SEMINARS IN
NEPHROLOGY

The Clinical Features of Thin Basement Membrane Nephropathy

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Thin basement membrane nephropathy (TBMN) is a common, lifelong condition affecting the kidneys that is characterized by microscopic glomerular hematuria, minimal or no proteinuria, and normal renal function. It often is discovered incidentally, and usually has an excellent prognosis. Many cases are familial and show autosomal-dominant inheritance. The defining characteristic is a glomerular basement membrane (GBM) that is thinned to about half its normal thickness on ultrastructural examination of the renal biopsy specimen. However, occasionally patients with TBMN develop marked proteinuria or renal impairment. It is unclear whether individuals with TBMN and impaired renal function represent part of the spectrum of TBMN associated with heterozygous *COL4A3* or *COL4A4* mutations, or if their disease is caused by mutations of other genes, or whether it is caused by a second coexistent renal lesion or is misdiagnosed Alport syndrome.
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Many terms have been used to describe Thin basement membrane nephropathy (TBMN). Each focuses on subtly different aspects, and some define slightly different groups of patients, but overall they refer to the same condition. Reyersbach and Butler[1] in 1954 described *congenital hereditary hematuria*, and Russell and Smith[2] in 1959 described *hereditary hematuria*, whereas Rome et al[3] called it *familial hematuric nephritis*. The first substantial study of what now is regarded as familial TBMN was the description of *familial benign hematuria* by McConville and McAdams,[4] who also described sporadic cases. The same term, or the variant *benign familial hematuria*, has been used widely since then.[5-19] Others have written of *familial benign essential hematuria*,[20,21] *benign essential (familial) hematuria*,[22] or *benign hereditary nephritis*,[23] clearly referring to the same entity. The terms *benign hemorrhagic nephritis*[24] and *benign primary hematuria*[25] make no reference to heredity although several cases in the latter report were familial. *Familial hematuria*[26] also has been used to refer to the same condition but this term includes Alport syndrome and thus lacks specificity.

The names thin membrane nephropathy,[27-29] *thin basement membrane disease*,[11,15,30-38] *thin glomerular basement membrane (GBM) nephropathy*,[39] and *thin basement membrane syndrome*[40] increasingly are used widely. *Thin basement membrane nephropathy*[41-63] is preferred here because it clearly refers to a renal condition and is based on observable ultrastructural changes. Some clinicians still prefer descriptive terms such as *familial hematuria* if there is no biopsy specimen and the family is too small to infer a benign prognosis. A caveat about the use of *TBMN* is that the GBM also is thinned in early Alport syndrome[64,65] and even in advanced Alport syndrome of the type prevalent in French Polynesia.[66]

Prevalence and Epidemiology

Indirect evidence suggests TBMN is common; large systematic population-based studies of the prevalence of TBMN are needed. Various biopsy studies of TBMN as the cause of hematuria are summarized in Table 1. Overall, TBMN is appreciably more common than immunoglobulin (Ig)A nephropathy, and is the commonest cause of isolated microscopic hematuria on renal biopsy examination. However, the selection criteria have varied in these studies and biopsy examinations have been performed more frequently in patients with microscopic hematuria and additional features that gave rise to concern. This is apparent in those series that found Alport syndrome disproportionately often. Any such bias underestimates the true frequency of TBMN. The series by Gauthier et al[41] often is cited as evidence for the high prevalence of TBMN. However, as those researchers pointed out, none of their cases had basement membrane thinning as the sole abnormality, and some may have had Alport syndrome.

Microhematuria on a single sample (or 2 samples close in

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Table 1 Prevalence of TBMN, IgA Nephropathy, and Alport Syndrome in Series of Patients Presenting With Hematuria

Study	Selection Method	Age Range	Total Number	TBMN	IgA	Alport Syndrome
Piel et al,[80] 1982	Unexplained hematuria	Children	57	65%	0%	35%
Yum and Bergstein,[105] 1983	Asymptomatic hematuria	3–47 y	19	37%	0%	21%
Trachtman et al,[81] 1984	Isolated microscopic hematuria	3–19 y	76	22%	11%	12%
Blumenthal et al,[7] 1988	Isolated microscopic hematuria	5–65 y	56	54%	23%	23%
Perry et al,[28] 1989	Glomerular hematuria	16–73 y	92	28%	21%	1%
Tiebosch et al,[62] 1989	Microscopic or macroscopic hematuria	16–65 y	80	23%	34%	0%
Tiebosch et al,[62] 1989	Isolated microscopic hematuria	16–65 y	54	31%	?	0%
Schröder et al,[19] 1990	Isolated, persistent microscopic hematuria	Children	65	51%	25%	12%
Tanaka et al,[106] 1996	Isolated microscopic hematuria	Adults	40	10%	40%	0%
Piqueras et al,[46] 1998	Glomerular hematuria (biopsy examination delayed if slight or no proteinuria)	Children	322	16%	24%	27%
Auwardt, et al,[63] 1999	Renal biopsy examinations of patients with IgA nephropathy or TBMN	5–68 y	102	70%	30%	NA
van Paassen et al,[58] 2004	Hematuria	Adults	210	34%	9%	0%
van Paassen et al,[58] 2004	Hematuria and subnephrotic proteinuria	Adults	244	5%	31%	0%

NOTE. N = number of patients in each series. ? = not stated; NA = not applicable.

time) has been found in 2.5% of English men,[67] 4.6% of Australian adults,[68] and 13% of US men and postmenopausal women.[69] The prevalence of persistent hematuria is not well known in adults, but occurs in 1% to 2% of children,[70,71] furthermore, most hematuria in children is glomerular.[72] If the prevalence of hematuria exceeds 1%, and TBMN is the most frequent cause, then the prevalence of TBMN causing hematuria must approximate 1% of the population. The higher frequency of thin GBMs in transplant donors (6.6%), who presumably are representative of the general population, implies that microhematuria does not occur in most individuals with thinned GBMs. If this is so, it adds another layer of complexity to the definition of TBMN and estimates of its prevalence.

Many series have shown TBMN occurs more commonly in females, both in children and adults,[4,5,8,12,18,20,28,29,40,46,58,63,73] but other investigators have not confirmed this.[7,20,39,54,58,62] In total, 388 of 615 (63%) of all the cases cited in these series were female. Whether this is a true biological difference or merely the result of a selection bias is not clear. Only 1 of these series routinely used genetic testing and some females reported elsewhere may have been undiagnosed carriers of X-linked Alport syndrome whereas the males with Alport syndrome were more likely to have been identified. A possible biological basis for the greater prevalence in females could be the tendency for GBM to be thinner in females than in males in both pathologic[74,75] and normal[76,77] kidneys. In contrast to these findings, a recent systematic study[78] could not confirm this gender difference.

Clinical Features

Persistent microscopic hematuria is the characteristic clinical feature of TBMN.[4,5,8,18,20,25,28,29,39,40,62,79-81] Hematuria has been documented for up to 30 years,[28] and from as young as age 1[4,8] to as old as age 86.[20] Exceptionally, hematuria may disappear with time.[73] Dysmorphic urinary erythrocytes are found readily,[28,29] and red cell casts,[28] including string casts, may occur. Episodes of macroscopic hematuria occur at some stage in 5% to 22% of patients.[8,18,28,29,39,46,47,62,79,81] Trachtman et al[81] found episodes of macroscopic hematuria to be less frequent in children with TBMN (12%) than in Alport syndrome (33%) or IgA nephropathy (88%). Piqueras et al[46] confirmed this finding.

Flank pain has been reported in 7% to 31% of adults with TBMN[28,29,47,73] and 7 cases have been reported with *loin pain-hematuria* syndrome.[82] A surprisingly high incidence of hypercalciuria or hyperuricosuria (39%) was found in one series of TBMN.[47] Nephrolithiasis was common in these patients and a family history of nephrolithiasis was noted in 51%. However, this observation has not been confirmed. Hypertension has been reported in 11% to 31% of adults,[12,39,58,63,73,79] but uncommonly in children.[54] Others simply have noted that blood pressure was normal.[7,40] In the absence of a uniform definition of hypertension or of contemporaneous controls, it is difficult to interpret these reports.

Proteinuria rarely is seen in children, but modest proteinuria (up to 1 g/d) has been found repeatedly in a substantial minority of patients (Table 2). The occasional patient reported to have *nephrotic range* proteinuria may have had focal segmental glomerulosclerosis or superimposed minimal change nephritis.[83] The frequency of proteinuria summarized in Table 2 may be skewed because several series excluded patients with greater than 1 g/d of proteinuria.

In an intriguing study, Thomas et al[84] examined glomerular permselectivity to polydisperse neutral dextrans. Despite

Table 2 Prevalence of Proteinuria in Series of Patients With TBMN

Study	Preponderant Age Group	Proteinuria
McConville and McAdams,[4] 1966	Children	Proteinuria only during episodes of gross hematuria
Schröder et al,[19] 1990	Children	No proteinuria (0%)
Piqueras et al,[46] 1998	Children	0/50 patients (0%)
Roth et al,[54] 2001	Children	≥ 1 + (33%)
Rogers et al,[20] 1973	Adults	No proteinuria (0%)
Dische et al,[79] 1985	Adults	6 had about 1 g/d proteinuria; 2 others had 2.5 and 9 g/d (8/14, 57%)
Abe et al,[40] 1987	Adults	± to ++ proteinuria (5/8, 63%)
Aarons et al,[29] 1987	Adults	.2–.5 g/d (45%)
Blumenthal et al,[7] 1988	Adults	Mean, .39 (range, .2–3.6) g/d
Perry et al,[28] 1989	Adults	Proteinuria, .92, 1, 1.4 g/d (3/26, 12%)
Tiebosch et al,[62] 1989	Adults	Proteinuria, .5–3.0 g/d (6/18, 33%)
Goel et al,[73] 1995	Adults	28% had proteinuria >.2 g/d
Nieuwhof et al,[39] 1997	Adults	32% > .25 g/d
Auwardt et al,[63] 1999	Adults	>1 g/24 h in 11% >.2 g/24 h in 42%
Badenas et al,[12] 2002	Adults	≥1 g/d in 6%
van Paassen et al,[58] 2004	Adults	5% nephrotic range, 15% 1–5 g/d

normal hemodynamics and minimal proteinuria, patients with TBMN had increased fractional clearance of neutral dextran with Stokes radius greater than 42 A. This increased fractional clearance of neutral dextrans predicts nephrotic range proteinuria but the discrepancy between predicted heavy proteinuria and observed minimal proteinuria remains unexplained.

Renal function is described uniformly as normal in children with TBMN,[19,54] whereas a small proportion of adults have some degree of renal insufficiency (see later, Table 3).

There are occasional reports of hearing loss in TBMN.[29] Until more experience is obtained with defined mutations it will remain unclear whether this is a feature of some forms of TBMN, an incidental finding, or unrecognized Alport syndrome, because hearing loss is a feature of X-linked Alport syndrome and the heterozygous *COL4A3* or *COL4A4* mutations that cause autosomal-dominant Alport syndrome.[85]

Complications of TBMN

Acute renal failure has been described in 1 patient with TBMN who was receiving warfarin; his biopsy examination showed widespread occlusion of tubules with erythrocytes and casts.[86] Coleman et al[87] described another patient with pulmonary hemorrhage and hematuria, mimicking Goodpasture's syndrome but without anti-GBM antibodies.

Differential Diagnosis

Acquired TBMN

Thin GBM has been described in minimal change nephrotic syndrome[42,58,83,88-90] and Coleman and Stirling[83] suggested that this thinning is acquired as a consequence of impaired production of the α3 to 4-5(IV) collagen network by podocytes. The GBM also is thinned moderately in some patients

Table 3 Prevalence of Renal Impairment in Series of Patients With TBMN

Study	Year	N	Age Group	Renal Function
Yoshikawa et al[8]	1988	50	Children	No renal failure (0%)
Schröder et al[19]	1990	33	Children	Normal (0%)
Roth et al[54]	2001	9	Children	Normal (0%)
Rogers et al[20]	1973	8	Adults	Normal (SCr 1.4 at age 86) (0%)
Dische et al[79]	1985	14	Adults	SCr 1.5, 1.6, and 3.6 mg/dL in 3 cases; ESRD in 1 (29%)
Abe et al[40]	1987	8	Adults	Normal (0%)
Blumenthal et al[7]	1988	30	Adults	Normal (0%)
Perry et al[28]	1989	26	Adults	SCr 1.6 mg/dL in 1 case (4%)
Goel et al[73]	1995	43	Adults	Normal (0%)
Nieuwhof et al[39]	1997	19	Adults	SCr > 1.6 mg/dL in 1 case (5%)
Auwardt et al[63]	1999	71	Adults	SCr >1.2 mg/dL in 7%
van Paassen et al[58]	2004	92	Adults	SCr >1.35 mg/dL in 4%

SCr, serum creatinine level; ESRD, end-stage renal disease.

with rheumatoid arthritis who have hematuria or proteinuria, which has led to the suggestion that gold sodium thiomalate treatment causes GBM thinning[91]

Alport Syndrome

Many cases of autosomal-recessive Alport syndrome are homozygotes or compound heterozygotes for the same *COL4A3* and *COL4A4* mutations that in the heterozygote state cause familial TBMN.[26,34] One difficulty that can arise in these families with autosomal-recessive disease is that the heterozygotes (who will have TBMN) do not necessarily have hematuria. Their detection is important for pointing to the mode of inheritance. The converse difficulty is recognizing occasional homozygotes or compound heterozygotes in a family with TBMN. If TBMN affects 1% of the population, there is an appreciable chance that an unrecognized carrier may marry into the family and from time to time a child with autosomal-recessive Alport syndrome will result.[15,34,48]

X-linked Alport syndrome is also an important diagnostic consideration. The risk for misdiagnosing or overlooking Alport syndrome is greatest if the family is small or comprises only female carriers or the adult men develop disease late or have atypical clinical features. Families with the onset of renal failure in adulthood typically are large[66,92,93] and family members often are unaware of their diagnosis. Skin or renal biopsy examination in at least 1 or 2 members of the kindred, with appropriate immunofluorescent and ultrastructural examination for type IV collagen chains or, alternatively, specific mutation analysis, usually will indicate the correct diagnosis.

Other Causes of Benign Familial Hematuria

When benign familial hematuria is defined by the occurrence of hematuria in several family members in whom none has developed renal failure or had a renal biopsy examination, there are several possible causes. Most cases are caused by TBMN, but others could have familial IgA nephropathy, rare inherited glomerulopathies, or even nonglomerular disease that has a familial basis, for example, hypercalciuria or hyperoxaluria. In some cases, patients with these conditions will have a less benign course than originally anticipated.

Natural History

Does TBMN Cause Renal Failure?

Our understanding that TBMN does not affect kidney function is inconsistent with several reports of an association with renal insufficiency.[28,39,58,63,79] Thus, TBMN occasionally progresses to renal failure, possibly through the development of segmental glomerulosclerosis[58] or possibly because it is caused by mutations in genes other than *COL4A3* or *COL4A4*, including *NPHS2*.[94] Other explanations are that the patient actually has unrecognized autosomal-recessive or X-linked Alport syndrome, or coincidental renal disease that worsens kidney function. Regardless of the explanation, it is wise to temper explanations to patients or parents with the caveat that there are exceptions to the generally excellent outlook for TBMN.

Does TBMN Predispose to Other Nephropathies?

A surprising number of case reports and small series describe TBMN in association with many other glomerulopathies,[95] especially IgA nephropathy.[49,96-102] Linossier et al[101] found abnormalities in the galactosylation of serum IgA1 in IgA nephropathy with normal-thickness GBM but no abnormality with a thinned GBM. Other nephropathies that have been associated, in decreasing frequency, with TBMN are as follows: minimal change disease,[42,58,88-90] membranous nephropathy,[103] mesangial proliferative nephropathy,[90,97] focal segmental glomerulosclerosis,[58,89] and anti-GBM nephritis.[104] In addition, TBMN has been described with the loin-pain hematuria syndrome.[82] Nonrenal conditions found associated with TBMN in individual cases or small series include aortitis,[43] Crohn's disease,[102] and rheumatoid arthritis.[91] These associations may be coincidental.

Hill et al[16] clearly showed that GBM lesions mimicking Alport syndrome or TBMN occur focally in a wide variety of nephropathies. These GBM alterations are presumably a consequence of membrane damage and attempted repair and should not be equated with the widespread uniform abnormalities seen in the hereditary basement membrane nephropathies.

Conclusions

TBMN is the commonest inherited renal condition and the commonest cause of glomerular hematuria. Proteinuria usually is minimal and renal function remains normal, but occasionally patients develop marked proteinuria or renal impairment. It is unclear whether individuals with TBMN and impaired renal function represent part of the spectrum of TBMN associated with heterozygous *COL4A3* or *COL4A4* mutations, or if their disease is caused by mutations of other genes, or whether it is caused by a second coexistent renal lesion, or to misdiagnosed Alport syndrome.

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