26 Inherited Glomerular Diseases

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In recent years the determined efforts of numerous investigators and the dedicated participation of patients, families and clinicians have led to the mapping and identification of numerous genetic loci involved in inherited glomerular disease and the functional characterization of their protein products. This information has generated important insights into the cell–cell and cell–matrix interactions required for normal glomerular structure and function, and the mechanisms by which genetically programmed disruptions in these interactions produce disease phenotypes. Additionally, our ability to predict prognosis and provide accurate genetic counseling has been greatly enhanced by this expansion of our knowledge base.

Inherited glomerular diseases can be roughly divided into two categories based on clinical presentation. Hematuria is typically the initial symptom of inherited diseases of glomerular basement membranes, with the exception of Pierson syndrome. In patients with inherited podocyte diseases the predominant clinical abnormality at presentation is proteinuria. This chapter will focus on inherited diseases of glomerular basement membranes, particularly Alport syndrome and thin basement membrane nephropathy, which together account for 30–50% of children with isolated glomerular hematuria referred to pediatric nephrology clinics for consultation (1–4).

The Glomerular Basement Membrane

The structural and functional characteristics of the normal glomerular capillary wall are discussed in detail elsewhere in this text. For the purposes of this chapter, this discussion will focus on the major protein components of glomerular basement membrane (GBM), type IV collagen and laminin, which form networks bridged by entactin/nidogen and heparan sulfate proteoglycans (agrin).

Type IV collagen. The type IV collagen protein family comprises six α chains that share several basic structural features: a collagenous domain of ~1,400 residues containing the repetitive triplet sequence glycine-X-Y (Gly-X-Y, with X and Y representing other amino acids); a carboxyterminal noncollagenous (NC1) domain of ~230 residues, including 12 completely conserved cysteine residues; and an aminoterminal noncollagenous sequence of 15–20 residues. The collagenous triplet sequence in each chain contains ~20 interruptions. The secreted form of type IV collagen is a heterotrimer composed of three α chains, resulting from self-association of NC1 domains and folding of the collagenous domains into triple helical structures. Amino acid sequences within the NC1 domains determine the specificity of chain association, resulting in three major trimeric species: α1α1α2, α3α4α5 and α5α5α6 (5). While the interstitial collagens, such as type I collagen, lose their NC1 domains after chain association and form fibrillar networks, type IV collagen trimers form open, nonfibrillar networks through NC1–NC1 interactions between two trimers and aminoterminal interactions of four trimers.

α1α1α2(IV) trimers are present in all basement membranes. α3α4α5(IV) and α5α5α6(IV) trimers are more restricted in their distributions in basement membranes (*Fig. 26-1*). In normal, mature human kidneys, α3α4α5(IV) trimers are found in GBM, Bowman's capsules and the basement membranes of distal tubules. α5α5α6(IV) trimers are present in Bowman's capsules and the basement membranes of distal tubules and collecting ducts of normal kidneys but are not found in GBM (6, 7). α5α5α6(IV) trimers are also found in normal epidermal basement membranes, but α3α4α5(IV) trimers are not. α3α4α5(IV) trimers are also found in several ocular and cochlear basement membranes, as discussed in the section on Alport syndrome below.

Each type IV collagen a chain is encoded by one of six distinct genes, COL4A1 – COL4A6, which are arranged in pairs on three chromosomes (*Fig. 26-2*). COL4A1 and COL4A2 encode the α1(IV) and α2(IV) chains, respectively, and are located on chromosome 1. The α3(IV) and α4(IV) chains are respectively encoded by the COL4A3 and COL4A4 genes on chromosome 2, while the α5(IV) and α6(IV) genes are encoded by the COL4A5 and COL4A6 genes on the X chromosome. The paired genes are arranged in a 5′-5′ orientation, with intervening sequences of varying length that contain regulatory elements.

Laminin. Laminin also forms networks based on heterotrimeric subunits. Each subunit consists of an α, β and

Figure 26-1

Immunofluorescene microscopy. Normal distribution of the α(IV) chains in renal and epidermal basement membranes. (See color plate 8)

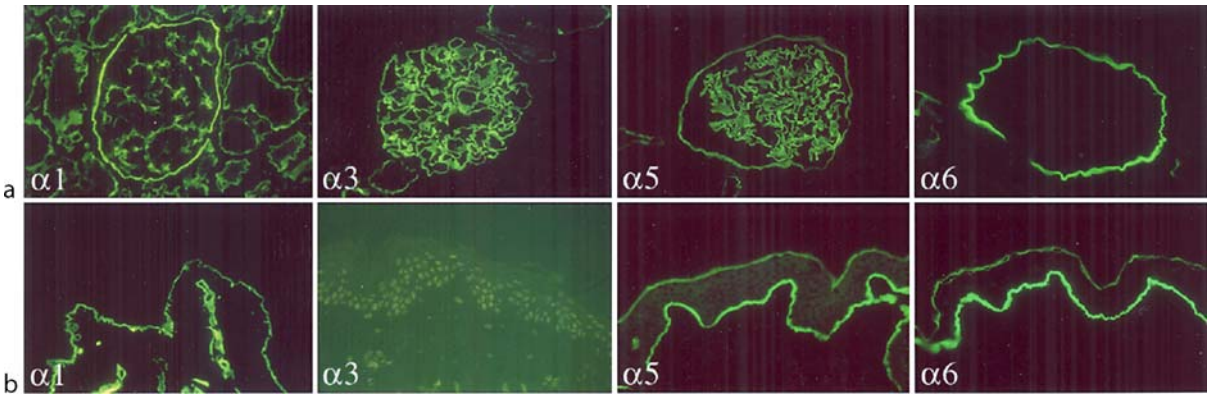
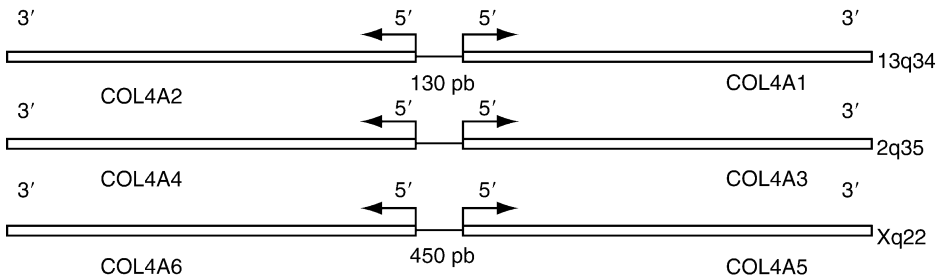


Figure 26-2

Schematic representation of the distribution of type IV collagen gene on chromosomes 13, 2, and X.



γ chain. There are 11 known laminin chains (α1–5, β1–3, and γ1–3), each encoded by a distinct gene, that form 15 heterotrimeric isomers. Laminin-521 (previously known as laminin 11) has the composition α5β2γ1 and is the laminin form found in GBM (8).

Glomerular Basement Membrane Disorders

To date, mutations affecting two of the major proteins of GBM, type IV collagen and laminin, have been identified as causes of inherited glomerular disease. Mutations in type IV collagen cause Alport syndrome, some cases of thin basement membrane nephropathy, and HANAC syndrome, comprising hereditary angiopathy, nephropathy, aneurysms and muscle cramps (*Table 26-1*). Mutations in laminin have been implicated in Pierson syndrome.

Type IV Collagen Disorders

Alport Syndrome

Dominantly-transmitted hematuria was first described as a clinical entity in the early 1900s (9). Over the next 20 years, studies of this condition in successive generations of a single family described development of proteinuria and renal insufficiency in affected individuals, particularly males, and in 1927 Alport reported the association of nephritis with neural deafness in this family (10, 11). Numerous descriptions of families with hereditary nephritis were published in the 1950s and 1960s, leading ultimately to the observations that established Alport syndrome as a heritable disorder of type IV collagen. These signal events included the identification of unique ultrastructural alterations in Alport glomerular basement membranes (GBM) (12–14), the observation that Alport

Table 26-1
Type IV collagen disorders

Disorder	Inheritance	Locus	Gene product
Alport syndrome	X-linked	COL4A5	α5(IV)
	Autosomal recessive	COL4A3 or COL4A4	α3(IV) or α4(IV)
	Autosomal dominant	COL4A3 or COL4A4	α3(IV) or α4(IV)
Thin basement membrane nephropathy	Autosomal dominant	COL4A3 or COL4A4	α3(IV) or α4(IV)
HANAC syndrome	Autosomal dominant	COL4A1	α1(IV)

GBM exhibited abnormal reactivity with anti-GBM sera directed against antigens associated with type IV collagen (15–17), the mapping of the major Alport locus to the X chromosome (18), the discovery of a type IV collagen gene (COL4A5) on the X chromosome (19), and finally the description of COL4A5 mutations in families with X-linked Alport syndrome (20).

Genetics

There are three genetic forms of Alport syndrome. X-linked Alport syndrome (XLAS) is caused by mutations in the COL4A5 gene and is the predominant form of the disease, accounting for ~80% of patients. Affected males are hemizygotes carrying a single mutant COL4A5 allele. Affected females carry a normal COL4A5 allele as well as a mutant allele and are therefore heterozygotes. About 15% of patients with Alport syndrome have the recessive form of the disease (ARAS), due to mutations in both alleles of the COL4A3 or COL4A4 gene. These patients are either homozygotes who have the identical mutation in both alleles of the affected gene (and who may have consanguineous parents) or compound heterozygotes who have inherited different mutations in the affected gene from their parents. About 5% of patients have autosomal dominant Alport syndrome (ADAS) caused by heterozygous mutations in COL4A3 or COL4A4. Most individuals with heterozygous COL4A3 or COL4A4 mutations are asymptomatic or exhibit isolated, nonprogressive microscopic hematuria associated with thin glomerular basement membranes (thin basement membrane nephropathy, or TBMN). For reasons that are as yet uncertain, some people with heterozygous mutations in COL4A3 or COL4A4 have a progressive course leading to chronic renal failure or end-stage renal disease, and are thus considered to have ADAS.

Several hundred different mutations in the COL4A5 gene have been identified in patients and families with XLAS (21–23). While the great majority of these mutations are unique, a small group of missense mutations accounts for a large portion of XLAS patients in the U.S. (24). Reported mutations include large rearrangements (~20%), small deletions and insertions (~20%), missense mutations that alter a glycine residue in the collagenous domain of the α 5(IV) chains (~30%), other missense mutations (~8%), nonsense mutations (~5%) and splice-site mutations (~15%) (21–23). The COL4A5 genotype has a powerful effect on the course of XLAS in affected males (22, 23). Large deletions, nonsense mutations and small mutations that alter the translational reading frame are associated with a 90% probability of progression to ESRD by age 30 (22, 23). This risk is 70% in patients with a splice-site mutation and 50% in those with a missense mutation (22, 23). The position of a glycine substitution may also affect the XLAS phenotype (23). These genotype-phenotype correlations are not apparent in females with XLAS, perhaps as a result of the overwhelming influence of random X-chromosome inactivation on disease course in XLAS females (25).

A similar variety of mutation types has been described in patients and families with ARAS (21, 26–30). Because of small patient numbers, genotype-phenotype correlations in ARAS have not been described.

Clinical Features

Gender and genotype are the major determinants of the severity of renal, cochlear and ocular disease in Alport syndrome. Males with XLAS, and patients of either gender with ARAS, inevitably progress to end-stage renal disease (ESRD) and the majority develop sensorineural deafness. The pacing of these events is influenced by the nature of the underlying disease mutation. While the majority of women with XLAS have mild disease manifestations, ESRD and severe deafness develop in a significant minority. Patients with ADAS exhibit relatively slow progression of renal and cochlear dysfunction, and ocular findings are much less common than in XLAS and ARAS (31, 32).

Renal. Persistent microscopic hematuria is the cardinal clinical feature of Alport syndrome, occurring in 100% of males with XLAS, 95% of females with XLAS

and in all patients with ARAS (22, 25). Hematuria is likely present from infancy in XLAS males and in patients with ARAS. Episodic gross hematuria is not unusual, especially during childhood (33). Some children with Alport syndrome have virtually constant gross hematuria.

Overt proteinuria typically appears during later childhood or adolescence in XLAS males and in ARAS patients and increases progressively, often into the nephrotic range (33–35). About 75% of XLAS females ultimately develop proteinuria of some degree (25). Most children with Alport syndrome have normal blood pressures, but hypertension is common in adolescent males with XLAS and teen-aged ARAS patients.

In XLAS males, the probability of ESRD is 50% by age 25, 80% by age 40 and 100% by age 60 (22). COL4A5 genotype has a powerful effect on rate of progression to ESRD in XLAS males. Large deletions and nonsense mutations confer a 90% probability of ESRD before age 30, compared to a 70% risk with splice site mutations and a 50% risk with missense mutations (22).

Women with XLAS exhibit a lower but substantial risk of progression to ESRD than XLAS males. According to one study of a large cohort of XLAS females, the risk of ESRD is 12% by age 45, 30% by age 60 and 40% by age 80 (25). Proteinuria and sensorineural deafness are risk factors for ESRD in XLAS females (36). COL4A5 genotype does not have measurable effects on the rate of progression to ESRD in XLAS females, perhaps due to the overwhelming influence of X-inactivation balance (25). The epidemiology of ESRD in ARAS is probably similar to XLAS males, although comparable data is lacking. It takes ~50 years for 50% of ADAS patients to develop ESRD, twice as long as XLAS males (31).

Cochlear. Hearing is normal at birth and during early childhood. Symmetrical deficits in sensitivity for high frequency sounds often become detectable by audiometry in late childhood. In XLAS males the probability of hearing loss is 50% by age 15, 75% by age 25 and 90% by age 40 (22). COL4A5 genotype influences the probability of hearing loss, with 90% of those with deletions, nonsense mutations and splice site mutations exhibiting deafness before age 30, compared to 60% of those with missense mutations (22). In XLAS females the probability of hearing loss is 10% by age 40 and 20% by age 60 (25). The majority of patients with ARAS develop deafness, although precise data on timing is not available.

Over time, the hearing deficit progresses into the frequency range of conversational speech. Because the deficit typically does not exceed 60–70 dB and speech discrimination is preserved, hearing aids are effective in most affected individuals.

Ocular. Anomalies of the lens, retina and cornea are common in Alport syndrome, especially among males with XLAS and patients with ARAS, often becoming apparent during adolescence and young adulthood (37). About 15% of XLAS males exhibit anterior lenticonus, in which the central portion of the lens protrudes into the anterior chamber (22). While this lesion is often asymptomatic, it may be associated with reduced visual acuity, and cataracts and even rupture of the lens may occur. Alteration of retinal pigmentation, consisting of whitish-yellowish perimacular flecks, occurs in about 15% of XLAS males (22), often in association with lenticonus. Corneal abnormalities include recurrent corneal erosions (38, 39) and posterior polymorphous dystrophy (40).

Other. The association of XLAS with smooth muscle tumors (leiomyomas) of the esophagus, tracheobronchial tree and, in women, the external genitalia, has been described in several dozen families (41–43). Symptoms such as dysphagia, postprandial vomiting, epigastric or retrosternal pain, recurrent bronchitis, dyspnea, cough, and stridor often appear in late childhood. The Alport syndrome-diffuse leiomyomatosis complex arises from X-chromosomal deletions involving COL4A5 and the proximal portion of the adjacent COL4A6 gene (44).

Mental retardation, midface hypoplasia, and elliptocytosis have been described in a small number of XLAS males who carry deletions that extend downstream of the 3′ end of the COL4A5 gene (45).

Pathology

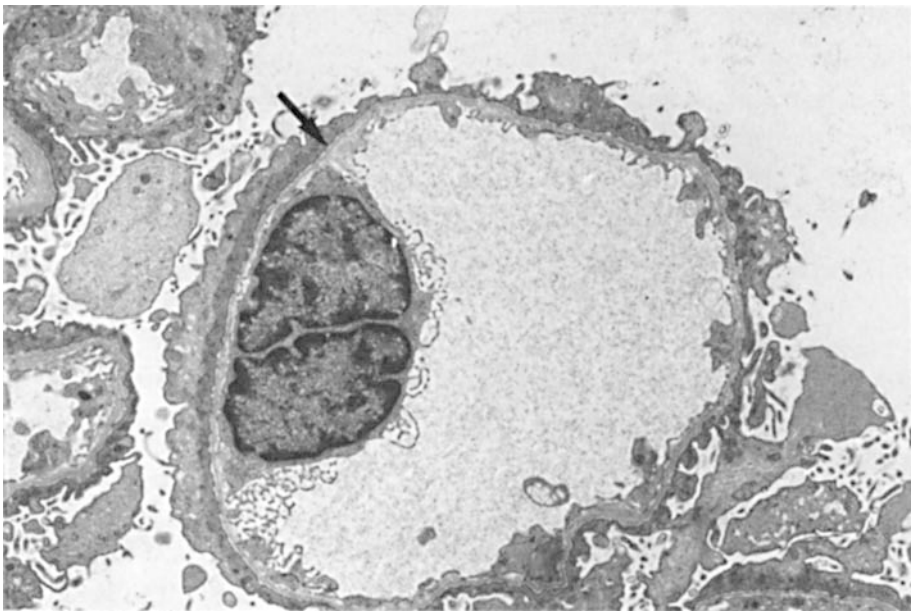
The clinical features of Alport syndrome originate in changes in basement membrane structure and function initiated by absence or abnormalities of α3α4α5(IV) and α5α5α6(IV) networks.

Renal. Light microscopic abnormalities are unusual in children with Alport syndrome who are less than 5 years of age. Mesangial hypercellularity and matrix expansion, and eventually focal segmental glomerulosclerosis, are common in older children and adolescents, especially boys. Tubular atrophy and interstitial fibrosis develop progressively after age 10 in boys with Alport syndrome (46).

Electron microscopy may reveal pathognomonic changes, depending on the patient's age and gender. The earliest abnormality is diffuse attenuation of the GBM; consequently, differentiation of Alport syndrome from thin basement membrane nephropathy by routine renal biopsy processing may be difficult in children (*Fig. 26-3*). To further complicate matters, some families with Alport syndrome due to COL4A5 mutations, GBM attenuation is the only ultrastructural abnormality. However, the great majority of boys with XLAS and both boys and girls with

Figure 26-3

Electron micrograph. Lead citrate and uranyl acetate stain (×4,800). Alport syndrome. Thin and regular GBM (*arrow*) with attenuated lamina densa. Epithelial foot processes are extensively fused.



ARAS develop the classic Alport GBM lesion, consisting of diffuse thickening accompanied by "basket-weave" transformation of the lamina densa, intramembranous vesicles and densities, scalloping of the epithelial surface of the GBM and foot process effacement (*Fig. 26-4*). The percentage of GBM displaying this lesion increases progressively with age in boys with XLAS (34). Females with XLAS display a range of GBM alteration, from focal GBM attenuation to diffuse thickening and basket-weaving, and there is no consistent correlation of GBM findings and age (34).

Routine immunofluorescence is normal or shows nonspecific immunoprotein deposition. Because disease-causing mutations result in abnormal expression of α3α4α5(IV) and α5α5α6(IV) networks in basement membranes in most Alport patients, specific immunostaining for type IV collagen α chains is useful for both diagnosis and differentiation of XLAS and ARAS (47) (*Figs. 26-5* and *26-6*). Expression of the α3(IV), α4 (IV) and α5(IV) chains is completely absent in ~80% of XLAS males, and 60–70% of females with XLAS exhibit mosaic expression of these chains (*Fig. 26-5*). In most patient with ARAS, GBM is nonreactive with antibodies to the α3(IV), α4(IV) and α5(IV) chains, and Bowman's capsules and tubular basement membranes are also negative for the α3(IV) and α4(IV) chains (48) (*Fig. 26-6*). However, immunostaining for α5(IV) chains in Bowman's capsules and tubular basement membranes is positive, because in these basement membranes expression of α5α5α6(IV) networks is preserved. It is important to note that altered immunostaining for the α3(IV)-α6(IV) chains in patients with XLAS and ARAS is not age-dependent. Therefore, this method can provide diagnostic information even in patients who are too young to display characteristic abnormalities in GBM ultrastructure.

Normal epidermal basement membranes (EBM) express the α5α5α6(IV) network but not the α3α4α5(IV) network. Epidermal basement membranes show negative staining for α5(IV) chains in about 80% of XLAS males, and mosaic expression of α5(IV) is observed in 60–70% of XLAS females, allowing diagnosis of XLAS by skin biopsy (49, 50) (*Fig. 26-5*). Skin biopsy is not useful for diagnosis of ARAS, since expression of α5(IV) in epidermal basement membranes is normal (48) (*Fig. 26-6*).

Cochlear. The hearing loss of Alport syndrome arises from cochlear dysfunction (51). Normal cochleae in mice, dogs and humans express type IV collagen α3, α4, and α5 chains in the spiral limbus, spiral ligament and in the basement membrane interposed between the organ of Corti and the basilar membrane (52–55). However, expression of these chains is absent in cochleae of ARAS mice (52), XLAS dogs (53) and men with XLAS (55). Careful examination of well-preserved cochleae from men with XLAS and deafness revealed a zone of separation

Figure 26-4

Electron micrograph. Lead citrate and uranyl acetate stain (×11,250). Alport syndrome. Thickened GBM showing splitting of the lamina densa and presence of granulations.

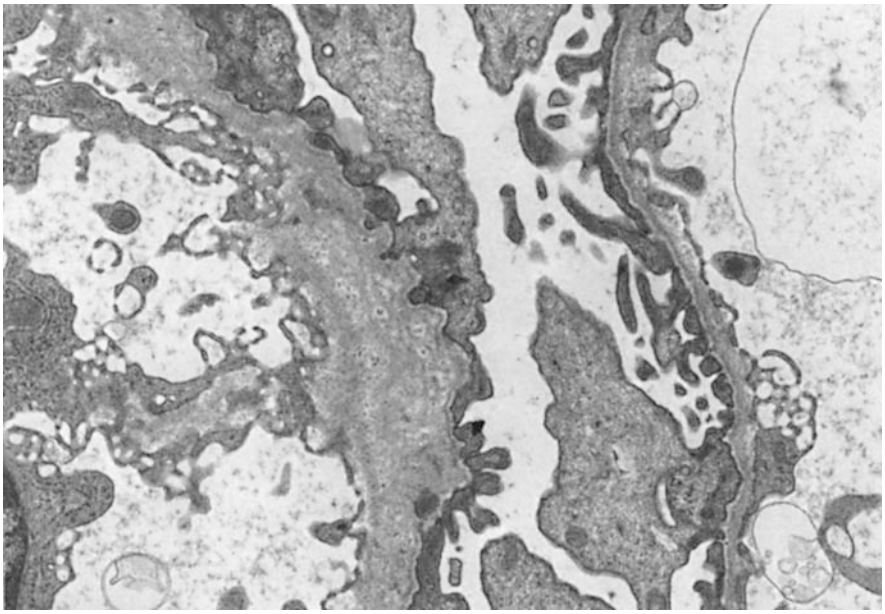
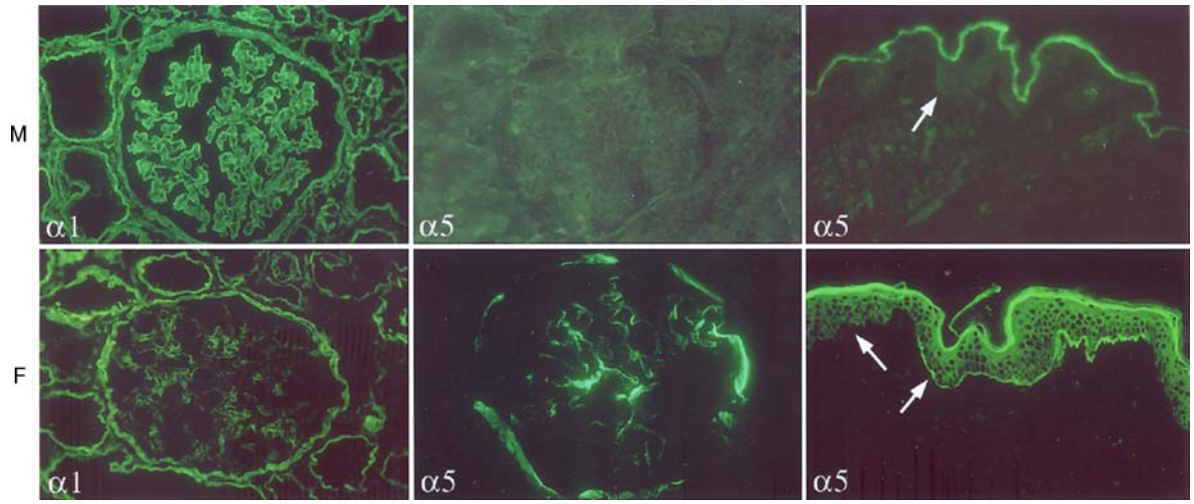


Figure 26-5

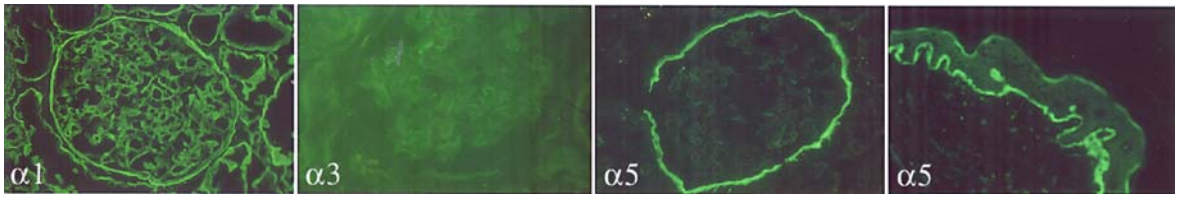
Immunofluorescene microscopy. Distribution of the α(IV) chains in renal and epidermal basement membranes of male (A-C) and female (D-F) patients affected with X-lined Alport syndrome. C: absence of epidermal basement membrane labeling (*arrow*). F: Distcontinuous epidermal basement membane labeling (*arrows*). (See color plate 9)



between the organ of Corti and the underlying basilar membrane, and cellular infiltration of the tunnel of Corti and the spaces of Nuel (56). These changes are not observed in similarly well-preserved cochleae obtained from normal individuals or patients with other causes of deafness. The structural changes observed in Alport cochleae may be associated with defective attuning of basilar membrane motion and hair cell stimulation, resulting in reduced

Figure 26-6

Immunofluorescene microscopy. Distribution of the α(IV) chains in renal and epidermal basement membranes of patients affected with autosomal recessive Alport syndrome. (See color plate 10)



acuity of hearing. Similar changes have not been observed in cochleae from mice or dogs with Alport syndrome, although deafness in these models is minimal or absent.

Ocular. The α3, α4, and α5(IV) chains are normal components of several basement membranes in the eye, including the corneal basement membrane, Descemet's membrane, lens capsule, the internal limiting membrane of the retina, and the retinal pigment epithelium basement membrane (54, 57–59). The ocular manifestations of Alport syndrome likely arise from absence or abnormality of α3α4α5(IV) networks in these basement membranes. The lens capsules of Alport patients with anterior lenticonus exhibit marked attenuation and focal areas of dehiscence, suggesting that the lens capsule lacks the mechanical strength to maintain normal lens shape (58, 60, 61).

Diagnostic Considerations

Accurate diagnosis of Alport syndrome and differentiation of this condition from other causes of familial and sporadic glomerular hematuria are based upon careful clinical evaluation, reliable pedigree data and thoughtful consideration of the relative merits of skin biopsy, kidney biopsy and molecular analysis.

In a child with isolated hematuria, a positive family history of hematuria in the absence of a history of ESRD suggests a diagnosis of thin basement membrane nephropathy (TBMN). Two rare causes of familial hematuria associated with macrothrombocytopenia, Epstein and Fechtner syndromes, can be excluded if the platelet count is normal. Familial IgA nephropathy (62) and membranoproliferative glomerulonephritis (63) are uncommon causes of familial hematuria.

In the absence of a family history of hematuria, the differential diagnosis of glomerular hematuria includes Alport syndrome, TBMN, IgA nephropathy, membranoproliferative glomerulonephritis, membranous nephropathy, lupus nephritis, postinfectious glomerulonephritis and Henoch-Schonlein nephritis. Associated clinical findings (e.g., rash, arthritis) or laboratory findings (e.g., hypocomplementemia) will suggest diagnoses other than Alport syndrome in many of these patients.

While results of hearing evaluation are likely to be normal in young children with Alport syndrome, audiometry may be very useful in children over 6–8 years of age. Ophthalmologic assessment may also provide valuable information, although ocular lesions are more prevalent in Alport patients with advanced disease, and less likely to be present in the population of young patients in whom differential diagnosis of hematuria may be more difficult.

Tissue studies can complement clinical and pedigree information that is insufficient to clearly differentiate Alport syndrome from other diagnoses. Skin biopsy with immunostaining for the α5(IV) chain, as described above, may be diagnostic, especially when clinical and pedigree data strongly suggest a diagnosis of XLAS. Normal expression of the α5(IV) chain in epidermal basement membrane can be explained in several ways: (1) the patient has XLAS, but his or her COL4A5 mutation does not abolish α5(IV) expression; (2) the patient has a form of Alport syndrome (ARAS or ADAS) in which expression of α5(IV) in epidermal basement membranes is not affected; or (3) the patient does not have Alport syndrome. Whereas skin biopsy is useful only if it provides definitive confirmation of a diagnosis of XLAS, renal biopsy carries the advantage of enabling the diagnosis of XLAS, ARAS and non-Alport kidney disease, particularly if type IV collagen immunostaining is applied.

Mutation detection rates of 80–90% are attainable in males with XLAS using direct sequencing of COL4A5 (64). Comparable data for detection of COL4A3 and COL4A4 mutations in patients with ARAS are lacking. COL4A5 mutation analysis has been commercially available in Europe for some time, and has recently become available in the United States. Laboratories providing type IV collagen gene sequencing can be found through the GeneReviews website (www.genereviews.org) and through the website of the Alport Syndrome Foundation (www.alportsyndrome.org).

Treatment

There have been no controlled therapeutic trials in human Alport syndrome. Consequently, treatment recommendations must be derived from animal studies and anecdotal reports. In murine ARAS several interventions have proven efficacious, including angiotensin antagonism (65–67), TGFb-1 inhibition (68), chemokine receptor 1 suppression (69), administration of bone morphogenic protein-7 (70), blockade of matrix metalloproteinases (71) and bone marrow transplantation (72, 73). Inhibition of angiotensin converting enzyme (ACE) treatment resulted in prolongation of survival in dogs with XLAS (74). In uncontrolled studies of human Alport subjects ACE inhibition reduced proteinuria, at least transiently (75, 76).

Cyclosporine treatment also resulted in prolongation of survival in male XLAS dogs (77). Cyclosporine treatment diminished proteinuria and appeared to stabilize renal function in a small, uncontrolled study of Alport males (78). However, apparent acceleration of renal fibrosis was suggested by the results of another study of cyclosporine treatment in Alport patients (79).

At the present time, angiotensin antagonism aimed at suppression of proteinuria appears to be the least risky of available treatment options. There is as yet no evidence that initiation of angiotensin blockade can delay the onset of overt proteinuria in Alport patients who have isolated hematuria. With advancing disease, management of hypertension and other complications of nephrotic syndrome and renal insufficiency is required.

Renal Replacement Therapy

Patients with Alport syndrome typically have excellent outcomes following renal transplantation (80). Two issues require the special attention of transplant physicians involved in the care of Alport patients. First, evaluation of potential related donors must identify affected individuals who may be at risk for development of significant renal insufficiency. Second, posttransplant monitoring must allow early diagnosis of posttransplant anti-GBM nephritis, a complication of transplantation that is unique to Alport syndrome.

Familiarity with the genetics of Alport syndrome and the signs and symptoms of the disease is required for informed donor evaluation. Since 100% of males with XLAS have hematuria (22), the absence of hematuria excludes Alport syndrome in male relatives of XLAS patients. About 95% of females with XLAS have hematuria (25), so there is only a 5% chance that a female without hematuria is affected. Given that by age 60 there is an estimated risk of ESRD of 30% in women with XLAS (25), female members of XLAS families who have hematuria should generally be discouraged from kidney donation.

Anti-GBM nephritis occurs in ~3% of transplanted Alport males (80). The onset of anti-GBM nephritis typically occurs during the first year after transplantation, and usually results in irreversible graft failure within weeks to months of diagnosis. There is a high rate of recurrence in subsequent allografts. In XLAS males the primary target of anti-GBM antibodies is the α5(IV) chain (81, 82). Females with XLAS who require transplantation are at little or no risk of developing anti-GBM nephritis. However, both males and females with ARAS can develop anti-GBM nephritis after transplantation. The α3(IV) chain is the primary target of anti-GBM antibodies in ARAS patients (81, 83). Goodpasture auto-antibodies and anti-GBM antibodies from transplanted Alport patients target distinct epitopes on the carboxyterminal noncollagenous (NC1) domain of the α3(IV) chain (84).

Renal allograft biopsy with routine immunofluorescence should be performed early in the evaluation of Alport patients who develop hematuria or increased creatinine after transplantation, or if circulating anti-GBM antibodies are detected. Anti-GBM nephritis after renal transplantation should be treated with cytotoxic therapy and plasmapheresis, although such therapy has been unsuccessful in the majority of reported patients.

Thin Basement Membrane Nephropathy

Historically, families displaying autosomal dominant transmission of isolated, nonprogressive hematuria were classified as having "benign familial hematuria" (85–87). Affected patients typically exhibited no renal parenchymal abnormalities apart from thinning of glomerular basement membranes (GBM) observed by electron microscopy (88–93). The more inclusive term "thin basement membrane nephropathy" (TBMN) has gradually displaced benign familial hematuria as the preferred designation for hematuria associated with thin GBM, because it encompasses sporadic cases of hematuria associated with thin GBM; familial or sporadic cases of thin GBM in which hematuria is accompanied by proteinuria, hypertension and/or renal insufficiency; and benign familial hematuria.

Thinning of GBM is a pathological description rather than a distinct entity. Depending on the timing of renal biopsy, GBM attenuation may be observed in patients with hemizygous or heterozygous mutations in COL4A5

(X-linked Alport syndrome, or XLAS), biallelic mutations in COL4A3 or COL4A4 (autosomal recessive Alport syndrome, or ARAS), heterozygous mutations in COL4A3 or COL4A4 (the carrier state of ARAS) and mutations at nontype IV collagen loci (94). The natural history of hematuria associated with thin GBM is determined by the underlying mutation, perhaps in combination with remote modifier genes. Hemizygous mutations in COL4A5 and biallelic mutations in COL4A3 and COL4A4 result in progressive GBM thickening, proteinuria and renal failure. Heterozygous mutations in COL4A3 or COL4A4 are usually associated with persistent GBM attenuation, isolated hematuria and benign outcomes. Heterozygous mutations in COL4A5, in women with XLAS, are associated with a wide range of prognostic outcomes, as described in the section on Alport syndrome. Perhaps this spectrum of outcomes reflects differences in the cellular responses provoked by complete absence of α3α4α5(IV) networks from GBM (hemizygous XLAS and ARAS), mixed α3α4α5(IV)-positive and α3α4α5(IV)-negative GBM (heterozygous XLAS) and homogeneous reduction in GBM content of α3α4α5(IV) networks (heterozygous COL4A3 or COL4A4 mutations).

Clinical Features

Persistent microscopic hematuria, associated with normal blood pressure, renal function and urine protein excretion, is the characteristic feature of TBMN in childhood (2, 3). TBMN is not specifically associated with hearing loss, ocular defects or other extrarenal abnormalities.

Proteinuria has been reported in up to 30% of adults with thin GBM (92, 95–99). About 5–7% of adult patients with TBMN have elevated serum creatinine levels (95, 98, 99).

Pathology

Diffuse attenuation of the lamina densa and GBM, with preservation of normal podocyte anatomy, is the characteristic histological abnormality in TBMN. Glomerular obsolescence or sclerosis may be observed in adult patients with TBMN, including some with heterozygous COL4A3 or COL4A4 mutations (98, 100).

GBM width is dependent on age and gender. The lamina densa and GBM increase rapidly in width between birth and 2 years of age, followed by a more gradual increase during childhood and adolescence (101). Adult men exhibit greater GBM widths than adult women (102).

Because different investigators have used different techniques to measure GBM width, a standard definition of "thin" GBM does not exist. In children the threshold is 200–250 nm (1, 3, 103), while the adult threshold ranges from 250 to 330 nm (92, 104).

Routine immunofluorescence studies of renal biopsy material from patients with TBMN are typically unremarkable. Immunostaining using specific antibodies against α3(IV), α4(IV), and α5(IV) chains yields normal results in patients with TBMN (88, 89, 105).

Diagnostic Considerations

IgA nephropathy, TBMN and Alport syndrome together account for the majority of children with glomerular hematuria seen in pediatric nephrology clinics (1–4). Thorough clinical evaluation, including detailed pedigree analysis, can assist in determining which children need tissue studies and which can be followed prospectively without biopsy. Obtaining urinalyses on first-degree family members may provide valuable information, since adults with familial hematuria may be unaware that they are affected (106).

When a child has isolated microscopic hematuria, a family history of dominantly transmitted hematuria and a negative family history for renal failure, a clinical diagnosis of TBMN is reasonable, and renal biopsy is unnecessary. These children should be followed prospectively every 1–2 years. If proteinuria or hypertension develops, renal biopsy should be considered.

In children who have persistent microscopic hematuria but do not have affected relatives, renal biopsy is often informative. In those children whose renal biopsy findings are limited to GBM attenuation, the clinician's challenge is to differentiate TBMN and Alport syndrome. Audiometry and ophthalmologic examination may be helpful in older children but these studies will usually be normal in young children with Alport syndrome. Abnormal results of immunostaining for the α3(IV), α4(IV) and α5(IV) chains suggests a diagnosis of Alport syndrome. While normal immunostaining results cannot entirely exclude Alport syndrome, they can help support a suspected diagnosis of TBMN.

The role of molecular analysis of the COL4A3, COL4A4 and COL4A5 genes in patients with suspected TBMN remains to be determined. Since the finding of a heterozygous mutation in COL4A3 or COL4A4 cannot guarantee a benign prognosis (100, 107–109), the need for follow-up examination of such patients would not be precluded.

Treatment

Since TBMN usually has a benign outcome, treatment is rarely indicated. Patients with TBMN who have proteinuria are theoretically candidates for angiotensin blockade.

Hereditary Angiopathy with Nephropathy, Aneurysms and Cramps (HANAC Syndrome)

Mutations in the COL4A1 and COL4A2 genes have not been found in patients with Alport syndrome or TBMN (110). Recently, missense mutations in the COL4A1 gene were described in three families displaying an autosomal dominant hereditary angiopathy associated with nephropathy, aneurysms and muscle cramps (HANAC syndrome) (111). The mutations affect three highly conserved glycine residues in the collagenous domain of the α1(IV) chain. Retinal arteriolar tortuosity and retinal hemorrhages were common to affected individuals in all three families, as were intracranial aneurysms, leukoencephalopathy and elevated creatine kinase levels. In two families, affected individuals had muscle cramps. Renal findings in affected individuals included microscopic and gross hematuria in one family, mild renal insufficiency in two families and renal cysts in all three families.

Renal biopsy in affected individuals with hematuria showed no abnormalities of GBM structure or type IV collagen expression. However, basement membranes of Bowman's capsules, tubules and interstitial capillaries exhibited irregular thickening, splitting into multiple layers and focal interruptions.

Laminin Disorders

Pierson Syndrome

The association of congenital nephrotic syndrome with eye abnormalities in siblings was first described by Pierson in 1963 (112). Affected infants died within the first year of life with ESRD. Subsequent reports of additional patients described variable abnormalities on fetal ultrasound, including kidney enlargement and hyperechogenicity, oligohydramnios, placental enlargement and/or pulmonary hypoplasia (113, 114). Infants surviving to term exhibited congenital nephrotic syndrome, with renal biopsy findings of mesangial sclerosis and diffuse GBM abnormalities, accompanied by ocular globe enlargement (buphthalmos) with reduction in the size and reactivity of pupils (microcoria). Additional ocular findings in some patients included cataract, posterior rupture of the lens capsule and retinal abnormalities. Some affected children were also found to have muscular hypotonia, central nervous system hemangioma and genital abnormalities (115, 116).

The gene for Pierson syndrome was mapped to chromosome 3p14-p22 and identified as LAMB2, the gene encoding the laminin β2 chain, by Zenker and colleagues in 2004 (113). Subsequent reports indicate that LAMB2 mutations may be associated with isolated congenital nephrotic syndrome and with mild variants of Pierson syndrome (117–121). The absence of the laminin β2 chain in transgenic mice results in massive proteinuria along with retinal and neuromuscular abnormalities (122). In these mice, proteinuria precedes the appearance of podocyte abnormalities, suggesting that the GBM contributes to the barrier function of the glomerular capillary wall.

Type III Collagen Nephropathies

Nail-Patella Syndrome (Hereditary Osteo-Onychodysplasia)

Nail-patella syndrome (NPS) is a rare autosomal dominant disorder characterized by dystrophic nails, hypoplasia or absence of the patellae, dysplasia of the elbows and iliac horns, and renal disease (123, 124). Affected individuals may also exhibit glaucoma and sensorineural deafness (125, 126). The disorder affects about 1 in 50,000 individuals. The severity of renal involvement, which occurs in 30–40% of patients, determines prognosis.

Genetics

Targeted disruption of the LIM homeodomain transcription factor gene Lmx1b in mice resulted in hypoplastic nails and absent patellae as well as renal disease, suggesting a possible locus for human NPS (127). LMX1B, the human homologue of Lmx1b, and the NPS locus were found to map to chromosome 9q34, and heterozygous mutations in LMX1B were identified in NPS patients (128, 129). A variety of LMX1B gene defects have been identified in NPS patients, including missense, splicing, insertion/deletion and nonsense mutations (128–134). The results of *in vitro* experiments in which the transcriptional effects of mixing wild-type and mutant LMX1B protein are measured, along with the variety of observed mutation types, suggest that the NPS phenotype results from haploinsufficiency rather than a dominant-negative mechanism (130, 135). Mutations in the homeodomain of LMX1B protein and female gender may confer an increased risk of renal involvement (126).

LMX1B protein is specifically expressed in glomerular podocytes, beginning at the S-shaped body stage of glomerular development (127). Lmx1b-null mice exhibit marked reduction in GBM expression of the α3 and α4

chains of type IV collagen, and the slit diaphragm proteins podocin and CD2AP (136–138). However, changes in expression of these putative targets of LMX1B were not observed in kidneys of patients with NPS nephropathy (139), perhaps because patients with NPS are heterozygous for LMX1B mutations, leaving the mechanisms for the renal effects of LMX1B mutations uncertain.

Clinical Features

Renal. Less than half of NPS patients have clinical renal disease (140, 141). Symptoms include microscopic hematuria and mild proteinuria, and typically appear in adolescence or young adulthood. Occasional patients develop nephrotic syndrome and hypertension. The nephropathy is typically mild, with about a 10% risk of progression to ESRD. Marked differences in the severity of the nephropathy can be observed in related patients, suggesting the influence of superimposed factors.

Nails. Nail abnormalities occur in over 90% of patients and are usually apparent from birth (142). Fingernails, especially on the thumb and index finger, are more severely affected than toenails. The nails may be absent or dystrophic with discoloration, koilonychias, longitudinal ridges or triangular lunulae.

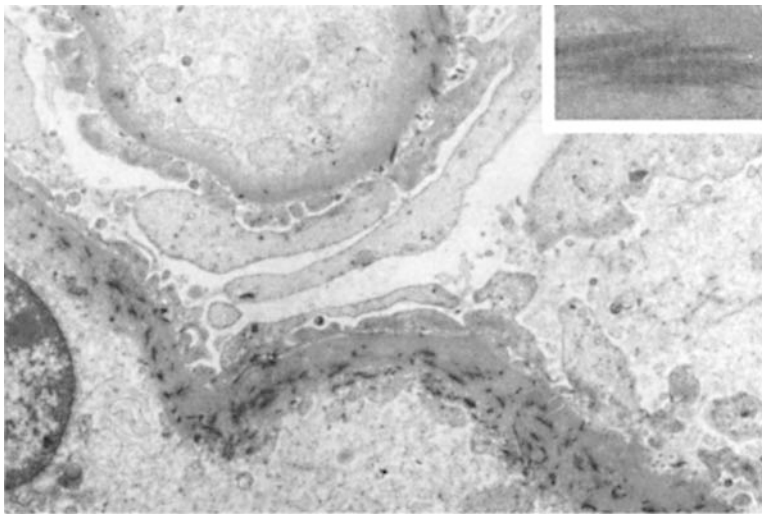
Skeletal defects. Over 90% of NPS patients exhibit aplasia or hypoplasia of the patellae (142). Associated symptoms may include knee pain, effusions, dislocations and osteoarthritis. Dysplasia of the elbows occurs in over 90% of patients (142). Anomalies such as hypoplasia of the radial head with dislocation, posterior processes at the distal ends of the humeri, hypoplasia of the olecranon and elongation of the neck of the radius may be associated with mild to severe limitation in extension, pronation and supination of the forearm. About 80% of patients display osseous processes projecting posteriorly from the iliac wings, known as iliac horns, which are pathognomonic for NPS (142).

Pathology

The nephropathy of NPS has no specific features by light microscopy or routine immunofluorescence. Focal segmental glomerulosclerosis and deposits of IgM and C3 may be observed, depending on the severity of renal involvement. Characteristic lesions are observed by electron microscopy (143, 144). With standard staining techniques the GBM and mesangium exhibit multiple lucencies, imparting a "moth-eaten" appearance. Staining with phosphotungstic acid reveals clusters of cross-banded collagen fibrils within these lucent areas (*Fig. 26-7*). These collagen fibrils have been observed in NPS patients with no clinically evident renal disease, and there is no correlation between the extent of GBM changes and patient age, severity of proteinuria or degree of renal functional impairment (130, 131). Staining of NPS kidneys with antibodies against type III collagen produced irregular, discontinuous labeling of GBM in normal-appearing glomeruli and focally intense staining of sclerotic glomeruli (139).

Figure 26-7

Electron microscopy. Phosphotungstic acidstain (×10,500). Nail patella syndrome. Irregular distribution of fibrillar collagen within the GBM. Inset shows the typical periodicity of interstitial collagen (×48,000).



Treatment

There is no specific therapy for NPS renal disease. Kidney transplantation has been carried out successfully, and recurrence of disease apparently did not recur. Selection of living donors must be performed with care, since NPS is an autosomal dominant disorder.

Collagen Type III Glomerulopathy

Renal disease associated with glomerular deposits of type III collagen has been described in patients who have no extrarenal abnormalities (145–148). In comparison to NPS patients, subjects with collagen type III glomerulopathy have relatively severe renal findings, more extensive histological changes and greater glomerular type III collagen accumulation.

Clinical Features

Patients with collagen type III glomerulopathy can present in childhood or in adulthood. Early presentation is associated with a more severe disease course. Proteinuria is common to the juvenile and adult forms of the disease. In children, proteinuria progresses to nephrotic syndrome and is accompanied by hypertension and the development of renal failure (145, 148). Microangiopathic hemolytic anemia has been described in some patients. Patients presenting in adulthood exhibit more gradual increase in proteinuria and loss of renal function (147).

Pathology

Light microscopy shows enlarged glomeruli with mesangial expansion and glomerular capillary wall thickening due to subendothelial accumulation of poorly staining material. Routine immunofluorescence studies are unremarkable or show nonspecific immunoprotein deposits. Electron microscopy shows deposits of electron-lucent material in mesangial matrix and GBM. Staining with phosphotungstic acid demonstrates fibrillar collagen in these deposits which is identified as type III collagen by specific immunostaining.

Hereditary Nephritis with Thrombocytopenia and Giant Platelets: Epstein and Fechtner Syndromes

Epstein and Fechtner syndromes are allelic, autosomal dominant disorders that have some features in common with Alport syndrome, such as hematuria, progressive nephropathy and sensorineural deafness (149, 150). However, these conditions are distinguished clinically from Alport syndrome by the invariable presence of thrombocytopenia and giant platelets. In addition, granulocytes of patients with Fechtner syndrome display cytoplasmic inclusions known as Dohle-like bodies, and these patients may develop cataracts. In some patients ultrastructural changes in GBM resemble those of Alport syndrome (151, 152). However, glomerular expression of type IV collagen α3, α4 and α5 chains is normal in these patients (152).

Despite the similarities with Alport syndrome, Epstein and Fechtner syndromes are genetically distinct disorders. Following the mapping of the Epstein and Fechtner loci to chromosome 2q11–13 (153, 154), heterozygous mutations in MYH9, the gene that encodes nonmuscle myosin heavy chain IIA (NMMHC-IIA), were identified in patients with these disorders, as well as in patients with two other conditions featuring giant platelets, Sebastian syndrome and May-Hegglin anomaly, and in nonsyndromic hereditary deafness (DFNA17) (155–158). NMMHC-IIA is expressed in podocytes (159), but the mechanism by which mutations in this protein might adversely affect podocyte function is unknown.

Hereditary Metabolic Disorders with Primary Glomerular Involvement

Fabry Disease

Anderson-Fabry disease is a rare X-linked disorder of glycosphingolipid metabolism resulting from deficiency of the lysosomal hydrolase a-galactosidase A. Clinical aspects of this disease are discussed in Chapter 51.

Renal tissue from all hemizygous patients demonstrates characteristic glycolipid accumulation within every glomerular, vascular and interstitial cell and within distal tubular cells, regardless of age at biopsy. Two intermingled cell populations, normal cells and cells exhibiting glycolipid accumulation, are observed in heterozygous females. Degenerative renal changes develop with age. They initially affect vessels and consist of round fibrinoid deposits resulting from smooth muscle cell necrosis. These changes are followed by nonspecific vascular, glomerular and tubulointerstitial lesions (160). Enzyme replacement appears to result in decreased glycolipid storage in renal cells and stabilization of renal function (161, 162).

Other Glomerular Lipidoses

Nephrosialidosis is a rare autosomal recessive condition caused by neuraminidase deficiency. Clinical and radiologic features include dysmorphic facies, visceromegaly, mental retardation, skeletal anomalies, marrow foam cells and cherry-red spot on fundoscopy. Renal involvement consists of proteinuria and progression to ESRD early in life (163). Renal biopsy findings include podocyte and proximal tubular cell vacuolization. By electron microscopy many of these vesicles appear empty, but others contain flocculent or membrane-like electron-dense material. Wheat germ agglutinin binds to cytoplasmic material in podocytes and tubular cells, indicating the presence of compounds with terminal sialic (neuraminic) acid moieties (164).

Silent accumulation of glycolipids or mucopolysaccharides has been described in patients with Gaucher disease, Niemann-Pick disease, I-cell disease and GM1 gangliosidosis (165). Clinical renal disease during childhood is unusual in patients with these disorders.

Hereditary Metabolic Disorders with Secondary Glomerular Involvement

Familial Amyloidosis

Hereditary amyloidosis encompasses a group of autosomal dominant disorders characterized by extracellular accumulation of protein fibrils arranged in an antiparallel β-pleated sheet configuration. These disorders are classified according to the protein composing amyloid fibrils and/or the type of mutation in the corresponding gene. Transthyretin variants have been found in most affected families, but variants of cystatin C, gelsolin, apoliprotein A1, fibrinogen and lysozyme have described in other kindreds (166). Symptomatic renal involvement is unusual during childhood.

Familial Mediterranean fever is an autosomal recessive disorder described primarily, but not exclusively, in several ethnic groups originating in the Mediterranean region. The disease is characterized by recurrent episodes of fever, abdominal pain, joint pain, pleuritis and pericarditis. Renal amyloidosis of the AA type may result in proteinuria and eventual renal failure. Renal amyloidosis of the AA type may be associated with the autosomal dominant disorders *Muckle-Well syndrome* and *tumor necrosis factor receptor-1 associated periodic syndrome (TRAPS)* (167).

Alpha-1 Antitrypsin Deficiency

Chronic liver disease due to deficiency of alpha-1-antitrypsin (α1AT) may be associated with glomerulonephritis in children (168–170). Renal biopsy reveals diffuse or focal segmental membranoproliferative glomerulonephritis, type I in most cases, associated with subendothelial deposits composed of immunoglobulin and complement. Renal manifestations include proteinuria, hypertension and renal failure. Regression of nephrotic syndrome and glomerular lesions after liver transplantation has been observed (171).

Alagille Syndrome

Alagille syndrome is an autosomal dominant disorder with variable penetrance that causes cholestasis in childhood, associated with characteristic facies, cardiac malformations, vertebral abnormalities, posterior embryotoxon, hypogonadism, growth retardation and high-pitched voice. The disease results from mutations in *Jagged1*, which encodes a ligand for the Notch1 receptor (172). Accumulation of lipid vacuoles in mesangial matrix, mesangial cells and GBM has been observed in some patients (173) (› *Fig. 26-8*). The extent of mesangiolipidosis correlates with the severity of cholestasis. Although the glomerular lesions are present early in life, renal symptoms in childhood are unusual. Progression to ESRD may occur in affected adults.

Hereditary Lecithin-Cholesterol Acyltransferase (LCAT) Deficiency

LCAT deficiency is a rare autosomal recessive disorder characterized by the inability to esterify plasma cholesterol, leading to deposition of unesterified cholesterol in tissues, including the kidney (174). Progression to ESRD usually occurs in the fourth or fifth decade. Glomerular lesions include accumulation of foam cells of endothelial and mesangial origin and massive accumulation of lipids within the mesangial matrix and subendothelial GBM (174).

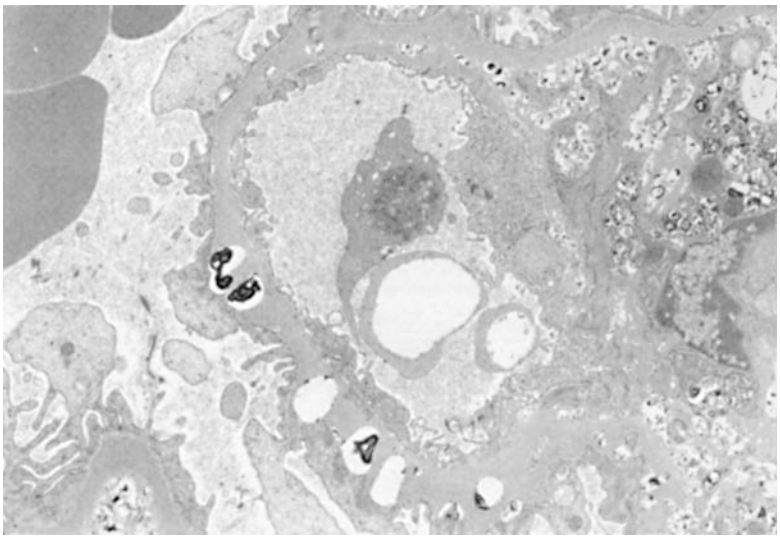
Lipoprotein Glomerulopathy

Lipoprotein glomerulopathy is characterized by intraglomerular lipoprotein thrombosis and high plasma concentrations of apolipoprotein E (175). The disease is usually detected in adults, but onset of symptoms during childhood has been described (176). Renal symptoms range from proteinuria to nephrotic syndrome, and progression to ESRD occurs in some patients. Recurrence of glomerular lesions after renal transplantation has been observed (177). Mutations in apolipoprotein E have been found in patients with this disorder (178).

Glomerular lipidosis has also been reported in patients with *familial hypercholesterolemia* resulting from defects in the LDL receptor, in *type III hyperlipoproteinemia*, and in patients with *cholesterolic polycoria*. Renal symptoms usually appear in adulthood in patients with these disorders.

Figure 26-8

Electron microscopy. Lead citrate and uranyl acetate stain (×8,600). Alagille syndrome. Massive accumulation of lipid vacuoles within mesangial cells and matrix. Irregular distribution of lipid vacuoles within the GBM.



Familial Juvenile Megaloblastic Anemia

Familial juvenile megaloblastic anemia (Imerslund-Grasbeck syndrome) is a rare autosomal recessive disorder caused by selective vitamin B12 malabsorption. Anemia is detected in infancy or early childhood and is associated with mild, nonprogressive proteinuria. Most cases arise from mutation in the gene for either cubilin (chromosome 10) or amnionless (chromosome 14), which are components of the intestinal receptor for the vitamin B12-intrinsic factor complex as well as the receptor that mediates proximal tubular reabsorption of filtered protein (179).

Other Hereditary Diseases with Glomerular Involvement

Charcot-Marie-Tooth (CMT) Disease

CMT disease is a genetically heterogeneous, familial peripheral neuropathy resulting in progressive symmetric atrophy and weakness of distal muscles and sensory deficits. Autosomal dominant and X-linked forms have been described, due to mutations in the myelin protein zero gene on chromosome 1, peripheral myelin protein 22 gene on chromosome 17, and the connexin 32 gene on the X chromosome (180). Proteinuria and progression to ESRD associated with focal glomerulosclerosis occur in some patients (181). Since some of these patients are also deaf, CMT disease could potentially be misdiagnosed as Alport syndrome. No specific ultrastructural changes in GBM have been described in patients with CMT disease.

Cockayne Syndrome

Cockayne syndrome is an autosomal recessive disorder characterized by growth retardation, neurologic abnormalities, premature aging, senile facies, sensorineural deafness, cataracts, retinopathy, sun sensitivity and dental caries (182). The disorder arises from mutations in genes involved in DNA nucleotide excision repair (183). Renal symptoms including hypertension, proteinuria and renal insufficiency occur in about 10% of patients, associated with diffuse, homogeneous GBM thickening (184).

Hereditary Acro-Osteolysis with Nephropathy

Hereditary acro-osteolysis is a rare disorder characterized by arthritic episodes and progressive resorption of carpal and tarsal bones. Familial (dominant or recessive) and sporadic cases have been reported. Hypertension, proteinuria and progressive renal failure occur in some patients (185). Renal biopsy findings include arteriolar thickening and sclerosis and focal glomerulosclerosis.

Other Syndromes with Renal Involvement

Renal abnormalities, typically cystic renal dysplasia and/or tubulointerstitial lesions, are found in most patients with *Bardet-Biedl syndrome (BBS)*, a genetically heterogeneous, autosomal recessive disorder whose cardinal features included obesity, polydactyly, mental retardation, retinal dystrophy and hypogonadism (186). Glomerular symptoms such as proteinuria and questionable glomerular changes have been described in a few patients (187). Mutations in several genes involved in the functioning of primary cilia have been linked to BBS (188).

Alstrom syndrome is an autosomal recessive disorder characterized by cone-rod dystrophy, obesity, progressive sensorineural deafness, dilated cardiomyopathy, insulin resistance syndrome and developmental delay. Renal tubular dysfunction and tubulointerstitial lesions have been observed in some patients (189). Renal disease due to vascular lesions and secondary glomerulosclerosis occurs in some patients with *familial dysautonomia.*

Hereditary Glomerulopathies Without Extrarenal Symptoms

Fibroncectin Glomerulopathy

Fibronectin glomerulopathy is associated with massive accumulation of fibronectin derived mainly from the soluble plasma isoform, transmitted as an autosomal dominant trait (190–192). A substantial fraction of cases arises from mutations in the gene FN1 (193), which is located on chromosome 2 and encodes fibronectin, but another locus appears to exist at chromosome 1q32 (194). Clinically, the disease is characterized by proteinuria of variable magnitude, typically first observed in early adulthood. Subsequently, patients develop hypertension and renal insufficiency, with gradual progression to ESRD.

Other Familial Glomerulopathies

Persistent proteinuria with the abrupt development of rapidly progressive renal failure, malignant hypertension and microangiopathic hemolytic anemia during the third or fourth decade of life, transmitted as an autosomal dominant trait, has been described in several families (195). Renal biopsy findings included diffuse vascular injury, ischemic glomerular changes, and glomerular deposits of IgM and C3. The cause(s) of this disorder is apparently unknown.

Mitochondrial Cytopathies

Mitochondrial cytopathies are a heterogeneous group of disorders resulting from genetic defects in enzymatic complexes of the respiratory chain, leading to impaired oxidative phosphorylation and energy production. The most common renal defect is the de Toni-Debre-Fanconi syndrome, associated with nonspecific abnormalities in tubules and intersititium on renal biopsy, but glomerular lesions such as focal segmental glomerulosclerosis, collapsing glomerulopathy and crescentic glomerulonephritis may also occur (196). Proteinuria has been found in patients with maternally inherited diabetes and/or deafness and in patients with complete or incomplete MELAS syndrome (*m*itochondrial *e*ncephalopathy with *l*actic *a*cidosis and *s*troke-like episodes).

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