Clinical Evaluation of Pediatric Patients Diagnosed with Membranous Glomerulonephritis

Çocukluk Çağı Membranöz Glomerülonefrit Tanılı Hastaların Klinik Değerlendirmesi

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ABSTRACT

Objective: Membranous nephropathy (MN) is a rare immune complex disease in pediatric population then adults. The prognosis of MN is variable, ranging from spontaneous complete remission to end-stage renal disease (ESRD). The lack of large multicenter studies precludes the possibility of examining in detail the treatment options and clinical outcomes in these patients. The present study aimed to expand the literature on the clinical findings, treatment, and prognosis of MN in pediatric patients.

Material and Methods: This single-center retrospective study included 13 patients with a diagnosis of primary and secondary membranous nephropathy.

Results: The mean age of the sample was 12.29±3.67 years. Complete remission occurred in 7 (53.8%) patients (of which 1 case was spontaneous remission), and partial remission occurred in 4 (30.8%) patients. In long-term follow-ups; one patient had chronic kidney disease (CKD) and one patient had end-stage renal disease (ESRD). At the last-follow up, proteinuria was noted in 6 (46.2%) patients and microscopic hematuria was noted in 4 (30.8%) and 9 patients were still using low-dose steroids.

Conclusion: The current findings have not identified any significant risk factors associated with the prognosis of MN in pediatric patients, but are thought to contribute to the limited data on pediatric MN. Most of the available data on the natural history, treatment options, and long-term outcomes of MN in the pediatric population consists of small, uncontrolled case series. Therefore, we think that larger-scale clinical trials are necessary to clearly elucidate the factors related to the prognosis of pediatric MN.

Key Words: Childhood, Membranous glomerulonephritis, Nephrotic syndrome, Nephritic syndrome

ÖZ

Amaç: Membranöz nefropati (MN), pediatrik popülasyonda erişkin dönemden daha nadir görülen bir immün kompleks hastalığıdır. MN'nin prognozu, spontan tam remisyondan son dönem böbrek hastalığına (SDBY) kadar değişkendir. Çok merkezli geniş çalışmaların olmaması, bu hastalarda tedavi seçeneklerinin ve klinik sonuçların ayrıntılı olarak incelenmesi olasılığını engellemektedir. Bu çalışma, pediatrik hastalarda MN'nin klinik bulguları, tedavisi ve prognozu hakkındaki literatür verilerine katkı sağlamayı amaçlamaktadır.

Gereç ve Yöntemler: Bu çalışmaya primer ve sekonder MN glomerülonefrit tanılı 13 çocuk hasta dahil edilmiştir.

Bulgular: Yaş ortalaması 12.29±3.67 yıldı. Yedi (%53.8) hastada (1 olgu spontan remisyon) tam remisyon, 4 (%30.8) hastada kısmi remisyon meydana geldi. 13 hastanın 2'sinde (%15.4) böbrek yetmezliği gelişti. Son kontrolde 6 (%46.2) hastada proteinüri, 4 (%30.8) hastada mikroskobik hematüri saptandı ve 9 hasta halen düşük doz steroid kullanıyordu.

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Conflict of Interest / *Çıkar Çatışması*: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. Approval was obtained from the Clinical Research Ethics Committee of Sami Ulus Obstetrics, Gynecology and Pediatrics Training and Research Hospital (E-22/06-356 / 15.06.2022).

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How to cite / *Atıf yazım şekli* : Karakaya D, Yazılıtaş F, Kargın Çakıcı E, Güngör T, Çelikkaya E and Bülbül M. Clinical Evaluation of Pediatric Patients Diagnosed with Membranous Glomerulonephritis . Turkish J Pediatr Dis 2023;17:341-346.

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Received / Geliş tarihi : 17.01.2023
Accepted / Kabul tarihi : 13.04.2023
Online published : 24.05.2023
Elektronik yayın tarihi
DOI: 10.12956/tchd.1236249

Sonuç: Mevcut bulgular, pediatrik hastalarda MN'nin prognozu ile ilişkili herhangi bir önemli risk faktörü belirlememiştir, ancak pediatrik MN ile ilgili sınırlı verilere katkı sağlayacağı düşünülmektedir. Pediyatrik popülasyonda MN'nin doğal seyri, tedavi seçenekleri ve uzun dönem sonuçları ile ilgili mevcut verilerin çoğu küçük, kontrolsüz vaka serilerinden oluşmaktadır. Bu nedenle, pediatrik MN'nin prognozu ile ilgili faktörleri açık bir şekilde aydınlatmak için daha büyük ölçekli klinik araştırmaların gerekli olduğunu düşünüyoruz.

Anahtar Sözcükler: Çocukluk çağı, Membranöz glomerülonefrit, Nefrotik sendrom, Nefritik sendrom

INTRODUCTION

Membranous nephropathy (MN) is an immune complex disease. The prevalence of MN in adults is much higher than in the pediatric population (1,2). The incidence is 8 to 10 cases per 1 million population worldwide (3). MN has a wide range of clinical manifestations, from subnephrotic proteinuria to severe proteinuria and nephrotic syndrome.

MN can develop primarily (idiopathic) or secondary to systemic diseases, neoplasms, chronic infections, or drugs (4,5). It is often associated with concomitant diseases in children, such as systemic lupus erythematosus (SLE), hepatitis B or C infection, and drug use (4). After excluding secondary causes, idiopathic MN (IMN) is extremely rare. There are few data on the prognosis and optimal treatment of MN in children and adolescents.

The prognosis of MN is variable, ranging from spontaneous complete remission to end-stage renal disease (ESRD) (6-8). The lack of large multicenter studies precludes the possibility of examining in detail the treatment options and clinical outcomes in these patients. The present study aimed to expand the literature on the clinical findings, treatment, and prognosis of MN in pediatric patients.

MATERIALS and METHODS

This single-center study was carried out in the pediatric nephrology department of a tertiary pediatric hospital. The records of MN patients aged <18 years at the time of diagnosis between 1 January 2010 and 1 January 2022 were retrospectively reviewed. MN was diagnosed based on histopathological renal biopsy findings. Gender, age at presentation, family history, physical examination findings, and laboratory results were obtained from the patients' medical records, and were then analyzed. Physical examination findings included body weight, height, blood pressure, and the presence or absence of edema. Hypertension was defined according to the American Academy of Pediatrics 2017 Hypertension Guideline, based on gender, age, and height percentiles (9).

Laboratory findings included the serum creatinine, albumin, and cholesterol levels, complement 3 (C3) and complement 4 (C4) levels, the phospholipase A2 receptor (PLA2R) antibody level, anti-nuclear antibody (ANA) and anti-double stranded DNA (dsDNA) positivity, and hematuria. Hematuria was defined as the presence of >5 erythrocytes in urine sediment in a microscopic field. Proteinuria was defined as urinary protein level >4 $mg/m^{-2}/h^{-1}$ or a protein/creatinine ratio >0.2 g g^{-1}. Proteinuria in the nephrotic range was defined as a urinary protein level >40 $mg/m^{-2}/h^{-1}$ or a protein/creatinine ratio >2 g g^{-1}. Complete remission was defined as proteinuria <4 $mg/m^{-2}/h^{-1}$ and a protein/creatinine ratio <0.5 g g^{-1}, and partial remission was defined as a ≥50% decrease in proteinuria, as compared to baseline. The estimated glomerular filtration rate (eGFR) was calculated using the Schwartz equation. Chronic kidney disease (CKD) was defined as an eGFR <60 $mL/min^{-1}/1.73\ m^{-2}$ based on 2 consecutive exams performed ≥3 months apart (10).

Light and immunofluorescence microscopy were used for pathological evaluation of renal tissue samples. The presence or absence of interstitial disease and predominant immunoglobulin accumulation in the subepithelial space were noted with renal biopsy results. Antibodies against IgM, IgA, IgG, C4, C3, C1q, lambda, kappa, and fibrinogen were used to stain renal tissue sections.

Treatment and follow-up times were recorded for each patient. For the treatment of MN prednisolone was used together with angiotensin-converting enzyme (ACE) inhibitors for antiproteinuric effect, and second-line immunosuppressive agents (cyclophosphamide, cyclosporine, tacrolimus, mycophenolate mofetil, azathioprine and rituximab) were used according to the response to prednisolone. The study approval was obtained from the Clinical Research Ethics Committee of Sami Ulus Obstetrics, Gynecology and Pediatrics Training and Research Hospital (E-22/06-356 / 15.06.2022).

Statistical analysis

Data were analyzed using IBM SPSS Statistics for Windows v.21 (IBM Corp., Armonk, NY, USA). Data are presented as mean ± SD. The level of statistical significance was set at $p<0.050$.

RESULTS

The study included 13 patients with a mean age at presentation of 12.29 ± 3.67 years (range: 3-16 years); 3 of the patients were aged ≤10 years. The female-to-male ratio was 1.6:1. Mean follow-up time was 35.23 ± 21.69 months. In total, 7.7% of the patients had a family history of proteinuria, hematuria, or CKD. Among the patients, 5 had an underlying secondary cause of MN, as follows: hepatitis B virus infection (n = 2); hepatitis C virus infection (n = 1); SLE (n = 2). At presentation 7 (53.8%) patients had microscopic hematuria, 10 (76.9%) had peripheral edema, 11 (84.6%) had nephrotic-range proteinuria, 3 (23.1%) had hypertension, and 3 (23.1%) had macroscopic hematuria.

Table I: Baseline characteristics of the children diagnosed with MN

Characteristic	Value
Gender female*	8 (53.3)
Patient age, years,†	12.29±3.67
Follow up time, months,†	35.23±21.69
Family history*	1 (7.7)
Seconder MN*	5 (38.46)
HCV	1 (7.7)
HBV	2 (15.4)
SLE	2 (15.4)
Presenting clinical symptoms*	
Edema	10 (76.9)
Macroscopic hematuria	3 (23.1)
Microscopic hematuria	7 (53.8)
Elevated blood pressure	3 (23.1)
Nephrotic proteinüria	11 (84.6)
Laboratory findings	
24-hour protein excretion,†	202.98±124.95
Nephrotic range proteinuria*	11 (84.6)
Hypoalbuminemia*	9 (69.2)
Serum albumin levels, gr/dl,†	2.49±1.31
Serum creatinine levels, mg/dl,†	0.6±0.13
eGFR, mL/min/1.73 m^2,†	104.69±16.34
Renal insufficiency*	2 (15.4)
Treatment responses	
Complete remission*	7 (53.8)
Partially remission CKD*	4 (30.8)
KBH*	2 (15.4)

:** *n (%),* **†:** *mean ± SD,* ***eGFR: *estimated glomerular filtration rate*

At the time of presentation mean 24-h protein excretion was 202.98 ± 124.95 mg/m^{-2}/h^{-1} and 84.6% of the patients had nephrotic-range urine protein excretion. In all, 9 (69.2%) patients had hypoalbuminemia and hypercholesterolemia, with a mean serum albumin level of 2.49 ± 1.31 g dL^{-1}. The mean serum creatinine level was 0.6 ± 0.13 mg dL^{1} and the mean eGFR was 104.69 ± 16.34 mL/min^{-1}/1.73 m^{-2}. PLA2R antibodies were present in 3 (23.1%) of the 4 patients that were tested. In addition, only the 2 patients with SLE had low C3 and C4 levels. Moreover, ANA and anti-dsDNA positivity were noted in the 2 patients that developed MN secondary to SLE (Table I). Patients with primary and secondary MN, it was observed that there was no significant difference between the initial symptoms of the patients (hypertension, edema, nephrotic level proteinuria, hematuria), and laboratory findings (albumin, creatinine, and eGFR) (p>0.050).

The mean interval between referral to pediatric nephrology and kidney biopsy was 13.46 ± 4.73 day. The mean glomeruli count was 27.46 ± 15.40. Characteristic histopathological findings of MN were observed in glomeruli in all specimens. Thickening of the glomerular basement membrane was noted in 9 (69.23%) patients, of which 6 had glomerulosclerosis and 2 had tubulointerstitial minimal infiltration and tubular atrophy. Biopsy findings showed that 8 (61.5%) patients had subepithelial deposits and 5 (38.5%) had intramembranous changes.

Table II: Biopsy findings in patients with MN

Characteristic	Value
İnterstisial infiltration*	2 (15.4)
Tubular atrophy*	2 (15.4)
Presence of thickening of GBM*	9 (69.2)
Mesangial enlargement*	3 (23.1)
Glomerular sclerosis*	6 (46.1)
Subepithelial deposits*	8 (61.5)
İntramembranous deposits*	5 (38.5)
Presence of thickening of the CBM*	5 (38.5)

:** *n (%),* ***CBM: *Capillary basement membrane,* ***GBM:*** *Glomerular basal membrane*

Among these patients the predominant immunoglobulin in the subepithelial or intramembranous deposits was IgG in the 4 (30.8%), 5 (38.5%) patient had combined IgG and IgM deposition, and 4 (30.8%) had IgG, IgM, and IgA deposition (Table II).

In total, 3 (23.1%) patients were given antiviral treatment, 10 (76.9%) received an ACE inhibitor or angiotensin receptor blocker (ARB), and 10 (76.9%) patients were given prednisoloneas the first-line immunosuppressive therapy. Additional immunosuppressive therapy was not used in cases developing secondary to viral infection. The criteria for the use of prednisolonewere persistence of proteinuria after initiation of treatment with an ACE inhibitor and/or ARB. Mean duration of prednisone treatment was 16.4 ± 19.8 months. Among the patients treated with prednisolone, 8 subsequently received ≥1 second-line drug, as follows: cyclophosphamide (n = 3); cyclosporine (n = 5); tacrolimus (n = 2); mycophenolate mofetil (n=1) and azathioprine (n = 1). The 1 patient that was positive for the PLA2R antibody and resistant to treatment was given rituximab. During the study period there was a lack of consistent criteria and clinical guidelines for the administration of these agents. The cumulative duration of secondary immunosuppressive therapy was 35.50 ± 17.91 months for cyclosporine, 15.00 ± 12.72 months for tacrolimus, 6 months for cyclophosphamide, and 32.00 ± 8.48 months for mycophenolate mofetil/azathioprine. In all 3 patients with positive phosphalipase A2 receptor antibody; in addition to corticosteroid treatment, calcineurin inhibitors (CNI) were preferred as the first choice, and rituximab treatment was given in one of them. In other primary MN cases, as a second immunosuppressive (IS) treatment; CNI was and MMF was preferred.

Complete remission occurred in 7 (53.8%) patients (of which 1 case was spontaneous remission), and partial remission occurred in 4 (30.8%) patients. At the last follow-up visit the mean creatinine level was 0.91 ± 0.41 mg dL^{-1}, the mean eGFR was 92.41 ± 35.35 mL/min^{-1}/1.73 m,$^{-2}$ and the mean albumin level was 3.29 ± 0.98 g dL^{-1}. Proteinuria was noted in 6 (46.2%) patients and microscopic hematuria was noted in 4 (30.8%). At the last follow-up visit 9 patients were still using low-dose steroids. Hypertension was present in 5 patients (38.46%) and

Table III: Distribution and treatment of patients with MN

Patent Number	Age	Seconder MN	Etiology	Phosphalipase A2 receptor antibody positivity	Treatment	Remission	Complication
1	13	-	-	+	CS + CSA + Cyclophosphamide	CR	-
2	12.6	+	SLE	-	CS + Azathioprine	CR	-
3	3	+	Hepatitis B	-	Antiviral	-	ESRD + Thrombosis (Moyamoya disease)
4	15	-	-	-	CS + CSA	PR	-
5	7	+	Hepatitis C	-	Antiviral	PR	-
6	10	-	-	-	CS + CSA + Cyclophosphamide	PR	HT
7	12.9	-	-	+	CS + CSA + Tacrolimus + Rituximab	CR	HT
8	13.6	+	SLE	-	CS + Cyclophosphamide + MMF	-	CKD
9	15.6	-	-	+	CS + CSA + Tacrolimus	CR	Renal vein thrombosis
10	13.4	-	-	-	CS	CR	-
11	16	-	-	-	-	CR	-
12	14.9	-	-	-	CS	PR	-
13	12.9	+	Hepatitis B	-	An#viral	CR	-

MN: *Membranous nephropathy,* ***eGFR:*** *Estimated glomerular filtration rate,* ***CS:*** *Corticosteroid,* ***CSA:*** *Cyclosporine,* ***SLE:*** *Systemic lupus erythematosus,* ***ESRD:*** *End stage renal disease,* ***HT:*** *Hypertension,* ***CR:*** *Complete remission,* ***PR:*** *Partial remission*

edema was present in 3 (23.07%). In long-term follow-ups; one patient had CKD and one patient had ESRD. None of the clinical features at presentation, including age, gender, presence of hematuria, nephrotic-range proteinuria, or hypertension, had any predictive value for renal insufficiency. Treatment-related complications were as follows: elevated serum creatinine with cyclosporine (n = 1); and leukopenia with cyclophosphamide (n = 1). Steroid related complications as decreased bone density developed in 3, short stature developed in 1 and cataract developed in 1 patient respectively. In all, 2 patient had a history of thromboembolic events. Renal vein thrombosis was found in one patient and Moyamoya disease was found in the other. A summary of baseline characteristics and the treatments administered of MN patients is given in the Table III.

When primary MN cases with and without phosphalipase A2 receptor antibody were compared, there was no significant difference between long-term treatment responses (amount of proteinuria, albumin level, eGFR) and complete/partial remission rates. Similarly, when the cases secondary to lupus were compared with the others, it was observed that there was no significant difference between the long-term response to treatment (amount of proteinuria, albumin level, eGFR, creatinine) and the frequency of remission.

DISCUSSION

MN occurs less frequently in children than in adults. Its estimated incidence is 8-10 cases per million (11). The present single-center retrospective study included 13 MN patients over a 12-year period. Data in the literature on the prognosis of MN are limited. The present study evaluated patients in terms of prognostic factors, but a significant risk factor for renal insufficiency was not identified.

Mean age in the present study coincided with adolescence, as reported earlier (1). In 75%-80% of patients MN occurs in the absence of identifiable causes and is therefore referred to as primary MN (11). Immunohistology and disease course can differ significantly between those with primary and secondary MN; however, in children the association between MN and secondary causes is more common than primary MN (1,11,12). Particularly in patients aged <10 years the MN lesion is more often secondary to a systemic condition, with hepatitis B infection or systemic lupus SLE being the most common (3). In the present study underlying secondary causes, including hepatitis B and C virus infection, and SLE, were noted in 38.4% of the patients. While adult primary MN is seen twice as often in boys than in girls, there is no gender difference similar to our study in pediatric population generally (12).

Although MN is thought to have a more insidious onset than other glomerular diseases, it is known that approximately 80% of the cases may show signs of nephrotic syndrome (13). Hematuria accompanying proteinuria is more common in children than adults. In this study, the most common form of presentation of the patients was nephrotic syndrome. In addition, 7 (53.8%) patients had microscopic hematuria and 3 (23.1%) patients had macroscopic hematuria. Also studies on

the presence of hypertension at the time of admission in MN patients have reported that approximately 25% of them have hypertension at the time of diagnosis (1). Similarly, 3 (23.1%) patients were hypertensive when MN was diagnosed in our study. As previously reported, also in the present study the creatinine level and eGFR at the time of presentation were normal for age (1,12). In addition, patients with primary and secondary MN, it was observed that there was no significant difference between the initial symptoms of the patients (hypertension, edema, nephrotic level proteinuria, hematuria), and laboratory findings (albumin, creatinine, and eGFR) ($p>0.050$).

Autoantibodies to the M-type PLA2R initially described in adult MN patients have now been identified in children and adolescents with MN, and serve as a useful diagnostic and monitoring tool in such patients. Between 70% and 80% of patients presumed to have primary MN have PLA2R1 antibody positivity (1,11). A small percentage of patients with secondary MN also have anti-PLA2R1 antibody positivity. More importantly, it was reported that PLA2R antibody positivity has prognostic significance (1). Patients with positive PLA2R antibody titers at the time of biopsy have a lower rate of complete remission (14). Beck and Salant (15) also observed that PLA2R1 antibody titers became undetectable before proteinuria completely remitted. Anti-PLA2R1 immunosuppressive therapies have been shown to reduce PLA2R antibody titers (16). In the present study PLA2R antibody positivity was noted in 3 (23.1%) of the 4 patients tested, of which 2 had normal levels after treatment; however, complete remission of proteinuria was not observed in 1 of these patients despite a decrease in antibodies.

Based on immunofluorescence and electron microscopy, MN is morphologically characterized by thickening of the glomerular basement membrane, subepithelial immune complex deposits, and deletion of the podocyte foot process (17). Endocapillary proliferation, crescents, and necrosis are rare, except for cases with SLE. IgG deposits are subepithelial and located on the outer surface of the glomerular capillary wall (11). In addition to subepithelial deposits, the presence of electron-dense immune deposits at mesangial and/or subendothelial positions are suggestive of secondary MN. Characteristic histopathological findings of MN were observed in glomeruli in all specimens in the present study and thickening of the glomerular basement membrane was detected in 9 (69.23%) patients. In total, 6 of the presented patients had glomerulosclerosis, of which 2 also had minimal tubulointerstitial infiltration and tubular atrophy. Moreover, 8 (61.5%) patients had subepithelial deposits based on biopsy findings and 5 (38.5%) had intramembranous changes.

The first step in the treatment of MN is to differentiate between primary and secondary MN, as the treatment of secondary MN is directed towards the underlying cause. Next is supportive therapy and targeted therapy, if MN is primary. Evidence supports the use of an ACEI/ARB in cases of primary MN, and supportive treatment is recommended immediately following diagnosis to minimize protein excretion (11). In the present study antiviral treatment was administered to 3 (23.1%) patients and 10 (76.9%) patients received an ACEI or ARB. Some children diagnosed with MN can require nothing more than conservative treatment, unless severely symptomatic, but immunosuppressive therapy should be considered in patients at high risk for progressive disease or severe nephrotic syndrome (1, 11). Cyclosporine or tacrolimus are considered alternative first-line therapeutic agents.

The extent to which pediatric MN responds to steroid monotherapy is unclear. Several case series show that pediatric MN can eventually respond to corticosteroids. Valentini et al. (18) observed in a small series of idiopathic MN cases that 50% did not respond to steroids, whereas 50% had a complete or partial response. In the present study 10 (76.9%) patients were given immunosuppressive therapy with prednisolone as the first-line therapy, but 8 of these patients required ≥1 second-line drugs, as follows: cyclophosphamide (n = 3); cyclosporine (n = 5); tacrolimus (n = 2); mycophenolate mofetil (n=1) and azathioprine (n = 1).

Therapeutic agents such as rituximab are a new therapeutic option that should be considered for the treatment of primary MN (11). Some case reports describe the use of rituximab for pediatric primary/idiopathic MN. According to Malatesta et al. (19), 2 adolescent MN patients with nephrotic proteinuria and an elevated anti-PLA2R level failed to achieve remission with steroids, but were subsequently successfully treated with rituximab. In the present study rituximab was given to 1 patient with PLA2R antibody positivity that was treatment resistant, but complete remission was not achieved.

The natural course of MN is highly variable. Although spontaneous disease remission can occur in 30% of patients, MN-associated nephrotic syndrome can negatively affect renal survival, with 33% of patients progressing to ESRD within 10 years of diagnosis, although progression to ESRD is rare in the pediatric population (6,20,21). Other established risk factors for progression to ESRD included age, male gender, and a low GFR at presentation (22). It was also reported that the initial serum creatinine level alone is important for predicting progression to CKD (23).

In the present study 7 (53.8%) patients had complete remission (of which 1 had spontaneous remission) and 4 (30.8%) had partial remission. Furthermore, renal insufficiency developed in 2 (15.4%) of the 13 patients; one patient had CKD and one patient had ESRD. Evaluation of patients with and without renal insufficiency showed that there was no significant difference for age, gender, hematuria, nephrotic level proteinuria, or hypertension at first admission. The present study has some limitations, including a small patient population and retrospective design.

In conclusion, the present findings did not identify any significant risk factors associated with the prognosis of MN in

pediatric patients, but they do make a valuable contribution to the limited data on pediatric MN. Most of the available data on the natural history, treatment options, and long-term outcomes of MN in the pediatric population come from small, uncontrolled case series; therefore, we think larger scale clinical research is necessary to more clearly elucidate the association between risk factors and the prognosis of pediatric MN.

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