SEMINARS IN
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The Epidemiology of Thin Basement Membrane Nephropathy

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The prevalence of this basement membrane nephropathy (TBMN) may be approximated from the known frequencies of glomerular hematuria in the population, and from the prevalence of autosomal-recessive Alport syndrome and its known relationship to TBMN. These approaches confirm that TBMN affects more than 1% (but <10%) of the population, making it the commonest inherited renal disease, and one of the commonest conditions affecting the kidney after infections, hypertension, and stones. TBMN is the most frequent cause of persistent glomerular hematuria. Although we do not advocate mass screening for hematuria to detect TBMN, we strongly support investigating hematuria that is discovered incidentally. Individuals with TBMN and isolated hematuria should be evaluated initially by a nephrologist and subsequently reviewed by their family doctor. Those with proteinuria, hypertension, or renal impairment are at risk for progressive renal impairment and should by examined carefully for features of Alport syndrome or an additional glomerular or tubulointerstitial lesion, undergo a renal biopsy examination, be treated symptomatically, and be monitored by a renal physician.
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Thin basement membrane nephropathy (TBMN) is characterized clinically by persistent glomerular hematuria, minimal proteinuria, normal renal function, and a benign course. Ultrastructural examination of the renal biopsy specimen typically shows a thinned glomerular basement membrane (GBM) and many individuals have a positive family history of hematuria or of TBMN itself.[1]

The similarity of clinical features and GBM ultrastructure in individuals with TBMN and in carriers of autosomal-recessive Alport syndrome first suggested these were the same condition or at least caused by mutations in the same genes.[2] Studies subsequently confirmed that 40% of individuals with TBMN had hematuria segregating with the locus for autosomal-recessive Alport syndrome (*COL4A3*/*COL4A4*)[3] and that identical *COL4A3* and *COL4A4* mutations (in the homozygous or compound heterozygous form) cause both conditions.[4]

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Prevalence of TBMN

Although the diagnosis of TBMN usually is made on the basis of persistent glomerular hematuria (with minimal proteinuria and normal renal function), or, less commonly now, on the renal biopsy examination showing a thinned GBM, the majority of affected individuals remain undiagnosed. However, the prevalence of TBMN still may be approximated from the known frequencies of persistent glomerular hematuria in the community and of TBMN in archival series of renal biopsy examinations from patients with isolated hematuria, and from the prevalence of autosomal-recessive Alport syndrome and its known relationship to TBMN.

How Common is Persistent Glomerular Hematuria in the Community?

The prevalence of hematuria and persistent hematuria have been studied repeatedly in pediatric and adult populations.[5-10] *Persistent* usually has been defined as present on 2 occasions, and persistent hematuria occurs consistently in up to 6% of both children and adults. The persistence of hematuria in TBMN is not known but reasonably might refer to hematuria on 2 occasions at least 2 years apart. The persistence of hematuria is important in the definition of TBMN

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because it distinguishes the glomerular bleeding caused by TBMN from that found with post-streptococcal glomerulonephritis. The finding of persistent hematuria in the absence of proteinuria and together with normal renal function will exclude most other conditions such as immunoglobulin (Ig)A glomerulonephritis and Alport syndrome. Relatively few studies have examined persistent hematuria in the community by phase-contrast microscopy to determine its origin,[11] but all those that do, confirm that it usually originates from the glomerulus. Furthermore, these studies show that about 1% to 4% of the population have persistent glomerular hematuria. Any direct correlation with the prevalence of TBMN must, however, be tempered by the observations that there are other causes for this, some individuals with TBMN have no hematuria, some have intermittent hematuria, and some have proteinuria and renal impairment that usually precludes this clinical diagnosis. (This also raises the question of how TBMN is defined, and whether someone with the mutation that causes TBMN but without the clinical phenotype should be considered affected.)

How Common is TBMN in Series of Renal Biopsy Examinations?

TBMN also is diagnosed when there is GBM thinning without lamellation or immune deposits on ultrastructural examination of the renal biopsy specimen.[12] However, the current practice is that individuals with isolated hematuria suspected to have uncomplicated TBMN do not undergo a biopsy examination.

Nevertheless, there are several very large series reported from patients with isolated hematuria in previous decades when they were much more likely to undergo a biopsy examination. Many of these studies have been Australasian,[13-15] possibly because of our enthusiasm for urinary phase-contrast microscopy, our very low renal biopsy examination complication rate, and a predominantly government-funded health system. For example, one unit that performed nearly 1,000 renal biopsy procedures annually described a small series of 70 biopsy procedures performed for isolated glomerular hematuria, of which 37 (53%) showed TBMN and 21 (30%) showed IgA disease. In another study of 111 patients with isolated hematuria, 75 (68%) had a renal biopsy examination, TBMN was present in 27 (36%) (and in possibly another 31 with normal or non-IgA mesangial proliferative glomerulonephritis) and IgA disease was diagnosed in 17 (23%). In our own unit, between 1988 and 1991, a total of 110 renal biopsy examinations were performed that showed TBMN and only 27 in which IgA disease was found. These series all confirm TBMN is more common than IgA glomerulonephritis, and that TBMN accounts for more individuals with persistent hematuria. Even so, biopsy series will underestimate the likelihood of TBMN because many affected individuals are undiagnosed. In our experience, there is at least one undiagnosed individual in each family with TBMN for everyone who has been identified, and, of course, many affected families still are unrecognized.

How Often is TBMN Found Incidentally in Renal Biopsy Specimens When it is Not Suspected Clinically?

The prevalence of TBMN also has been estimated from measurements of GBM width in renal biopsy specimens when TBMN is not suspected clinically. For example, the GBM width was measured in biopsy specimens from 76 normal renal allografts immediately after transplantation (the cadaver donors had not been tested for hematuria). This study found thinning in 5.2% or 9.2% of biopsy specimens depending on the definitions used.[16] The higher frequency was obtained using criteria that overlapped with normal GBM width and, hence, is an overestimate.

The policy in our own renal unit toward individuals suspected of having TBMN has also changed and these patients have not undergone a biopsy examination in the past decade. However, all biopsy examinations performed since 2001 have been screened routinely for TBMN by measuring GBM width. Between 2001 and 2003, 156 patients underwent a biopsy examination and their GBM width was measured. Sixteen (10%) had TBMN (15 with additional glomerular or tubulointerstitial lesions, and 1 with uncomplicated TBMN), and 12 others (8%) had IgA glomerulonephritis. In the same time period, 2 new patients from unrelated families with Alport syndrome were diagnosed, making a total of 11 known families at our hospital.

How Common is the Carrier State of Autosomal-Recessive Alport Syndrome?

The third approach to determining the prevalence of TBMN is to consider that TBMN represents the carrier state for autosomal-recessive Alport syndrome. One estimate holds that autosomal-recessive Alport syndrome affects 1 in 40,000 individuals, which corresponds to a 1% frequency of the carrier state in the community. However, if only 50% of individuals with TBMN are carriers of autosomal-recessive Alport syndrome (in which case compound heterozygotes have hematuria rather than renal failure and the Alport phenotype), then TBMN will affect more than 1% of the population.

Because we know mutations in TBMN often affect the *COL4A3*/*COL4A4* genes, it theoretically is possible to examine DNA from members of the community for mutations in these genes and hence determine the genetic frequency of TBMN. However, these genes are too large, there may be a further gene locus, the mutations are different in each family, and most mutation detection techniques are too laborious, expensive, and insensitive to be able to do this.

How Common is TBMN?

These 3 approaches confirm that TBMN affects more than 1% (but <10%) of the community, making it the commonest inherited renal disease, and one of the commonest conditions affecting the kidney after infections, hypertension, and stones.

In addition, TBMN is the commonest cause of persistent glomerular hematuria. It is the most frequently diagnosed glomerular abnormality (apart from possibly diabetes) and is more common than the next most prevalent disease, IgA glomerulonephritis. TBMN occurs much more often than Alport syndrome (which is found in .002% of the population).[17]

How common is TBMN in our patients with chronic kidney failure? The cause of end-stage renal disease in many patients is unclear and the renal biopsy examination in an end-stage kidney usually is unhelpful diagnostically. Typically uncomplicated TBMN does not cause renal impairment but we have shown previously that 7% of our patients undergoing a biopsy procedure have some degree of impaired renal function.[1] We suspect in many cases this occurs because of a coincidental or secondary glomerular or tubulointerstitial lesion. Family studies and, in time, genetic studies will reveal how often TBMN contributes to our population of patients with chronic kidney failure.

Epidemiology of TBMN

TBMN has been reported in all races and although it obviously is studied better in developed countries, recent reports show it also is common in Chinese people[18] and there are occasional reports in Africans.

Patients with TBMN usually present in childhood or in adulthood with median ages at presentation of 7 and 37 years,[1] respectively. Although hematuria caused by TBMN has been recognized in infants and the elderly, it is not clear whether hematuria truly is persistent throughout the patient's lifetime or diminishes with increasing age. The issue of whether TBMN (or at least hematuria caused by TBMN) is more common in women than men also still is unresolved.[1]

Should We Screen the Population for Hematuria to Detect TBMN?

Current guidelines for urine screening are concerned primarily with proteinuria as a risk factor for renal impairment.[10] Recommendations on screening for hematuria have focused on the need to detect a urologic malignancy and other researchers have concluded screening is warranted only in the elderly or other at-risk individuals.[19-21]

Nevertheless, urinary testing by dipstick is common. It is performed frequently during pregnancy, as a screening test for a urinary tract infection in unwell patients, for life insurance purposes, and at the time of all hospital admissions in many countries. There have been repeated discussions in the literature about the significance of a positive result.[22-25] A recent review recommends that positive results be confirmed and the glomerular or nonglomerular nature of the bleeding determined.[26] If isolated hematuria is present, the patient should be reviewed by their family doctor, but if proteinuria or renal impairment also occur, the patient must be seen by a nephrologist. Nonglomerular hematuria should be investigated with a helical computed tomography scan and urinary cytology, and a cystoscopy should be performed if the patient is older than 50 years or there is a risk for bladder cancer.

Although we do not advocate mass screening for hematuria to detect TBMN, we strongly support investigating hematuria that is discovered incidentally. We suggest performing phase-contrast urinary microscopy to confirm the hematuria and show its glomerular (or nonglomerular) origin. The patient should be asked about a family history of hematuria, renal failure, and Alport syndrome, and examined for hypertension and the ocular manifestations of Alport syndrome (lenticonus and retinopathy). Their serum creatinine and urinary protein levels should be measured. Other causes of familial and persistent hematuria should be excluded clinically and by laboratory testing (Tables 1 and 2). Importantly, other relatives should be examined for hematuria to confirm its familial nature[27] (testing both parents is the most useful strategy), and to identify as many affected individuals as possible to avoid unnecessary anxiety and excessive investigations at a later time.

A renal biopsy examination usually is reserved for individuals with atypical clinical features such as proteinuria or renal impairment, and when IgA glomerulonephritis, X-linked Alport syndrome, or an additional glomerular or interstitial lesion cannot be excluded. When GBM thinning is shown, this must be distinguished from the thinning seen in other inherited (X-linked Alport syndrome in boys and girls) and noninherited glomerular diseases (IgA disease, glomerular injury, and minimal change glomerulonephritis).

Table 1 Causes of Persistent Familial Hematuria

Glomerular Hematuria	Nonglomerular Hematuria
TBMN	Polycystic kidney disease
IgA disease	Sickle cell disease or trait
Alport syndrome	Familial hypercalciuria
Autosomal-dominant hereditary nephritis with hematologic abnormalities (Fechtner syndrome)	
Nail patella syndrome	
Mesangiocapillary glomerulonephritis type II	
Focal segmental glomerulosclerosis (usually low counts only)	
Fabry disease (usually low counts only)	

Table 2 Some Laboratory Investigations to Aid in the Diagnosis of Individuals With Glomerular Hematuria

Screening for proteinuria (or microalbuminuria)
Examination of urine of first-degree relatives for hematuria
Serum IgA levels
ANA, antidouble stranded DNA antibodies
Complement components, C3 and C4
Antineutrophil cytoplasmic antibodies
Hepatitis C
Antistreptolysin titre
Cryoglobulins
Anti-GBM antibodies
C3 nephritic factor

How Should We Follow-Up Individuals with TBMN?

Currently there are no guidelines on an appropriate protocol for review of patients with TBMN. It has been suggested that individuals with TBMN and isolated hematuria may be evaluated initially by a nephrologist and subsequently by their family doctor. Those with proteinuria, hypertension, or renal impairment are at risk for progressive renal impairment[28] and should be examined carefully for features of Alport syndrome or an additional glomerular or tubulointerstitial lesion, undergo a renal biopsy examination, be treated symptomatically, and be monitored by a renal physician. Although these recommendations reflect our current practice, they have not been evaluated formally.

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