Alport's syndrome

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Alport's syndrome is of interest to geneticists because it has probably been the subject of more hypotheses regarding its inheritance than any other disease. The two cardinal features of hereditary nephritis and perceptive deafness were first clearly recognised by Alport in a family he reported in 1927.¹ He acknowledged the help of A E Garrod and Alexander Fleming in the investigation of this family. His family had been the subject of several earlier incomplete reports,^{2–5} the latest of which had recognised the severe course of the disease in males with early death from renal failure, and the relatively benign course in females. The disorder attracted no further interest until Perkoff and Stephens studied an extensive Mormon family in the 1950s.^{6–8} These authors regarded the disease as an interstitial nephritis or pyelonephritis with proteinuria, haematuria, pyuria, and urinary casts. Many affected members of their family had a progressive perceptive high tone hearing loss that was either clinically significant or was detected on audiography.

Clinical features

There have now been over 200 families reported with Alport's syndrome, from which have emerged a clinical picture of a disease presenting with macroscopic or microscopic haematuria, with or without proteinuria or casts. Some, but not all, patients show a progressive perceptive hearing loss. Some families with a hereditary nephritis but without hearing loss probably suffer from the same disorder, which when associated with glomerular ultrastructural changes similar to those in true Alport's disease have been described as having an Alport-like syndrome. Although Perkoff and Stephens emphasised the proteinuria and pyuria in their patients, later studies have shown haematuria to be the more specific sign of affected family members.^{9–11}

Since microscopic haematuria may be intermittent, repeat testing may be necessary before expression of the disease can be excluded, especially in a female. Nevertheless there is failure of penetrance in females with some 12 to 13% of obligate female heterozygotes showing no haematuria or other signs of the disease.^{12 13}

In most families the haematuria and proteinuria progress relatively rapidly in males, with death from renal failure before the age of 30 years. In females progression is much slower so that renal failure only supervenes, if at all, in later life. There is a minority of atypical families in which males consistently survive beyond 30 years.¹³

In over 30 of the reported families at least some affected members show ocular lesions, involving either the lens or the macula. The lens abnormality is most characteristically anterior, or less often posterior, lenticonus which leads to a progressive visual deterioration.¹⁴ Other lens lesions include spherophakia, keratoconus, lens capsule rupture, and cataracts. The macular lesion is typically pigmentary, but occasionally whitish lesions have been observed. It is probably more common than reports suggest as not all patients receive a detailed ophthalmological examination.

Pathology and pathogenesis

Microscopically, the renal lesion appears to be a non-specific glomerulonephritis,¹⁵ chronic pyelonephritis,^{6 8} or interstitial nephritis.^{16 17} In addition, there are often excessive numbers of lipid foam cells that may even form macroscopic yellow streaks in the lower cortex^{15 17} (fig 1). Later workers looking at biopsy material rather than at necropsies have shown progressive glomerular changes and late development of interstitial nephritis.¹⁸ Kaufman *et al*¹⁹ found the earliest lesion to be focal thickening of the glomerular basement membrane. There is no evidence for any immune mechanism in the aetiology of these renal lesions.

FIG 1 Lipid filled foam cells (appearing black in this photograph) in the kidney of a patient with Alport's disease. (From Krickstein et al. *Arch Pathol* 1966;82:510-5. Fig 4. (Copyright 1966, American Medical Association, with the permission of Dr Krickstein and the American Medical Association.)

The suggestion of a glomerular basement membrane lesion from light microscopy has been confirmed by electron microscopy and by studies with antisera to glomerular basement antigens (anti-GBM antisera). Several groups have described focal thickening of the glomerular basement membrane on electron microscopy, with splitting of the lamina

densa leaving clear spaces containing electron dense particles²⁰⁻²⁹ (fig 2). These abnormalities may be interspersed with regions of normal or even thinning of the basement membrane, and were found in both renal biopsy and necropsy material from patients with true Alport's syndrome, and also some patients with Alport-like hereditary nephritis without deafness

FIG 2 Electron micrograph of renal biopsy of a three year old boy with Alport's syndrome showing thinning and splitting of the basement membrane. (Kindly supplied by Professor R A Risdon.)

Focal splitting may also be observed in benign familial haematuria, nephrotic syndrome, or glomerulonephritis, but never with the widespread lesions of Alport's or Alport-like syndrome.²⁶ Habib *et al*²⁹ emphasise the progressive nature of the glomerular lesions with young patients often showing only non-specific thickening or thinning of the membrane without splitting.

Anti-GBM antisera have been used in the analysis of urinary proteins or renal histological preparations. Lubec has used such sera, including anti-GBM antisera from patients with Goodpasture's syndrome, to demonstrate a protein giving an abnormal immunoprecipitation band in urine from Alport's syndrome patients, and has advocated this as a diagnostic test.³⁰⁻³¹ Several groups have undertaken immunofluorescent studies of renal tissue with Goodpasture anti-GBM antisera. Both polyclonal and monoclonal antisera show either complete failure to bind to renal tissue from Alport's syndrome patients, or reduced binding compared to the binding by normal kidney.²⁹⁻³²⁻³⁵ The degree of loss of Goodpasture antiserum binding correlates with disease severity.³⁴ Rabbit and guinea pig anti-GBM antisera do bind to Alport's syndrome renal tissue,²⁹ suggesting that a GBM antigen specifically recognised by Goodpasture antiserum is lost. This is confirmed by the observation that the antigen recognised by Goodpasture antisera is determined by the 'non-collagenous' globular domain of type IV collagen.³⁶⁻³⁹ Loss of this antigen is inherited in an X linked dominant manner³⁷ and is also associated with absence of serum amyloid P component.⁴⁰ Studies on the biochemical composition of glomerular basement membranes in Alport's syndrome provide indirect²⁹⁻⁴¹ and direct³⁸ evidence of a collagen defect.

Genetics

Alport,¹ in his paper of 1927, referred to the disease he described as being hereditary. More precise genetic analysis has been hampered by the greater severity in males, who consequently have few children. Nor did earlier studies recognise the undoubted genetic heterogeneity of the syndrome. These two factors resulted in some curious segregation ratios explained by successive authors by a variety of genetic hypotheses. The earliest of these was the suggestion of partial sex linkage by Perkoff and Stephens in their large Mormon family (family P). Graham⁴² postulated autosomal dominant inheritance with incomplete penetrance and sex influence with intrauterine death of half of all affected males. Shaw and Glover,⁴³ in a reanalysis of family P and a new large family of their own, supported

Graham's hypothesis with an additional proposition. This was of non-random disjunction leading to preferential segregation of the chromosome bearing the gene to the oocyte rather than the polar body in oogenesis, and with the X rather than the Y chromosome in spermatogenesis. They offered no evidence, or even suggestions, as to the possible mechanisms for such a remarkable phenomenon. Over a decade later, MacNeill and Shaw⁴⁴ included family P, along with 34 other published families, in a new analysis. This excluded partial sex linkage but supported autosomal dominant inheritance with increased penetrance of the gene in sons of affected mothers owing to an unfavourable intrauterine milieu (a theory also put forward by Preus and Fraser⁴⁵). MacNeill and Shaw⁴⁴ argued that their data supported the preferential segregation hypothesis earlier proposed by Shaw and Glover with the modification that the proportion of affected offspring of affected mothers was greater when the mother was symptomatic. Earlier, Arnott *et al*¹⁴ postulated another theory, that of a common X linked modifier gene, that has not been subsequently substantiated.

In 1973 Mayo⁴⁶ showed that the families used by MacNeill and Shaw were heterogeneous and should not be pooled. O'Neill and Atkin¹⁰⁻⁴⁷ proposed X linked dominant inheritance for family P with an advantage of the sperm bearing the X chromosome compared to the Y chromosome.

Menlove *et al*^{48-48a} have reported linkage of X linked dominant adult Alport's syndrome in three Utah families, including family P, to random DNA probes on the X chromosome long arm. The closest linkage observed was to *DXS3* at Xq21.3-q22. The maximum lod score between Alport's syndrome and *DXS3* was 8.27 at $\theta=0.170$.

Apart from family P, several other families have been strongly suggestive of dominant X linkage,¹¹⁻²⁴⁻⁴⁹⁻⁵⁰ as is the evidence discussed above for X linkage of the ultrastructural changes in glomerular basement membrane, and for the loss of Goodpasture GBM antigen. Nevertheless, there have also been about 40 families with clear father to son transmission, including the earliest reported such family, that of Poli,⁵¹ and several large subsequent families,⁴³⁻⁵²⁻⁵⁶ as well as many more smaller families.

Apart from autosomal and X linked dominant inheritance there is also some rather doubtful evidence for a possible rare autosomal recessive form of Alport's syndrome. In most families for which recessive inheritance has been suggested, the parents have not been adequately investigated, and the known occasional failure of penetrance in females makes it impossible to exclude maternal

transmission. However, there are at least five families in which only sibs appear to be affected and the parents are consanguineous.^{24 29 57}

Other factors suggestive of genetic heterogeneity include the occurrence of families with lenticular or macular defects already discussed, interfamilial differences in age at death of male patients,^{9 13 58} and Alport's syndrome with thrombocytopathia (Fechtner syndrome).⁵⁹ Hasstedt *et al*,⁶⁰ in a review of 23 Utah families, proposed a classification of Alport's syndrome with six categories: type I, juvenile cases, either X linked or autosomal dominant; type II, a definite X linked dominant juvenile form; type III, an X linked dominant adult form; type IV, pure hereditary nephritis without deafness; type V, autosomal dominant with thrombocytopathia; and type VI, a definite autosomal dominant juvenile form.

An alternative, extended, provisional classification of Alport's syndrome, excluding hereditary nephritis without deafness, which is itself very heterogeneous, and the unclassifiable families, is proposed in the monograph *The genetics of renal tract disorders*.¹³

- I Autosomal dominant juvenile.
- II X linked dominant juvenile.
- III Autosomal dominant adult.
- IV X linked dominant adult.
- V Autosomal dominant with lenticular lesions.
- VI X linked dominant with lenticular lesions (one family only⁶¹).
- VII Autosomal recessive (unconfirmed).
- VIII Autosomal dominant with macrothrombocytopathia.

Glomerular basement membrane splitting and failure to bind Goodpasture anti-GBM antisera is certainly seen in type II and possibly in some other types as well.

One unresolved question is that although the loss of the collagen type IV globular domain antigen in the basement membrane appears to be X linked, the type IV collagen structural genes are themselves autosomal. This would imply that the defect may lie in a gene for an enzyme that modifies collagen IV after its translation. There is clearly still a great deal of research to be undertaken in clarifying the distinct disorders comprising Alport's syndrome and in the elucidation of their molecular basis.

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