

# The Risks of Thin Basement Membrane Nephropathy

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Most individuals with thin basement membrane nephropathy (TBMN) have an excellent prognosis. For these patients, the only hazards are the anxiety related to misconceptions about the diagnosis and the inconvenience, expense, and wastefulness of unnecessary investigations. However, there also are specific genetic implications for individuals with TBMN because, on average, half their offspring inherit the causative mutations and most of these have hematuria. In addition, despite the generally excellent outcome, some individuals with TBMN develop hypertension, proteinuria, or renal impairment. In some cases, renal failure is caused by apparently progressive but otherwise uncomplicated TBMN, and in others it results from a secondary or coincidental glomerular or tubulointerstitial renal lesion. In particular, TBMN appears to predispose to immunoglobulin (Ig)A glomerulonephritis, and the outcome for these patients is worse than for those with TBMN alone. The risks for patients with TBMN in relation to pregnancy and transplantation have not been well-studied but are described elsewhere in this issue.

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Most individuals with thin basement membrane nephropathy (TBMN) have an excellent prognosis. However, some TBMN patients develop renal failure<sup>1-3</sup> and the only criteria to identify those at risk are the presence of hypertension, proteinuria or any degree of renal impairment,<sup>4</sup> or the demonstration of a second glomerular or tubulointerstitial lesion on renal biopsy examination.

## Nonmedical Risks

The most common hazard for the individual with TBMN is the anxiety related to misconceptions about this diagnosis and the inconvenience, expense, and wastefulness of unnecessary investigations. On the other hand, when TBMN is suspected clinically but is not confirmed by renal biopsy examination the diagnostic uncertainty also may result in worry for the individual. Now that the nature of TBMN and its prognosis are better understood it is uncommon (and usually unjustified) for affected individuals to have difficulty in obtaining life insurance or any particular type of employment.

## Genetic Implications

There are, however, genetic implications in making the diagnosis of TBMN. TBMN is an autosomal-dominantly inherited condition,<sup>5-7</sup> and about two thirds of cases have another family member with hematuria.<sup>7</sup> On average, the causative mutation occurs in half of the offspring of an affected parent and equally often in males and females. Females seem to come to medical attention more often than males, possibly because their normally thinner glomerular basement membrane (GBM) is attenuated further by the mutations' effects, resulting in hematuria more frequently.<sup>1</sup> Nevertheless, some individuals with mutations that cause TBMN do not have hematuria (nonpenetrance) and fewer than half the offspring of an affected individual have an abnormal sediment. In addition, we now understand that TBMN represents the carrier state for autosomal-recessive Alport syndrome at least in some cases,<sup>7-9</sup> but it is not clear how often the offspring of 2 parents with TBMN develop renal failure and the other clinical features of autosomal-recessive Alport disease.

## Clinical Complications

### Hematuria

The hematuria in TBMN usually is microscopic, persistent, and dysmorphic, reflecting its glomerular origin.<sup>10</sup> Sometimes the hematuria is intermittent, which can interfere with the identification of affected family members. Occasionally, the hematuria is macroscopic and there are rare reports of

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TBMN associated with *loin-pain hematuria* syndrome, of urinary red cells blocking the renal tubules and causing acute tubular necrosis, and even of iron deficiency.<sup>11-13</sup>

### Hypertension, Proteinuria, and Renal Impairment

The most serious complications of TBMN are the development of hypertension, proteinuria, and renal impairment. These are treated symptomatically because there is no specific therapy for TBMN.

How common are these complications? We reviewed the clinical features associated with TBMN in 6 pediatric studies and 11 studies in adults<sup>1</sup> in which TBMN was biopsy examination-proven in the index case or a family member, patients were not selected on the basis of clinical features, and in which X-linked Alport syndrome was excluded on family history and the absence of typical clinical associations. Hypertension, proteinuria, and renal impairment did not occur in any of the children in these reports but were present to a variable extent in the adult series.

We went on to show that although proteinuria and renal impairment occurred in our own adult patients who had undergone a renal biopsy procedure, these features were much less common in their affected family members who did not undergo a biopsy examination (who were diagnosed on the basis of hematuria or disease haplotypes). Thus, proteinuria greater than 500 mg/d was present in 21% of our 71 patients with biopsy examination-proven disease, but in only 4% of their 45 family members who did not undergo a biopsy examination ( $P < .02$ ), and impaired renal function was present in 7% our patients who underwent a biopsy examination but in none of their affected family members ( $P$  is not significant). These results indicate TBMN usually is uncomplicated in children, and in adults, hypertension, proteinuria, and hypertension are uncommon but are overrepresented in published series of hospital-based patients.

### Hypertension

Hypertension is a common accompaniment of TBMN in adults but it is not clear how often this relationship is coincidental and how often it is causal.<sup>1</sup>

### Proteinuria

Most patients with TBMN have no proteinuria but, on the other hand, proteinuria is the only manifestation of TBMN in 8% of patients.<sup>14</sup> When proteinuria occurs it does not correlate with the amount of GBM thinning.<sup>15</sup> Why does hematuria occur without proteinuria? Hematuria in TBMN arises from the leakage of red cells through transient gaps in the thinned GBM into Bowman's space,<sup>10</sup> and these gaps should allow proteinuria too. One explanation for the absence of protein in the urine is that protein loss occurs commonly through the glomerular membrane breaks in TBMN but all of it is resorbed by the tubular cells.

Other mechanisms of proteinuria in TBMN include the losses associated with glomerulosclerosis, and from coincidental glomerular or tubulointerstitial disease.

### Renal Impairment

Renal impairment is uncommon in TBMN, and the contribution of TBMN to the number of patients with end-stage renal disease in national registries is unknown. This is partly because the renal biopsy specimen appearance in end-stage kidney disease is nonspecific and patients might have been described as having *familial glomerulonephritis*, which usually implies Alport syndrome.

The only known risk factors for renal impairment in TBMN are proteinuria, hypertension, and a coexistent glomerular or tubulointerstitial lesion. It is not possible to determine which patients with TBMN will develop renal failure until they have proteinuria or hypertension. In our experience only occasional individuals from affected families have renal impairment so this is not related to the nature of the underlying mutations, but modifying genes such as podocin or nephrin which encode slit pore structural proteins, may play a role.<sup>16,17</sup>

Renal impairment in patients with TBMN can be explained by progression of the TBMN itself, by predisposition to a further glomerular or tubulointerstitial lesion, by coincidental renal disease, or by the misdiagnosis of immunoglobulin (Ig)A glomerulonephritis or X-linked Alport syndrome.<sup>18-24</sup> Many patients with TBMN have more glomerulosclerosis than expected for their age and this may contribute to renal impairment. In addition, a coexistent glomerular or tubulointerstitial lesion frequently is found in the kidney biopsy specimen. We recently reviewed all biopsy examinations performed in our unit during the years 2001 to 2003 ( $n = 362$ ). The policy of our nephrologists at the time was not to perform a biopsy examination on patients suspected clinically of having uncomplicated TBMN. This differed from our earlier practice when most patients with hematuria underwent a biopsy procedure.<sup>21</sup>

For these 3 years, all nontransplant biopsy examinations ( $n = 246$ ) for which there was sufficient tissue ( $n = 156$ , 63%) were examined routinely by electron microscopy. The GBM width was averaged over 100 measurements in 12 micrographs magnified 6,300 $\times$  by a computerized system. TBMN was diagnosed when the GBM width was less than 250 nm. It was present in 16 biopsy specimens (10%) from 6 males and 10 females with a median age of 48 years (range, 35-72 y). Only 1 of the 16 patients had uncomplicated TBMN with the typical clinical features of persistent microscopic hematuria, no proteinuria, and normal renal function. The other 15 patients with TBMN all had additional glomerular or tubulointerstitial lesions. Their median urinary red blood cell (RBC) count was 180,000 RBC/mL (range, 6 to >500,000 RBC/mL), 9 (60%) had proteinuria levels greater than 500 mg/24 h, and 7 (47%) had renal impairment (serum creatinine level > .11 mmol/L). The additional diagnoses on biopsy examination were IgA disease ( $n = 7$ ), focal segmental glomerulosclerosis ( $n = 2$ ), pauci-immune glomerulonephritis ( $n = 1$ ), minimal change glomerulonephritis ( $n = 1$ ), acute tubular necrosis/allergic interstitial nephritis ( $n = 3$ ), or another unidentified glomerulonephritis ( $n = 1$ ). These data indicate that coexis-

**Table 1** Diagnostic Features That Distinguish TBMN From X-Linked Alport Syndrome and IgA Disease

Diagnostic Feature	TBMN	X-Linked Alport Syndrome		IgA Disease
		Boys <10 y	Carrier Females	
Persistent dysmorphic haematuria	92%	100%	100%	<100%
Proteinuria <500 mg/d	73% to 96%	<100%	70% to 90%	<60%
Normal renal function	93% to 100%	<100%	70% to 90%	70%
Family history of hematuria	50% to 67%	85%	85%	5%
No family history of Alport syndrome	100%	15%	15%	100%
Uniformly thinned GBM	100%	<100%	<100%	0%
$\alpha$ 3(IV), $\alpha$ 4(IV), $\alpha$ 5(IV) chains in GBM	100%	80%	80%	100%
Linked to COL4A3/COL4A4 locus	40%	0%	0%	0%
Mutations in COL4A3 or COL4A4	33%	0%	0%	0%

tent renal lesions are common in TBMN, and often result in proteinuria and renal impairment.

Is the second lesion coincidental or does TBMN predispose to further pathology? In some cases, such as with acute tubular necrosis or allergic interstitial nephritis, the additional renal lesions clearly are coincidental but in other cases this is not necessarily true. Why is IgA glomerulonephritis so common in TBMN? To understand this, we examined whether IgA glomerulonephritis occurred equally often in TBMN as in other glomerular diseases. In the renal biopsy procedures performed between 2001 and 2003, there were 31 patients diagnosed with IgA disease. It was the only finding on renal biopsy examination in 24 cases, and occurred together with TBMN in 7 cases (23%). Thus, IgA disease occurred about twice as often with TBMN as expected by chance alone (10%) ( $P < .05$ ), but it did not occur together with any other form of glomerulonephritis. These observations suggest that TBMN predisposes to mesangial IgA deposition.

Where an additional glomerular or tubulointerstitial lesion occurs together with TBMN the clinical features and course usually reflect the superimposed pathology. This typically means that the prognosis is different from that seen with TBMN alone. However, it is not obvious whether the converse also is true or that TBMN worsens the outcome for other diseases. For example, we have shown previously in a small series that patients with TBMN and IgA disease do not necessarily have more proteinuria, hypertension, or renal impairment than those with IgA disease alone.<sup>21</sup>

## Misdiagnosis

The diagnosis of TBMN usually is made clinically (Table 1). TBMN must be distinguished from X-linked Alport syndrome in boys and female carriers (the disease usually is obvious in adult men) and IgA disease because of the very different prognoses for these conditions and because of the possibility of treatment for IgA disease. X-linked Alport syndrome is relatively uncommon but the clinical and ultrastructural features in boys and female carriers closely resemble those seen in TBMN.<sup>25</sup> IgA disease is common and the clinical features often resemble those in TBMN.

The clinical diagnosis of TBMN depends on the demonstration of persistent dysmorphic hematuria, with minimal

proteinuria and normal renal function, in the absence of a positive family history of X-linked Alport syndrome or renal failure, and any other obvious explanation. In some cases, for example, when there are atypical clinical features such as marked proteinuria or renal impairment and when IgA glomerulonephritis and X-linked Alport syndrome cannot be excluded, a renal biopsy examination is warranted. Confirmation of the diagnosis of TBMN by the demonstration of genetic linkage to the COL4A3/COL4A4 locus or mutation screening of these genes rarely is performed.

Although the clinical criteria for the diagnosis of TBMN are useful they have not been evaluated formally. Furthermore, about 8% of individuals with TBMN do not even have hematuria,<sup>14</sup> and proteinuria is sometimes greater than 500 mg/d (4% in our affected family members who did not undergo a biopsy examination), and although renal function may be impaired in published reports, this again is uncommon in individuals who did not undergo a biopsy examination.<sup>1</sup> In addition, only 50% of affected individuals know of another family member with hematuria, but this increases to 67% when more family members are studied. Families are not always aware of distant relatives with Alport syndrome or renal failure and, regardless, 15% cases of X-linked Alport syndrome are caused by de novo mutations.

Individuals with TBMN must be distinguished from those with IgA glomerulonephritis who often have the characteristic synpharyngitic macroscopic hematuria, or fluctuating urinary RBC counts as well as proteinuria.<sup>26</sup> The demonstration of microalbuminuria also may help differentiate between TBMN and IgA disease.<sup>27</sup> The distinction from X-linked Alport syndrome can be more problematic. It often is easier to make a positive diagnosis of X-linked Alport syndrome than to exclude TBMN. Individuals with X-linked Alport syndrome are more likely to have proteinuria and renal impairment, and possibly hearing loss, lenticonus, and the dot-and-fleck retinopathy depending on their age, sex, and disease penetrance.

A renal biopsy examination usually is not required to diagnose TBMN but it remains the gold standard. Renal biopsy interpretation also can be difficult. Although the GBM in TBMN is thinned on ultrastructural examination, this appearance also occurs in boys and carrier females with X-linked Alport syndrome.<sup>28</sup> Likewise, the  $\alpha$ 3(IV),  $\alpha$ 4(IV), and

$\alpha 5(IV)$  collagen chains are all present in TBMN and although typically absent from X-linked Alport syndrome, about 20% of males with X-linked disease can have a normal GBM composition.<sup>29-31</sup> The thinned GBM seen in TBMN (and the mesangial IgA deposits seen on immunohistochemistry) of the renal biopsy specimen will, however, distinguish TBMN and IgA disease.

Genetic studies for TBMN are definitive and differentiate TBMN from both X-linked Alport syndrome and IgA disease, but they are insensitive, laborious, costly, and available only in specialized centers internationally.<sup>32,33</sup> The most useful genetic tests in patients suspected of having TBMN are those that diagnose or exclude X-linked Alport syndrome. These either show a *COL4A5* mutation or exclude linkage to the *COL4A5* locus.<sup>33,36</sup> In the United States, there are several very large families with X-linked Alport syndrome caused by C1564S or L1649R mutations in which affected individuals have normal hearing. It has been suggested that testing for these mutations should be performed in potential renal donors and in other cases for which X-linked Alport syndrome cannot be excluded.<sup>34</sup>

When a renal biopsy examination is not performed, TBMN may be confused with X-linked Alport syndrome or IgA glomerulonephritis, but there is also the risk for overlooking a coexistent glomerular or tubulointerstitial lesion. However, in most, but not all, patients, the presence of atypical clinical features will alert the clinician to the possibility of a further renal abnormality.

## Pregnancy

Although TBMN is the commonest glomerular lesion worldwide, the effect of pregnancy is not well studied. There are only a few reports of pregnancy in patients with non-IgA mesangial proliferative glomerulonephritis, most of whom have had TBMN.<sup>35,36</sup> In our experience, the outcome for most individuals with TBMN (and their babies) is better than in these series.

## Transplantation

Many nephrologists currently use kidneys from donors with TBMN, and this practice appears to have no obvious adverse outcomes for the donors or recipients, at least in the short term.<sup>37</sup> However, the real risks of donation and the outcome for allograft recipients are unknown, and, in particular, it is not clear whether they are more prone to the development of glomerulosclerosis, proteinuria, hypertension, or renal impairment in the long term.

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