CHAPTER

17 Alport Syndrome, Fabry Disease, and Nail-Patella Syndrome

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Hereditary glomerular diseases have diverse and often covert patterns of inheritance and varied clinical presentations. They are more common than is generally appreciated. Vigilance and awareness of these subtleties are important for prompt and accurate diagnoses, which allow for optimal management and timely genetic counseling.

ALPORT SYNDROME

Alport syndrome (AS), formerly called hereditary nephritis, is a disorder characterized by hematuria, proteinuria, progressive renal failure, variable sensorineural hearing loss, and ocular abnormalities. On a histologic examination, irregularities of the glomerular basement membrane (GBM) constitute the primary disease feature. Cecil Alport's archetypal kindred[1] had dominantly inherited kidney disease that was characterized in both sexes by hematuria and urinary erythrocyte casts, variable proteinuria, and by hearing loss and renal failure in males. Affected males died in adolescence of uremia, whereas females lived to old age.

The Present Definition of Alport Syndrome and the Molecular Defect Definition

For this chapter, AS will be defined as progressive, hereditary, hematuric, nonimmune glomerulonephritis that is characterized ultrastructurally by progressive irregular thickening, thinning, and lamellation of the GBM and genetically by a mutation in COL4A3, COL4A4, or COL4A5.

The Genetic Classification of Alport Syndrome

Between 2% and 5% of males with end-stage renal disease (ESRD) and probably less than 1% of females have AS. Various estimates place the gene frequency between 1:5,000 and 1:53,000, respectively.[2] The true prevalence may be higher because affected patients with subtle hearing loss are easily overlooked. There are three main genetic types of AS: X-linked Alport syndrome (XL-AS), autosomal recessive Alport syndrome (AR-AS), and autosomal dominant Alport syndrome (AD-AS), which are classified based on the mode of inheritance as described in Table 17.1. The severity of symptoms varies from person to person and with age and gender. Large kindreds show modes of inheritance and kindred-specific phenotypes that clearly reflect the genetic heterogeneity of AS. Thus, although the demonstration of a family history of glomerulonephritis among affected persons within a kindred may be helpful to ascertain, demonstration of a causative mutation remains the gold standard for genetic diagnosis.

X-Linked Alport Syndrome Caused by a Mutation in *COL4A5* (OMIM 301050)[3]

XL-AS is the most common form of AS, accounting for 80% of cases. XL-AS results from a mutation in the COL4A5 gene located at Xq22.3, which encodes the α_5 chain of type IV collagen (α_5[IV]). Hematuria from birth occurs in 100% of hemizygous males[4,5,6] and 90% to 100% of heterozygous female carriers of XL-AS.[5,7,8] Disease expression is phenotypically very heterogeneous. ESRD is inevitable in males but occurs at widely different ages in different families. The age of ESRD tends to run true within a family, but even within a family there can be quite wide variability. Knowing the mean age of ESRD in males in a family is useful from a prognostic standpoint. Moreover, extrarenal manifestations, such as hearing loss and ocular defects, tend to occur more commonly, more severely, and at an earlier age in kindreds whose males develop ESRD early.[4]

Because they are late symptoms, it is unwise to equate chronic renal failure and ESRD with Alport gene penetrance. We define penetrance of ESRD as the fraction of a population at risk in whom ESRD eventually develops. For males in each Alport kindred, ESRD penetrance generally coincides with hematuria penetrance. In Figures 17.1 and 17.2, representations of the probability of ESRD and hearing loss in boys and girls with XL-AS are shown. Inactivation of the X chromosome likely explains both incomplete hematuria penetrance among females heterozygous for XL-AS and their low probability of ESRD and hearing loss.[9] Jais et al.[7] found a cumulative prevalence of ESRD of 12% in female carriers of XL-AS by the age of 40 years.

17.1 Genetic Classification of Alport Syndrome

Description	OMIM	Gene	Comment
X-Linked Alport Syndrome	301050	COL4A5	Most common form of Alport syndrome accounting for 80% of cases. A heterogeneous condition with progressive renal insufficiency and timing of ESRD occurring between childhood and adult. Hearing loss and eye problems are common but severity is variable. More severe phenotype in affected males.
COL4A5 and Contiguous Gene Defects			
Alport Syndrome with Diffuse Leiomyomatosis	308940	COL4A5-COL4A6	Alport syndrome with diffuse leiomyomatosis.
Alport Syndrome, Mental Retardation, Midface Hypoplasia, Elliptocytosis (AMME)	300194/95	COL4A5 with FACL4/ AMMECRI	Contiguous gene deletion affecting genes located 3′ of the COL4A5 gene.
Autosomal Recessive Alport Syndrome (ARAS)	203780	COL4A3/COL4A4	This form of Alport syndrome accounts for 15% of cases. Most cases result in the early onset of ESRD. Hearing and eye problems are common, with both males and females being equally affected.
Autosomal Dominant Alport Syndrome (ADAS) without Hematologic Defects	104200	COL4A3 or COL4A4	A milder disease with the later onset of renal impairment, and a lower incidence of hearing loss and eye problems.
Familial Thin Basement Membrane Disease and Benign Familial Hematuria	141200	COL4A3 or COL4A4	A milder disease, with no hearing loss or occurrence of eye problems.

One consequence of X linkage is that twice as many females as males with a nephritis gene will be born if there are no prenatal effects and if reproductive fitness is independent of gender of the gene-carrying parent. In kindreds with XL-AS and early onset of ESRD, most affected children obtain the gene from their mothers, and the sex ratio of gene-carrying newborns approaches 1:1.

X-Linked Alport Syndrome Caused by a Deletion in *COL4A5* with Damage to Contiguous Genes (OMIM 308940 and 300194/5)

In this form, AS is associated with other features caused by an extension of the deletion outside COL4A5. Alport syndrome with diffuse leiomyomatosis (smooth muscle tumors) (Online Mendelian Inheritance in Man [OMIM] 308940)[3] stems from a deletion embracing the 5′ ends of COL4A5 and COL4A6.[2,10] The AMME syndrome (OMIM 300194/5)[3] consists of AS, midface hypoplasia, mental retardation, and elliptocytosis and has been described in several families with deletions of COL4A5 that extend beyond the 3′ end of the gene.[11–14]

Autosomal-Recessive Alport Syndrome Caused by Homozygous Mutations Mutations in *COL4A3* or *COL4A4* (AR-AS, OMIM 203780)

AR-AS is allelic with familial thin basement membrane nephropathy (TBMN). This form of AS accounts for 15% of

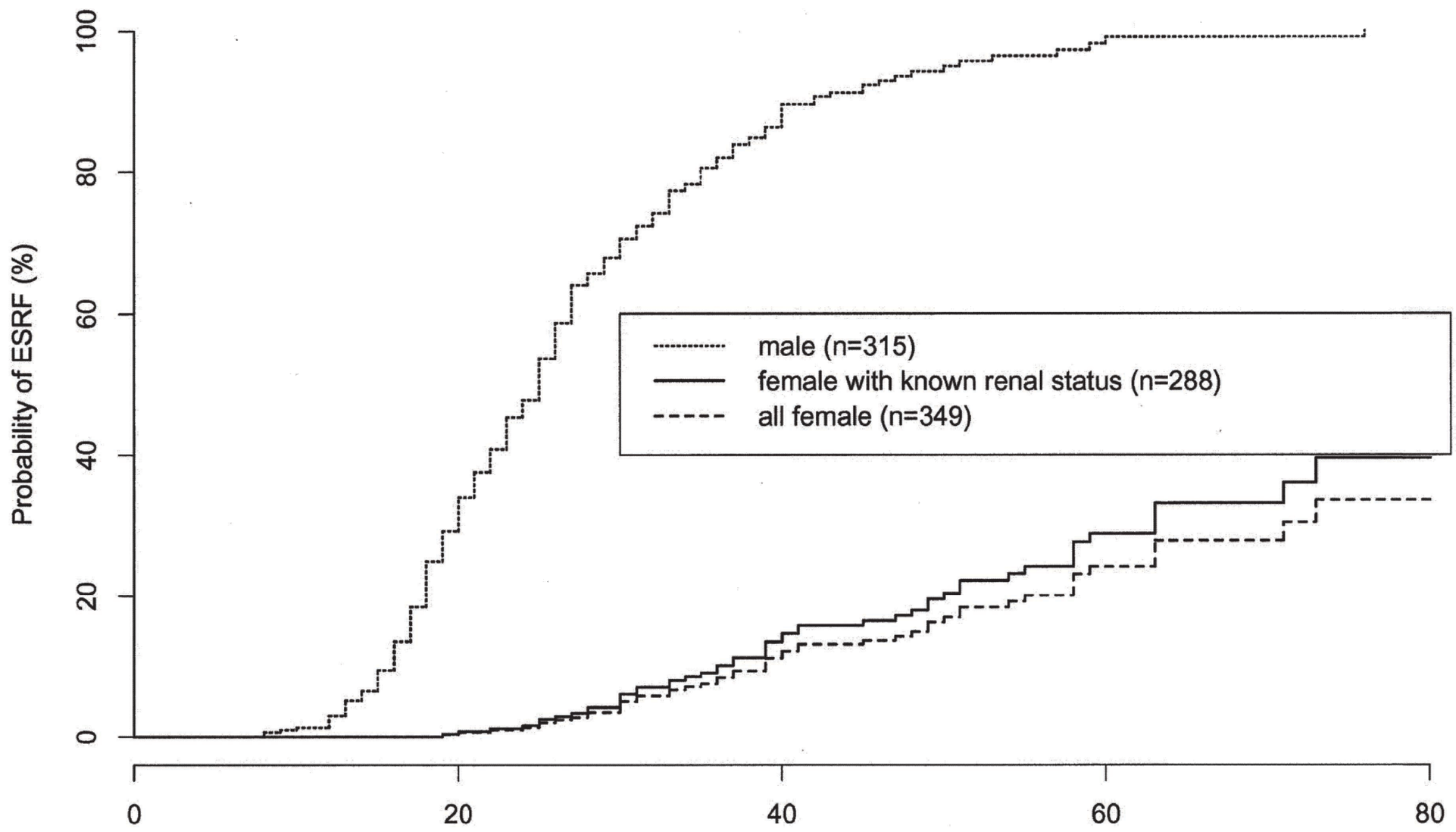

FIGURE 17.1 Probability of end-stage renal disease (ESRD) in 315 boys and men and 288 girls and women with the *COL4A5* mutation. In the third curve, girls and women with incomplete clinical data were added because they were not in ESRD at last follow-up. (Reprinted from Jais JP, Knebelmann B, Giatras I, et al. *J Am Soc Nephrol.* 14:2603-2610;2003 with permission from the publisher, American Society of Nephrology.)

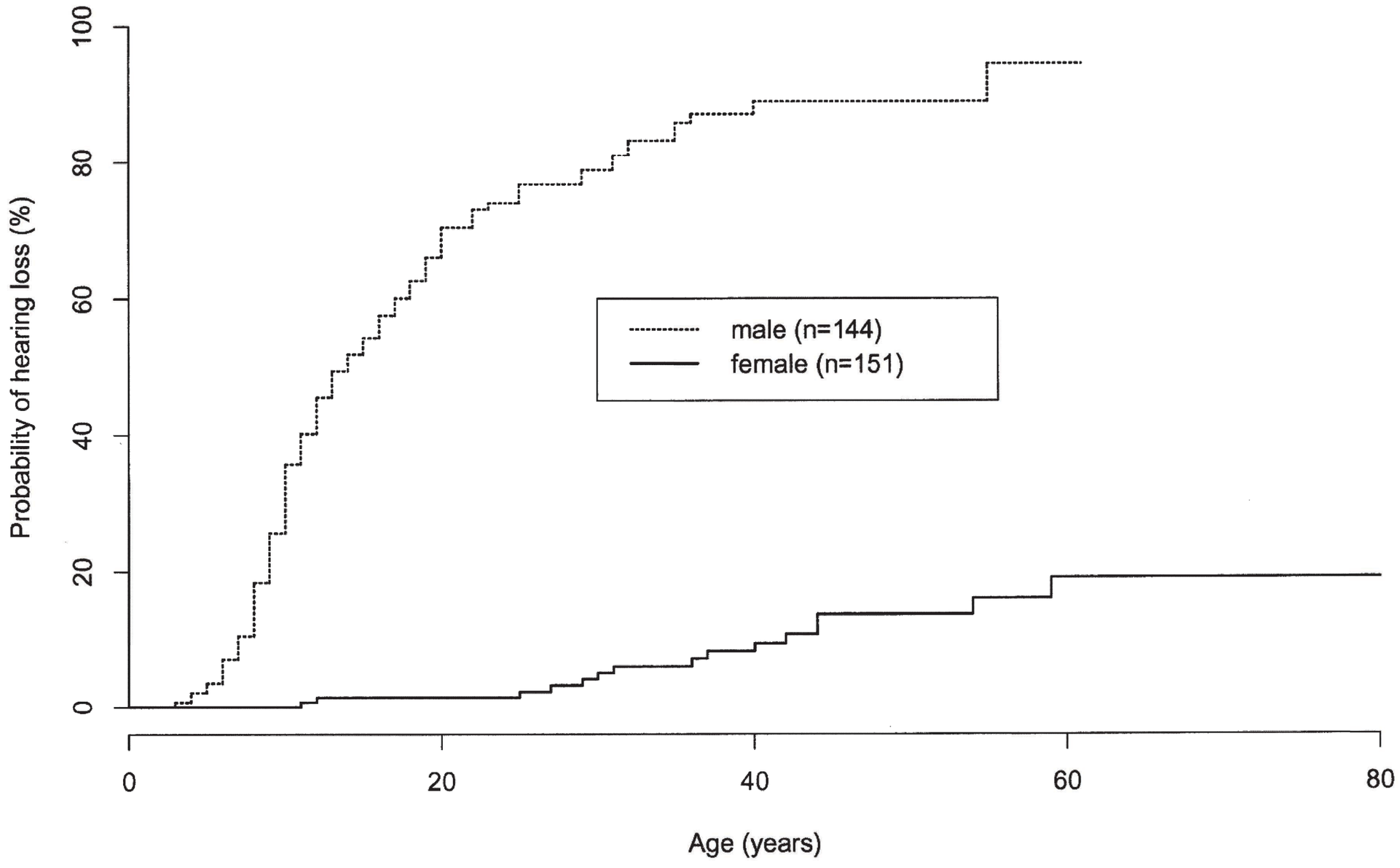

FIGURE 17.2 Probability of hearing loss in 144 boys and men and 151 girls and women with the *COL4A5* mutation. (Reprinted from Jais JP, Knebelmann B, Giatras I, et al. *J Am Soc Nephrol.* 14:2603-2610;2003 with permission from the publisher, American Society of Nephrology.)

AS cases. AR-AS results from mutations affecting both alleles of the COL4A3 gene or the COL4A4 gene. To date, most examples of AR-AS syndrome have resulted in early ESRD, but this may reflect ascertainment bias.[15–17] Males and females are equally severely affected, and hearing and ocular defects are usual. It is not yet clear whether all AR-AS or all TBMN is caused by mutations of these genes.

Autosomal-Dominant Alport Syndrome without Hematologic Defects (AD-AS, OMIM 104200)

AD-AS is a relatively rare genetic form of AS. It is linked with a heterozygous mutation of either the COL4A3 gene or the COL4A4 gene. Only a few families have been described to date. One well described family had relatively mild renal impairment and no hearing loss, eye signs, platelet abnormalities, or leiomyomatosis.[18] The mutation in this family is a splice site mutation in COL4A3.[19] In a study of eight families with heterozygous mutations affecting the COL4A4 gene none had ocular problems, and a low incidence of hearing anomalies was observed.[20] Loss of renal function occurred at a later age than the X-linked form.

Familial Thin Basement Membrane Nephropathy or Benign Familial Hematuria (OMIM 141200)

In 1997, Lemmink et al.[21] linked the occurrence of heterozygous mutations in the COL4A3 and COL4A4 genes with familial TBMN. These conditions are associated with the maintenance of long-term normal renal function and the absence of hearing loss or ocular problems. More recently, Pierides et al.[22] described 11 large pedigrees in which heterozygous COL4A3/COL4A4 mutations were associated with microscopic hematuria before the age of 30 and late development of proteinuria and ESRD due to focal segmental glomerulosclerosis.

Genotype–Phenotype Correlation in Alport Syndrome

COL4A5 Mutations

XL-AS is both clinically and genetically heterogeneous. To date, more than 590 mutations and potential mutations have been described in the COL4A5 gene associated with XL-AS.[23,24] Among affected male patients, the age at ESRD typically ranges between the second and third decades of life. However, in milder cases, ESRD may be delayed until the fifth or sixth decade. Similarly, deafness occurs at variable ages and a wide variety of ocular abnormalities have been reported among patients.[2] Several large studies from Europe, the United States, and China have assessed a genotype–phenotype correlation in XL-AS.[2,4,25,26,27] The COL4A5 mutation type appears to be one factor associated with renal disease severity and extrarenal manifestations. In male-affected patients large deletions, non-sense, and frame shift mutations have been associated with more severe disease manifestations, such as earlier age at ESRD onset, hearing loss, and the occurrence of eye abnormalities compared to patients with missense mutations.[4,25,26] Early renal failure and retinopathy have also been reported to associate with the occurrence of certain specific mutations, including some missense mutations.[28] The position of the mutation and the affected domain of collagen α_5(IV) also appears to affect disease severity. An earlier age at onset of ESRD was shown to associate with a more 5′ gene location in one study.[26] The distance of the mutation from the NC1-domain was shown to affect severity.[25] Glycine substitutions occurring in exons 1 through 20 resulted in a less severe phenotype compared to those affecting exons 21 through 47.[25] This effect was attributed to the fact that the triple helix formation starts at the C-terminal of the NC1-domain and proceeds in a zipperlike manner to the N-terminal end.[29] Similar studies in affected women and girls have failed to demonstrate any genotype–phenotype correlation.[7] However, it should be stated that phenotypic variability is also common among affected family members of the same gender who carry the same germline mutation. This intrafamilial variability may be attributed to both the environment and the effect of other genes.

COL4A3 and COL\4A4 Mutations

To date, 71 mutations or potential disease-associated sequence variants have been described in the COL4A3 gene, and 56 have been described in the COL4A4 gene.[23] Although AR-AS associated with homozygous mutation in either COL4A3 or COL4A4 results in the early onset of ESRD with typical hearing loss and eye problems, heterozygous mutations in the COL4A3/COL4A4 genes are associated with the less severe phenotype associated with benign familial hematuria and familial TBMN. Due to the innate genetic complexity of these disorders, not surprisingly, no genotype–phenotype correlation has been described.

Clinical variability in disease expression has been described for both male and female patients with AD-AS who carry a heterozygous mutation in either COL4A3 or COL4A4. However, no significant genotype–phenotype correlations have been described in AD-AS.[20] This may relate to the small number of families that have been identified with this genetic form of AS.

Pathogenesis

Type IV collagen, a major constituent of basement membranes, is comprised of six chains: α_1(IV) through α_6(IV). The type IV collagen chains assemble into three different heterotrimers in the mammalian basement membrane: $\alpha_1,\alpha_1,\alpha_2$; $\alpha_3,\alpha_4,\alpha_5$; or $\alpha_5,\alpha_5,\alpha_6$, respectively. The $\alpha_3,\alpha_4,\alpha_5$ form is synthesized by the podocytes in the glomerulus, and this heterotrimer of type IV collagen is also the predominant form of collagen found in the basement membrane of the ears, eyes, and lungs.[30] Mutation affecting any of the corresponding genes—namely, COL4A3, COL4A4, or COL4A5—will have a consequential effect on the integrity of the type IV collagen. In the GBM in Alport syndrome, the normal $\alpha_3,\alpha_4,\alpha_5$ collagen network is replaced by the fetal $\alpha_1,\alpha_1,\alpha_2$ network, which

is less resistant to degradation, thus resulting in the gradual deterioration of the GBM and in the clinical features of AS.[31]

Pathology

Kidney

There are no pathognomonic lesions seen with light microscopy in AS.[32,33] Lipid-laden interstitial foam cells are seen in the cortex of some but not all biopsy specimens. Foam cells are typically absent from biopsies taken early in the disease process.[34,35] Direct immunofluorescence is initially negative, whereas a faint deposition of immunoglobulin (Ig)G, IgM, and/or C3 may be observed with the progression of the glomerular segmental lesions.[36] The most definitive diagnostic information is provided by electron microscopy (EM) and by differential immunostaining for collagen α(IV) chains with specific monoclonal antibodies, which is discussed further under immunopathology.

Electron microscopy. The classic ultrastructural lesion of AS is characterized by an irregular thinning and thickening of the GBM, splitting and lamellation of the GBM with the loss of the normal lamina densa, small granules within the GBM, and an irregular outer and inner contour of the GBM (Fig. 17.3).[36] Distortion of the lamina densa may be extreme at times, amounting to a basket weave appearance in which the lamellae branch and rejoin in a complex triangle.[37] Focal or diffuse foot process fusion is common. The ultrastructural changes are common to all variants of AS. However, the extent of GBM thickening and lamellation is gender and age dependent. Moreover, there is considerable variability between affected individuals regarding the presence of these characteristic ultrastructural findings and even between affected individuals from the same family.[36] It should be emphasized that GBM splitting with variable thickness and an irregular outer contour is not specific for AS; such changes may be seen with other renal injuries, as reviewed by Haas.[36] Therefore, the combined use of EM and immunohistology for the detection of the collagen α_3(IV), α_4(IV), and α_5(IV) chains increases the specificity for AS diagnosis. Use of these combined methods permits AS diagnosis in most cases.[36]

Immunopathology. Staining for α_3(IV), α_4(IV), and α_5(IV) collagen chains with monoclonal antibodies distinguishes between the various forms of AS including XL-AS, AR-AS, and TBMN as depicted in Table 17.2. In particular, the absence

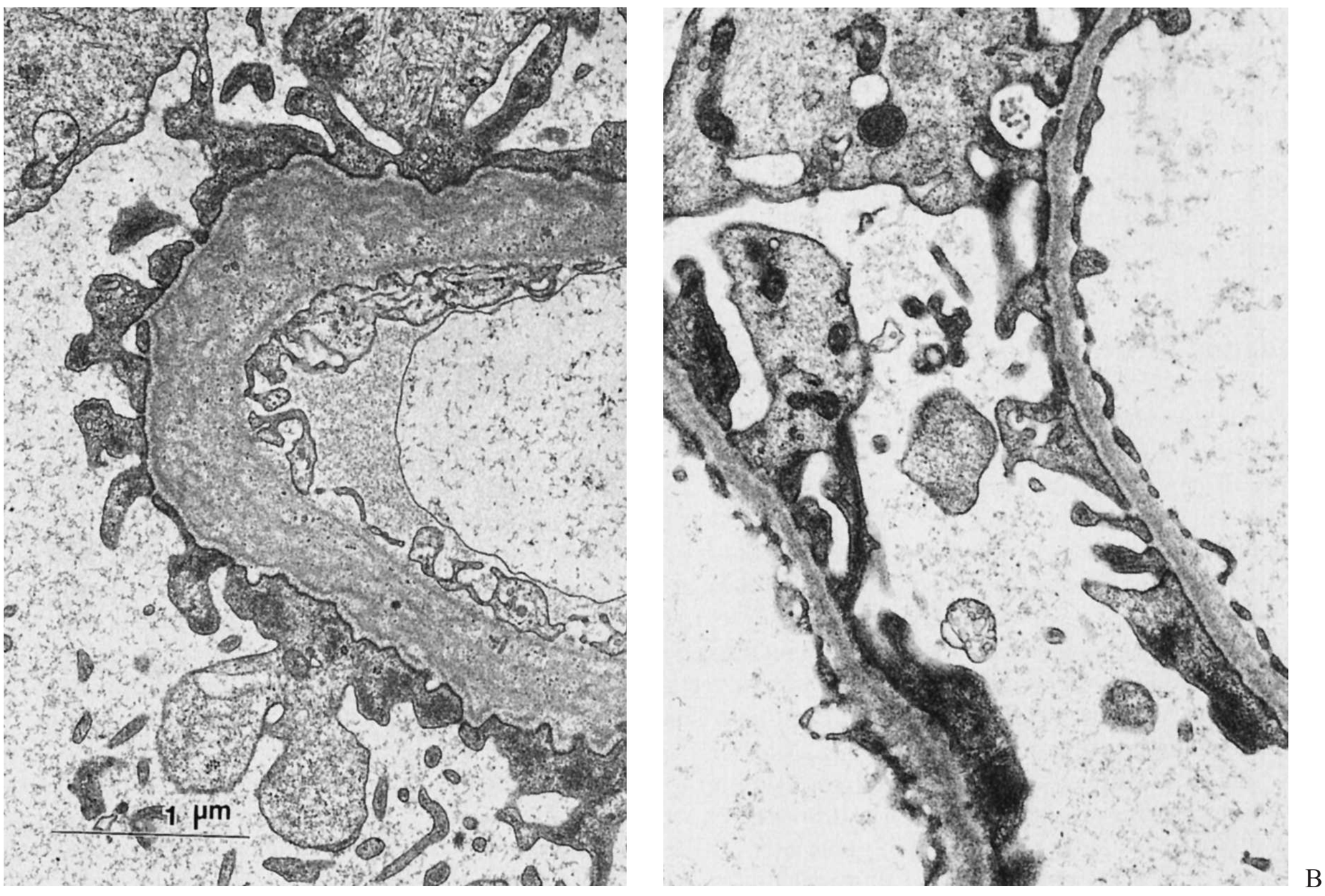

FIGURE 17.3 **A:** Glomerular ultrastructure in Alport syndrome. Electron micrograph of a renal biopsy specimen from a man in Utah kindred M, illustrating a widened lamina densa of the GBM (GBM). The lamina densa is split into several layers, between which may be seen numerous small electron-dense granules. **B:** Electron micrograph, at same magnification as **(A),** from an affected woman with familial thin GBM disease. The uniform thinning of the GBM can be appreciated by comparison with the width of the epithelial foot processes. (Electron micrographs courtesy of Dr. M.E. Hammond, University of Utah, Salt Lake City.)

17.2 Staining for α_3(IV) and α_5(IV) in Thin Basement Membrane Nephropathy (TBMN) and Alport Syndrome Variants

	α_3(IV)			α_5(IV)			
	GBM	BC	TBM	GBM	BC	TBM	EBM
Normal/TBMN	+	+	+	+	+	+	+
Alport variants[a]							
X-linked carrier (heterozygote)	Discont	Discont	Discont	Discont	Discont	Discont	Discont
X-linked male	–	–	–	–	–	–	–[b]
Autosomal recessive	–	–	–	–	+	+	+

[a]Infrequent exceptions to these patterns have been noted on renal biopsies.
[b]Up to approximately 50% of individuals in each of these categories will show normal staining for α_5(IV) on skin biopsy.
GBM, glomerular basement membrane; BC, Bowman capsule; TBM, distal tubular basement membrane; EBM, epidermal basement membrane; Discont, discontinuous staining (mosaic pattern).
Reproduced from Haas M. Arch Pathol Lab Med. 2009;133:224–232 with permission from the publisher American College of Pathologists.

of GBM staining for α_3(IV) and α_5(IV) is indicative of AS: either XL-AS in male subjects or AR-AS in both genders.[36] It should be noted that in 15% to 20% of XL-AS kindreds, α_3(IV) and α_5(IV) staining remains normal. This may result from the presence of certain missense mutations that cause only minimal disruption to the collagen chain structure. Both α_3(IV) and α_5(IV) are normally expressed in TBMN. Readers are referred to a comprehensive overview of differential α(IV) staining patterns for differentiation of the various forms of AS and TBMN by Haas.[36]

Skin

Skin biopsies are far less invasive than renal biopsies and may provide useful diagnostic information based on immunofluorescence analysis in certain patients. A normal epidermal basement membrane (EBM) contains α_5(IV) but not α_3(IV) or α_4(IV) chains. Thus, in AR-AS, α_5(IV) is present in EBM.[38] Absence of staining for α_5(IV) is highly specific of XL-AS in male patients. A pronounced pattern of discontinuous α_5(IV) staining is observed in some heterozygous carriers of XL-AS. However, it should be noted that a significant proportion of XL-AS patients, both male and female, retain a normal EBM staining of α_5(IV).[36] Thus, the diagnostic value of skin biopsies that demonstrate a positive staining for α_5(IV) is limited. Moreover, skin biopsy staining cannot be used for the diagnosis of AR-AS as expression of α_3(IV), and α_4(IV) is normally absent in EBM.

Cochlea

The inner ear is much less amenable to a histopathologic study than the kidney. Specific lesions in AS include a zone of separation between the basilar membrane and the overlying basement membrane of the organ of Corti and the presence of cells filling the tunnel of Corti and the extracellular spaces of Nuel.[39] Cellular infilling of the tunnel of Corti and spaces of Nuel likely represents a persistence of the fetal cochlear structure.[39]

Eye

In the anterior lenticonus, the basement membrane of the anterior lens capsule is thinned and more fibrillar than normal,[40,41] allowing for an anterior bulging of the cortex of the lens, most prominently in the pupillary region. The collagen α_3(IV), α_4(IV), and α_5(IV) chains may be present or lacking in the anterior lens capsule of AS patients.[42]

Another common ocular manifestation is perimacular "dot and fleck" retinopathy, which consists of whitish or yellowish flecks or granulations in a perimacular distribution.[43]

Smooth Muscle

In Alport-leiomyomatosis syndrome, the orderly hyperplasia of smooth muscle may involve the trachea and bronchi, all muscle layers of the esophagus, the clitoris, and the uterus. True leiomyomas, characterized by disorderly smooth muscle proliferation, have been found in the trachea and lungs, the esophagus, the upper part of the stomach, the clitoris, the vagina, the vulva, and the perineum.[10] Malignant transformation has not been observed. Ultrastructurally, basement membranes are normal in the esophageal tissue.[10]

Clinical Features of X-Linked and Autosomal Recessive Alport Syndrome

Renal Symptoms and Signs

Hematuria is the cardinal feature, persistent and present from birth, in 100% of affected males[4] and in 90% to 100%

of heterozygous females.[7] Hematuria is a sine qua non for the diagnosis of AS in males. Single or recurrent episodes of gross hematuria have been reported in 60% to 70% of males.[4] They may follow sore throats or other infections in children and may be the presenting symptom.[44]

Microscopy reveals dysmorphic red cells, renal tubular cells, and red cell casts in the urine. Urinary tract infections are no more frequent than in the general population. Proteinuria develops in 95% of affected males and in 75% of female heterozygous patients and is of variable degrees, ranging from barely detectable in early stages to nephrotic range[4] in some patients in advanced stages. As in other renal diseases, heavy or increasing proteinuria implies a worse prognosis.[4,44] Nephrotic syndrome may occur in severely affected patients. The serum complement concentration is normal.

Renal function initially remains normal for years and then wanes inexorably to renal failure. The age at which ESRD develops is very variable and spans from childhood or adolescence in families with severe (usually truncating) mutations to the fourth or fifth decade in some families with very mild (usually missense) mutations.[4,26] In the past, families in which ESRD developed in males at a mean age of 30 years or younger were classified as "juvenile" Alport families (about 70% of XL-AS), whereas others in which ESRD occurred at a mean age over 30 years were called "adult" Alport families (about 30% of XL-AS).[45] However, even within a family, the age of ESRD may be widely variable. As renal function declines, hypertension develops and worsens. Rarely, crescentic glomerulonephritis has been described and accompanied by rapidly progressive renal failure.[46]

In XL-AS, renal failure is inevitable for affected males, whereas only 30% to 40% of females develop ESRD, generally in later adulthood. In a European study of 195 XL-AS families, 12% of gene-carrying women developed ESRD by the age of 40 years, 30% developed ESRD by age 60, and 40% developed it by age 80 years (Fig. 17.1).[7] However, this may be an overestimate because in that study, about a third of gene-carrying women, possibly the less severely affected, were lost to follow-up. Many females remain asymptomatic carriers, only manifesting microscopic hematuria with or without low-grade proteinuria.[7,9] There is no correlation between the severity of the disease in women and men from the same family, and no genotype–phenotype correlations in women, which is likely due to the random inactivation of X-chromosomes in women.[7,9] The clinical manifestations of AR-AS are indistinguishable from XL-AS, with hematuria, proteinuria, and renal failure developing equally in males and females. ESRD occurs in all affected men and women, usually before the age of 30 years.[2,8]

Sensorineural Hearing Loss

Sensorineural hearing loss occurs in 50% to 80% of males with XL-AS and in 20% to 30% of heterozygous females, as shown in Figure 17.2.[4,7,8] It is never present at birth but starts to develop in childhood; initially, there is high-frequency hearing loss that is detectable only by audiometry, but it progresses and becomes clinically detectable in boys at an average age of 11 years.[2] Deafness develops at varying ages, often concurrently with the progression to ESRD, but in some cases 10 or more years later.[4,47] There is some correlation between the severity of the renal disease and the severity of hearing loss; families without hearing loss appear to have less severe renal disease than those with hearing loss.[44] However, there is also variability within AS families; while some affected family members develop hearing loss, other affected members may have apparently normal hearing even after ESRD.[47] Hearing loss generally occurs less frequently, less severely, and at an older age in carrier females (Fig. 17.2),[7,8,48] although some women and girls may have a profound loss. In the European study of XL-AS families, the risk of deafness by the age of 40 years was only 10% for women, but after the age of 60 years, 20% of the women had developed hearing loss.[7]

There is no anatomic abnormality of the tympanic membrane or ossicular chain; middle ear pressures are normal and air conduction is normal. Hearing loss is usually worse above 1,000 Hz, with an abnormal short increment sensitivity index, negligible tone decay, and normal brainstem auditory evoked responses,[48] thus proving cochlear rather than neural dysfunction. Caloric test results are normal, but more subtle testing reveals impaired vestibular function[48]; flat intensity function curves locate the lesion in the end organ itself. Hearing loss is thought to be due to structural lesions of the capillary basement membrane of the stria vascularis in the cochlea where the collagen α_3(IV), α_4(IV), and α_5(IV) chains are normally expressed.

Renal disease with hearing loss, even if familial, should not be equated with AS. Several genetic diseases affect the ear and the kidney, and chronic renal failure itself has been associated with impaired hearing. Hearing loss from the time of birth is unlikely to be due to AS.[4,47,49]

Ocular Features

A wide range of eye abnormalities have been reported, including anterior lenticonus, dot and fleck retinopathy, corneal endothelial vesicles (posterior polymorphous dystrophy) and erosions, macular holes, retinal detachment, and more recently, bull's eye and vitelliform maculopathy.[50] Eye abnormalities are usually not observed in children but develop in late adolescence and young adults. The most frequent are anterior lenticonus and dot and fleck retinopathy, which appear to be specific for AS.[2,28] The retinopathy consists of yellowish or whitish spots around the macula, sparing the fovea. Loss of the foveal reflex with alterations in macular pigmentation may be observed, as well as more peripheral pigmentary disturbances, either white or dark.[50] Visual acuity is unaffected by the presence of these retinal lesions. Their reported frequency varies and depends in part on whether a thorough eye exam is performed. In a smaller study, the retinopathy was found in 90% of affected males,[2] whereas other studies report it in 50% to 60% of men and in about 15% of women in XL-AS.[4,7,28]

Anterior lenticonus is a conical protrusion on the anterior aspect of the lens due to thinning of the lens capsule; it is less common than the dot and fleck maculopathy, occurring in 20% to 40% of men with XL-AS and is usually, but not invariably, bilateral. It is easy to recognize when it is fully developed. The red reflex is present, but it is impossible to see the fundus clearly because of the severe refractive error. Examination through a dilated pupil with a strong convex lens in the ophthalmoscope reveals an "oil drop" bulging the anterior surface of the lens. Lesser degrees of lenticonus may be difficult to diagnose even by slit-lamp examination.[51] Severe degrees of lenticonus cause grave visual impairment, are not correctable by glasses or contact lenses, and require lens replacement. Lenticonus is usually associated with early onset renal failure and more severe mutations in COL4A5.[4,28] It is rare in women with XL-AS.[7,8] Lenticonus is almost always accompanied by dot and fleck retinopathy,[52] but the retinopathy can be found in the absence of lenticonus. Ocular findings in AR-AS are similar to those seen in XL-AS men.[2] In one study, 91% of subjects with AR-AS had retinopathy and 82% had lenticonus.[8]

Autosomal Dominant Alport Syndrome

AD-AS is characterized by wide intra- and interfamilial variability in severity, but usually it is a milder disease.[2,19,20,53] It has been described in more detail in recent years, and causative heterozygous mutations have been shown in both COL4A3 and COL4A4 genes.[2,19,20,53] Although microhematuria is present in 95% to 100% of gene carriers, proteinuria is observed in about 50% of carriers at an age between 20 and 40 years, and ESRD is observed in 24% at a mean age of 51 years, but increases to 80% among patients older than 60 years.[20] ESRD has not been documented before the age of 31 years, and the overwhelming majority (93%) occurs after the age of 40 years.[20] Manifestations are similar in men and women. Hearing loss occurs in about 20%, with the onset usually after the age of 40 years. Ocular lesions have so far not been observed in AD-AS.[20]

Esophageal and Genital Leiomyomatosis

In several kindreds and in isolated patients, hematuric nephropathy was associated with striking muscular hypertrophy or leiomyomas of the esophagus.[54–57] In females, there was also hypertrophy of the clitoris, vulva, and adjacent structures. Hearing loss and cataracts were common, and anterior lenticonus was occasionally present.[57] Cataracts, which are not a feature of AS alone, were frequently severe and of early onset, and were sometimes congenital. Alport-leiomyomatosis syndrome has been comprehensively reviewed.[55,57]

Inheritance is X-linked dominant with deletions having been shown in the adjacent 5′ ends of COL4A5 and COL4A6.[56,58–60] In cases examined by electron microscopy, lamellation and granulation were seen in renal but not in esophageal basement membranes.[55] Clinically, affected patients suffer from dysphagia, odynophagia, regurgitation with respiratory symptoms, and bleeding. Occasionally, esophageal leiomyomatosis may be asymptomatic. The renal disease is similar to that in XL-AS men or women.[55]

Aortic Abnormalities

Aside from isolated case reports of aortic disease in males with AS, recently five males with a severe form of XL-AS were described who manifested thoracic aortic dissection at ages 25 and 32 years (two cases), ascending aortic aneurysm with rupture at age 32 (one case), aortic insufficiency requiring a replacement of the aortic root and valve at age 23 (one case), or asymptomatic dilatation of the ascending and descending aorta at age 21 years.[61] All five patients had ESRD by age 20 years, three had sensorineural deafness, and two had anterior lenticonus. Supporting the contention that aortic disease is a manifestation of AS was the finding of absence of collagen α_5(IV) from the aortic media in transgenic mice with XL-AS. A ruptured abdominal aortic aneurysm at age 36 and a ruptured intracranial aneurysm at age 14 years had been previously reported in two males with XL-AS.

Rare or Chance Associations

Many strange associations with AS have been described. Often, the diagnosis of AS was insecure, and in others, a coincidence noted on a few cases was not confirmed in larger studies. Further examples are needed to confirm these associations.

Diagnosis

The path to the correct diagnosis lies through a carefully collected, extended family history and a personal examination of the urinary sediment, specifically for hematuria. The proband will often be a child with unexplained hematuria or an adolescent to middle-aged male with ESRD with a vague history of kidney disease in brothers or relatives on the maternal side. A systematic urinalyses may reveal several relatives with hematuria.

There are several points to remember:

Microscopy of urine sediment—do it yourself!

Family history—extend to as many generations and collaterals as possible.

Age of ESRD in males helps to clarify the phenotype.

Female gene carriers—look for hematuria, although not all carriers have it.

When a member on the line of descent in a well-studied kindred is found to have hematuria, a renal biopsy is generally superfluous. The poorer the family history and the more remote the nearest affected relative, the stronger the case for a biopsy. Typical extrarenal features, specifically anterior lenticonus or retinal pigmentary changes in the patient or family, strengthen the presumption of AS and diminish the need for a biopsy. Linkage studies can identify gene carriers with near certainty in large families, but this is frequently

not practical for routine diagnosis due to the need to study several affected family members. About 15% of XL-AS cases are due to new mutations and, therefore, the family history will be negative.[2,62] In these patients, AS is diagnosed or suspected based on a renal biopsy performed for unexplained hematuria with or without proteinuria.

Molecular genetic testing is now generally available for mutation detection in the COL4A5, COL4A4, and COL4A3 genes. Acceptable samples for analysis include buccal swabs or blood samples. Detection of COL4A5 mutations by targeted mutation panel screening identifies the most commonly occurring mutations in this gene with almost 100% detection efficiency.[62] In addition, whole gene sequence analysis is available and has an efficiency of approximately 80% for mutation detection. Detection of large COL4A5 deletions or duplications requires more complex testing, which is offered by specialized clinical laboratories. Carrier testing and prenatal diagnosis may be performed once a mutation has been identified. Molecular genetic screening of both COL4A3 and COL4A4 genes by direct sequence analysis is likewise currently available through several clinical laboratories with an estimated efficiency of 80% for mutation identification. Screening for large deletions/duplications in these genes is less readily available outside of research laboratories.

Treatment

Kidney Disease

No specific treatment is known to affect the underlying pathologic process or to alter the clinical course of kidney disease. One uncontrolled series reported a surprising benefit of cyclosporine[63]; however, this was not confirmed in other studies. Despite a reduction of proteinuria with cyclosporine, renal function deteriorated and significant lesions of cyclosporine nephrotoxicity were seen on repeated renal biopsies.[64,65] Angiotensin converting enzyme inhibitors (ACEI) have been used in both hypertensive and non-hypertensive Alport children with proteinuria.[66,67] They variably reduced proteinuria and appeared to stabilize the decline of GFR. Although there is no proof of efficacy of these agents in AS, they are being widely used to suppress proteinuria in AS children.[68] Control of hypertension is necessary on general grounds and should follow the guidelines for children with renal disease. Patients with deteriorating renal function are monitored and treated as the general population with chronic kidney disease. When ESRD occurs, dialysis and transplantation pose no particular problems.

Transplantation is the treatment of choice for these young and otherwise healthy patients and has had excellent outcomes. Recurrent disease does not occur, but a small proportion of males (3% to 5%) developed de novo anti-GBM glomerulonephritis, which usually does not respond to plasmapheresis and cyclophosphamide and results in graft loss in 90% of cases.[69–71] The autoantibodies are directed against the collagen α_3(IV) and/or α_5(IV) chains, which are missing in the native kidneys. Why anti-GBM disease develops only in a minority of transplanted patients is unknown, but may depend on the specific mutation. It is not possible to predict which patients will develop this complication, but once this has occurred, the risk of recurrence in a subsequent transplant is very high.[71]

Hearing and Vision

Great care should be taken to avoid adding insults from drug cytotoxicity to the advancing aural injury. Improvement or stabilization of hearing loss in AS patients has occasionally been noted after transplantation[44,72]; others noted no benefit.[73] An interpretation of these findings is difficult because dialysis and the uremic state have been associated with reversible hearing loss. There is fair success with hearing aids. When hearing loss worsens, the patient will become more dependent on lip reading and other visual cues. Visual acuity should be monitored at intervals in those with or at risk of lenticonus, and consideration should be given to early lens extraction and intraocular lens implantation. Steroid doses should be kept low after transplantation, and patients should be monitored regularly for cataracts; poor vision is a disproportionate handicap to the deaf.

Genetic Counseling

Inheritance is X-linked dominant in 80% to 85% of families, is autosomal recessive in about 15%, and is autosomal dominant in 1% to 5%.[62] As a group, men with AS have about 30% fewer children than do men without AS; many men with more severe disease will sire no offspring.

An incomplete penetrance of AS in females must always be kept in mind.[74] In kindreds with X linkage, daughters of affected males will all be gene carriers regardless of their urinalysis results. Each clinically normal daughter of dominant gene carriers (mothers in kindreds with X linkage, and parents of either sex in kindreds with autosomal dominance) has a 50% chance of having an undetected Alport gene. Information from genetic tests or from urinalyses of the next generation may help decide whether these females have inherited a gene.

Differential Diagnosis

Conditions with Hearing Loss

Many conditions affect both the ear and the kidney, perhaps because of simultaneous embryogenesis or because of structural and physiologic homology.[75] For instance, hearing loss and proteinuria with a histologic picture of focal segmental glomerulosclerosis (FSGS) have been described in patients with mitochondrial cytopathies.[76] Here we discuss the most important hereditary conditions that might be confused with AS.

Autosomal-Dominant Alport-Like Syndrome Caused by Mutations in *MYH9*

Epstein and colleagues[77] first described a syndrome (OMIM 153650) that looked like a variant of AS with nephropathy,

sensorineural hearing loss, thrombocytopenia, and giant platelets. Subsequently, several kindreds have been described. When there were inclusions in leukocytes and cataracts in addition to nephropathy, deafness, and giant platelets, the term Fechtner syndrome (OMIM 153640) was used.[78] Other families had giant platelets, thrombocytopenia, and leukocyte inclusions but no nephropathy or deafness; this disorder was called May-Hegglin anomaly after the first descriptions in 1909 and 1945 (OMIM 155100). Other families have autosomal dominant hereditary hearing loss without any other manifestations (DFNA 17, OMIM 603622). All of these seemingly different disorders are caused by mutations in the MYH9 gene on chromosome 22q11-13, which encodes for the nonmuscle myosin heavy chain IIA (NMMHC-IIA), and are therefore variable expressions of the same disease.[79,80] Mutations in the motor domain of NMMHC-IIA are associated with a severe phenotype with severe thrombocytopenia and a high risk of glomerulopathy, ESRD, and deafness before the age of 40 years, whereas mutations in the tail domain are milder and often cause only giant platelets with mild thrombocytopenia, with a low risk of developing cataracts or hearing loss late in life.[79,80] However, as in other genetic disorders, there is significant intrafamilial variability in the severity of manifestations, possibly mediated by modifying genes or environmental factors.[80]

Clinical and Laboratory Features of MYH9 Disorders

The hallmark of this disease is macrothrombocytopenia from birth; all patients also have neutrophilic inclusions, although in some cases they are small and difficult to see on routine peripheral blood smears. The bleeding tendency is generally mild and depends on the degree of thrombocytopenia; platelet counts are usually between 25,000 and 100,000 per microliter. Bleeding times may be normal or substantially prolonged.

Glomerulopathy develops in 30% to 70% of patients with MYH9-related disorders at a mean age of 23 years.[80,81] Patients present with proteinuria, which is in the nephrotic range in more severe cases, and/or microhematuria, and often progress to ESRD before the age of 40 years.[80] When a renal biopsy was performed, it usually showed nonspecific light microscopic findings, including mesangial cell and matrix expansion, focal segmental, or global glomerulosclerosis and tubulointerstitial fibrosis.[80,82] Electron microscopy showed a focal and segmental effacement of foot processes and a loss of the interpodocyte slit diaphragm, as well as irregular thickening, splitting, thinning, and even a basket weave appearance of the GBM,[80] which may lead to confusion with AS. A renal biopsy is not necessary for the diagnosis of an MYH9-related disorder.

Sensorineural hearing loss and, sometimes, cataracts usually develop in parallel with the renal disease in patients with severe mutations (in the motor domain or at position 702 of the NMMHC-IIA gene), similar to AS.[79] The differentiation is made clinically by the finding of giant platelets, thrombocytopenia, and autosomal dominant inheritance. Individuals from families with milder mutations (in the tail domain of the gene) may develop presenile cataracts and hearing loss later in life.

Treatment

The treatment or prevention of bleeding complications is with platelet transfusions, with or without adjunctive desmopressin (DDAVP). Corticosteroids, intravenous immunoglobulin, and splenectomies have no role because this is not an autoimmune-mediated disease. The management of the renal disease is nonspecific; drugs that block the renin-angiotensin system are used for patients with hypertension and proteinuria. Drugs that are potentially harmful to the inner ear, lens, or kidneys must be avoided. Subjects who progress to ESRD are good candidates for renal transplantation.

Hereditary Interstitial Nephritis with Hearing Loss

One large kindred with autosomal-dominant inheritance of high-tone hearing loss, proteinuria, casts, and pyuria, but without hematuria, has been described.[83] Biopsy findings in four siblings were interpreted as interstitial nephritis. Renal impairment was generally mild, although renal failure supervened late in life in four men and in one woman. Familial reflux nephropathy was not excluded as a possible cause of this disorder.

Conditions with Normal Hearing

Familial Thin Basement Membrane Nephropathy (Benign Familial Hematuria, OMIM 141200)

Familial hematuria does not always have an ominous prognosis, and large families in which renal impairment never occurred have been described. Rogers and colleagues[84] delineated an entity characterized by uniform thinning of the GBM and prolonged survival without the deterioration of renal function. Familial TBMN is the best name for this condition, which occurs in about 1% of the general population.[36,85,86] In several reports, about 40% of cases have been shown to result from heterozygous mutations in the COL4A3 or COL4A4 genes.[21,85–88] It is not clear whether other genes can cause TBMN or whether the failure to detect mutations in these genes in some families resulted from incomplete penetrance, concurrent conditions causing hematuria, or the limitations of mutation analysis.

TBMN displays autosomal-dominant inheritance[89,90] and represents the carrier state for AR-AS.[22,36,85,86] Clinically, it manifests hematuria from childhood, usually microscopic and continuous, but it may be punctuated by episodes of visible hematuria, particularly during or after an upper respiratory tract infection. Hearing is normal and ocular lesions do not occur. In most individuals, there is no or only minimal proteinuria, blood pressure is normal, and renal

function remains normal.[84,85,91] Flank pain occurs in some patients,[85,91] and TBMN appears to be one of the causes of the so-called loin pain–hematuria syndrome.[92,93] Although familial TBMN does not lead to ESRD in most cases, a few families have been reported in whom significant proteinuria, hypertension, and ESRD developed in older individuals (>50 to 60 years of age), without hearing loss or ocular manifestations.[22,94,95] Because these cases of late onset ESRD were also caused by COL4A3 and COL4A4 mutations, these observations blur the line between benign familial hematuria and AD-AS, in which hearing loss occurs in only some individuals late in life and ocular changes are not seen.[20,36,53] Moreover, recently, five families with a clinical diagnosis of benign familial hematuria have been found to carry a heterozygous missense mutation in the COL4A5 gene, whereas that same mutation caused AS with late onset ESRD in other families,[96] possibly due to the effect of other modifier genes.

In classical TBMN, renal biopsy specimens, apart from the presence of erythrocytes in the Bowman space and in tubules, appear normal by light microscopy.[36,84] Immunofluorescence examinations also reveal normal findings.[84] The characteristic ultrastructural finding is uniform with diffuse thinning of the lamina densa of the GBM. The overall width of the GBM is reduced from 300 to 400 nm to approximately 200 nm.[36,84] Breaks may be seen in the GBM through which red cells can cross.[84] There is no widespread splitting or lamellation of the GBM, although very localized (<5% of GBM length) splitting may be observed.[36]

Even with adequate material for high-resolution electron microscopy, the distinction from AS is not always clear. Biopsies in early stages of AS can show uniform thinning while lacking abnormally thick areas and lamellation, which develop later in the course of the disease.[36,62] In these cases, immunofluorescence staining for α_3(IV) and α_5(IV) may allow the differentiation. These chains are absent from the GBM in about 80% of AS but are always present in TBMN, although at reduced levels.[36,62] Renal biopsies from individuals with late onset proteinuria and chronic renal failure have shown focal-segmental and global glomerulosclerosis in addition to diffusely thin GBM.[85,94,95]

In practice, in the absence of genetic testing, features that help distinguish TBMN from AS include male-to-male transmission, normal hearing and longevity of several affected family members, and characteristic biopsy findings in at least one member of the family. In small families or patients with new mutations, only long-term follow-up will allow for a precise diagnosis.

Familial Immune Glomerulonephritis

A familial incidence is occasionally noted in many forms of glomerulonephritis, including IgA nephropathy,[97] systemic lupus erythematosus, membranous nephropathy,[98] IgM mesangial proliferative glomerulonephritis,[99] focal segmental glomerulosclerosis,[100,101] membranoproliferative glomerulonephritis,[102] and partial lipodystrophy.[103] Congenital complement deficiencies, most commonly C3, predispose an individual to membranoproliferative nephritis.[104] The distinction from AS is evident on a renal biopsy, although the clinical features can be very similar in children or young adults presenting with hematuria with or without proteinuria.

Hereditary Interstitial Nephritides

Familial Juvenile Hyperuricemic Nephropathy (FJHN, OMIM 162000). This entity is a chronic interstitial kidney disease with autosomal dominant inheritance. It is characterized by decreased uric acid excretion, hyperuricemia in childhood and clinical gout beginning in adolescence, the development of chronic kidney disease in the third or fourth decade of life, and slow progression to ESRD by the fourth to seventh decade.[105,106] Besides hyperuricemia, decreased urine concentrating ability is observed early in life, and children may present with polyuria and enuresis.[105,106] Hypertension develops later, but proteinuria is absent or slight and the urine sediment is normal or contains only a few urate crystals or epithelial cells. Renal ultrasound shows normal size or small kidneys, sometimes with multiple small medullary cysts, in which case autosomal dominant medullary cystic kidney disease (MCKD) type 2 was diagnosed until advances in molecular genetics showed that both FJHN and MCKD type 2 are caused by mutations in the uromodulin gene on chromosome 16 and therefore are the same disease.[107] Chronic interstitial nephritis is histologically nonspecific. Sometimes intratubular crystal deposits and a thickening of the tubular basement membranes are seen. There is no specific treatment for this renal disease, but allopurinol will help prevent the development of progressive tophaceous gout.[106]

A similar autosomal dominant interstitial nephropathy with early onset hyperuricemia was recently found to be caused by mutations in the renin (REN) gene on chromosome 1 (OMIM 613092).[106,108] Individuals with REN mutations have decreased renin production, predisposing them to hypotension, hyperkalemia, and acute kidney injury, which is similar to patients receiving ACEI. Children with these mutations also suffer from anemia due to decreased renin and angiotensin production.[108] Gout is common in these families and is due to decreased urate excretion. The pathogenesis of both disorders involves the accumulation of abnormally produced uromodulin or renin in tubular cells, leading to tubular cell death and subsequent tubular atrophy.

There is a third form of autosomal dominant chronic interstitial kidney disease with unknown mutations that is not associated with gout or anemia. Some of these families have been linked to chromosome 1, but REN mutations have not been found.[106]

FABRY DISEASE (OMIM 301500)

Fabry or Anderson–Fabry disease was identified over a century ago, in 1898. This inborn error (also called angiokeratoma corporis diffusum, ceramide trihexosidosis) is a rare

metabolic disorder that particularly affects vascular endothelium, leading to renal, cardiac, and cerebrovascular manifestations and early death. Fabry disease is the only known X-linked sphingolipid storage disease. Lack of α-galactosidase, a lysosomal hydrolase crucial in glycosphingolipid metabolism, causes an accumulation of neutral glycosphingolipids in many tissues.

Epidemiology

The disease is panethnic, and estimates of incidence range from about 1 in 40,000 to 60,000 males,[109,110] but may be higher.[111] Fabry disease affects males more severely than females, although many carrier (heterozygous) females also have symptoms and some have severe organ manifestations because of random X-chromosomal inactivation.[112,113]

Genetics

Inheritance is X-linked and the gene coding for α-galactosidase A (GLA) is situated at Xq22.1 on the long arm of the X chromosome, just centromeric to the AS locus. The GLA gene is a relatively small gene of ~12-kb containing seven exons. To date, over 600 mutations that cause Fabry disease have been identified, including missense, nonsense, small deletions and insertions, large gene rearrangements, and splice mutations.[23] The mutations are spread throughout the entire GLA gene, and most are "private," occurring in one or a few affected families. An analysis of data from the Fabry Outcome Survey (FOS) has suggested a correlation between genotype and clinical severity.[114] Most mutations result in the typical phenotype, but several missense mutations produced signs and symptoms confined to the heart, called "cardiac variant," or produced no symptoms at all.[115] A higher incidence of a splice mutation, IVS4-919G→A, has been reported in Japanese and Taiwanese patients with a late onset cardiac phenotype.[116,117] Moreover, patients carrying this splice mutation have recently been shown to also have a higher incidence of renal and ocular abnormalities, suggesting that the effects of this mutation are not restricted to the heart.[117]

Genotype–phenotype correlations are complex in Fabry disease because the same mutation can lead to both classic and atypical disease, even within the same family.[118,119] Patients with atypical variants of Fabry have been found to exhibit missense mutations that lead to a reduction but not an absence of α-galactosidase A activity.[120] In contrast, an increased incidence of GLA loss of function mutations has been demonstrated in children with ocular manifestations of disease.[121]

The complexity of genotype–phenotype interactions in Fabry disease is further complicated by the potential influence of modifier genes. Polymorphisms in the endothelial nitric oxide synthase gene (NOS3) have been associated with left posterior wall thickness of the heart in patients with Fabry disease and the cardiac phenotype.[122] Polymorphisms in the vitamin D receptor gene (VDR) have also been associated with variability in the Fabry phenotype.[123]

Pathogenesis

α-Galactosidase hydrolyzes neutral glycosphingolipids with terminal α-galactosyl residues. If the enzyme is defective, several glycosphingolipids, particularly globotriaosylceramide (GL-3, or ceramide trihexoside), will accumulate in many cell types, especially vascular endothelial and smooth muscle cells and also in cardiac myocytes, renal glomerular and tubular cells, and cardiac conduction fibers. Patients with a reduction in α-galactosidase A activity have a less extensive accumulation of GL-3 than patients with an absence of activity.

Pathology

Kidney

In early stages (children and adolescents), light microscopy may only show a vacuolization of podocytes and distal tubular epithelia.[124] As the lipids deposited in these cells are dissolved out with routine processing, the cells that contained them appear as foam cells (Fig.17.4). However, foam cells are not specific for Fabry disease and can be seen in other lysosomal storage diseases or in nephrotic syndrome. The accumulation of GL-3 starts in utero and affects all glomerular cell types but is greatest in podocytes.[125] Deposits can also be seen in distal and, to a lesser degree, proximal tubular epithelial cells, as well as in endothelial and vascular smooth muscle cells of arteries and arterioles.[124] In more advanced stages, light microscopy shows focal segmental and, later, global glomerulosclerosis with tubular atrophy and interstitial fibrosis, all of which are nonspecific findings.[124] However, electron microscopy reveals striking stacks or whorls of dense, flat, osmiophilic inclusions in the lysosomes of blood vessels and of glomerular and tubular epithelial cells with a periodicity of 35 to 50 Å (Fig. 17.5). These myelin bodies are 1 to 3 μm in diameter, showing a characteristic "zebra" or "onion-skin" appearance, and are strongly suggestive of a diagnosis of Fabry disease.[126,127]

Nonrenal Tissues

The most striking changes are in blood vessels and are similar to those just described for the kidney. Thromboses can occur in many organs, leading to tissue infarction, and seem to occur as a result of platelet aggregation on areas of sphingolipid accumulation in the endothelium and vascular smooth muscle cells. Aside from ischemic sequelae, the heart may show extensive glycosphingolipid deposition in myocytes and valvular fibrocytes. A left ventricular endomyocardial biopsy can reveal severe hypertrophy and a vacuolization of myocardial fibers, in some cases surrounding normal appearing arterioles.[128] On electron microscopy, lamellar inclusion bodies can be seen in vacuoles, similar to the zebra bodies in renal epithelial cells.[128] All four chambers of the heart may enlarge, the mitral and tricuspid valves thicken, and the mitral valve may prolapse. In advanced stages, prominent cardiac fibrosis develops. Cerebral vessels are strikingly involved, leading to stroke in young subjects. Glycosphingolipid accumulation in neural tissue is confined

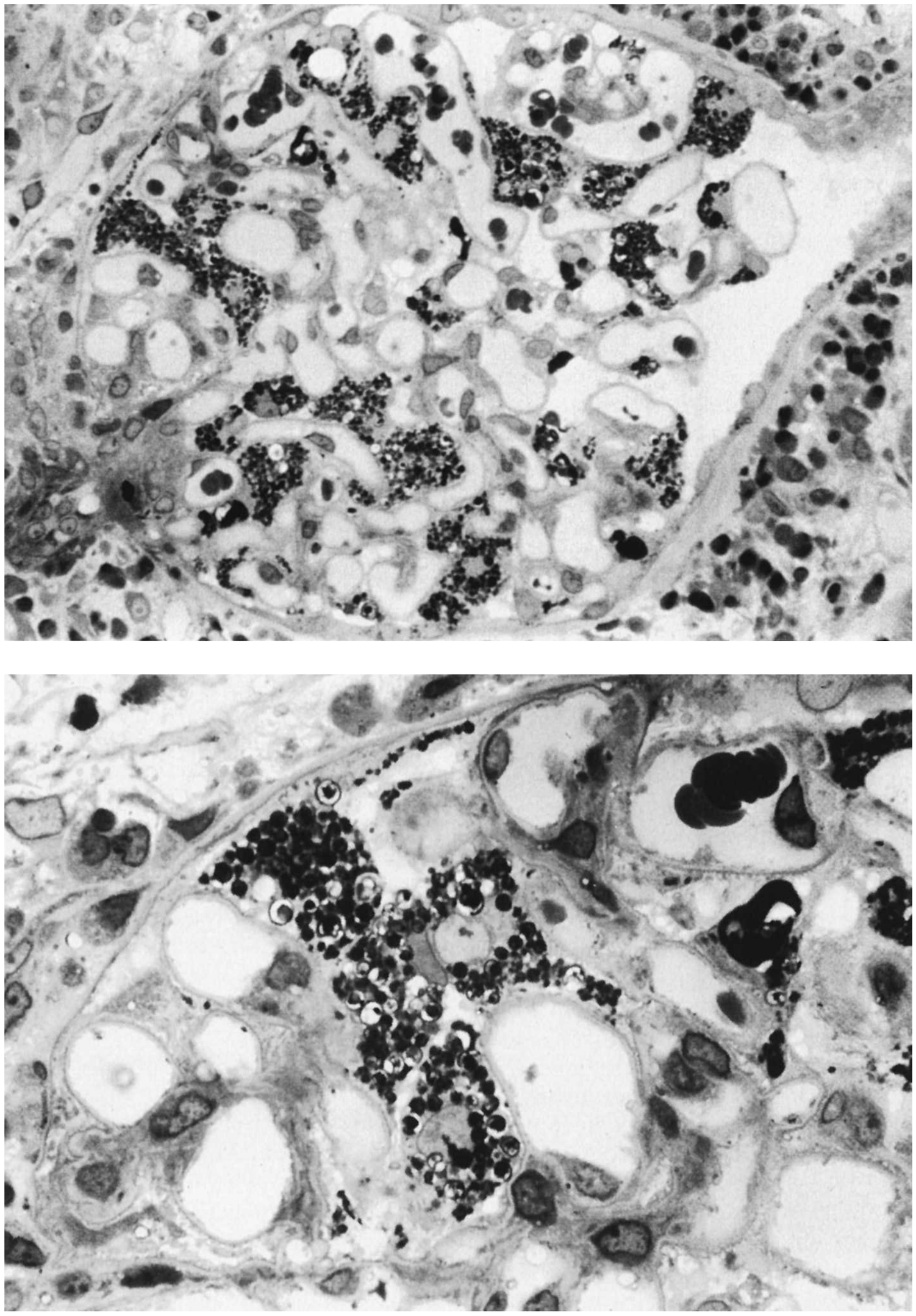

FIGURE 17.4 **A:** Foam cells in the renal glomerular epithelium in Fabry disease. (Magnification ×400.) **B:** Lipid deposits in the renal glomerular epithelium. (Magnification ×1,000.) (The glomerulus was embedded in epoxy resin and was stained with toluidine blue.) (Photographs courtesy of Dr. Melvin M. Schwartz, Rush-Presbyterian-St. Luke's Medical Center, Chicago.)

to the perineurium of the peripheral nerves, autonomic neurons, dorsal root ganglia, and some primary somatic afferent neurons. Accumulation also occurs in the cornea.

Clinical Features and Course

Extrarenal Manifestations

In childhood and early adolescence, affected individuals experience agonizing pain in the limbs, more marked distally.[109] Pain can be chronic and/or acute, with episodic crises often precipitated by changes in temperature, exercise, or stress. They occur in 80% to 90% of male patients in the first decade and in about 10% to 70% of female patients, often in the later course of the disease.[129,130] A typical pattern of pain is acroparesthesia or burning sensations in the palms of the hands or soles of the feet. They become less intense or may even disappear in later life. In severe attacks, pain radiates proximally and may even simulate an acute abdomen. The pain is a result of damage to small nerve fibers caused by the accumulation of GL-3 in the nerve axons and dorsal root ganglia.

Hypohidrosis is a nearly constant feature, leading to heat and exercise intolerance. Some patients suffer from hyperhidrosis. Other common nonspecific complaints in children and adults are abdominal cramps and diarrhea, which are likely caused by autonomic neuropathy. Progressive sensorineural hearing loss, often associated with tinnitus or vertigo,

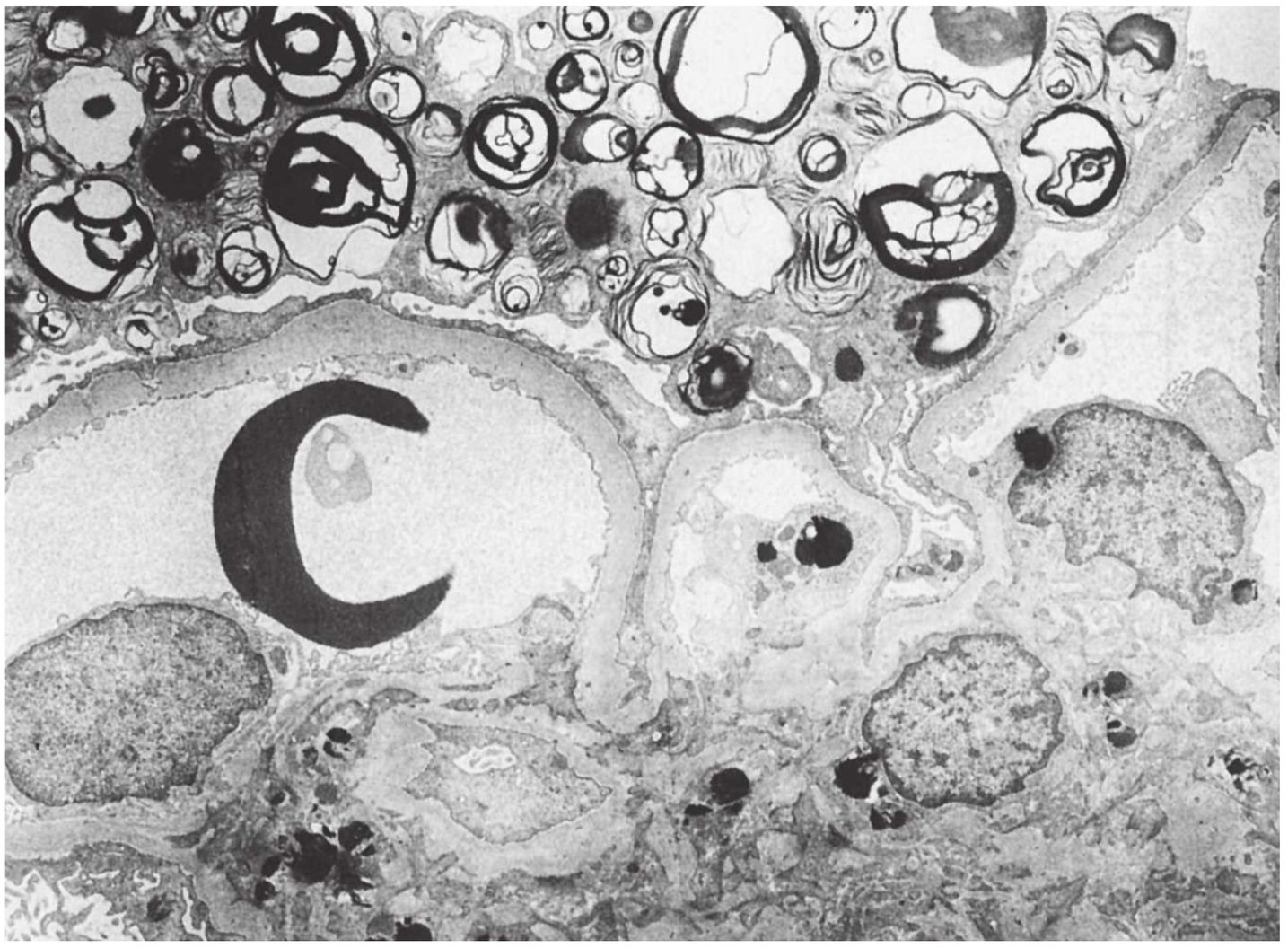

FIGURE 17.5 Myelin figures in Fabry disease. An electron micrograph of glomerular capillary loops with ultrastructural changes characteristic of Fabry disease. (Magnification ×5,500.) Many whorled "myelin figures" or "zebra bodies" are visible in the glomerular visceral epithelial cells. (Photograph courtesy of Dr. Daniel Terreros, Salt Lake City VA Medical Center, Salt Lake City, Utah.)

has also been reported to occur commonly in young male and female patients; its severity appears to be correlated with the peripheral nerve manifestations of the disease.[131,132]

Angiokeratomas, apparent as slightly raised, cherry red to black, nonblanching macules or maculopapules 1 to 3 mm in diameter, are small hyperkeratotic areas of dilated blood vessels. They appear in adolescence and progressively increase on the lower trunk and back, being particularly marked on the scrotum and bathing suit area (Fig. 17.6). Usually, they appear in groups or in generalized forms but they can be isolated. About 30% of carrier females have at least minimal angiokeratomas.[133] Angiokeratomas are not specific for Fabry disease because they also occur in other lipid storage diseases, and their absence does not rule out a diagnosis of Fabry disease.[134]

Cardiac involvement manifests as left ventricular hypertrophy, and some patients are erroneously diagnosed with idiopathic hypertrophic cardiomyopathy.[135] Left ventricular hypertrophy usually develops in the third and fourth decades of life and in the absence of significant hypertension.[113,135,136] In one echocardiographic study, left ventricular hypertrophy was found in 61% of men and in 18% of women who were older than 30 years of age.[135] Patients may present with congestive heart failure and/or severe mitral regurgitation.[134] The accumulation of glycosphingolipids in the cardiac conduction

FIGURE 17.6 Angiokeratomas of the anterior abdomen of a man hemizygous for Fabry disease.

system leads to arrhythmias or conduction defects requiring pacemaker and/or defibrillator implantation.[131] Cardiac and cerebral ischemic episodes can occur at an early age, in the third and fourth decades of life, often preceding the diagnosis of Fabry disease.[137] Therefore, Fabry disease is an important consideration in young patients with an unexplained stroke. One retrospective chart review of 447 Fabry patients reported that cardiac events, strokes, or transient ischemic attacks had occurred in 49% of males at a mean age of 36 years and in 35% of females at a mean age of 44 years.[131]

Cardiovascular events become more common in patients with ESRD. The Fabry registry, a voluntary international registry of 2,712 subjects with Fabry disease, reveals that after the onset of renal replacement therapy, 50% of men experienced a cardiac event or stroke (by a mean age of 48 years) compared with 20% of men without the need for renal replacement therapy (with a mean age of 36 years).[138] In this registry, there were significantly fewer women receiving renal replacement therapy (N = 27, versus 186 men), but 10 of them (37%) had a cardiac event or stroke by a mean age of 51 years. Cardiac involvement is the most common cause of death in both men and women.[139] In this recent study, the median age of death was 54.3 years for men and 62.0 years for women.[139]

Cornea verticillata is a distinctive whorled corneal opacity that is very similar to the opacities that can occur with prolonged chloroquine or amiodarone therapy.[140,141] It is the most common ocular manifestation of Fabry disease, occurring in about 70% of adult patients and 50% of child patients.[121] Opacities appear within the first few years of life and are generally asymptomatic; they are diagnostic of Fabry disease (unless the patient is on long-term treatment with chloroquine or amiodarone). Posterior radial cataracts eventually occur in 50% of patients but scarcely interfere with vision. Retinal vascular tortuosity is observed in about 50% of males, 22% of females, and 27% of children, but by itself it is not diagnostic of the disease.[121] Retinal vascular occlusion and ischemic optic atrophy may cause a visual loss.[142,143]

Female heterozygotes have very variable and often milder manifestations, but some are as severely affected as males. In the Fabry registry mentioned previously, 70% of the 1,077 enrolled females had symptoms and signs of Fabry disease with a median age at symptom onset of 13 years.[113] Twenty percent of females experience a major cerebrovascular, cardiac, or renal event at a mean age of 46 years. Although more severely affected women are more likely to have enrolled in the registry, these data clearly show that a significant number of affected women have serious disease manifestations.

Renal Manifestations

Urinary concentration defects may be the earliest functional manifestation of Fabry renal disease, leading to polyuria and nocturia. A nephrology referral is more typically initiated because of the development of proteinuria. Proteinuria may begin in the teenage years and becomes more frequent when patients reach their 20s and 30s, and may be in the nephrotic range.[144] Microscopy of the urine sediment may show red blood cells, renal tubular cells, casts, and lipids. Lipid droplets with their characteristic "Maltese cross" appearance under polarization microscopy may be found even when proteinuria is slight. Electron microscopy of the urine sediment may show "myelin bodies" morphologically identical to those seen in the lysosomes of renal tubular cells on renal biopsy specimens (Fig. 17.7). Renal ultrasound studies have revealed an increased incidence of renal sinus and parapelvic cysts compared to healthy controls; the pathophysiology is unclear.[145]

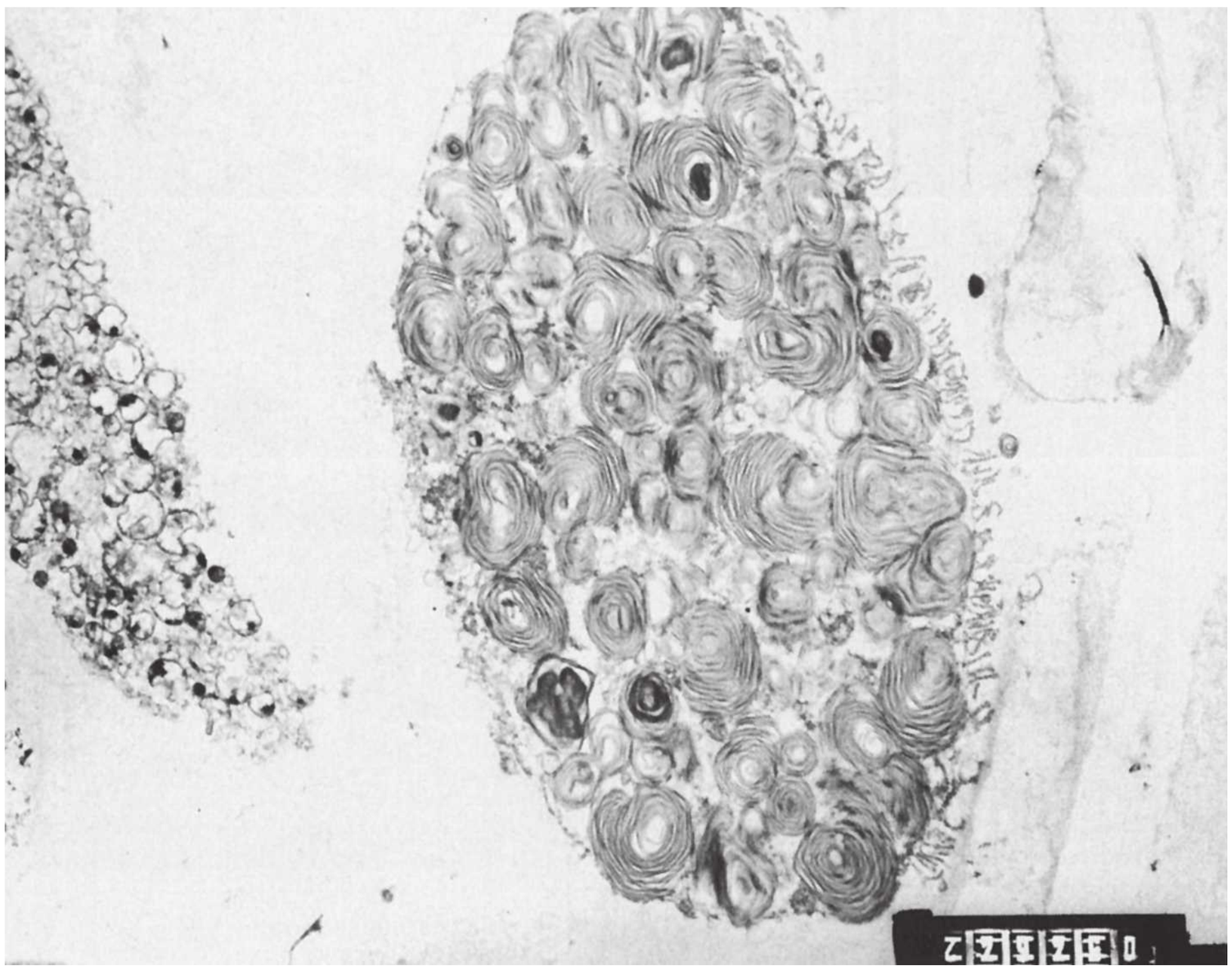

FIGURE 17.7 Urinary myelin bodies. An electron micrograph of a cell in the urine of a female heterozygous for Fabry disease. It is filled with myelin figures. (Uranyl acetate and lead citrate stain; ×20,000.) (Photograph courtesy of Dr. Melvin M. Schwartz, Rush-Presbyterian-St. Luke's Medical Center, Chicago.)

The progression to ESRD is near universal in males in their third to sixth decade of life, but occasionally occurs in their teenage years.[144,146] The mean age at the onset of ESRD in a study of 105 males was 39 years, and all patients who survived to age 55 developed ESRD.[144] Fewer women develop ESRD, and often at an older age than males,[131,147,148] although some of them develop ESRD as early as men.[113] The strongest predictor for a more rapid decline in GFR is the degree of proteinuria. Data on the natural history (i.e., the disease course before enzyme replacement therapy) comes from the Fabry registry and shows that men with a urine protein to creatinine ratio of 1.5 or greater lose GFR at a rate of 5.6 mL/min/1.73 m^2 per year, compared to 1.3 mL/min/1.73 m^2 per year for those with lesser degrees of proteinuria.[148] In the same study women had a slower decline, averaging 1.3 mL/min/1.73 m^2 per year if their urine protein to creatinine ratio was greater than 1.2; women also were about 5 years older at enrollment, and fewer women exhibited the higher levels of proteinuria.[148] Hypertension is a late manifestation, usually developing after GFR starts to decline, and is also associated with faster GFR decline, at least in men.[144,148]

Diagnosis

The most important step is to consider the diagnosis of Fabry disease. The index patient in most families goes undiagnosed for years or decades. In affected males with fully expressed disease, the constellation of symptoms and signs is highly suggestive. The diagnosis is confirmed if there is low α-galactosidase A activity in plasma or leukocytes. The test in leukocytes is more sensitive and is therefore preferred. The enzyme activity in Fabry leukocytes is usually under 4% of normal, and often undetectable in men, but it may be normal in women.[113,131] Therefore, direct genetic analysis is often required to make the diagnosis in women. A biopsy of the skin or kidney that demonstrates the characteristic glycolipid deposits may establish the diagnosis if no other means is available. Sometimes a kidney biopsy is performed for the evaluation of proteinuria, and the finding of "zebra bodies" in glomerular cells leads to the diagnosis of Fabry disease.[149] In such cases, family screening should be done in order to identify additional gene carriers with or without symptoms who might benefit from therapy (see the text that follows).

Prenatal Diagnosis

The severity of Fabry disease in males and in a proportion of females is the principal motivation for prenatal diagnosis. An analysis of α-galactosidase A activity in fetal cells obtained from chorionic villous tissue can confirm the disease in a male fetus; genetic mutation analysis should also be done, particularly in female fetuses because they can have residual enzyme activity. A mutation analysis can be performed on chorionic villi or cultured amniocytes.[150]

Treatment

Until recently, Fabry disease management was limited to symptomatic and palliative treatment, but this has changed with the availability of the recombinant human α-galactosidase A enzyme, agalsidase. Two different intravenous agalsidase formulations have been obtained: one from human fibroblasts (agalsidase α), and one from Chinese hamster ovary cells (agalsidase β). Both preparations underwent clinical trials that documented the feasibility, efficacy, and safety of the treatment. Based on observations made during these trials, both agalsidase α (Replagal) (0.2 mg per kilogram every other week) and agalsidase β (Fabrazyme) (1.0 mg per kilogram every other week) have been approved in Europe, but only agalsidase β was approved in the United States.[151,152]

A recent review identified 48 prospective clinical studies of enzyme replacement therapy (ERT), 22 each for agalsidase α and β and 4 with pooled treatments.[132] The longest reported treatment duration and follow-up was 4.5 to 5 years.[132,153] Overall, these studies showed that treated patients had a sustained decrease in plasma GL-3 levels and sustained endothelial GL-3 clearance as seen on skin, kidney, or heart biopsies.[153,154] The safety profile was favorable. Neuropathic pain and quality of life usually improved, even in dialysis patients. However, no effect on the incidence of strokes could be demonstrated in any study.[132] The effect on renal disease progression depended on the stage at which ERT was begun. If patients had more than 1 g proteinuria per day and/or decreased GFR ($<$ 60 mL/min/1.73 m^2), ERT was usually unable to halt the progression.[136,147,153] However, there was long-term stabilization of renal function in patients who were treated before they developed significant proteinuria. Similarly, a reduction in left ventricular hypertrophy was achieved only in patients without significant cardiac fibrosis, arguing for an early initiation of ERT.[132] A point to keep in mind is that ERT is extremely expensive.

Supportive treatment is also important for patients with Fabry disease. The debilitating pain may be considerably eased by phenytoin or carbamazepine. Excess glycosphingolipids can be removed by plasmapheresis with a temporary symptomatic benefit.[155] Given the limited benefit of ERT in patients with proteinuria, aggressive antiproteinuric therapy with angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers in addition to ERT is both feasible and recommended.[136,156] The goal is to reduce proteinuria to less than 500 mg per day and to reduce the rate of GFR decline to less than 1 mL/min/1.73 m^2 per year.

When ESRD supervenes, both hemodialysis and peritoneal dialysis can be carried out with no specific problems. In studies from both the United States and Europe, the 3-year survival of dialysis patients with Fabry disease was worse compared with nondiabetic dialysis patients of similar age.[157] Renal transplantation is the treatment of choice for Fabry patients. In the most recent study of 197 kidney transplant recipients with Fabry disease, 5-year graft survival was similar to that of a matched cohort of recipients with other causes of ESRD, but 5-year patient survival was worse (81% versus 90%).[158] The most common reported cause of death was myocardial infarction. Few patients, if any, in these reports had received ERT. Although ERT is safe in kidney transplant

recipients and small studies show symptomatic benefit, it is currently unknown whether ERT will improve the prognosis of Fabry patients with ESRD.[157] Graft loss due to recurrent Fabry nephropathy has so far not been documented.[157]

Variants and Diseases Related to Fabry Disease

Recently, a variant form of Fabry disease was identified with manifestations primarily limited to the heart[128,159]; these "cardiac variants" lack the classical disease symptoms, and present in the sixth or seventh decade of life with left ventricular hypertrophy (LVH) and/or cardiomyopathy. These patients may also have proteinuria, but their renal function is typically normal for age. Of note, cardiac variants have residual α-galactosidase A activity due to missense mutations and lack the systemic vascular endothelial glycosphingolipid deposition characteristic of classically affected patients. Screening of 230 consecutive Japanese male patients with LVH and 153 British male patients with hypertrophic cardiomyopathy by plasma α-galactosidase A assays revealed that 3% and 3.9%, respectively, were previously unrecognized cardiac variants.[128,159]

There is mounting evidence that renal disease with ESRD can also occur in the absence of other typical organ manifestations. Nakao et al.[160] screened 514 male Japanese hemodialysis patients and identified 6 with exclusively renal manifestations. Interestingly, these subjects had residual α-galactosidase A activity, but reached ESRD at an age similar to patients with full-blown disease. These may be examples of a renal variant.

Angiokeratoma corporis diffusum with glycopeptiduria is an autosomal-recessive disorder resulting from a deficiency of α-N-acetylgalactosaminidase.[161,162] Features are similar to Fabry disease, with angiokeratomas and peripheral neuropathy. Both a severe infantile onset and a milder adult onset form of the disease have been described.

Finally, renal ultrastructural lesions identical to those in Fabry disease have been described in patients on long-term treatment with hydroxychloroquine, chloroquine, and amiodarone.[163] These drugs can inhibit several lysosomal enzymes, including α-galactosidase A. This complication of drug therapy has been called iatrogenic phospholipidosis and seems to be limited to the kidney and cornea. After the removal of the offending agents, a variable improvement in renal parameters has been reported.[163]

NAIL-PATELLA SYNDROME (NPS) (OMIM 161200)

Nail-Patella syndrome (NPS) is a rare autosomal dominant disorder first described by Little in 1897, which is characterized by the tetrad of dysplastic nails, hypoplastic or absent patellae, iliac horns, and deformities of the elbow. Other names include hereditary onycho-osteodysplasia (HOOD), Fong's syndrome, Turner-Keiser syndrome, and Osterreicher-Turner syndrome. It shows wide variability in phenotypic expression and organ involvement within and between families. Renal involvement is observed in about 40% of cases and appears to cluster in certain families.[164,165] Renal failure has been reported to occur in 1% to 15% of patients.[164,165]

Epidemiology and Genetics

The incidence of NPS has been reported to approach 1 in 50,000 live births.[165–167] The condition was linked to the ABO blood group locus as early as 1955[168]; fine mapping established the locus at 9q34.1.[3,169,170] The gene was identified in 1998 as the LMX1B gene,[170] which codes for a transcription factor that is essential for a wide range of developmental processes including dorso-ventral patterning of the limb, differentiation of dopaminergic and serotonergic neurons, patterning of the skull, and normal development of the kidney and eye as recently reviewed by Dai et al.[171] These developmental processes apparently require the function of two normal LMX1B genes because a mutation in one of them results in NPS, which is likely due to haploinsufficiency.[172,173]

To date, over 160 mutations[23,81] have been reported in patients with NPS. In 10% to 15% of families, no mutation is found; about 12% of cases have no family history and may be either new mutations, subclinical disease in the parent, or due to somatic mosaicism of the parent.[165,174] Most negative studies attempting to demonstrate genotype–phenotype correlations in NPS have been small. One larger study of 106 subjects from 32 NPS families demonstrated that individuals with LMX1B mutations affecting the homeodomain had significantly more frequent and higher values of proteinuria compared to those individuals carrying LIM domain mutations.[164] The genetic basis for the wide inter- and intrafamilial phenotypic variability is unknown but may involve modifier genes or polymorphisms in the target genes of LMX1B.[165]

Renal Pathology

Light Microscopy of renal biopsy specimens is nonspecific and often demonstrates normal findings. The only consistent but nonspecific glomerular feature is focal GBM thickening.[175,176] In more advanced stages, when renal functional impairment is present, light microscopy findings include focal segmental glomerulosclerosis, proliferative glomerulonephritis with crescents, and hyalinization of glomeruli.[175–177]

Immunofluorescence microscopy is negative or shows presumably a nonspecific trapping of IgM and complement.[175] Staining of the GBM for collagen α_3(IV) and α_4(IV) chains, podocin, synaptopodin, CD2AP, α3 integrin, and nephrin is normal.[165]

Ultrastructural changes are characteristic and specific and have been found in all NPS patients. The GBM is irregularly thickened and contains lucent areas and areas of fluffy low-density material, giving the appearance of a "moth-eaten" basement membrane. Overlying pedicles are effaced.

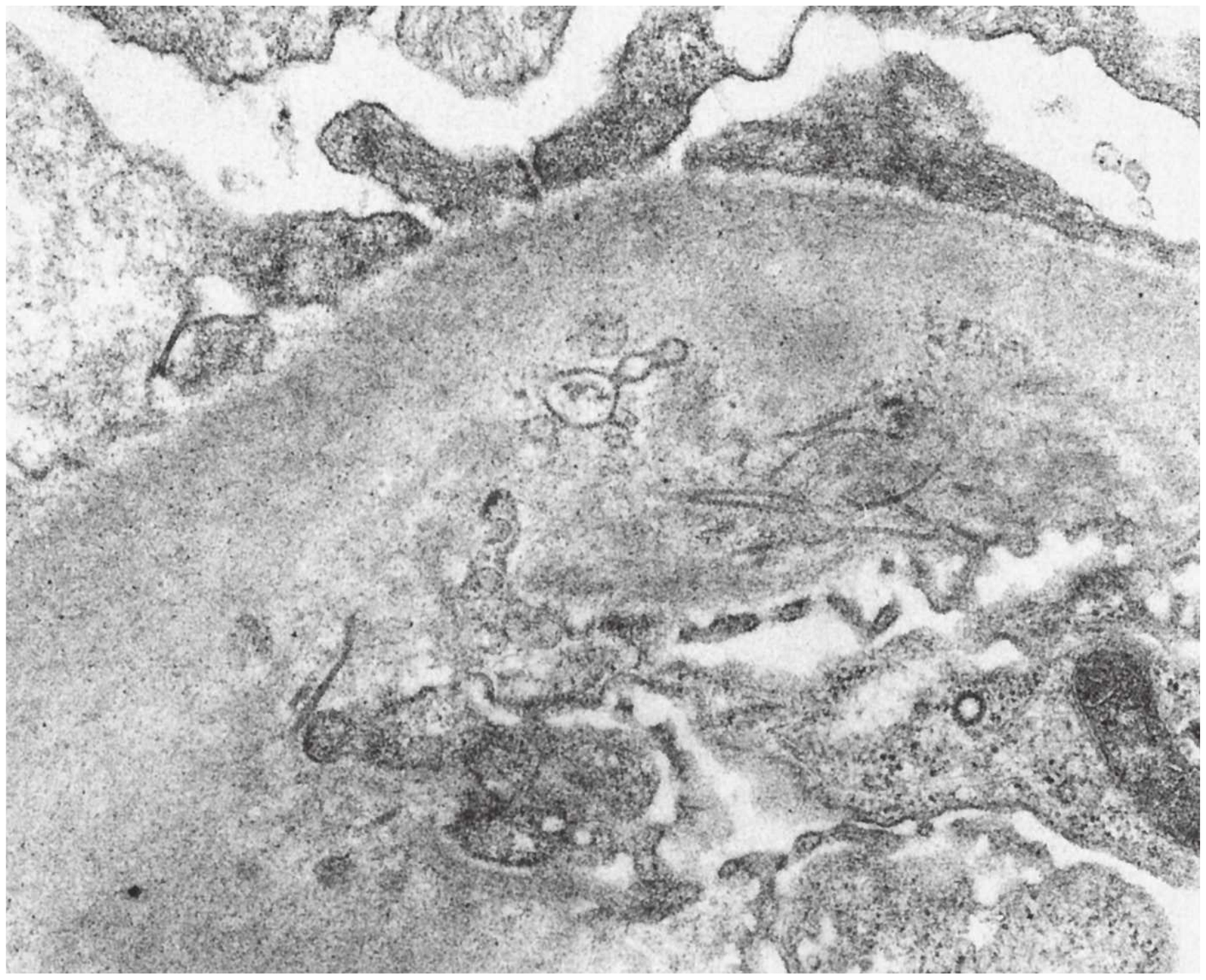

FIGURE 17.8 Glomerular basement membrane (GBM) in nail-patella syndrome (NPS). A high resolution (magnification ×55,000) electron micrograph of the GBM showing fluffy lucencies expanding the GBM and blurring its endothelial margin. Several collagen fibrils are visibly embedded in the GBM. (Photograph courtesy of Dr. Daniel Terreros, Salt Lake City VA Medical Center, Salt Lake City, Utah.)

Patches of dense fibrillar material with a periodicity of collagen are scattered throughout the entire thickness of the GBM (Fig. 17.8).[175–178] The Bowman capsule and tubular basement membranes are not specifically affected, but the mesangium may show fibrillar collagen similar to that in the GBM and is usually accompanied by mesangial cell proliferation. Although similar mesangial lesions have been seen in other conditions such as diabetes, membranoproliferative glomerulonephritis, amyloidosis, and glomerulosclerosis, in these conditions the material is not collagen and can be distinguished by its relatively weak staining with phosphotungstic acid.

NPS has been associated with other glomerular lesions, including membranous nephropathy,[179] systemic vasculitis,[180] IgA nephropathy,[181] Goodpasture syndrome,[182] hemolytic-uremic syndrome,[183] and bilateral renal stones.[184] The significance of these associations is unknown, but perhaps the abnormal structure or abnormal immunogenicity renders the GBM more vulnerable to other insults.

Clinical Features and Course

Extrarenal Manifestations

Patients with NPS have a lean body mass, which is more apparent in adolescents and young adults. This decrease in muscle mass is more prominent in the dorsal parts of the upper arms and in the upper legs. Other abnormalities include lumbar lordosis and scoliosis. The classic tetrad of NPS consists of dystrophic nails (Fig. 17.9), patellar and lateral femoral condylar hypoplasia (Fig. 17.10), hypoplasia of the radial head and capitellum of the elbow (Fig. 17.11), and bilateral iliac horns (Fig. 17.12).

Nail dystrophy is present at birth in more than 90% of those affected and is the most constant feature of NPS.

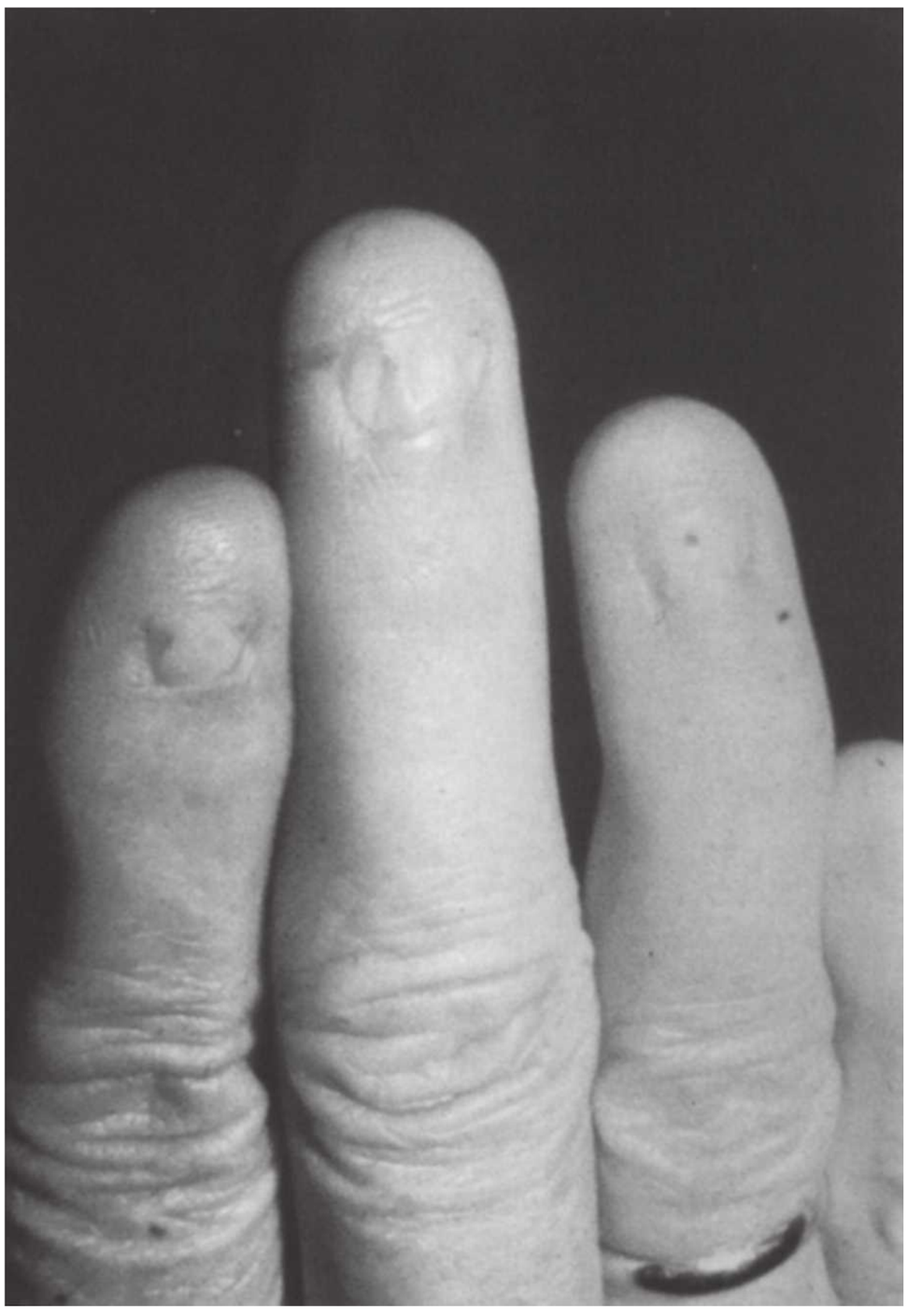

FIGURE 17.9 Characteristic nail changes of nail-patella syndrome (NPS). All the nails are small. The long finger shows the typical central triangular dystrophy with its base at the lunula. Usually, the changes are more marked toward the radial side of the hand.

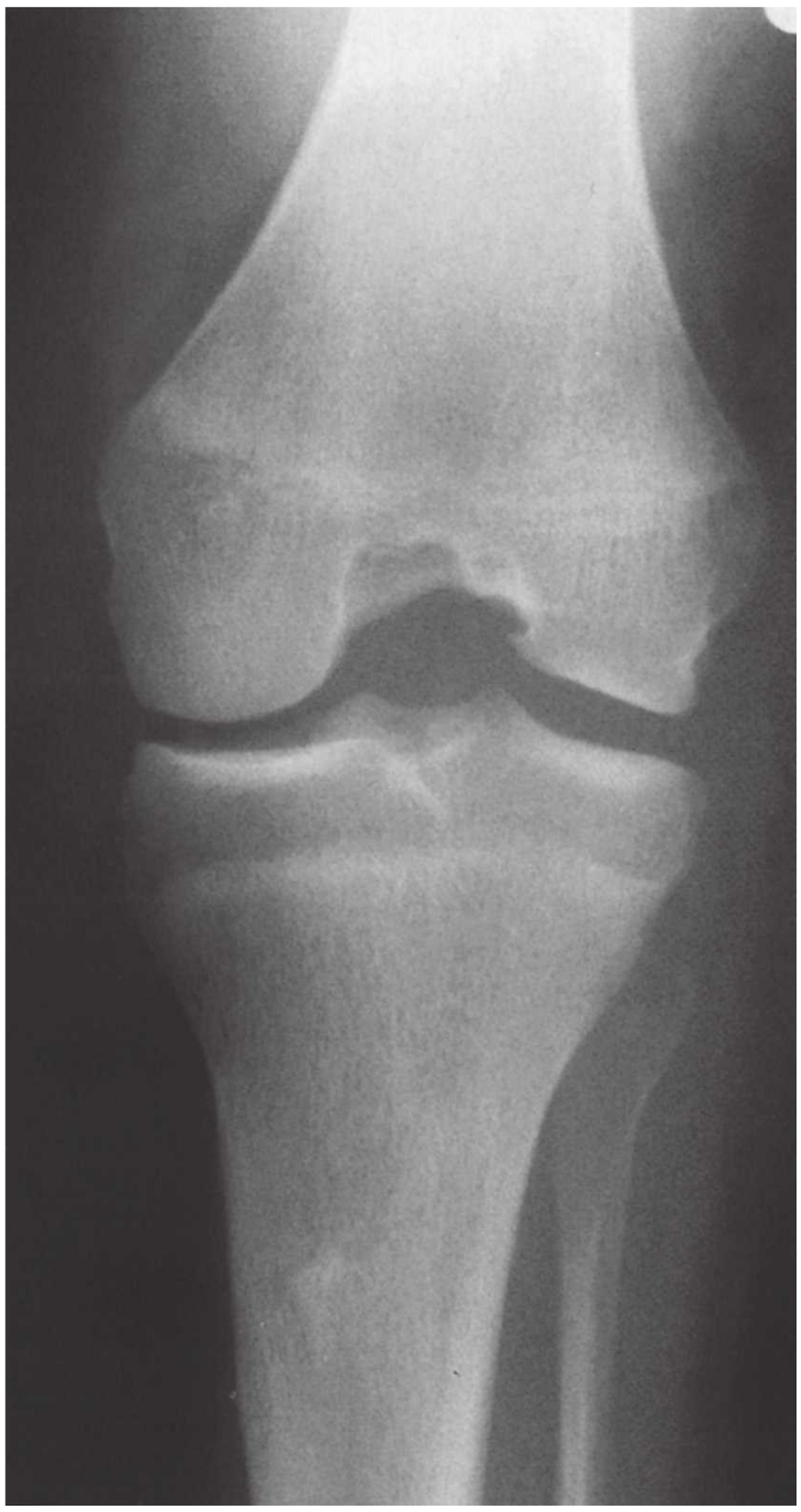

FIGURE 17.10 An absence of patella in nail-patella syndrome (NPS). A radiograph of the left knee of a 19-year-old girl with NPS. The patella is congenitally absent and the lateral femoral condyle is hypoplastic.

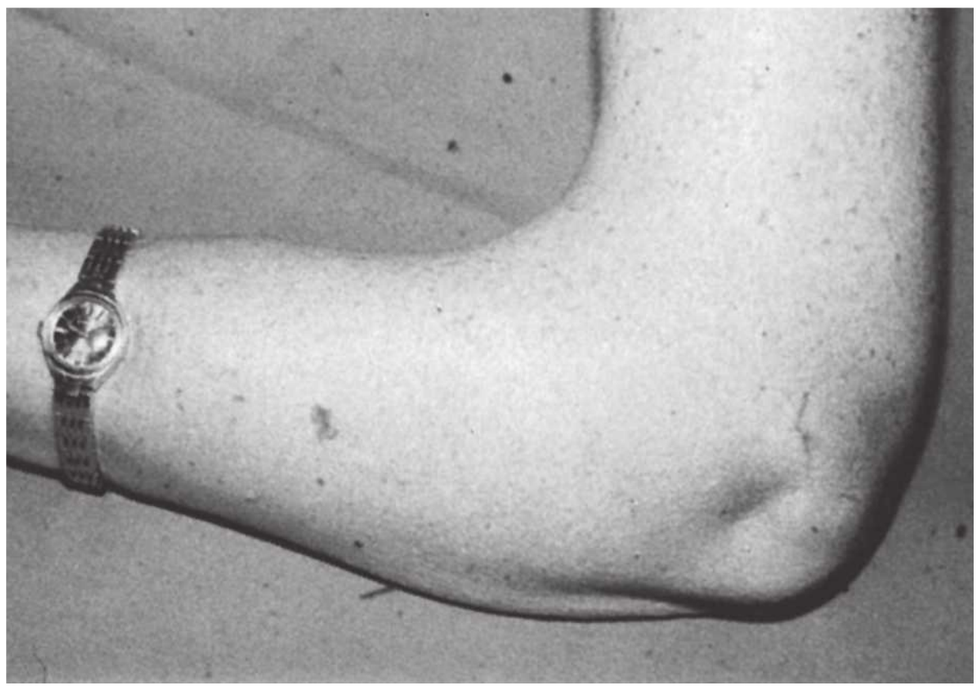

FIGURE 17.11 An elbow contracture in nail-patella syndrome (NPS). The left elbow of a 44-year-old woman with NPS and end-stage renal disease (ESRD) (same patient as in Fig. 17.9). She is holding her elbow as straight as possible. A web of soft tissue fills the antecubital fossa.

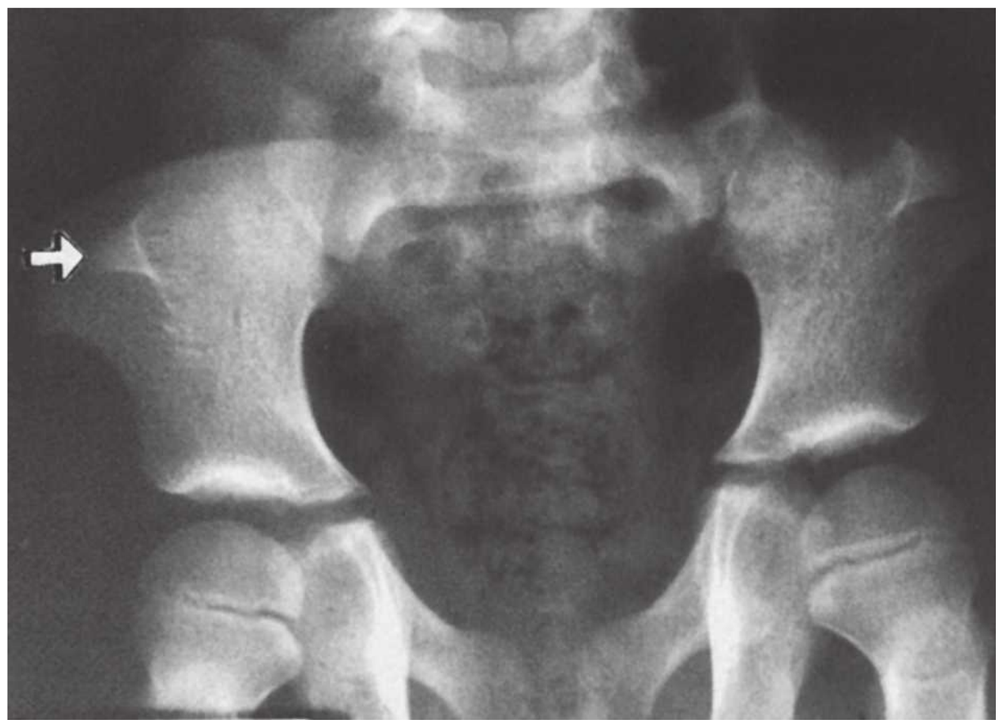

FIGURE 17.12 Iliac horns. A pelvic X-ray film of an 8-year-old girl with nail-patella syndrome (NPS) (same patient as in Fig. 17.10, but 11 years earlier). The *arrow* indicates the characteristic iliac horn, which is visible medial to the outer margin of the blade of the ileum. The radiograph incidentally shows a fusion defect and lumbarization of S1.

The presence of a triangular nail is a pathognomonic sign for NPS. The lunula appears stretched toward the free border of the nail, and the central portion of the nail is deformed. Commonly, affected nails are smaller than normal and may even be absent. Fingernails are more affected than toenails, and thumb and radial-side digits are more affected than ulnar-side digits. Furthermore, longitudinal ridging, splitting, spoon-shaped, and flaky nails have been associated with NPS.

The patella is small, misshapen, or absent in more than 90% of patients (Fig. 17.10). Concurrent hypoplasia of the lateral femoral condyle and poor development of the vastus medialis muscle may lead to recurrent subluxation or dislocation of the patella, knee instability, and knee pain complicated by patello-femoral arthrosis. Involvement of the elbow is almost as common, with hypoplasia of the radial head and capitellum being characteristic. This predisposes the patient to posterior subluxation of the radial head. Synechiae may lock the elbows in a permanent and disabling flexion (Fig. 17.11).

Conical bony horns projecting from the back of the blade of the ileum are seen in about 80% of patients and is considered pathognomonic of NPS. Often palpable in thin subjects, they are readily seen radiographically (Fig. 17.12).

Although not part of the classic tetrad, the most common presentations to orthopedists are foot or ankle deformities (club feet) and/or hip dysplasia.[164,185] Usually, these deformities require surgical correction.

More recently, ocular involvement and sensorineural hearing impairment have been described in patients with NPS. The most common pathologies are glaucoma, isolated glaucomatous alteration of the optic disk, and ocular hypertension, which are found in 35% of individuals in one study.[164] The mean age of these patients was 63 years, and glaucoma was rare under the age of 40 years. Cataracts were found in 8% of subjects,

including congenital cataracts in two siblings. Other anomalies were iris pigmentation (Lester sign) and corneal abnormalities. Unilateral or bilateral hearing impairment was detected by audiometric testing in 46% of patients at a mean age of 47 years.[164]

Renal Manifestations

It is the renal manifestations of NPS that influence mortality, occurring in 12% to 55% of the patients.[166] Between 5% and 14% develop ESRD.[166] The first and most typical sign of renal disease is moderate proteinuria with or without hematuria. Proteinuria may occur at any age and may resolve spontaneously, remain stable, or progress to renal failure at variable ages.[166] Nephrotic syndrome may also sometimes occur.[165,175]

The relationship between the somatic features of NPS, the clinical signs of nephropathy, and the GBM lesion is perplexing. There appear to be families with the somatic features in whom nephropathy does not develop, and other families with clinical renal disease and typical renal ultrastructural findings but no somatic manifestations. In a genotype–phenotype correlation study, Bongers et al.[164] presented evidence that the LMXB1 mutation position is involved with the risk of developing nephropathy. However, even families that clearly express the full spectrum of somatic and renal features, including proteinuria and the progression to ESRD, may have affected individuals without renal clinical manifestations. Other individual patients have shown musculoskeletal features and the typical renal ultrastructure but no clinical renal abnormalities.[177,178,186] Thus, the origins of variable phenotypic expression in NPS remain unclear.

Diagnosis

Typically, NPS is readily recognized clinically. If doubt remains, radiographs of the knees and pelvis usually show absent, rudimentary, or deformed patellae and bilateral iliac horns.

Renal biopsy is rarely required to make the diagnosis of NPS. It may be justified in patients with an atypical disease in whom another potentially treatable glomerulonephritis may coexist.

Prenatal Diagnosis

In families with a defined mutation, chorionic villous sampling can potentially be used for a mutation analysis[187]; in large families without an identified mutation, but with sufficient members to be informative, linkage could be sought with polymorphic markers near 9q34.[188] The typical renal ultrastructural features of NPS were found in an 18-week abortus,[189] and the diagnosis of NPS has been made by intrauterine kidney biopsy.[190] Skeletal anomalies may be recognized by fetal sonography.[191,192]

Treatment

As long as we cannot correct the molecular defect of NPS, treatment for all aspects is supportive. Orthopedic surgery to relieve contractures and to fuse or realign joints confers major benefits. Knee, ankle, and foot surgery is frequently helpful, whereas elbow surgery is rarely needed.[185] The treatment of renal disease is as in other patients with chronic kidney disease. ACEI may be of benefit in patients with proteinuria. Hemodialysis, peritoneal dialysis, and transplantation have been carried out successfully. In three patients who have had a biopsy of the allograft,[193,194] there was no evidence of recurrence of NPS lesions or of anti-GBM nephritis. Most intriguing, in a single patient,[194] nail lesions appeared to improve after transplantation.

Variants and Diseases Related to Nail-Patella Syndrome

More than 20 patients showing the renal ultrastructural features of NPS without the somatic findings have been described.[195–197] In seven families, inheritance appeared to be autosomal recessive. It is possible that these cases were examples of collagen III glomerulopathy, as previously described.[198] There is also some evidence for an autosomal dominant NPS-like syndrome without extrarenal symptoms.[199] These GBM diseases might be due to a partial expression of NPS or another type of hereditary glomerulopathy.[167]

A girl with a heterozygous complete deletion of the COL5A1 gene at 9q34 and underexpression of α_1(V) chains had dysplastic nails, normal patellae, but other mesenchymal and ectodermal features more suggestive of Goltz syndrome than of NPS.[200]

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