Clinical and morphological aspects of thin glomerular basement membrane disease

Jakub Żurawski[1], Wiesława Salwa-Żurawska[1], Aldona Woźniak[1], Elżbieta Bortkiewicz[2], Janusz Maciejewski[2], Ilona Idasiak-Piechocka[3], Bartosz Urbański[1]

[1]Chair and Department of Clinical Pathomorphology, Karol Marcinkowski Medical University in Poznań
[2]Department of Paediatric Cardiology and Nephrology, Karol Marcinkowski Medical University in Poznań
[3]Chair and Department of Nephrology, Transplantology and Internal Medicine, Karol Marcinkowski Medical University in Poznań

The report presents the results of investigations carried out in 63 patients (49 children and 14 adults) with thin glomerular basement membrane disease. Of 49 children, 13 came from nine families with family members suffering from kidney diseases (mostly manifested by haematuria).
In the group of children, the most frequent initial clinical symptom (noted in 29 cases) was isolated haematuria, more rarely (in eight cases) haematuria and proteinuria, and (in seven cases) nephrotic syndrome. Isolated proteinuria was observed in another three children.
In the adults, only in five patients was isolated haematuria the initial symptom of the disease; more frequently (in seven cases), they presented with isolated proteinuria. In two patients, proteinuria and haematuria were noted.
In the two groups of patients, in addition to markers of thin glomerular basement membrane disease, the authors also observed markers indicative of other glomerulopathies: in seven children and four adults focal segmental glomerulosclerosis (FSGS) without any other glomerular pathologies (with the exception of thin glomerular basement membrane disease). Also in cases in which in addition to thin glomerular basement membrane disease other glomerular pathologies were present (mesangial hypercellularity, mesangial glomerulonephritis), matrix expansion was detected; this phenomenon might be considered a harbinger of glomerular sclerosis. In general, although not in each and every case, these pathologies were associated with duration of the disease.

Introduction

Thin glomerular basement membrane (TGBM) syndrome is also referred to as benign familial haematuria.

Initially, the disease was believed to be an inherited, familial condition characterized by haematuria, which does not lead to renal failure; in addition, family history lacks any information on uraemia prevalence in the family of the patient [1]. It appears, however, that thin glomerular basement membranes are also noted in individuals who have no kidney diseases in their family medical history. Thin membranes have been detected in patients who – in addition to haematuria – present with other symptoms, and some of these individuals develop renal failure [2]. For this reason, the description of the syndrome has been markedly extended. At present, it is believed to constitute a disease entity characterized by a variable clinical presentation, either familial or sporadic, most frequently having a benign course,

but at times its course may be progressive [3–5]. The syndrome is considered the most common congenital kidney disease. It is observed in more than 1%, but less than 10%, of the general population [6]. The presence of thin glomerular basement membranes is also characteristic in Alport syndrome, especially in the early stage of the disease. A differential diagnosis to discriminate between the two disease entities continues to be the subject of an extensive discussion in the literature. In Alport syndrome, in addition to characteristic clinical signs and renal failure, which develops as a rule, the most significant findings focus on morphological features that differ from those observed in thin glomerular basement membrane disease.

Characteristic observations in thin glomerular basement membrane disease include absence of light-microscopically observed changes, with the exception of erythrocytes present in the tubules. Sometimes, immature glomeruli may be seen. In the later stage of the disease, one may also observe enlargement of the mesangial regions, glomerular sclerosis and interstitial lesions accompanied by tubular atrophy [1].

In the initial stage of Alport syndrome, the glomeruli may be unchanged in light microscopy. Situated side-by-side mature and immature glomeruli are detected more often as compared to thin glomerular basement membrane disease. With time, even in light microscopy one may detect segmental capillary loop thickening. Glomerular sclerosis appears earlier and more frequently. The presence of interstitial foam cells is a characteristic, although not specific, property. Focal fibrosis is also observed [1].

Immunofluorescence microscopy fails to provide any significant contributions in diagnostic management of thin glomerular basement membrane disease. At times, small IgG, IgM, IgA and C3 deposits are found within the loop.

A firm diagnosis of TGBM disease and Alport syndrome is established based on ultrastructural examinations.

In thin glomerular basement membrane disease, the only change is basement membrane thinning. It does not necessarily have to involve all the loops, but is seen in the majority of capillary loops. Thicker membrane segments are mostly situated in the paramesangial regions, and only infrequently are detected in the peripheral parts of the loops. At times, the membrane continuity is interrupted. The membranes generally have a smooth contour on both the endothelial and epithelial side [1]. In the majority of the loops, the membranes achieve at maximum 50% of the normal thickness. Their thickness is most frequently estimated as 100-250 nm [3, 7]. Other authors are of the opinion that thin glomerular basement membrane disease may be diagnosed when the membrane thickness does not exceed 200 nm [8]. The most significant observation is thinning of the lamina densa [1, 9].

The glomerular membranes are thinner in children than in adults, and also thinner in adult females than in males. Various authors propose different values for normal membrane thickness, but the most commonly accepted view holds that in children below three years of age, the basement membrane is up to 200 nm thick, in adult females 326 ±45 nm, and in males 373 ±42 nm [7, 10]. Fogo [3] defines basement membrane thickness in children in relation to their age. It is estimated that in one-year old children, the membrane is 110 nm thick, while in a 7-year old child, the relevant value is 222 ±14 nm.

Contrary to thin glomerular basement membrane disease, patients with Alport syndrome demonstrate thin membranes, but also normal-thickness and thickened membranes. The most significant finding, however, is membrane delamination noted in various – especially thickened – membrane segments [1, 3].

In the search for methods aiming at differentiating between the two syndromes, studies on basal membrane composition are also taken into consideration. To date, attention has been focused on type IV collagen evaluation. It has been observed that characteristic findings in Alport syndrome include changes in collagen chains 3, 4 and 5 (COL4A3, COL4A4, COL4A5) [11]. However, some patients with thin glomerular basement membrane disease also manifest changes involving these chains [12–15]. It has been demonstrated, nevertheless, that in TGBM, the changes more frequently involve collagen α3 and 4 chains (COL4A3, COL4A4), while in Alport syndrome they more often involve the α5 chain (COL4A5) [16].

Discussions on these differences are ongoing.

In patients with thin glomerular basement membrane disease, other types of glomerular and interstitial lesions are frequently noted [17]. In a group of 487 adult patients, Mandache and Gherghiceanu [8] observed frequent concomitant occurrence of glomerulonephritis and thin glomerular basement membrane disease. The authors believe that thin basement membranes predispose the patients to accumulate deposits of immunocomplexes. The opinion is shared by Forster *et al.* [14]. The latter authors also take into consideration the possibility of glomerulonephritis being not causally related to the presence of thin basement membranes, but rather constituting a consequence of incidental interposition

of inflammatory lesions on the damaged membranes.

Material and methods

The analysis included the results obtained in 63 patients with thin glomerular basement membrane disease, the majority of them (49) being children. A slight preponderance of girls (27) over boys (22) was observed. The age range of the paediatric patients was 1.5 to 17 years. The two youngest girls were 1.5 years old, while the oldest was 16 years of age. Of 27 girls, 12 were in the age group of 10 or more years and 15 were less than 10 years old. The youngest boy was 3 years old, and the three oldest male patients were 17 years of age. One-half of the boys (11) were above 10 years of age. The youngest group included five children: two girls aged 1.5 years, two girls aged 2 years and a 3-year old boy.

Thirteen children came from nine families with a history of kidney diseases, predominantly accompanied with haematuria. No renal failure was noted in these families. The group included seven girls and six boys. Twelve children of this group presented with isolated haematuria and one with haematuria and proteinuria.

Isolated haematuria was the initial symptom in the majority of children (29). Further symptoms, in descending order, included haematuria and proteinuria (n = 8) and nephrotic syndrome (n = 7). Nephrotic syndrome was the initial symptom in the two youngest girls. In three children, isolated proteinuria was the initial sign of the disease. In another child, the onset of the disease was signalled by acute renal failure, while another girl presented with signs suggestive of lupus erythematosus. The suggestion was not confirmed in further follow-up. Presently, on follow-up, the girl continues to be hypertensive.

In the paediatric group of patients, biopsy examinations were performed after 2 months to 13 years following the onset of symptoms.

Basic data on this group of patients are presented in Table I.

Females also predominated in the adult group consisting of 14 individuals (F : M = 9 : 5). The age range of females was 24 to 55 years, while for males it was 19 to 53 years. In the majority of cases (seven patients), the presenting symptom was proteinuria. Isolated haematuria was noted in five patients, and haematuria and proteinuria in two individuals. None of the patients reported familial kidney diseases during medical history taking. Their medical histories spanned several months to 30 years prior to biopsy.

Basic data on adult patients are illustrated in Table II.

Renal punch biopsy specimens were divided into three parts and subjected to examinations employing light microscopy, immunofluorescence and electron microscopy. Immunofluorescence tests were performed at the Department of Immunology, Chair of Clinical Pathomorphology (now the Chair of Clinical Immunology). Materials for all types of examinations were routinely processed. Histological sections were stained with haematoxylin and eosin and with Masson's trichrome and impregnated with silver salts according to the method developed by Jones. Immunofluorescence tests included reactions with antibodies against IgG, IgM, IgA, C3 and C1q.

The diagnosis of thin glomerular basement membrane disease was established based on electron microscopy. Membrane thickness, and especially the thickness of the lamina densa, was assessed by comparison with membrane thickness from the controls. The control group included kidney punch biopsy specimens originating from patients diagnosed with submicroscopic glomerulonephritis, mesangial hypercellularity and mesangial glomerulonephritis, in which no thin glomerular basement membrane disease was detected. When selecting the groups, the authors took into consideration (especially in the case

Table I. Basic data characterizing the group of children

SYMPTOMS	NUMBER OF PATIENTS	GENDER ♀	GENDER ♂	AGE ♀	AGE ♂	FAMILIAL OCCURRENCE
Haematuria	29	17	12	2-15	4-17	in 12 children (from 8 families)
Haematuria and proteinuria	8	4	4	4-16	4-17	in 1 child
Proteinuria	3	–	3	–	4-16	–
Nephrotic syndrome	7	4	3	1.5-5	6-17	–
Other (acute renal failure, hypertension, suspected LED)	2	2	–	6 and 8	–	–
Total	**49**					

Table II. Basic data characterizing the group of adult patients

Symptoms	Number of patients	Gender ♀	Gender ♂	Age ♀	Age ♂	Familial occurrence
Haematuria	5	3	2	32-54	19 and 53	–
Haematuria and proteinuria	2	1	1	30	47	–
Proteinuria	7	5	2	24-55	41 and 49	–
Total	**14**					

of the youngest children) the patient's age. Ten matching cases were selected for each control group; in the case of children, two control groups were formed (below and above 4 years of age), while one control group was established for the adult patients. The lamina densa thickness was assessed through measurements performed in electronograms and taken at three points of each capillary loop. The result of each measurement was divided by the magnitude of image enlargement. The resultant value in millimetres was converted to a result expressed in nanometres.

In the controls, the membrane thickness in children was 220-300 nm, and in adults above 350 nm.

The diagnosis of thin glomerular basement membrane disease was established when thinning was observed in at least 70% of the examined capillary loops, with the number of loops being not lower than 30, and the membrane thickness did not exceeded 110 nm in children up to 3 years of age, 150 nm in children above 7 years of age and 200 nm in adult patients.

Results

In the group of 49 children, as many as 29 patients demonstrated evidence of other glomerular pathologies. Seven children had mesangial hypercellularity, accompanied with matrix expansion, detected by electron microscopy in two patients. In another three children, electron microscopy demonstrated matrix expansion without an increase in the number of mesangial cells. Nine children were diagnosed as having mesangial glomeru-lonephritis, confirmed by immunofluorescence, which showed the presence of IgG, IgM, C3 and trace amounts of IgA. The composition of deposits was variable in particular cases. Of nine patients, two children additionally demonstrated mesangial matrix expansion, which was not proportional to the number of cells, but did not clearly predominate over the cellular component. In another seven cases, the diagnosis was an early stage of focal segmental glome-rulosclerosis (FSGS), and in three, submicroscopic glomerulonephritis.

Table III. Morphological changes in children (excluding markers of thin glomerular basement membrane disease) versus clinical symptoms

Symptoms	Hypercellularitas mesangialis	Hypercellularitas mesangialis + ↑ matrix mesangialis	↑ Matrix mesangialis	Glomerulonephritis mesangialis	Glomerulonephritis mesangialis + ↑ matrix mesangialis	FSGS incip.	Glomerulonephritis mesangialis
Haematuria (18/29)	4	2	2	3	2	5	-
Haematuria and proteinuria (3/8)	-	-	-	3	-	-	-
Proteinuria (2/3)	1	-	1	-	-	-	-
Nephrotic syndrome (6/7)	-	-	-	1	-	2	3

+↑ – matrix expansion
FSGS – focal segmental glomerulosclerosis

The compilation of morphological changes and clinical signs is presented in Table III.

The intensity of such changes as cell proliferation or mesangial matrix expansion was associated with duration of the disease in some cases only. An example of such an association may be seen in re-biopsy results of two boys. One of them was re-biopsied twice. The original biopsy, performed when the boy was 12 years old, revealed in addition to thin basement membranes also markers of mesangial glomerulonephritis. Four years later, the ultrastructural examination of material obtained by a re-biopsy additionally showed mesangial matrix expansion. Another re-biopsy done two years later (i.e. six years after the original biopsy) demonstrated markers of FSGS already visible under light microscopy.

In the other boy, the original biopsy was performed when the patient was 10 years old. Thin basement membranes were observed, as well as mesangial hypercellularity. A re-biopsy performed six years later showed FSGS.

In the group of 14 adult patients, apart from thin glomerular basement membranes, in 12 individuals other glomerular pathologies were detected, namely: mesangial hypercellularity in one patient and mesangial glomerulonephritis in seven individuals; in four of these seven adults, mesangial matrix expansion was additionally detected in some mesangial regions.

Another four patients were diagnosed with early stage FSGS without any markers indicating glomerulonephritis.

Table IV presents the compilation of morphological changes and clinical symptoms.

Detailed morphometric and statistical studies will constitute the subject of a separate report.

Discussion

In the two investigated groups – both in children and in adult patients – isolated haematuria, considered the most characteristic symptom of thin glomerular basement membrane disease, was not the only initial symptom at the onset of the disease. In the group of paediatric patients, isolated haematuria constituted the most common sign. This group also manifested – albeit much less frequently – proteinuria and haematuria, nephrotic syndrome and isolated proteinuria. In adults, the most common initial symptom was isolated proteinuria, followed in descending order by haematuria and haematuria with proteinuria. In this group, no markers of nephrotic syndrome were noted. In keeping with the commonly accepted principles [6], we concentrated meticulous attention on patients whose initial symptom of the disease was not haematuria. In all these cases, we examined extensive material and noted the presence of thin membranes in all the capillary loops. This allowed for establishing the diagnosis of thin glomerular basement membrane disease and for formulating a conclusion that the initial symptoms of the syndrome do not necessarily need to be limited to isolated haematuria. Similar conclusions are increasingly more often reached by other authors [5, 6, 18, 19].

In addition to the basic change, we relatively frequently detected in both the investigated groups markers of other glomerular pathologies – mesangial hypercellularity, mesangial glomerulonephritis, mesangial matrix expansion, glomerular sclerosis (also without signs of glomerulonephritis) and submicroscopic glomerulonephritis. Particular changes were detected in patients with various types of initial symptoms.

Table IV. Morphological changes in adults (excluding markers of thin glomerular basement membrane disease) versus clinical symptoms

Symptoms	Hypercellularitas mesangialis	Hypercellularitas mesangialis + ↑ matrix mesangialis	↑ Matrix mesangialis	Glomerulonephritis mesangialis	Glomerulonephritis mesangialis + ↑ matrix mesangialis	FSGS incip.	Glomerulonephritis mesangialis
Haematuria (4/5)	1	-	-	1	1	1	-
Haematuria and proteinuria (2/2)	-	-	-	1	1	-	-
Proteinuria (6/7)	-	-	-	1	2	3	-

+↑ – matrix expansion
FSGS – focal segmental glomerulosclerosis

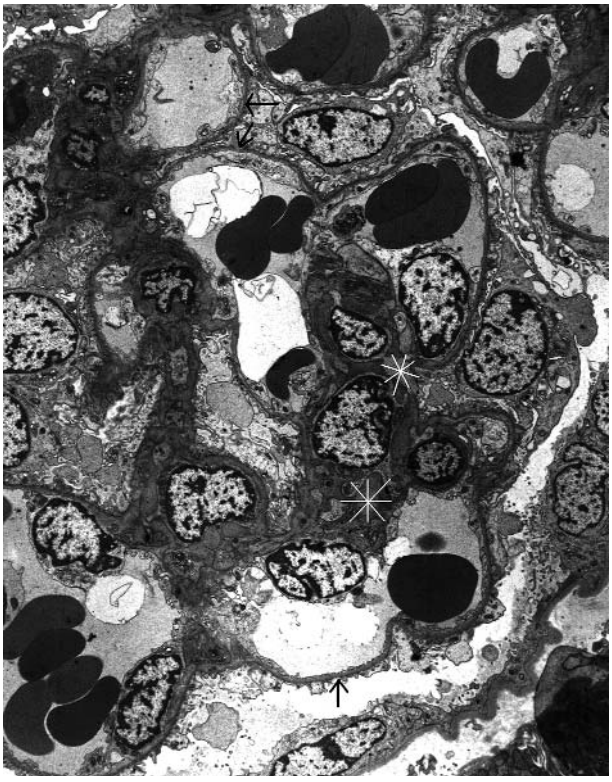

Fig. 1. Thinning of glomerular basement membranes (arrows). Mesangial regions (asterisks) merge (an increase in the number of cells – 6), magnification 4400 ×

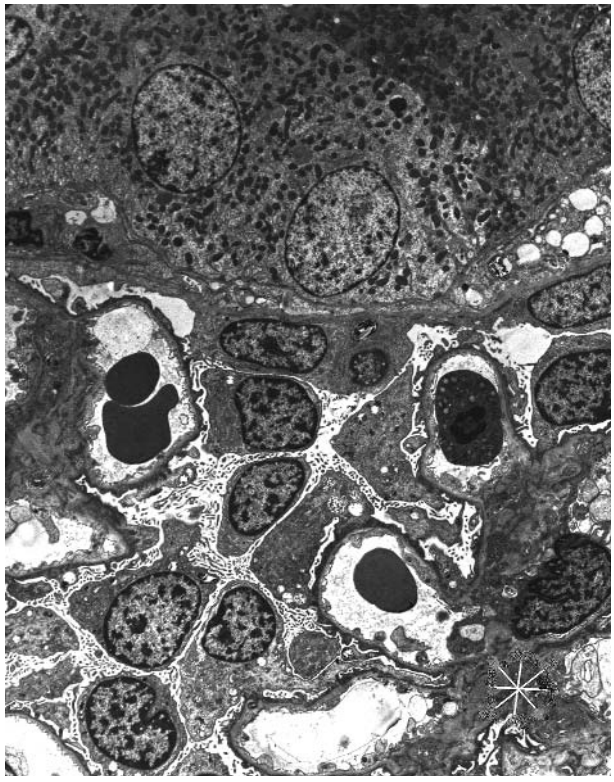

Fig. 2. An increased number of cells (5) in a mesangial region (asterisks), magnification 11 000 ×

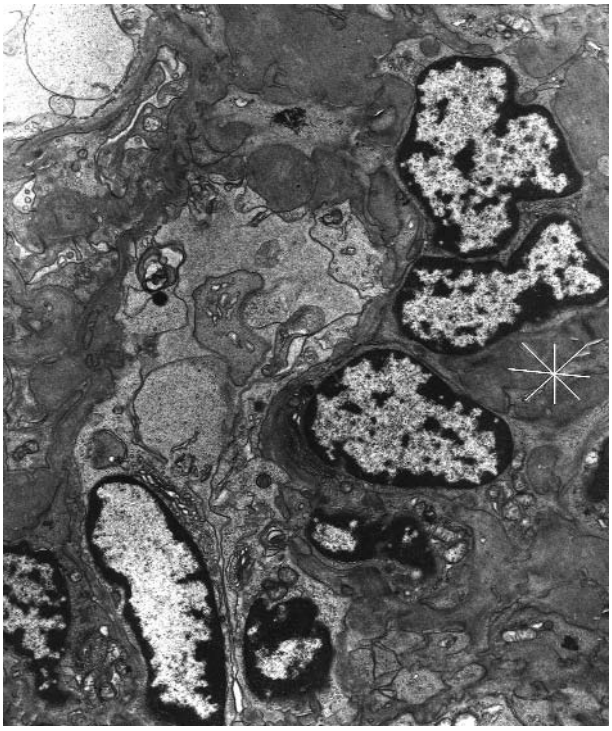

Fig. 3. A small mesangial region with marked matrix expansion (asterisks), magnification 1500 ×

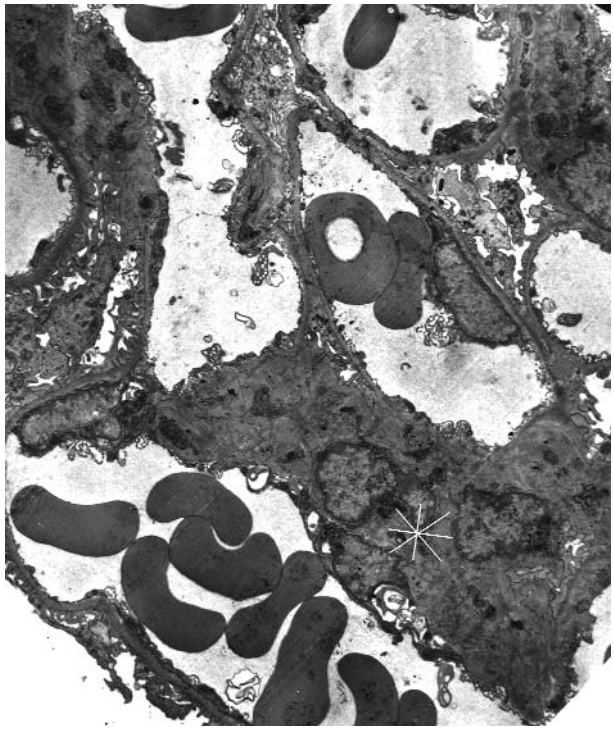

Fig. 4. A mesangial region with clearly visible matrix expansion (asterisks), magnification 5600 ×

We paid particular attention to mesangial matrix expansion and focal segmental glomerulosclerosis (FSGS) not accompanied by the presence of markers pointing to other glomerulopathies (apart from basement membrane thinning).

In the group of children with isolated haematuria, in five cases we detected early stage FSGS and in two cases mesangial matrix expansion in some mesangial regions. A similarly early stage of FSGS was observed in two children with isolated proteinuria.

In the adult group, markers of FSGS (without inflammatory lesions involving the glomeruli) were noted in four patients – one with isolated haematuria and three with isolated proteinuria.

The above data indicate that in patients with this syndrome, mesangial matrix expansion and FSGS are not always associated with proteinuria, as has been suggested by some authors [5]. The data may, however, support the notion that basement membrane thinning alone leads in time to an unfavourable event, which is glomerular sclerosis.

Mesangial matrix expansion that did not predominate over the cellular component accompanied markers of mesangial glomerulonephritis in two children with isolated haematuria and in four adults – one with isolated haematuria, one with haematuria and proteinuria and two with isolated proteinuria. A relatively frequent occurrence of these pathologies in the limited in number group of adult patients may be related to a longer disease course. One might also give some thought to the question to what degree concomitant mesangial glomerulonephritis and thin glomerular basement membranes favour development of glomerular sclerosis.

The results of repeated biopsies performed in two boys require a comment. The re-biopsies demonstrated intensification (albeit slow) of changes leading to sclerotization. It cannot be ruled out that the course of the disease might have been affected by mesangial glomerulonephritis diagnosed in one of the boys and mesangial hypercellularity observed in the other child.

Establishing a diagnosis of thin glomerular basement membrane disease in keeping with the presently adopted criteria (described in the section on investigative methods) seems to be easy. It should be emphasized that it is necessary to examine a sufficiently high number of glomerular capillary loops (at least close to twenty) and to assess the lamina densa thickness.

The literature on the subject is a forum for discussion on the age and gender-appropriate basement membrane thickness. We have summed up these controversies in the Introduction. There

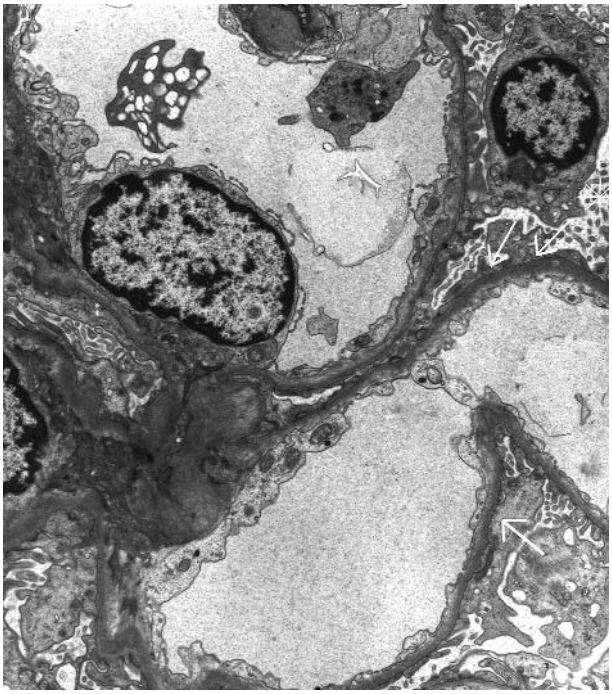

Fig. 5. A glomerular fragment. Uniform thinning of basement membranes and markers of proteinuria – loss of podocytes (arrows) and microvillous transformation of podocyte surfaces (asterisks), magnification 3500 ×

are no strict recommendations as to determining the degree of membrane thinning in order to diagnose thin glomerular basement membrane disease [14]. Generally, it is accepted that the diagnosis can be made when membrane thickness does not exceed 200 nm [8]. In keeping with the suggestions of Fogo and Kashagarian [3], we differentiated our assessment of membrane thinning in relation to the patient's age.

In the controls, the membrane thickness was clearly larger. The observed differences between the study and control groups were comparable to the results obtained by Klimek *et al.* [20].

The glomerular basement membranes are believed to reach their ultimate thickness at the age of 3 years. The group of our patients included five children below 5 years of age – two 1.5-year old girls, two 2-year old girls and a 3-year old boy. In the 2-year old girls and the 3-year old boy, the initial symptom at the onset of the disease was isolated haematuria. One of these girls, in addition to thin glomerular basement membranes, demonstrated markers of mesangial glomerulonephritis, while the other girl and the boy presented solely with thin basement membranes. In the two 1.5-year old girls, biopsies performed during the first episode of nephrotic syndrome showed lesions characteristic of submicroscopic glomerulo-

nephritis. The diagnosis of thin glomerular basement membrane disease in these two girls and in the 2-year old girl with mesangial glomerulonephritis may give way to doubt in view of the possibility of the patients suffering from early-phase Alport syndrome. To date, further longitudinal follow-up has failed to demonstrate disease progression; thus we may assume that in those cases we are indeed dealing with thin glomerular basement membrane disease. In such diagnostic considerations, however, the presence of thin basement membranes cannot be disregarded, since their thickness did not reach 110 nm.

In all the five children aged 1.5, 2 and 3 years of age, basement membrane thickness was clearly lower than in the controls, amounting in the majority of loops to 100 nm.

The above-presented results allow us to draw the following conclusions:

1) describing the above-presented syndrome as benign familial haematuria is incorrect, since familial incidence is observed in a percentage of cases only, and the initial symptoms are not always limited to haematuria;
2) irrespectively of initial symptoms at the onset of the disease, which may be variable, one may expect the changes to progress, including the stage of glomerular sclerosis;
3) thin glomerular basement membrane disease often appears concomitantly with markers of glomerulonephritis;
4) thin glomerular basement membranes are sometimes detected only in adult patients.

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Address for correspondence

Jakub Żurawski PhD
Chair and Department of Clinical Pathomorphology
Karol Marcinkowski Medical University in Poznań
ul. Przybyszewskiego 49
60-355 Poznań
phone/fax: +48 61 853 05 71