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## Idiopathic membranous nephropathy in children: A case report

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### Abstract

#### BACKGROUND

Minimal change disease is a common cause of nephrotic syndrome (NS) in children and has a good prognosis. Idiopathic membranous nephropathy (IMN), a rare cause of NS in children, may progress to chronic kidney disease. However, there is little data on how to evaluate and treat IMN in children.

#### CASE SUMMARY

In this article, we report the case of a 7-year-old boy with steroid-resistant NS. After cyclophosphamide pulse therapy combined with oral prednisone, the urinary protein results remained positive. Renal biopsy confirmed the pathological diagnosis of stage II MN, with positivity for phospholipase A<sub>2</sub> receptor. Other immunological and infectious diseases relevant to secondary MN were ruled out by laboratory tests. Subsequently, tacrolimus plus prednisone was administered, and the therapeutic effect was satisfactory.

#### CONCLUSION

IMN is rare in children. The main clinical manifestation is NS. The diagnosis depends on renal biopsy. There is little evidence-based data on the treatment of IMN in children. Therefore, large-sample randomized controlled trials need to be performed. Individualized treatment should be used to improve the prognosis of the disease.

**Key Words:** Idiopathic membranous nephropathy; Tacrolimus; Prednisone; Phospholipase A<sub>2</sub> receptor antibody; Renal biopsy; Children; Case report

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**Core Tip:** Here, we report the case of a school-age boy with idiopathic membranous nephropathy (IMN). IMN was diagnosed after treatment with steroids and immunosuppressants for several weeks by renal biopsy. This case highlights that individualized treatment can be used to improve the prognosis of the disease. Phospholipase A<sub>2</sub> receptor antibody levels may be valuable for early diagnosis, treatment monitoring, and follow-up.

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## INTRODUCTION

Idiopathic membranous nephropathy (IMN) is an uncommon cause of nephrotic syndrome (NS) in children, with an incidence of less than 5%[1]. The diagnosis of IMN depends on renal biopsy. IMN is an organ-specific (kidney) autoimmune disease, and its pathogenesis involves circulating antibodies binding to the intrinsic antigen on podocytes, which leads to subepithelial deposits of immune complexes[2]. To date, phospholipase A<sub>2</sub> receptors (PLA<sub>2</sub>Rs) on podocytes have been considered to be the primary antigen, and the rate of PLA<sub>2</sub>R positivity in the renal tissue of children with IMN is nearly 32%[3]. Circulating autoantibodies to PLA<sub>2</sub>R have been confirmed in approximately 80% of adults with IMN and are seldom detected in secondary MN[4]. Some studies have indicated that the titer of anti-PLA<sub>2</sub>R antibodies reflects disease activity and urinary protein levels. A high titer of antibodies is correlated with a great risk of deterioration in renal function and minimal chance of remission[5]. Although the possibility of spontaneous remission in children with IMN is greater than that in adults, personalized therapy must be adopted because there is no evidence-based standard treatment for IMN in children. Steroids and immunosuppressant drugs are popular treatment options for this disease; however, which immunosuppressant drug should be used and for how long still need to be determined[6].

There were no reports of tacrolimus in the treatment of idiopathic nephropathy in children. Here, we describe a child with IMN who presented with NS and was followed for a long period of time. Initially, high-dose methylprednisolone pulse therapy followed by prednisone therapy failed to eliminate the presence of urinary proteins. Renal biopsy and other specific tests were performed to confirm the diagnosis of IMN. Consequently, tacrolimus was added, and the therapeutic effect was satisfactory. By reviewing the literature on the therapeutic strategies for and prognosis of IMN in children, we aimed to better manage this disease.

## CASE PRESENTATION

### Chief complaints

A 7-year-old boy was admitted to our hospital (West China Second University Hospital of Sichuan University, Chengdu, Sichuan, China) in August 2020 with "repeated edema over the past 6 mo".

### History of present illness

Six months prior to admission, the patient developed facial edema and was diagnosed with idiopathic NS due to nephrotic proteinuria (24-h urinary protein 2.51 g), hypoproteinemia (albumin 20 g/L), and hyperlipidemia (serum cholesterol 6.29 mmol/L). At the same time, hematuria and leukocyturia were observed, without hypertension or abnormal renal function. Initially, the patient was treated with oral prednisone (2 mg/kg·d) and captopril (0.5-1.0 mg/kg·d) for 4 wk in another hospital (The First People's Hospital of Sichuan Liangshan Yi Autonomous Prefecture, Liangshan Yi Autonomous Prefecture, Sichuan, China). However, the presence of urinary proteins persisted. Subsequently, the urinary protein fluctuated between 1+ and 3+ after methylprednisolone pulse therapy (20 mg/kg·d) for 3 d followed by oral prednisone (2 mg/kg·d) for 2 wk. Captopril (1 mg/kg·d) was prescribed as maintenance therapy for the patient. Early-onset steroid resistance was considered; consequently, immunosuppressant drugs were added. The doctor administered cyclophosphamide (CTX) pulse therapy (8 mg/kg, used for two consecutive days, every 2 wk), and the prednisone was gradually tapered by 5-10 mg every 4 wk. After six CTX treatments, the urinary protein results remained positive. Because of the poor therapeutic effects, the patient was transferred to our hospital and was admitted to the Nephrology Department on October 28, 2020.

**Table 1 Results of laboratory tests performed at our hospital**

	Index	Result	Reference range
Blood count	White blood cell count ( $10^9/L$ )	7.23	3.6-9.7
	Hemoglobin (g/L)	120	110-146
	Platelet count ( $10^9/L$ )	379	100-450
Urinary chemistry	Urinary protein (g/24 h)	2.51	0-0.15
	Urinary protein	4+	Negative
	Urinary red blood cell count (cells/HP)	4+	0-3
	Urinary leukocyte count (cells/HP)	4+	0-5
	Pathological casts	Positive	Negative
Serum chemistry	Albumin (g/L)	20	35-50
	Total cholesterol (mmol/L)	6.29	< 5.18
	Triglyceride (mmol/L)	1.38	< 1.7
	Blood urea nitrogen (mmol/L)	4.76	3.2-7.1
	Serum creatinine ( $\mu\text{mol/L}$ )	35	17.3-54.6
Immunology	Immunoglobulin G (g/L)	2.21	5.29-21.9
	Immunoglobulin A (g/L)	0.39	0.41-3.95
	Immunoglobulin M (g/L)	0.96	0.48-2.26
	Immunoglobulin E (g/L)	17.2	< 90
	Complement C <sub>3</sub> (g/L)	0.98	0.7-2.06
	Complement C <sub>4</sub> (g/L)	0.18	0.11-0.61
	Complement C <sub>1q</sub> (mg/dL)	23.9	15.7-23.7

Note: Bold font indicates abnormal values.

### **History of past illness**

The patient had no history of other illnesses and no known allergies.

### **Personal and family history**

The patient did not have any relevant family history.

### **Physical examination**

The patient's temperature, arterial pressure, weight, height, respiration rate, and heart rate were 36.5 °C, 110/65 mmHg, 26 kg, 115.9 cm, 22 times per minute, and 95 times per minute, respectively. A moon face and eyelid edema were observed on October 28, 2020.

### **Laboratory examinations**

The laboratory test results revealed heavy proteinuria, hypoproteinemia, hyperlipidemia, leukocyturia, hematuria, and pathological casts (Table 1). The blood count, complement protein levels, and renal function were normal on October 28, 2020.

### **Imaging examinations**

The computerized tomography (CT) scan was normal. Urinary ultrasound showed a slightly enhanced echo in the bilateral renal parenchyma on October 28, 2020.

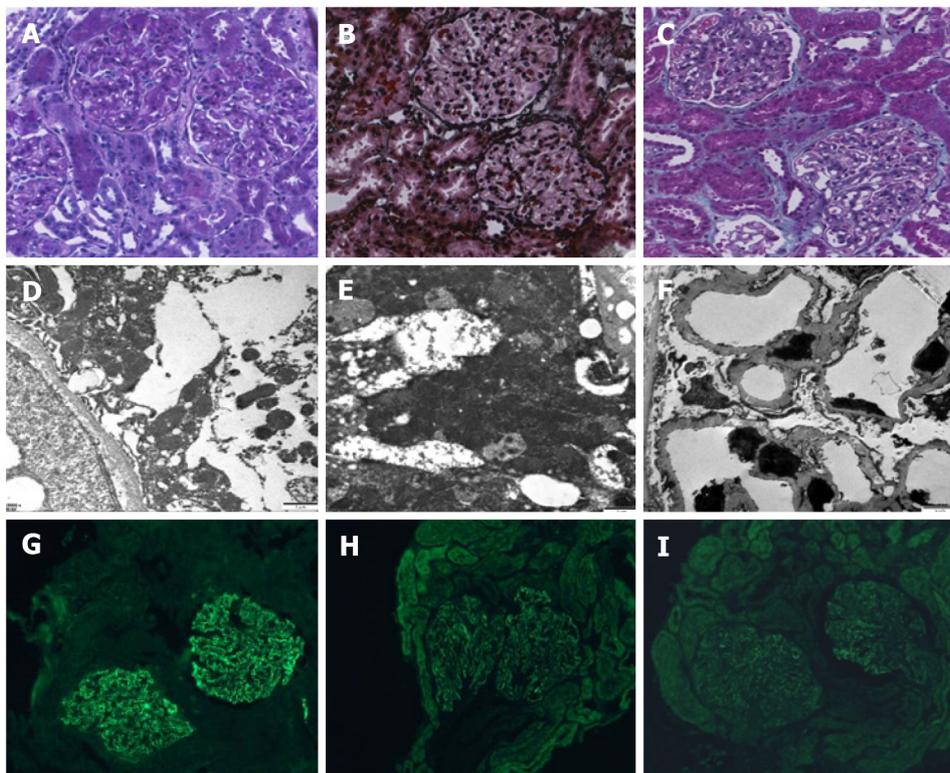
### **Pathological examination**

To further evaluate if the patient was steroid-resistant, renal biopsy was performed on October 30, 2020. No glomerulosclerosis, segmental sclerosis, or crescents was found. Obvious diffuse thickening of the basement membrane with several spiky formations, subepithelial deposition of fuchsinophilic protein, and vacuolar and granular degeneration in the renal tubular epithelial cells, without wire-loop lesions, were revealed by light microscopy. Irregular thickening of the basement membrane, along with electron-dense deposits in the subepithelial and intrabasal areas, and diffuse fusion of the foot processes

**Table 2 Results of urinalysis during follow-up**

Time of follow-up (d)	Urinary proteinuria	Urinary RBC count (cells/ $\mu$ L)	Urinary WBC count (cells/ $\mu$ L)	Urinary pathologic casts (cells/ $\mu$ L)
0	4+	1066	98	14
16	2+	280	9	0
60	3+	325	34	0
77	3+	1689	91.9	4.81
118	3+	1286	14	0
130	Negative	53	3	0
144	Negative	59	10	0

RBC: Red blood cell; WBC: White blood cell.



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**Figure 1 Representative images of pathological changes on renal biopsy.** Diffuse thickening of the basement membrane with several spiky formations, subepithelial deposition of fuchsinophilic protein, and vacuolar and granular degeneration of renal tubular epithelial cells were observed. A: Light microscopy (Periodic acid-Schiff,  $\times 400$ ); B: Light microscopy (Periodic acid-silver methenamine,  $\times 400$ ); C: Light microscopy (Masson staining,  $\times 400$ ); D-F: Irregular thickening of the basement membrane, electron-dense deposits in the subepithelial and intrabasal areas, and diffuse fusion of the foot processes (electron microscopy,  $\times 6000$ ); G: Depositions of immunoglobulin G (IgG) along the mesangial area and the capillary wall (immunohistochemical staining,  $\times 400$ ); H: Depositions of IgG<sub>1</sub> along the mesangial area and the capillary wall (immunohistochemical staining,  $\times 400$ ); I: Depositions of IgG<sub>4</sub> along the mesangial area and the capillary wall. Positivity for phospholipase A<sub>2</sub> receptor and negativity for thrombospondin type-1 domain-containing 7A are shown (immunohistochemical staining,  $\times 400$ ).

of epithelial cells were suggested based on electron microscopy. The immunofluorescence results were as follows: Immunoglobulin A (IgA) -, IgG +++, IgM +, C<sub>3</sub> +, complement C<sub>1</sub>q -, and fibrinogen -. Immunohistochemical staining for IgG subtypes indicated deposition of IgG<sub>1</sub> and IgG<sub>4</sub> along the glomerular capillary wall, with PLA<sub>2</sub>R + and thrombospondin type-1 domain-containing 7A -, as shown in [Figure 1](#).

#### Further diagnostic work-up

To exclude secondary MN, we performed analyses of anti-streptolysin O, autoantibodies, anti-neutrophil cytoplasmic antibodies, and complement proteins, tested for the hepatitis virus, syphilis,

**Table 3 Differences between idiopathic membranous nephropathy and minimal change disease in children**

		IMN	MCD
General features	Sex	Male	Male
	Age	Adolescence	Preschool age
Clinical manifestations	Nephrotic syndrome	Common	Common
	Leukocyturia	Some	Rare
	Hematuria	Some	Rare
	Hypertension	Some	Rare
	Renal failure	Some	Rare
Laboratory tests	Anti-PLA <sub>2</sub> R, antibody	Elevated	Normal
	Anti-THSD7A, antibody	Elevated	Normal
Treatment strategy	Prednisone	Mostly resistance	Mostly sensitive
	Immunosuppressant	Tacrolimus, cyclophosphamide, mycophenolate mofetil	Rare
	Biological agent	Rituximab	Rare

PLA<sub>2</sub>R: Phospholipase A<sub>2</sub> receptor; THSD7A: Thrombospondin type-1 domain-containing 7A; IMN: Idiopathic membranous nephropathy; MCD: Minimal change disease.

acquired immunodeficiency syndrome, and tuberculosis, and performed a urine culture, sputum culture, and plain chest CT scan, which were all negative.

## FINAL DIAGNOSIS

Renal biopsy confirmed the pathological diagnosis of stage II IMN. The pathological changes of IMN include thickened glomerular basement membranes under a light microscope, with immunofluorescence examination showing granular staining for IgG, IgM, C<sub>3</sub> and PLA<sub>2</sub>R along the periphery of glomerular capillary loops, and electron-dense subepithelial deposits under an electron microscope. After ruling out other immunological and infectious diseases relevant to secondary MN with other laboratory tests, IMN was identified.

## TREATMENT

In view of the patient's poor response to steroids and CTX, we changed the therapeutic strategy to include tacrolimus (0.07 mg/kg·d), and at the same time, prednisone was gradually decreased referencing 2019 Kidney Disease Improving Global Outcomes.

## OUTCOME AND FOLLOW-UP

On January 4, 2021, after 49 d of treatment using tacrolimus and prednisone, the urine protein results and urinary pathologic casts were negative. The red blood cell count in the urine decreased to 59 cells/ $\mu$ L, and the white blood cell count in the urine decreased to 10 cells/ $\mu$ L. Throughout a 5-mo follow-up period, the patient showed an uneventful clinical course, and the steroids were progressively decreased. Kidney function remained normal in the patient during follow-up. The urinalysis results during the follow-up are shown in [Table 2](#).

## DISCUSSION

IMN is a rare cause of NS in children. Here, we report the case of a school-age boy with steroid-resistant NS. IMN was diagnosed by renal biopsy, with PLA<sub>2</sub>R +. The therapeutic effect of tacrolimus plus prednisone was satisfactory. In this article, we described a 7-year-old boy with stage II IMN confirmed by renal biopsy and other laboratory tests. Initially, prednisone and CTX were given for several months,

but remission was not achieved. After tacrolimus was substituted for CTX, the proteinuria gradually became negative. IMN patients who present with NS need to receive steroid therapy for several weeks initially. If the therapeutic effect is not satisfactory, immunosuppressant drugs should be added to the treatment regimen for these patients. However, which immunosuppressant drug should be used and for how long are still unclear. Alkylating agents remain the only agents proven to be effective in preventing end-stage renal disease or death[6]. Rituximab may be considered for children who do not respond to hormonal or immunosuppressant therapy[6]. Other studies have reported that tacrolimus and CTX are superior to other immunosuppressant drugs in terms of complete remission rate, and tacrolimus monotherapy is also the safest and most effective choice for IMN with stable renal function[7]. A regimen of prednisone plus tacrolimus could undoubtedly yield a higher remission rate and long-term safety. More than 60% of patients can reach complete remission or partial remission in 24 mo, and relapse is rare[8]. In terms of other immunosuppressant drugs, the remission rate associated with the use of glucocorticoids and CTX in IMN is only 58.6%[9].

Minimal change disease (MCD) is a common cause of NS in children and has a good prognosis. However, IMN is rare and has a poor prognosis in children. Especially in children with IMN who present with NS, it is necessary to carefully evaluate and select a reasonable therapeutic strategy as early as possible to improve the prognosis. Due to the lower morbidity of IMN in children, there are few relevant data on therapeutic strategies for and evaluation of children with IMN, and there is a notable lack of large-sample randomized controlled trials (RCTs). Most of the current studies were retrospective studies or case reports. IMN in children is more common in men and in adolescents. Studies indicated that the most prominent clinical manifestation was NS, which was accompanied by various degrees of edema, hyperlipidemia, hypoalbuminemia, and nephrotic proteinuria[7]. Hypertension, hematuria, and renal injury were also observed[9]. All reported cases were resistant to hormones[10,11]. In children with MN, PLA<sub>2</sub>R-associated MN appears to be common. PLA<sub>2</sub>R antibody levels are closely associated with disease activity, whereas PLA<sub>2</sub>R antibody-negative patients often have a good prognosis[4]. MCD in children is common in male preschool children. NS is the main clinical manifestation, and it can be mitigated by hormone therapy in 90%-95% of cases[12]. We summarize the differences between IMN and MCD to better identify and address IMN at the early stage, as shown in Table 3.

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## CONCLUSION

IMN is rare in children. The main clinical manifestations are edema and NS. The diagnosis depends on renal biopsy. PLA<sub>2</sub>R antibody should be used to monitor treatment and follow-up. There is little evidence-based data on the treatment of IMN in children. Therefore, large-sample RCTs need to be performed. Individualized treatment should be used to improve the prognosis of the disease. In the future, for children who are not simple NS, we hope to detect serum PLA<sub>2</sub>R antibody to early predict MN and its prognosis.

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## FOOTNOTES

**Author contributions:** Cui KH collated the patient data and drafted the manuscript; Zhang H analyzed the patient's clinical course and outcomes, interpreted the findings, and critically reviewed the manuscript; Tao YH helped modify the manuscript; all authors read, critically reviewed, and provided feedback on the manuscript; and all authors approved the final manuscript.

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