified \( \alpha \)-Gal-A produced by a genetically engineered human cell line or Chinese hamster oocytes: relatively short-term studies have shown a significant treatment effect on clinical outcome measures.

Keywords: Anderson-Fabry disease, glycosphingolipidosis, hereditary renal diseases, chronic renal failure.
this reason, the diagnosis often is delayed or missed, especially in the presence of a silent family pedigree. Also, atypical clinical variants of AFd related to residual \( \alpha \)-Gal A activity have been reported, but the frequency of atypical cases has not been determined.\(^3\)\(^4\)

Usually, patients with AFd show 3 clinical phases, obviously more evident in hemizygous men than in heterozygous women,\(^1\) according to Lyon’s rule.\(^5\) The first phase occurs in childhood and adolescence and is characterized by acroparasthesia, myalgia, arthralgia, fever, cutaneous angiokeratomas, and corneal opacities. The second clinical phase is characterized by the appearance of renal involvement with microalbuminuria and subsequent proteinuria, lipiduria with Malta cross crystals in the urine sediment examined by polarized microscopy, and impairment in the urine concentration and diluting ability. In this stage, patients with AFd very often show glomerular hyperfiltration similar to the early phase of diabetic nephropathy. In the third clinical phase severe renal impairment is present with more or less late involvement of cardiovascular and cerebrovascular systems. The progression to ESRD is a common manifestation in hemizygous males in their third to fifth decade of life. Usually, death occurs from severe cerebral and/or cardiovascular complications in patients undergoing chronic dialytic therapies.\(^6\)

Renal involvement has been recognized as a complication of AFd since the original reports by Anderson and Fabry, both dermatologists, in the late 19th century. Renal involvement and renal dysfunction are the major cause of morbidity and mortality in male AF patients. The broad spectrum of renal lesions is a pathophysiologic continuum with progressive deterioration of renal function caused by progressive intracellular deposition of GL. All kinds of renal glomerular cells show evident GL inclusions, as well as endothelial cells of renal vessels, epithelial cells of the proximal tubule, Henle’s loop, distal tubule, and interstitial cells as well.\(^7\)

These pathologic features are evident in heterozygous women as well, despite the absence of clinical and functional renal impairment. Immunofluorescence microscopy is negative or nonspecific, except in the presence of superimposed immunologic glomerulonephritis.\(^8\) By electron microscopy, the intracellular GL deposits appear as typical osmiophilic inclusion bodies in the cytoplasm of all kinds of renal cells, characterized by concentric lamellation of clear and dark layers, with a periodicity of .35 to .50 nm. The osmiophilic myelin bodies are 1 to 3 nm in diameter, showing a characteristic onion-skin or zebra appearance, and showing a limited membrane when included in the cytoplasmic lysosomes.\(^9\) Female carriers may show typical onion-skin bodies in the renal cells despite the absence of functional and clinical evidence of renal disease.

As patients with AFd age, a progressive decrease in glomerular filtration rate is observed, which is caused by the progressive pathologic involvement of the epithelial cells of Bowman’s capsule, the mesangial cells and mesangial matrix, the endothelial cells, and the afferent and efferent glomerular arterioles. The expansion of the mesangial area reduces the surface of glomerular filtration, and the endothelial injury results in segmental glomerular sclerosis. Moreover, endothelial cells corresponding to damaged podocytes are submitted to additional hydraulic forces that also lead to segmental glomerular collapse and sclerosis.\(^10\)

Certainly, the diffuse and progressive involvement of venules and arterioles of the kidney with GL deposits in the endothelial cells and in the pericytes contributes to the progressive deterioration in renal function. In our opinion, the ischemic lesions, both glomerular and tubulointerstitial, are the main cause of ESRD.

In conclusion, the progressive impairment in renal function until ESRD appears mainly related to the progressive intracellular deposition of GL. This fact induces diffuse renal ischemic lesions as it happens in AFd patients in other districts, such as cerebrovascular and cardiovascular systems. The peculiar abundance in lysosomal structures that characterize the renal cells, and the peculiar functional role of the kidney, probably play a crucial role in promoting premature renal failure with respect to the severe involvement of other organs. In fact, in patients with AFd, death usually occurs as a result of cerebrovascular and/or cardiovascular complications connected to the progression of the metabolic disease in patients already undergoing chronic renal replacement therapies for renal failure.

ESRD

AFd is a rare cause of ESRD. In fact, in the analysis of the US Renal Data System Registry database, patients having ESRD caused by AFd amount to 0.0167% of all causes of ESRD.\(^6\) In the analysis of the ERA-EDTA registry, patients identified as having ESRD caused by AFd amount to 0.0188% of all causes of ESRD.\(^11\)

Despite these data, we believe that the prevalence of AFd among young men who initiate dialytic therapies before the age of 40 years is higher. In fact, the diagnosis of AFd often is missed, particularly in the absence of a previously identified family member.\(^1\) Recently, AFd has been identified in 1.2% of male Japanese patients with ESRD who previously were diagnosed with chronic glomerulonephritis. Interestingly, most of these patients (about 83%) did not show the typical clinical manifestations that could have facilitated their diagnosis.\(^12\) Recent data obtained in Italy by a screening of 1,765 male patients in chronic dialysis identified 0.23% of patients with low \( \alpha \)-Gal-A activity and AFd.\(^13\)

Although the incidence of AFd has not been determined in Italy and in Japan, it is evident from these studies that several patients with AFd who develop chronic renal insufficiency are missed, suggesting that AFd is underdiagnosed among renal dialysis and/or transplant patients.

Dialysis

Among patients with AFd, ESRD is a major cause of morbidity and is associated strongly with mortality. Data from the ERA-EDTA registry concerning patients with AFd who initiated dialysis between 1985 and 1993 suggest that these patients have a very poor survival rate.\(^11\) The prevalence and
demographic characteristics of patients with AFd on dialytic treatment in the United States are quite similar to those reported in the European study. The prevalence of patients with AFd on dialysis was very similar between the 2 registries, as was the gender distribution (women constituted approximately 12% of all patients with AFd with ESRD). US patients with AFd were more likely to choose peritoneal dialysis compared with European patients.

The prevalence of comorbid complications appears lower in US patients compared with their European counterparts, although this is not well documented. These clinical events are mainly severe cardiovascular complications, arrhythmia, congestive heart failure, myocardial infarction, severe cerebrovascular accidents, claudication, and hypertension.

US and European data show that the 3-year survival among patients with AFd in dialysis is poor, 63% and 60%, respectively, and the survival is significantly lower compared with nondiabetic controls.

Therefore, both in the United States and in Europe, patients with AFd who initiate dialysis show a worse survival compared with non-AFd controls; given the poor survival rate on dialysis we must consider different strategies to manage these patients, such as enzyme replacement therapy and renal transplantation.

**Renal Transplantation**

Renal transplantation is considered the optimal therapy for patients with ESRD. But in the past it was discouraged for AFd patients. Nevertheless, published reports are conflicting with respect to the patient and allograft outcomes in patients with AFd who undergo renal transplantation.

In fact, patients with ESRD caused by AFd are considered to have a very high risk for cardiovascular and cerebrovascular events, even if offered transplantation. On the contrary, a recent analysis of the US Renal Data System database has documented the excellent outcome of renal transplantation in 93 patients with AFd, despite their high risk for cardiovascular complications. One-, 5-, and 10-year graft survival rates in recipients with AFd were statistically similar to the graft survival rates in non-AFd patients. The incidences of delayed graft and rejection episodes were similar between AFd patients and controls matched on the basis of age, race, sex, year of transplantation, and cadaveric or living donor source. Aggressive management of cardiovascular and cerebrovascular risk factors before and after renal transplantation may be responsible for the good clinical outcomes.

In the past, kidney transplantation has been considered by some investigators as a possible way for correcting the α-Gal-A deficiency through enzyme replacement by a normal organ producing α-Gal-A. However, plasma α-Gal-A enzyme levels do not increase after kidney transplantation, and the decrease in substrate levels probably is related to increased clearance of substrate by the functioning kidney.

Finally, the recurrence of AFd in a renal allograft has been reported rarely. The demonstration of small amounts of GL deposits in the renal graft has been limited to vascular endothelial cells and in tubular epithelial cells, probably related to the high plasma and pre-urine substrate concentrations that locally overwhelm the α-Gal-A activity of the graft endothelial cells and tubular epithelial cells.

The literature reports only one AFd patient with an acute rejection after renal transplantation, perhaps caused by production of α-Gal-A antibodies, with widespread graft involvement. Extensive accumulation of GL deposits in all kinds of renal cells was reported in a male patient 5 years after kidney allograft; but the living donor was a human leukocyte antigen identical sister who was a heterozygotic carrier of AFd. The literature reports that allograft loss in renal transplant recipients with AFd was attributed to thrombotic events, infection, and chronic rejection, but not to renal recurrence of the systemic metabolic disease.

**Enzyme Replacement Therapy**

Progressive renal disease in AFd patients is treated by the dietetic and therapeutic strategies usually used in chronic renal failure. Dialysis and renal transplantation are required in AFd patients with ESRD: neither treatment modifies the progression of cardiovascular and cerebrovascular lesions because of the progressive and inexorable GL deposition and accumulation in all kinds of cells and tissues.

The only definitive treatment developed to date for AFd patients is enzyme replacement therapy with purified α-Gal-A enzyme produced by a genetically engineered human cell line (agalasidase alfa, Replagal; Transkeryotic Therapies, Inc.), and Chinese hamster oocytes (agalasidase beta, Fabrazyme; Synzyme Corporation).

Two clinical trials have documented the effectiveness and the safety of enzyme replacement therapy despite fundamental differences between the 2 trials, which were conducted independently. These studies, one by the Mount Sinai Study Group and the other by the National Institutes of Health, differed in the enzyme preparation used and in the dose used per infusion (intravenous). The studies also differed in their entry criteria. However, both trials showed significant decreases in urine sediment and plasma globotriosylceramide concentrations. The data reported in both trials during the brief period of therapy not only showed a good clinical control but also the potential for reversal of the disease outcome.

In symptomatic AF patients today, the decision to start enzyme replacement therapy clearly is shown; however, the tailored and appropriate therapeutic regimen, such as the best enzyme formulation, the frequency of infusion, the enzyme dose to achieve optimal clinical and pathologic benefit with minimal side effects, and at reasonable costs, still remains to be established.

The decision to initiate enzyme replacement therapy with agalsidase A among asymptomatic patients, children and young men, and heterozygous women still is debated and not yet defined. However, it is a very important issue because early intervention may offer the possibility to mitigate the pattern of systemic organ involvement and the clinical severity of the disease.
Appendix

SMIMAF Members

Chairman: Adalberto Sessa (U.O. di Nefrologia e Dialisi, Ospedale di Vimercate

Steering Committee: Cardiologo: Andrea Frustaci (Div. Di Cardiologia, Policlinico Universitario Gemelli, Roma); Dermatologo: Mario Aricò (Clinica Dermatologica, Università degli Studi, Palermo); Ematologo: Rosanna Abbate (Centro Trombosi, Università di Firenze, Ospedale Careggi, Firenze);

Gastroenterologo: Davide Festi (Bologna);

Nefrologo: Adalberto Sessa (U.O. di Nefrologia e Dialisi, Ospedale di Vimercate);

Neurologo: Walter Borsini (Clinica Neurologica II*, Università di Firenze, Ospedale Careggi, Firenze);

Oculista: Andrea Sodi (Clinica Oculistica II*, Università di Firenze, Ospedale Careggi, Firenze);

Patologo: Gianluca Vago (Anatomia Patologica, Ospedale Sacco, Milano);

Pediatra: Francesco Perfumo (U.O. di Nefrologia, Istituto G. Gaslini 5, Genova);

Laboratorio di Malattie Metaboliche: Barbara Bertagnolio (Istituto Neuroligico C. Besta, Milano);

V. Panichi, R. Puccini, D. Taccola: Nefrologia, Pisa;

G. Panzetta, S. Savoldi: Nefrologia, Trieste;

S. Pasquali: Nefrologia, Bologna;

E. Pelo: Citogenetica e Genetica, Firenze;

A. Peserico: Dermatologia, Padova;

G. Pistone, M. R. Bongiorno: Dermatologia, Palermo;

D. Procaccini: Nefrologia, Foggia;

C. Rovati, C. Comotti: Nefrologia, Trento;

P. Riboldi, Medicina Interna Centro Auxologico, Milano;

R. Ricci: Pediatria, Roma;

A. M. Savastano: Nefrologia, Foggia;

D. Simonetto: Nefrologia, Treviso;

C. Spisni, R. Di Vito: Nefrologia, Ortona (CH);

G. Tadini: Dermatologia, Milano;

F. Martinelli, M. Salvadori: Nefrologia, Firenze;

F. Giordano, M. Nebuloni, F. Pallotti: Anatomia Patologica, Messina;

A. Edefonti, R. Parini: Pediatria De Marchi, Milano;

G. Battini, A. Maglio, M. Meroni: Nefrologia, Vimercate (MI);

M. L. Battini: Firenze;

G. Bellinghieri: Nefrologia, Messina;

M. Bertella: Cardiologia, Vimercate (MI);

G. Bertolone, G. Canconi, P. Gatti: Nefrologia, Treviso;

A. Bucci, P. Napodano: Nefrologia, H. San Carlo, Milano;

Alberto Burlina: Pediatria, Padova;

L. Cagnoli, R. Mignani: Nefrologia, Rimini;

C. Cascone, C. Abaterusso: Nefrologia, Castelfranco Veneto;

M. Ciaccheri, G. Castelli: Cardiologia, Firenze;

B. Cianciaruso: Nefrologia, Napoli;

P. Coratelli, Pannarale: Nefrologia, Bari;

E. De Bella: Centro Emodialisi Villa Anna Maria, Roma;

D. Donati: Nefrologia, Varese;

A. Edefonti, R. Parini: Pediatria De Marchi, Milano;

S. Fedi: Centro Trombosi, Firenze;

C. Feletti, A. Giudicissi: Nefrologia, Cesena;

R. Furlan, F. Perego: Unità Sincopi e Disturbi della Posizione, Osp. Sacco, Milano;

O. Gabrielli, G. Coppa: Pediatria, Ancona;

R. Gatti, M. Filocamo: Laboratorio Malattie Metaboliche, Genova;

G. M. Ghiggeri: Nefrologia Pediatrica, Gaslini di Genova;

G. Giordano, M. Nebuloni, F. Pallotti: Anatomia Patologica, Vimercate;

F. Huber, P. Riegler: Nefrologia, Bolzano;

S. Iannaccone: Nefrologia, Avellino;

W. Martinelli, M. Salvadori: Nefrologia, Firenze;

G. Moneti: Laboratorio Biochimica, Firenze;

G. Montorfano: Laboratorio Biochimica, Milano;

5) Studiare gli alberi genealogici al fine di individuare precocemente i pazienti affetti, sia emizigoti che eterozigoti.

6) Definire la presenza di correlazioni genotipo/fenotipo mediante studio genetico delle famiglie affette.

7) Valutare l’efficacia e la sicurezza della terapia enzimatica sostitutiva attualmente disponibile.

8) Effettuare uno screening tra tutti i pazienti in trattamento dialitico senza diagnosi certa della causa dell’insufficienza renale cronica, mediante dosaggio plasmatico e leucocitario della α-galattosidasi A.

Laboratorio di Citogenetica e Genetica: Francesca Torricelli (U.O. di Citogenetica e Genetica, Piastra dei Servizi, Ospedale Careggi, Firenze);

Laboratorio di Biochimica: Bruno Berra (Istituto di Fisiologia Generale e Chimica Biologica, Milano);

Task Force: Erica Daina, Arrigo Schieppati, Elena Bresin, Giuseppe Remuzzi (Centro di Ricerche Cliniche per le Malattie Rare, Villa Camozzi, Ranica, BG);

Study Groups: da organizzare per ciascuna specialità su specifici argomenti di comune interesse.

Participating Investigators:

E. Ancarani, S. Feriozzi: Nefrologia, Viterbo;

R. Barone: Pediatria, Catania;

G. Battini, A. Maglio, M. Meroni: Nefrologia, Vimercate (MI);

M. L. Battini: Firenze;

G. Bellinghieri: Nefrologia, Messina;

M. Bertella: Cardiologia, Vimercate (MI);

G. Bertolone, G. Canconi, P. Gatti: Nefrologia, Treviso;

A. Bucci, P. Napodano: Nefrologia, H. San Carlo, Milano;

Alberto Burlina: Pediatria, Padova;

L. Cagnoli, R. Mignani: Nefrologia, Rimini;

C. Cascone, C. Abaterusso: Nefrologia, Castelfranco Veneto;

M. Ciaccheri, G. Castelli: Cardiologia, Firenze;

B. Cianciaruso: Nefrologia, Napoli;

P. Coratelli, Pannarale: Nefrologia, Bari;

E. De Bella: Centro Emodialisi Villa Anna Maria, Roma;

D. Donati: Nefrologia, Varese;

A. Edefonti, R. Parini: Pediatria De Marchi, Milano;

S. Fedi: Centro Trombosi, Firenze;

C. Feletti, A. Giudicissi: Nefrologia, Cesena;

R. Furlan, F. Perego: Unità Sincopi e Disturbi della Posizione, Osp. Sacco, Milano;

O. Gabrielli, G. Coppa: Pediatria, Ancona;

R. Gatti, M. Filocamo: Laboratorio Malattie Metaboliche, Genova;

G. M. Ghiggeri: Nefrologia Pediatrica, Gaslini di Genova;

G. Giordano, M. Nebuloni, F. Pallotti: Anatomia Patologica, Vimercate;

W. Huber, P. Riegler: Nefrologia, Bolzano;

S. Iannaccone: Nefrologia, Avellino;

P. Manna, L. Bignardi: Nefrologia, Parma;

S. Iannaccone: Nefrologia, Avellino;

W. Huber, P. Riegler: Nefrologia, Bolzano;

S. Iannaccone: Nefrologia, Avellino;

P. Manna, L. Bignardi: Nefrologia, Parma;

S. Iannaccone: Nefrologia, Avellino;

W. Huber, P. Riegler: Nefrologia, Bolzano;

References