ALPORTS NEPHRITIS

(A Report of Two Cases)

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Introduction

Alport's Syndrome is a progressive hereditary hematuric nonimmune glomerulonephritis characterised ultrastructurally by irregular thickening, thinning and lamellation of the glomerular basement membrane (GBM). Recent data suggest a considerable overlap in the ultrastructure, immunohistochemistry and molecular genetics of Alport's syndrome with Thin Membrane Nephropathy presenting as Benign Familial Hematuria, leading some workers to suggest that both the conditions are part of the same spectrum. [1].

Two cases of Alport's nephritis are presented to discuss these dilemmas and highlight the present knowledge of this disease.

Case Reports

CASE 1

A 1 1/2yr old male child with no family history of hematuria, deafness or defective vision presented with nephrotic syndrome. The child initially developed a nephritic picture with anasarca, oliguria, hematuria and non nephrotic proteinuria which progressed gradually into nephrotic syndrome. Renal function tests on 3 separate occasions were otherwise within normal limits. A diagnostic renal biopsy revealed prominence of mesangial regions in the glomeruli. Ultrastructural examination revealed the GBM to be extremely thin in most areas (Fig 1). The average thickness of the GBM was assessed at approx 230 nm. The adjacent visceral epithelium of the glomerulus showed extensive foot process effacement and associated microvillous transformation. However, a few areas showed thickening and weaving of the GBM. No deposits were seen in the subepithelial, subendothelial or mesangial regions. A diagnosis of Alport's nephritis- thin membrane variant was made. The patient was lost to follow up.

CASE 2

A 13 yr old female presented with recurrent hematuria of 5 yrs duration, nephrotic proteinuria and bilateral sensorineural deafness. Of the other siblings tested, 1 male sibling had 4+ proteinuria. No complaints related to an eye disorder were recorded. A renal biopsy was carried out which also showed mesangial predominance in glomeruli. The interstitium showed collections of foam cells (Fig 2). Transmission electron microscopy showed prominent widening of the glomerular GBM and a characteristic

basket weaving of the lamina densa. In a few areas there was separation of lamina rara interna and externa and lucent expansion

Fig. 1 : Case 1 : Ultrathin section of glomerulus showing thinning of basement membrane (arrowhead) (58000 x, lead citrate and uranyl acetate)

Fig. 2 : Case 2 : Photomicrograph of kidney showing mesangial prominence and interstitial foam cells (150 x, H & E)

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Fig. 3 : Case 2 : Ultrathin section of glomerulus showing basket weaving of basement membrane (arrow head) & central granular translucency (29000 x, lead citrate and uranyl acetate)

of the lamina densa with granularity (Fig 3). In most areas the overlying visceral epithelial cells showed extensive foot process effacement and some mesangial cell proliferation and interposition into capillary loops. The extent of GBM involvement was widespread but not seen prominently in the tubular basement membrane or Bowman's capsule.

Discussion

Guthrie in 1902 first described a family of hematuria exaggerated by infection and diet. Alport in 1927 noted its association with deafness [2]. Yoshikawa in 1982 described Alport's nephritis with no family history of renal disease or deafness [3]. Thin Membrane Nephropathy or familial benign hematuria can often resemble the early stages of Alport's nephritis and is differentiated by the absence of extrarenal manifestations and progression to chronic renal failure. However, thin membrane nephropathy has been seen to predispose to premature glomerular obsolescence with increased incidence of hypertension and late onset renal insufficiency. Case 1 is likely to be one such example. Males and females are both affected but nearly all males eventually progress to end stage renal disease by 40 yrs of age. The essential pathological features are progressive ultrastructural lesions of the GBM and absence of immune phenomena. The glomeruli are normal or may show increase in mesangial matrix and increase in cellularity. Localised thickening of the GBM and segmental sclerosis may be seen. The interstitium characteristically shows foam cells mainly in the cortex singly or in clusters.

Yoshikawa found foam cells only in patients greater than 10 years, as seen in Case 2. The ultrastructural changes are characteristic. The GBM is split into multiple interweaving lamellae enclosing electron lucent areas containing electron dense granules 500A in diameter and varying from scattered loops to widespread involvement. Similar changes may be seen in the TBM and the Bowman's capsule rarely. Splitting has been related to the degree of proteinuria and has also been described in patients with no family history of either renal or hearing disease [3]. It is however homogenous within a family of Alport's syndrome.

Thinning of GBM in Alport's nephritis has also been described, usually alternating with lamellated appearance. However Habib has described 5 cases in his series of Alport's syndrome with pure thinning of the GBM [5]. The differential diagnosis in this situation is with Thin Membrane nephropathy (Benign familial hematuria) which may occur in about 23% of patients with hematuria. The GBM shows extensive to severe thinning with an average cutoff width of about 264nm. Case 1 is likely to be one such thin membrane variant where nonrenal abnormalities and family history maybe absent, as brought out by other studies as well (6). Additional changes noted have been crenation of lamina densa and proliferation of mesangial cells with peripheral interposition as seen in Case 2. Foot process effacement over the lamellar lesions and microvillous transformation of visceral epithelial cytoplasm requires differentiation from minimal change disease, when presentation is with nephrotic syndrome.

The pathogenesis of the nephropathy in Alport's is related to a primary abnormality in basement membrane collagen network composed of alpha 3,4 and 5 chains of type IV collagen. Patients with Alport's have been found to lack the so called Goodpasture's antigen, which is a monomeric peptide residing in the noncollagenous domain (Nc-1) of type IV collagen [7]. Recent data suggest a complex rearrangement of major constituents of the glomerular basement membrane network with early deposition of fibrillar collagen proteins (8). Type IV collagen mutations have especially been seen in both autosomal recessive and x-linked Alport's syndrome and autosomal dominant thin membrane nephropathy. The spectrum of mutations accounts for the clinical heterogeneity of hereditary nephritis and especially Alport's syndrome [9].

In conclusion, the available data suggest that Alport's syndrome and thin membrane nephropathy in all likelihood are part of the same spectrum of the disease. The two cases presented, ultrastructurally, substantiate this overlap and serve as an indicator of

the complexity of the disease. The relation of these conditions to the worse prognosis highlights the need for a high index of suspicion in all childhood hematurias.

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