Thin Glomerular Basement Membrane Disease
: Light microscopic and electron microscopic studies

Benign recurrent hematuria usually indicates a good prognosis. This condition is associated with abnormally thin glomerular basement membranes. Of 680 renal biopsy cases in which lower urinary tract disease had been excluded by careful study, 25 cases from seven children and eighteen adults met the criteria for thin glomerular basement membrane disease, placing the incidence of the disease at 3.7%. The mean patient age was 32.4 years and the male to female ratio was 1 to 5.3. The primary finding was microscopic hematuria in eighteen patients and gross hematuria in five patients. Among eighteen patients who had microscopic hematuria, one patient also exhibited proteinuria and one patient suffered from acute renal failure due to acute drug-induced interstitial nephritis. Proteinuria was only found in one patient. All of the patients had normal renal function, with the exception of one who suffered from acute renal failure. The duration of hematuria from the time of detection to the date of biopsy ranged from 3 months to 30 years with a mean interval of 56.6 months. No apparent evidence of familial hematuria in any patient was noted. Under light microscopy most glomeruli were normal. However, five cases showed focal global sclerosis. Under immunofluorescence microscopy seventeen cases were negative for all immunoglobulins, for complement, and for fibrinogen. Eight cases showed nonspecific mesangial deposition of fibrinogen and/or IgM. Ultrastructurally, extensive diffuse thinning of the GBM was a constant finding. The mean thickness of the GBM was 203.2±28.3 nm (n=25) ; the thickness in adult (201.4 ±27.5 nm ; n=18) did not differ from that in children (208.1±32.0 nm ; n=7). *(JKMS 1997 ; 12 : 234~9)*

Key Words : *Benign recurrent hematuria, Thin glomerular basement membrane disease*

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INTRODUCTION

In 1966 McConville et al.(1) reported a benign form of familial hematuria, which is a heredofamilial disorder characterized by glomerular hematuria. It differs from Alport's syndrome in that affected individuals do not develop renal insufficiency and a family history of uremia is absent (2). Subsequent reports have confirmed the existence of a non-progressive nephropathy with hematuria (3,4). The renal histology in this condition was thought to be indistinguishable from other forms of isolated recurrent hematuria until Rogers et al.(3), using transmission electron microscopy, described marked generalized attenuation of the glomerular basement membrane (GBM) in these patients.

It is widely known that localized attenuation of the GBM can be identified in a variety of renal diseases, such as IgA nephropathy (5). However, diffuse thinning of the GBM appears to be confined to benign recurrent hematuria although it can be seen in the early stages of Alport's syndrome (6). The incidence of diffuse thin GBM disease is considered to be rare and published reports are scarce (4, 7).

Although thin GBM disease is benign for ultimate prognosis, the need for caution in predicting a prognosis is reinforced by one description of 12 patients with thin basement membrane nephropathy, three of whom had progressive renal disease, with end-stage renal failure in one (7). Careful follow-up of such patients and their relatives is required to determine whether thin GBM disease can be considered a benign disorder. Thin GBM disease can be viewed as a pathologic entity with multiple clinical expressions, including familial and sporadic forms, with either a benign or progressive course (2).

Twenty five cases of thin GBM disease were examined from among 680 patients whose renal biopsy specimens were analyzed by electron microscopy over a three year

period. The purpose of this study was to focus on the observed clinicopathological characteristics of the disease and to emphasize that the incidence of this condition is not rare.

MATERIALS AND METHODS

Thin GBM disease was defined as follows : 1. insignificant glomerular abnormalities which are apparently normal or show only minor changes by light microscopy (8); 2. diffuse thinning of the GBM to <280nm; 3. deposits of immunoglobulins and complement components that are not detectable by immunofluorescence and electron microscopy; 4. exclusion of Alport's syndrome which may accompany renal disease (9). Of the renal biopsy specimens examined by light, immunofluorescence, and electron microscopy at the Department of Pathology, Chungnam National University Hospital, between Oct. 1993 and Sept. 1996, twenty five cases satisfied the above criteria.

The portions of renal tissue submitted for light microscopy were serially sectioned and alternate sections were stained with hematoxylin and eosin, periodic acid-schiff, trichrome, and PA-silver stains. A portion of each specimen was quick frozen for subsequent direct immunofluorescent staining. For examination with transmission electron microscopy, tissue was fixed in 2.5% glutaraldehyde, postfixed in 1% osmium tetroxide, then embedded in epoxy resin. Ultrathin sections were stained with uranyl acetate and lead citrate, then examined on a Hitachi-600 transmission electron microscope. Electron photomicrographs of all cases were examined and only cases exhibiting diffuse thinning of the GBM were selected. The thickness of the GBM was measured only in the peripheral portions of the capillaries where the epithelial and endothelial cytoplasmic membranes were clearly visible. The distance between the epithelial and endothelial cytoplasmic membranes was considered as the thickness of the GBM. More than 20 measurements per case were made on a minimum of five peripheral glomerular capillary loops from photographic prints at 8,000x magnification. The GBM width was measured in 12 cases of minimal change nephrotic syndrome as a control group. GBM widths of the control group were 294 to 401 nm with a mean value of 335 nm (334.9±32.9 nm; n=12).

RESULTS

Of 680 renal biopsy cases in which lower urinary tract disease had been excluded by careful study, 25 cases met the criteria for thin GBM disease, placing the incidence of the disease at 3.7%. Relative details about the patients are summarized in Tables 1 and 2.

Twenty five cases of thin GBM disease from seven children and eighteen adults are presented separately to allow comparison between the two groups. The mean patient age was 32.4 years and the male to female ratio was 1 to 5.3. The primary finding was microscopic hematuria in eighteen patients and gross hematuria in five patients. Among eighteen patients who had microscopic hematuria, one patient also exhibited proteinuria and one patient suffered from acute renal failure due to acute drug-induced interstitial nephritis. Proteinuria was the only finding in one patient. All the patients had normal renal function with the exception of one who suffered from acute renal failure. The duration of hematuria from the time of detection to the date of biopsy could be identified in 17 patients. It ranged from 3 months to 30 years with a mean interval of 56.6 months. No apparent evidence of familial hematuria in any patient was noted.

Table 1. Clinicopathologic findings of thin GBM disease in children.

Case No.	Age/Sex	Chief complaint	Onset	IF	LM	GBM thickness(nm) (Mean±S.D.)
1	6/F	gross hematuria	?	−	NSA	236.6±14.9
2	10/M	gross hematuria	3 yr	−	NSA	234.2±22.7
3	14/F	micro. hematuria	4 mo	−	NSA	175.0±19.8
4	14/F	micro. hematuria	?	IgM± fib. ±	NSA	178.1±24.9
5	14/M	proteinuria	?	−	NSA	236.2±22.1
6	15/F	micro. hematuria	?	−	global sclerosis (4.3%)	169.1±11.8
7	15/F	gross hematuria	5 yr	fib. ±	NSA	226.6±18.2

* IF: Immunofluorescence study, LM: Light microscopic finding, NSA: No specific abnormalities, fib.: fibrinogen, micro.: microscopic

Table 2. Clinicopathologic findings of thin GBM disease in adults

Case No.	Age/Sex	Chief complaints	Onset	IF	LM	GBM thickness(nm) (Mean±S.D.)	Others
1.	23/M	micro. hematuria	3 mo	−	NSA	154.9±25.2	
2.	28/F	micro. hematuria	1 yr	−	NSA	185.3±27.3	focal mes. deposits
3.	32/F	micro. hematuria	1 yr	−	NSA	185.9±21.5	
4.	34/F	micro. hematuria	5 mo	−	NSA	219.8±31.3	
5.	35/F	micro. hematuria	1 yr	IgM± fib. ±	NSA	234.7±30.9	
6.	36/F	micro. hematuria	4 yr	−	NSA	190.5±39.2	
7.	37/F	gross hematuria	?	−	NSA	184.1±34.7	
8.	38/F	hypertension	?	−	NSA	226.2±21.0	mild arteriolar thickening
9.	39/F	micro. hematuria	?	−	global sclerosis(14.3%)	195.8±29.7	focal mesangial sclerosis
10.	41/F	micro. hematuria	4 yr	fib. ±	global sclerosis(5.0%)	152.4±14.1	
11.	43/F	micro. hematuria	4 yr	−	global sclerosis(8.7%)	189.8±18.4	
12.	45/F	gross hematuria	1 yr	IgM±	NSA	221.4±14.4	
13.	51/F	micro. hematuria	2 yr	−	NSA	227.3±21.9	
14.	51/F	micro. hematuria ARF	?	−	acute interstitial nephritis	221.3±32.1	
15.	55/F	micro. hematuria	20 yr	IgM± fib. ±	NSA	226.2±46.5	
16.	59/F	micro. hematuria proteinuria	3 yr	fib. ±	NSA	185.1±36.3	
17.	60/F	micro. hematuria	30 yr	−	global sclerosis(23.8%)	176.8±34.4	
18.	64/M	micro. hematuria	3 mo	−	NSA	248.0±17.0	

* ARF : Acute renal failure, mes. : mesangial

Under light microscopy most glomeruli were normal (Fig. 1), except for five cases which showed focal global sclerosis. Under immunofluorescence microscopy seventeen cases were negative for all immunoglobulins, for complement, and for fibrinogen. Eight cases showed nonspecific mesangial deposition of fibrinogen and/or IgM. Ultrastructurally, extensive diffuse thinning of the GBM ranging from 129 to 277 nm was a constant finding (Fig. 2). The mean thickness of the GBM was 203.2±28.3 nm (n=25). The thickness in adults (201.4 ±27.5 nm ; n=18) did not differ from that in children (208.0±32.0 nm ; n=7). There was little variation in the GBM thickness of capillaries within the same glomerulus, or between different glomeruli. The lamina densa was uniformly thin and had a relatively smooth contour. The lamina rara interna and externa were also thin, but occasionally irregular with a scalloped surface. Disruption of the GBM was not found. However, the presence of rare paramesangial electron dense deposits was found in one case. The overlying epithelial foot processes were relatively well preserved, but focally effaced. One case showed focal mesangial sclerosis.

DISCUSSION

The glomerular and tubular basement membranes are the principal barriers to filtration and reabsorption of water and other molecules in the nephron. These membranes are composed primarily of type IV collagen, laminin, fibronectin, sulphated proteoglycans, and collagen type I. Three common inherited diseases are associated with abnormalities of basement membrane proteins : Alport's syndrome, thin GBM disease, and adult polycystic kidney disease (10).

Thin GBM nephropathy, also called benign recurrent hematuria, is defined ultrastructurally by diffuse thinning of the GBM. Localized areas of GBM attenuation are frequently found in a variety of renal diseases including Alport's type of progressive hereditary nephritis. However, widespread attenuation appears to be confined to this disease. In contrast to Alport's syndrome, antibodies to the NC1 domain of collagen IV react with the GBM of patients with thin GBM disease, a finding that could be helpful in the differentiation of these conditions (11~13).

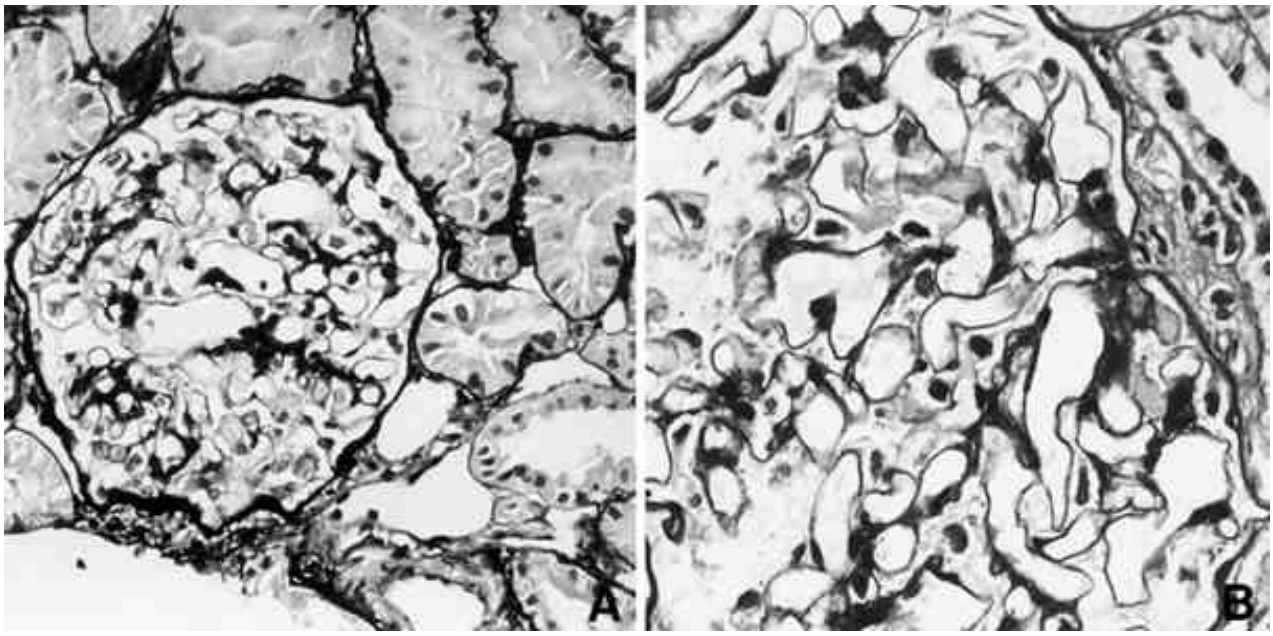

Fig. 1(A, B). Light microscopy of thin GBM disease showing no specific abnormalities (PA-silver ×200, PA-silver ×400).

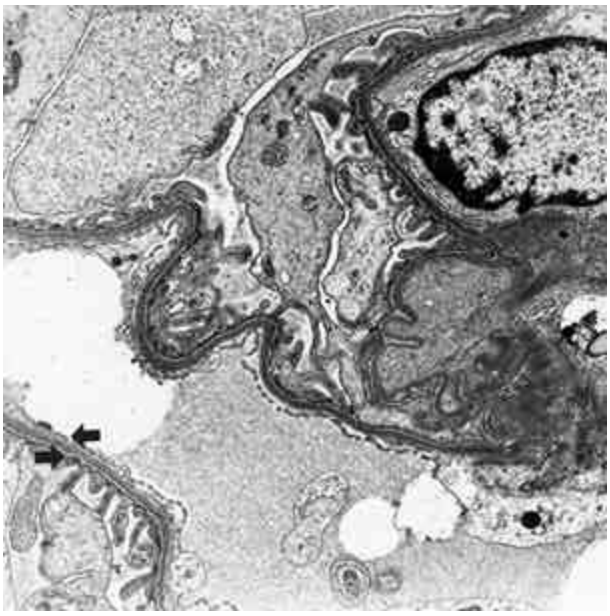

Fig. 2. Electron photomicrograph showing markedly attenuated GBM (arrrows). The overlying epithelial foot processes are relatively well preserved, but focally effaced (uranyl acetate and lead citrate, ×8000).

This disease is characterized clinically by a nonprogressive, frequently familial nephropathy with hematuria as the only sign of disease. Nonfamilial cases of thin GBM disease have been reported but prior studies have often lacked a rigorous testing of family members (14). Thinning of the GBM is a common finding in patients with isolated hematuria who lack any evidence of familial involvement (15). No apparent evidence of familial hematuria in any patient was noted in this study.

The cause of hematuria in this disease remains obscure. Rogers et al.(3) reported marked thinning of the GBM and disrupted peripheral capillary loops on electron microscopy in a patient with benign familial hematuria. In this study disruption of the GBM was not found. Yoshikawa et al.(16) suggested that a thin GBM is responsible for the escape of erythrocytes into Bowman's space, resulting in hematuria.

The incidence of the disease was reported to be rare among adults and more common in children (7). In the series of Trachtman et al. (17), 17 of 76 children (22%) with isolated hematuria who underwent renal biopsy exhibited GBM attenuation. Only five of these 17 children had a family member with hematuria. Based on several studies, it can be expected that approximately twenty percent of children presenting asymptomatic, isolated hematuria will prove to have thin GBM disease (17~19).

The number of reported cases of benign recurrent hematuria is small in Korea (20~21), however, it may be more prevalent than hitherto suspected (7). In addition, this condition is comparatively common in adults according to several reports (9, 22). Coleman et al.(23) observed that GBM lesions were the principal morphologic abnormalities in a comparatively large number of cases (approaching 10 percent). However, Abe et

al.(9) reported that the incidence of the disease in adults is 0.8%. To study the clinicopathologic characteristics of the disease strict criteria were applied in this study to exclude borderline cases. Cases in which GBM attenuation was the major finding were selected, although the degree of thinning was highly variable between cases. In this study the disease incidence was 3.7%.

Tiebosch et al.(22) observed that estimates of the thickness of the GBM that are based on measurements of only one glomerulus can indicate the presence of thin GBM nephropathy when thicknesses of less than 264nm are found. When a GBM thickness value of 264nm is used as a cutoff, the positive predictive value of the persistence of symptoms is 100 percent. However, in this study cases of less than 280nm thickness were included.

There is considerable disagreement regarding the natural history of renal disease associated with thin GBM. According to Goel el al.(24) there is no difference in GBM thickness between the sexes (male 258nm vs. female 251nm), but there is a significant negative correlation between age and GBM thickness, with older patients having the thinnest membranes. The disease was divided into two groups: a thin BM(270nm<GBM <320nm) group and an ultrathin group (<270nm). The ultrathin group (54%) showed a higher incidence of hematuria than the thin group (12%). Proteinuria occured more frequently in the thin group (65% vs. 8%) than in the ultrathin group. It was suggested that patients with ultrathin GBM had a greater loss of GBM anionic charge, which might result in both an alteration of flow characteristics within the glomerular capillaries and also increased fragility of the GBM with a likelihood of rupture and resultant macroscopic hematuria.

Other types of glomerular disease can be associated with thin GBM disease. Two unusual cases of IgA and IgM anti-GBM disease associated with diffuse thinning of the GBM were reported (25). Matsumae et al. (26) reported that segmental and diffuse thin GBM was seen in diabetics. The clinical and morphological characteristics of diabetics with and without thin-GBM were significantly different for DM duration (5.3±5.5 vs 9.8 ±6.5yrs), Ccr (67.0±25.5ml/ min vs 45.6±24.4ml/ min), the incidence of hematuria (52.9% vs 24.5%), and hypertension (13.3% vs 51.3%). The severity of microscopic hematuria correlated with the spread of the thin-GBM was also reported. Tina et al. (27) found the presence of rare paramesangial electron dense deposits in one case of idiopathic recurrent hematuria. Rare paramesangial electron dense deposits were also found in one case of this study. Acute drug-induced interstitial nephritis was present in another case. In this study two cases which exhibited proteinuria, microscopic hematuria, and exhibited focal segmental glomerulosclerosis were excluded although the GBM was diffusely thinned to 215 nm~244 nm.

The pathogenesis of diffuse attenuation of the GBM is unknown. The high frequency of familial disease suggests that it develops on the basis of an inheritable anomaly. However, the apparent onset of disease in adult life in many instances, and the existence of sporadic cases indicate that the abnormality is acquired, at least in some cases. Disruption of the membrane synthesis mechanism or catabolism may be the cause (19). The mean thickness of the GBM in cases of minimal change nephrotic syndrome increased with age (28). The GBM of children under 2 years of age is usually thin, regardless of underlying conditions, due to incomplete maturation of the GBM. The possibility that widespread thinning of the GBM may be the result of incomplete maturation of the GBM has been suggested (16).

The incidence of thin GBM disease is not rare in Korea. A more thorough examination of its frequency requires morphometric study of a consecutive, non-selected biopsy series, ideally compared with a larger group of age- and sex-matched control subjects (22). Thorough examination of family members regarding renal symptoms is necessary in order to clarify a possible genetic correlation in thin GBM disease. In addition, discrimination of this disease from nephropathies which cause idiopathic recurrent hematuria is essential in management of patients. Careful follow-up examinations for proteinuria, hypertension, or a decrease in GFR are warranted and any new finding should prompt re-evaluation of the patient and the need for a renal biopsy.

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