Long-term Prognosis of thin Glomerular Basement Membrane Nephropathy in Children: A Retrospective Single Center Study

Myung Hee Lim, M.D.
Hee Jung Bae, M.D.
Kyung Mi Jang, M.D.
Yong Hoon Park, M.D.

Department of Pediatrics, Yeungnam University Hospital, Yeungnam University College of Medicine, Daegu, Korea

Corresponding author:
Yong Hoon Park, M.D., Ph.D.
Department of Pediatrics, Yeungnam University College of Medicine, Daegu, 170 Hyeonchung-ro, Nam-gu, Daegu 42415, Korea
Tel: +82-53-620-3536
Fax: +82-53-629-2252
E-mail: yhpark@ynu.ac.kr

Purpose: Thin glomerular basement membrane nephropathy (TBMN) is, along with the IgA nephropathy, the most common cause of asymptomatic hematuria in Korean children. TBMN is usually a benign renal disease not requiring treatment and is associated with a good prognosis, but some cases hematuria is indicative of a state of progressive renal insufficiency. We aimed to retrospectively evaluate clinical manifestations and renal prognosis of patients with TBMN.

Methods: Among the 428 renal biopsies performed on children at Yeungnam University Hospital between January 2000 and February 2017, 167 patients were diagnosed as having TBMN. We retrospectively investigated 167 pediatric patients and identified 59 children with follow-up duration >3 years.

Results: Among 59 patients, there were 33 boys and 26 girls. Mean age of onset of hematuria was 7.18±2.64 years, and mean time from onset of disease until a renal biopsy was performed was 2.48±2.10 years. There were no clinical features or laboratory findings among studied children to indicate decreased renal function during follow-up; however, one case progressed to chronic kidney disease (CKD) due to an unknown cause. There were seven patients among these related a positive family history of hematuria or renal insufficiency.

Conclusion: Although almost all patients had normal renal functions during follow-up, there were one patient who progressed to CKD and seven patients with family history of hematuria or renal insufficiency. Moreover, four among the 428 patients over 17 years underwent repeat renal biopsies, which showed results different from their earlier biopsies. Thus, large-scales studies may be required to determine long-term prognosis of TBMN in children, and further evaluation for Alport syndrome in TBMN cases is essential.

Key words: Hematuria, Children, Thin basement membrane nephropathy, Alport syndrome, School urinalysis screening

Introduction

Annual school urinalysis screening (SUS) has been routinely performed in Korea since 1998 in Korea. A simple urinary dipstick method is used to detect proteinuria, hematuria, and urinary glucose[1]. This method has helped in screening various renal diseases for further investigation and is helpful to predict and follow-up for preventing progressive chronic renal disease. Advantages of early detection of glomerulonephritis in children have been recogni-

zed in Japan as well, for which the School Health Law of Japan was passed in 1974[2].

Hematuria is a common finding associated with renal and urinary tract disease in the pediatric age groups and is often a signal indicating either benign or serious renal pathologies. Some studies have reported that children with isolated hematuria comprised 60.1% of 1,044 school children who underwent renal biopsy in nationwide SUS with 14 hospitals[3]. Asymptomatic microscopic hematuria is often multifactorial in origin. Thin basement membrane nephropathy (TBMN) is likely to be present in a significant proportion of asymptomatic children with isolated, persistent, or recurrent microscopic hematuria[4].

TBMN is characterized by persistent glomerular hematuria, minimal proteinuria, and normal renal function and is the most common cause of inherited renal disease, noted in approximately 1% of the world population[5]. TBMN is usually associated with a good prognosis as a benign renal disease, but some adults were reported that they presented other glomerular diseases such as early stage Alport syndrome, immunoblogulin A nephropathy (IgAN), or mesangial proliferative glomerulonephritis (MPGN), and eventually progressed to renal insufficiency[5].

We studied the spectrum of the clinical and histopathological presentations of pediatric patients diagnosed with TBMN who visited or were referred to our clinic for any cause, and attempt to discover long term outcome of pediatric TBMN.

Materials and methods

We retrospectively investigated 428 renal biopsy cases in children between 12 months and 17 years of age between January 2000 and February 2017 at Yeungnam University Hospital.

Among 428 pediatric patients, we analyzed 167 children who were diagnosed with TBMN, and among the 167 patients we identified 59 children who were followed-up for >3 years.

TBMN was diagnosed based on histopathological findings normal findings using light microscopy, no deposits noted using immunofluorescence microscopy, and diffuse thinning of the glomerular basement membrane (GBM) using electron microscopy.

We reviewed data such as gender distribution, age at the time of diagnosis, age of onset of hematuria, referral route, family history, blood pressure, conventional laboratory tests, and renal biopsy data. Glomerular filtration rate was calculated based on the Schwartz equation, estimated from the patient's height and serum creatinine concentration. All statistical data were analyzed using the SPSS program version 23.0 software, and a P-value <0.05 was considered significant.

Results

Among the 428 renal biopsy cases in children between 12 months and 17 years of age studied at Yeungnam University Hospital, 167 patients (39.01%) showed TBMN, 77 (17.99%) showed IgAN, 63 (14.71%) showed minimal change disease (MCD), 38 (8.87%) showed Henoch-Schonlein purpura nephritis (HSPN), 14 (3.27%) showed focal segmental glomerulosclerosis (FSGS), 9 (2.10%) showed lupus nephritis, 8 (1.86%) showed renal transplantation-related conditions such as acute rejection or calcineurin inhibitor toxicity, 7 (1.63%) showed MPGN, 6 (1.40%) showed post-infectious glomerulonephropathy (PIGN), 5 (1.16%) showed Alport syndrome, 4 (0.93%) showed membranous glomerulonephropathy (MGN), 2 (0.46%) showed Wilm's tumor, 7 were cases presenting with miscellaneous conditions including inappropriate renal specimens with no glomerulus obtained during biopsy, while 21 cases showed no pathology.

Among 428 patients, 25 underwent repeat renal biopsies due to prolonged hematuria or proteinuria and three of these patients showed findings that differed from those obtained at the time of their first biopsy (1 case was found to change from HSPN to MPGN, 1 case from HSPN to IgAN, and 1 case from MCD to IgAN).

1. Patient demographics

Among 167 TBMN patients, 59 pediatric patients whose follow-up duration was >3 years were identified. All patients were Korean, and we studied 33 boys and 26 girls. Mean age of hematuria onset was 7.18±2.64 years, and only 10 patients were found to have gross hematuria. Mean age at the time of diagnosis was 9.66±2.84 years (range 2.76-16.06

years). Mean age of boys was 10.23±2.90 years, and that girls was 8.93±2.65 years, which was not statistically significant (*P*=0.082).

Hematuria was incidentally detected through school urinary screening (SUS) in most patients (76.3%). In 15.3% cases, asymptomatic isolated hematuria was incidentally detected when the patient presented for another unrelated problem, and 8.5 % cases presented with symptomatic hematuria (fever, abdominal pain, frequency, pyuria, among others) (Table 1).

All patients were found to have microscopic hematuria, but only two patients demonstrated additional proteinuria at their first visit. Almost all patients showed normal renal function with serum creatinine measuring 0.58±0.14 mg/dL and an estimated glomerular filtration rate (eGFR) of 141.57±30.49 mL/min/1.73m^2, with only one patient showing poor renal function (serum creatinine 1.21 mg/dL at 13 years of age, eGFR=62.27 mL/min/1.73m^2).

2. Renal biopsy

Light microscopy findings were essentially unremarkable in all cases. Electron microscopy showed diffuse thinning of the GBM (mean minimum GBM thickness was 161.24±41.10 nm, and mean maximum GBM thickness was 193.39±51.39). No electron-dense deposits were found in any case, and foot processes were well preserved. Immunofluorescence microscopy did not show any abnormalities or deposits.

3. Clinical features

Mean duration of time from the onset of hematuria until a renal biopsy was performed was 2.48±2.10 years, and mean follow-up duration from the first visit was 7.25±3.09 years. During follow-up, only one patient among 59 showed the development of renal insufficiency from the time of onset of disease, and she eventually progressed to a state of chronic kidney disease (CKD) stage 4. She received anbiotensin-converting enzyme (ACE) inhibitors, cyclosporine A, and angiotensin II receptor blockers (ARB). However, the remaining 58 patients did not receive corticosteroids, immunosuppressants, or any other treatment.

All patients were normotensive and clinically stable with microscopic hematuria and did not show any abnormalities with respect to immunoglobulins, complement components, serological tests [rheumatoid factor, antistreptolysin O titer (ASO), or hepatitis B surface antigen (HBsAg)]. Except one patient who developed CKD, all patients demonstrated normal serum creatinine and albumin levels during follow-up.

Among 59 patients, five patients showed hypercalciuria based on estimation of the urine calcium-creatinine ratio at the time of their first visit. Among these five patients, four were confirmed to be normal based on a repeat urinalysis, while one patient did not undergo a follow-up study.

Among 59 patients, two had only family history of hematuria and five related positive family history of chronic kidney disease, and one had family history of both hematuria and renal insufficiency (Table 2, Fig. 1).

No patient demonstrated history consistent with Alport syndrome such as signs and/or symptoms of deafness, or nephritis leading to renal failure; however, three patients were screened for mutations in the *COL4A5* gene and all three showed no mutation (One showed a hemizygous change on the *COL4A5* gene exon 2, but it was proved to be a case of polymorphism and not a pathogenic change). One patient who had shown poor eGFR at the first visit also related family history of CKD (mentioned in Table 2). She underwent genetic testing for the *COL4A5* gene but did not show any mutation.

4. Renal outcomes

We found that while 49 of 59 patients showed persistent

Table 1. Referral Causes of Patients Visiting our Clinic for Renal Biopsy

	Isolated microscopic hematuria	Gross and microscopic hematuria	Total
SUS	40	5	45 (76.3%)
Asymptomatic isolated hematuria detected incidentally	6	3	9 (15.3%)
Symptomatic hematuria*	3	2	5 (8.5%)
	49 (83.1%)	10 (16.9%)	59

*Patients with a symptomatic hematuria have fever, frequency, abdominal pain, etc.

microscopic hematuria at their last visit, only one patient demonstrated proteinuria. Renal function determined by

Table 2. Details of the Family History of Seven Patients

	Relaionship	Problem
Patient 1	Grandmother	CKD of unknown cause, received renal transplantation
Patient 2	Father	Microscopic hematuria, but not evaluated
	Sibling	Microscopic hematuria, improved without treatment
Patient 3	Father	Microscopic hematuria, but not evaluated
	Aunt	CKD of unknown cause, received renal transplantation
	Sibling	Gross and microscopic hematuria, improved without treatment
Patient 4	Uncle	CKD of unknown cause, who received hemodialysis
Patient 5	Father	CKD of unknown cause
	Sibling	CKD of unknown cause
Patient 6	Father	Microscopic hematuria, but not evaluated
Patient 7	Grand father	CKD due to hypertension, received renal transplantation
	Uncle	IgA nephropathy

eGFR was within normal reference range from the onset of disease to the time of their last visit in 58 patients. There was no significant change in eGFR values between their first and last visit (1st visit eGFR=141.57±30.49 mL/min/1.73m^2, last visit eGFR=142.23±36.16 mL/min/1.73m^2, $P=$ 0.895). Only one patient with an eGFR of 62.27 mL/min/1.73m^2 at the first visit, showed a gradual decline in her eGFR, which eventually decreased to 23.30 mL/min/1.73m^2.

Discussion

TBMN is, along with the IgAN, the most common cause of isolated microscopic hematuria in the pediatric age groups, as well as in adults[5]. Renal biopsy can confirm the presence of TBMN in patients who present with asymptomatic hematuria, minimal proteinuria, and normal renal function. This asymptomatic glomerular disease, also
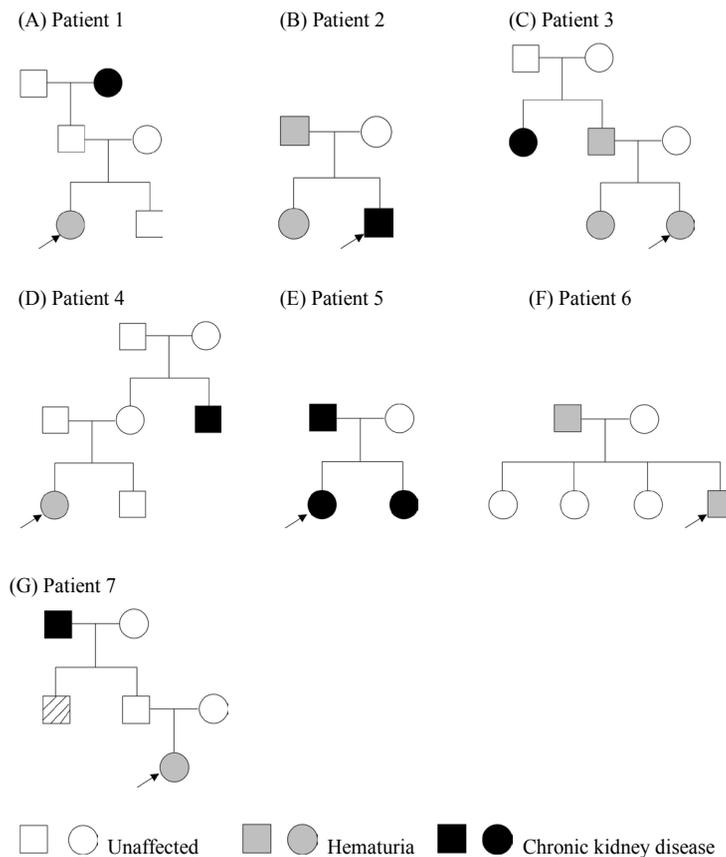

Fig. 1. Pedigree of seven patients. Arrows refers to the child with biopsy proven thin glomerular basement membrane nephropathy.

known as "familial benign hematuria," or "hereditary hematuria" is a nonprogressive disease associated with a pertinent family history as the name suggests. It is usually noticed incidentally when a patient presents to the clinic for an unrelated problem, or a routine medical examination such as a school urinary screening program[4].

It has been reported that some adults with TBMN have a poor prognosis, and the mechanism causing renal impairment associated with TBMN is usually unknown. Presumably, it is related to a misdiagnosis of IgAN, Alport syndrome, or other related conditions at the time of the patient's first visit, or the onset of a secondary disease condition.

Although electron microscopy reveals typical features of the GBM in patients diagnosed with TBMN, the features of pure TBMN are indistinguishable from the thin GBM observed in patient with early stages of Alport syndrome[5]. This relates to the fact that uniform thinning of the GBM is a histopathological finding common to those diagnosed with TBMN and Alport syndrome.

GBM is an acellular extracellular matrix demonstrating properties of a viscous gel primarily composed of type IV collagen. There are no definite criteria to define the normal GBM thickness. However, reportedly, the GBM thickness is 150 nm at birth, 200 nm at 1 year of age, and reaches its adult-level thickness at 11 years of age[5].

TBMN is currently explained as a genetic condition related to the GBM, as a common inherited disorder of type IV collagen. Type IV collagen genes, primarily, *COL4A3*, *COL4A4*, and *COL45* were discovered in the early 1990s, and 40% of TBMN cases are known to be associated with the *COL4A3* and *COL4A4* genes. *COL4A3*/*COL4A4* heterozygous mutant carriers are known to demonstrate a good renal prognosis, although 38% a relatively high number of these patients develop CKD and 19.5% progress to end-stage renal disease (ESRD)[6].

Although TBMN overlaps with Alport syndrome in terms of histopathological findings, the two are genetically heterogenous conditions. Many patients are carriers of mutations related to the autosomal recessive Alport syndrome. About 85% of patients diagnosed with Alport syndrome show mutations in the *COL4A5* gene located on the X-chromosome. This mutation is X-linked with patients progressing to a stage of ESRD. As opposed to TBMN, patients diagnosed with Alport syndrome usually show a poor prognosis manifested by increasing proteinuria and progressive renal impairment. Moreover, although not observed in all patients, many patients with Alport syndrome often demonstrate systemic clinical manifestations, such as ocular defects, and hearing loss among others[7].

Our study focused on the renal prognosis of pediatric patients diagnosed with TBMN. There were no clinical features or laboratory findings observed during follow-up to indicate decreased renal function in 58 patients diagnosed with TBMN. However, one patient revealed poor renal function with microscopic hematuria and proteinuria [blood 3+, red blood cells (RBC) many/high-power field (HPF), protein 2+, and eGFR=62.27] noted at the time of her first visit and a progressive decline in renal function (RBC 2-3/HPF, protein 2+, and eGFR=23.30) noted during the last year of her follow-up. She related a positive family history of CKD in her father and sister, which prompted genetic testing for the *COL4A5* gene, but no such mutation was detected.

Although almost all patients (58 patients except one) were observed to have normal renal function from the time of their first visit to the last one, seven patients among these related a positive family history of hematuria or renal insufficiency. Moreover, four among the 428 patients over 17 years underwent repeat renal biopsies, which showed results different from their earlier biopsies. However, there is no consensus with regard to the long-term outcomes of these patients. We could not evaluate gene studies in all patients, and there is no certainty of a good renal prognosis even though, to date, they have shown a good outcome.

We propose that establishing a diagnosis of TBMN based on immunological examination of type IV collagen and chromosome/gene studies could be an ideal method to estimate renal prognosis in patients.

A limitation of this study is the exclusion of 108 patients because of the follow-up duration smaller than 3 years, and the limited availability of family medical records about renal disease which lead to low prevalence of familial association. The exact impact of excluding data is unknown, but it is possible that it may lead to some bias. Larger scale studies over a longer duration would be required to determine the long-term prognosis of TBMN in children.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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