Glomerular basement membrane thinning is a common ultrastructural feature of minimal change disease.

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Introduction

Thinning of the glomerular basement membrane (GBM) is typical of familial renal diseases such as Alport’s Syndrome and benign familial haematuria. (Savij et al 2003) Thin GBM is also found sporadically in immune complex-mediated diseases such as IgA nephropathy, possibly as a part of the nephritic process or as a coincidental finding. (Berthoux et al 1996; Cosio et al 1994) Thin GBM is not usually recognised in descriptions of minimal change disease (MCD) or, when it is, it may be regarded as artefactual. (Savij et al 2003) Our subjective experience of MCD suggested that GBM thinning is common, a finding that is increasingly supported by others. (Marquez et al 1999; Danielewicz & Wagrovska 1998) Our initial aim was to determine whether the GBM was thinned in MCD and then, if our hypothesis was confirmed, to apply a simple technique to measure the GBM width in subsequent diagnostic cases.

Case Study

To test whether the GBM is thinned in MCD we previously measured the mean GBM width in 8 cases of uncomplicated MCD with no history of familial disease. (Coleman & Stirling 1991) For each case we measured the width of ~50 random 3 μm lengths of GBM in each of 3 glomeruli to give a total of 150 measurements as previously described. (Coleman et al 1986) Mean GBM thickness was calculated for each micrograph, each glomerulus and each case overall. One-way analysis of variance was used to give a total of 150 measurements as previously described. (Coleman et al 1986)

Discussion

Our results indicate most cases of MCD have GBM thinning, accordingly we now routinely measure GBM width in MCD cases using a simplified procedure as detailed below. We speculate that the lesion may involve changes in the amount and distribution of the alpha-3, -4 and -5 collagen IV subtypes that form the bulk of the GBM. Thus, the GBM thickness changes are probably acquired on the basis of visceral epithelial cell dysfunction involving regulation of collagen IV production within the basement membrane layer. (Berthoux et al 1996; Akazawa et al 2005) Our results show that tissues from MCD cases are regularly used as ‘normal’ controls in both quantitative and qualitative studies, including the measurement of GBM. (Basta-Jovanovich et al 1990; Akazawa et al 2005) Our current strategy for measuring GBM thickness is to take a series of 5 × 6 random electron micrographs with a final magnification of x6000. Using Scion image analysis software (version 4.0.3.2) we generate an overall mean GBM width and thickness profile from approximately 75-100 GBM width measurements. To date, the majority of MCD cases examined using this technique have consistently shown GBM thinning (Figures 1, 2 & 3). Such findings indicate that GBM abnormalities are a real and common pathological feature of MCD, not a random or artefactual finding.

Method

GBM thickness, normal range (Coleman et al 1986): single glomerulus 349-439 nm; three pooled glomeruli 356-432 nm

Results

Glomeruli with significant GBM thinning were present in 7 of the 8 cases. Significant inter-glomerular GBM variability was found in 3 cases and significant intra-glomerular GBM variability was found in 2 cases (Table 1).

Table 1. Analysis of GBM variability in MCD

<table>
<thead>
<tr>
<th>Case</th>
<th>GBM means</th>
<th>Single glomeruli</th>
<th>Interglomerular variability</th>
<th>Mean of pooled GBM</th>
<th>Intraglomerular variability</th>
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Female aged 41, nephrotic syndrome, normal creatinine, normotensive. Direct immunofluorescence for IgA, IgG, IgD, Clq, kappa, lambda, fibrinogen and albumin showed no significant reactions. Electron microscopy showed foot process effacement, generally uniform but moderately thinned GBM with no textural abnormalities (Figures 2 & 3). There was no other glomerular abnormality.

Diagnosis: minimal change disease.

Figure 1 Case study: low power image to show general glomerular features

The GBM shows moderate thinning with no textural abnormalities, the mesangium is unremarkable. Foot processes are extensively effaced.

Figure 2 Case study: electron micrograph showing a typical area of thin GBM

The GBM shows moderate thinning with no textural abnormalities. The membrane is ~167 nm thick at the point indicated (arrow). Foot processes are effaced.

Figure 3 Case study: GBM thickness profile compared to normal control GBM

GBM mean thickness was calculated at 274 nm (SD 97, n=95). The maximum GBM thickness was 628 nm; the minimum thickness was 139 nm

Acknowledgement

We thank Mr Richard Davey for technical assistance.

References


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Figure 2 Case study: electron micrograph showing a typical area of thin GBM

Figure 3 Case study: GBM thickness profile compared to normal control GBM