Alport's syndrome

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Creation Date: April 2001
Update: April 2003

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Abstract
*Alport's syndrome (AS) is a generalized inherited disorder of basement membranes, particularly those of glomeruli, that involves type IV collagen. The progression of the renal disease is more severe in male patients. Males present hematuria in early childhood, very often experience progressive sensorineural deafness while school-age, and usually develop end-stage renal disease in their early twenties, with or without ocular abnormalities. Females present a variable clinical course and only a few of them are severely affected, because AS has an X-linked inheritance. The mutation occurs in a gene located on the X chromosome: the normal allele on the other X chromosome in females partially compensates for the genetic disorder. The inherited defect of the classical X-linked AS affects the alpha5 chain of the type IV collagen gene (*COL4A5*), which has been mapped to chromosome Xq22, while inherited mutations in alpha3 and alpha4 chains of type IV collagen (*COL4A3 *and* COL4A4*), which map to chromosome 2, are responsible for the less frequent recessive form of AS. AS accounts for approximately 2.5% of male patients with end-stage renal failure in the USA, 1.1% of patients in India and 0.64% in Europe. Race, ethnicity or geography are probably not predictive factors of AS; establishing the true etiology of renal disease in patients with end-stage renal disease is hard and probably explains the above-mentioned frequencies.*

Keywords
renal disease, hematuria, ocular abnormalities, glomerular basement membrane defect, sensorineural deafness, X-linked inheritance Xq22 locus, COL4A5 gene

Disease name
Alport's syndrome (AS)
Familial hematuric nephritis with nerve deafness

History
In 1927, Cecil Alport was the first medical doctor to draw attention to familial persistent hematuria, associated with some degree of sensorineural deafness, and different severities of renal impairment in males and females. Nowadays, AS is defined by:
- a positive familial history of microhematuria with or without renal failure;
- sensorineural deafness;
- characteristic ocular abnormalities;

and typical electron microscopy-detected

- alterations of the glomerular basement membrane (GBM);

although all four features do not need to coexist to make the diagnosis.

Frequency

AS accounts for approximately 2.5% of male patients with end-stage renal failure in the USA,1.1% of patients in India, and 0.64% in Europe.

Clinical description

Family hematuria

In a German study, 10% of patients with hematuric glomerulonephritis were found to have relatives with renal disease, in their, and half of them were diagnosed as having classic forms of AS. However, it is well known that the absence of other affected subjects in a family does not exclude a genetic disease, since the patient may be the result of a *de novo* gene mutation.

Hematuria and proteinuria

All affected patients, both males and females, show persistent microhematuria and/or episodes of macroscopic hematuria even as of the childhood (males at an average of 3.5 years; females at 9 years). Episodes of gross hematuria are not common in adult patients, whereas they may accompany upper airway infections in children. No patient has proteinuria prior to the onset of microhematuria. The proteinuric range varies from only just detectable during the early stages of the nephropathy to an overt nephrotic syndrome. Almost all males (98%) and 67% of females have proteinuria to some degree. High or increasing values of proteinuria imply a poorer prognosis.

Hypertension

It has been reported that 75% of male and 35% of female patients present suffer from hypertension, very often in association with impaired in renal function.

Renal impairment

By an average age of 25 years, 94% of males and 3% of females present renal insufficiency with an elevated serum creatinine. In those patients with impaired renal function, the average age at which serum creatinine starts to rise is 18 years for males, and 31 years for females. The rapidity of progression to end-stage renal disease may show an interkindred variability; usually, the average time after detection of chronic renal impairment, is 2.2 years for males and 8.6 years for females. However, progression to end-stage renal failure occurs in 100% of males but only 15% of females.

Sensorineural hearing loss

Patients with AS usually present mild to moderately severe sensorineural hearing loss, and they must undergo an audiometric evaluation to detect their bilateral defect, because they rarely have true deafness.

Bilateral sensorineural deafness in a patient with persistent microhematuria is highly suggestive of AS, even in the absence of relevant family history. Usually, hearing loss appears in school-age boys; serial audiograms show progressive deterioration.

Adult patients retain some hearing capacity, although some of them require a hearing aid, and the impairment is more or less stable with time.

Sensorineural deafness results from structural lesions of the capillary basement membrane of the stria vascularis, that are similar to those found in the glomerular capillary basement membranes (thickening and lamellation due to the mutations in amino-acids chains of collagen IV). Hearing loss is usually for frequencies above 3000 Hz. This characteristic deafness is seen in 83% of males and 57% of females with an average deficit of 50-60 decibels.

Ophthalmic lesions

Eye defects occur more frequently in male patients and ophthalmic lesions may precede the appearance of deterioration in renal insufficiency.

Bilateral anterior lenticonus is the most specific lesion and spherophakia may merely be marked lenticonus. Posterior lenticonus is less common. The lenses are normal at birth and lenticonus develops during the teens. The mutation in type IV collagen components of the ocular lens explains the ultrastructural lesions and the fragility of the lens capsule.

Characteristic ocular abnormalities in AS are macular flecks, consisting of yellowish or whitish spots around the fovea, which give rise to "fundus albipunctatus". A structural thickening defect in Bruch's membrane could explain the pathogenesis of the retinal flecks (thickning of the basement membrane).

Lenticonus and macular flecks are described in 72% of males and 38% of females. However, the absence of these ocular features does not exclude the diagnosis of AS.

A few families with hereditary nephritis and ocular defects without sensorineural deafness have been reported, but this dissociation of manifestations is unusual.

Treatment

Clinical trials of treatment for AS do not exist. It is possible to hypothesize a beneficial effect of angiotensin-converting enzyme inhibition on renal function and on the progression to end-stage renal disease. Disease progression corresponds to fibrosis of the renal interstitium. Canine and murine models of AS might be useful to increase knowledge on the possibility of genetic therapy.

Both hemodialysis and peritoneal dialysis are used to treat patients with end-stage renal failure.
Kidney transplantation in AS patients is usually successful, but some authors have reported that about 10% of transplanted patients develop anti-GBM nephritis in the graft. It has been hypothesized that the defective α5 chain of type IV collagen may increase the risk of developing anti-GBM nephritis.

Etiology
In the past, some authors classified AS as a chronic tubulointerstitial renal disorder, because of the presence of tubular lesions of varying severity with chronic renal inflammatory cells, interstitial fibrosis, several foam cells in the renal interstitium and evident intimal thickening in small arteries.
As a matter of fact, AS is a mixed nephropathy with features of glomerular lesions evolving to glomerulosclerosis, combined with an evident tubulointerstitial reaction The typical abnormalities of the lamina densa of GBM described by electron microscopy studies suggested that the genetic mutation responsible for AS occurs in a structural component of type IV collagen of the basement membrane: a similar mutation may explain glomerular and extrarenal lesions involving collagen IV structures of the kidney, the inner ear and the eye.
Basement membrane type IV collagen in AS
Type IV collagen is the major structural component of some basement membranes, and it is responsible for the mechanical stability and integrity of the extracellular matrix. Six different amino acid of α chains type IV collagen whose components are assembled differently have been identified in a number of specialized basement membranes, including the GBM. Interactions among the various α chains appear to be specific and result in the formation of characteristic networks in basement membranes of different tissues. It has been documented that αl (IV) and α2 (IV) chains are present in all human basement membranes, whereas α3 (IV) and α4 (IV) chains are only present in specialized basement membranes of the kidney, inner ear, retina and lens capsule. Recently, α5 (IV) and α6 (IV) chains were identified, and found to be involved in basement membrane structures. On the basis of its derived amino acid sequence, α5 (IV) chain appears to be involved in the GBM structure, making it a candidate gene for AS. Thus, the contradiction has been solved: while AS clearly appeared to be X chromosome related, the previously known type IV collagen genes were autosomal. In fact, the genes encoding αl and α2 chains of type IV collagen are located on chromosome 13q34, those coding for α3 and α4 chains of type IV collagen genes are located on chromosome 2q35-37, while the genes for α5 and α6 chains of type IV collagen are located on chromosome Xq22.
AS Genetics
AS displays genetic heterogeneity. In most AS patients the mutation is X-linked, *i.e.*, it occurs in a gene located on the X chromosome. The pattern of AS inheritance is dominant because both males and females are affected; obviously, the progression of the disease is more severe in males.
Nowadays, different mutations in the α5 chain of type IV collagen have been documented in different kindreds. The different genetic mutations may be important and could probably explain the different clinical courses observed for different patients: juvenile form *versus* adult form of the disease. However, X-linked inheritance was documented in about 85-92% of kindreds. Some evidence suggesting an autosomal recessive form was first obtained by genetic studies; recently, mutations in the α3 and α4 chains of type IV collagen genes on chromosome 2 have been detected. These kindreds are characterized by affected siblings, both male and female, and healthy parents, often consanguineous.

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