



Nephrotic syndrome: what's new, what's hot?

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While the incidence of nephrotic syndrome (NS) is decreasing in Korea, the morbidity of difficult-to-treat NS is significant. Efforts to minimize treatment toxicity showed that prolonged treatment after an initial treatment for 2–3 months with glucocorticosteroids was not effective in reducing frequent relapses. For steroid-dependent NS, rituximab, a monoclonal antibody against the CD20 antigen on B cells, was proven to be as effective, and short-term daily low-dose steroids during upper respiratory infections reduced relapses. Steroid resistance or congenital NS are indications for genetic study and renal biopsy, since the list of genes involved in NS is lengthening.

Key words: Nephrotic syndrome, Rituximab, Prednisolone

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Introduction

Nephrotic syndrome (NS) in children is a disease of glomerular filtration barrier failure, manifesting with severe proteinuria leading to hypoalbuminemia, hypercholesterolemia, and generalized edema. In this work, recent advances regarding idiopathic pediatric NS are reviewed.

Incidence

The prevalence of NS is 12–16 per 100,000 children¹⁾ with an annual incidence of 2–7 cases per 100,000 children. According to the Health Insurance Review and Assessment service (HIRA, <http://www.hira.or.kr>) of Korea, 4,342 patients younger than 20 years were treated for NS in 2009, while in 2013 the number of NS patients decreased to 2,795 (Fig. 1). Korean data show male to female ratio is 1.78–2.22 and prevalence of 37.0 in 2009 and 25.8 in 2013 per 100,000 children. Notably, prevalence according to HIRA may not be accurate because secondary NS, such as in Henoch-Schönlein nephritis, is not excluded, and the Korean Standard Classification of Disease (KCD-6), on which the HIRA data is based, is coded by individual users; nevertheless, prevalence of NS seems to be decreasing in Korea. Since it is known that NS is more common in developing countries, the decrease in NS in this country may be natural.

Clinical course

Twenty percent of idiopathic NS does not respond to steroid treatment. In addition to steroid resistance, frequent relapses and steroid dependence are concerns. Younger age, male gender, a history of atopy, longer time to first remission, a shorter time from remission to first relapse, and glucocorticoid receptor gene *NR3C1* GR-9beta+TthIII-1 variants have

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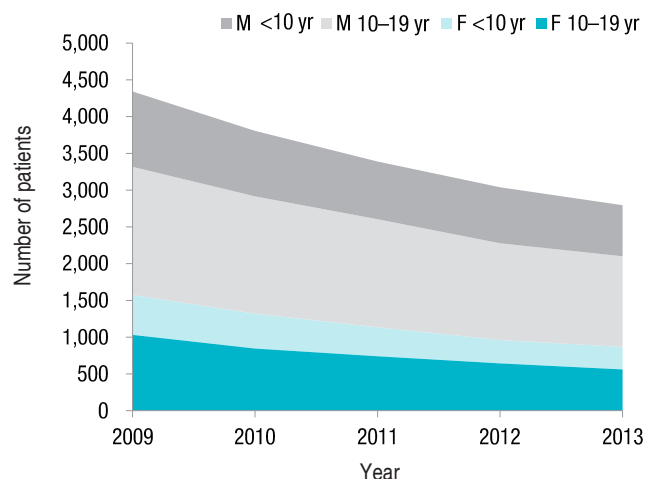


Fig. 1. Number of patients younger than 20 years old treated for nephrotic syndrome from 2009 to 2013, according to the Health Insurance Review and Assessment service (<http://www.hira.or.kr>).

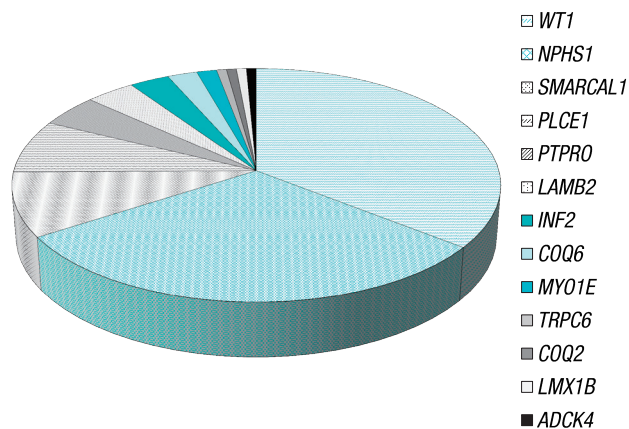


Fig. 2. Genetic causes of steroid-resistant and congenital nephrotic syndrome in children: The PodoNet Registry Cohort of Europe⁹. *NPHS2* was excluded, since it is rare in Korea.

been linked to frequent relapse and steroid dependence²⁻⁵. One-third of patients do not have frequent relapses, and remission status at 6 months after initial presentation is a predictor of non-frequent relapser⁶. In the 3 years after initial presentation, the relapse rate will decrease, and 80% will be in remission in 8 years⁶.

More than 15% of steroid-resistant NS (SRNS) will progress to end-stage renal disease (ESRD). Some of these will be found to have genetic NS (Table 1); detection of genetic causes in NS is an indication for cessation of immunosuppressive medications, because genetic NS does not respond to these, and inevitably progresses to ESRD. In contrast to idiopathic SRNS or focal segmental glomerulosclerosis (FSGS), with a recurrence rate of up to 50% after kidney transplantation (KT), genetic NS typically does not recur after KT⁷.

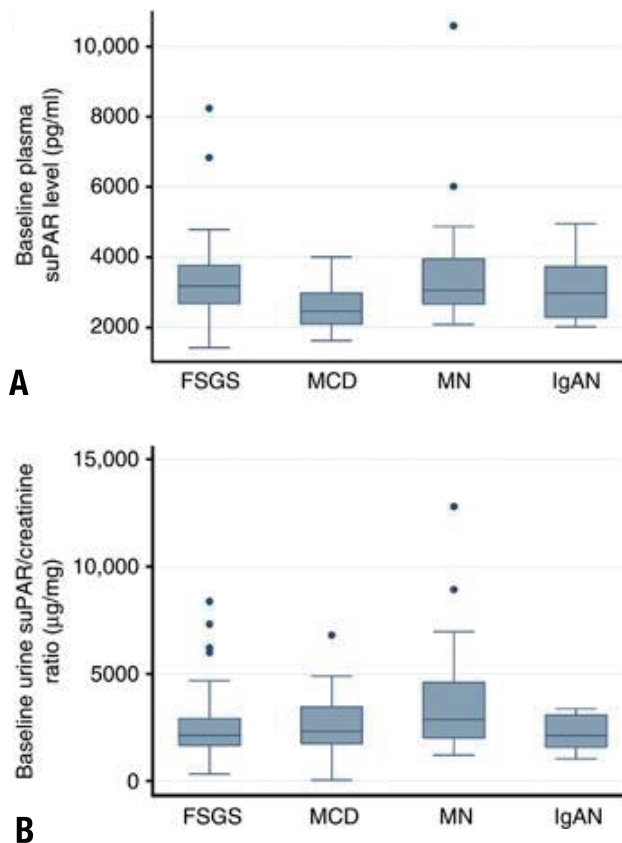


Fig. 3. Baseline plasma and urine soluble urokinase-type plasminogen activator receptor (suPAR) concentrations by pathological diagnosis. (A) Baseline plasma suPAR concentration from 183 Nephrotic Syndrome Study Network (NEPTUNE) participants is plotted by diagnosis. Although minimal change disease (MCD) participants had a statistically significantly ($P<0.01$), lower median plasma suPAR concentration, as compared with all the other groups, this difference did not persist after adjustment for differences in estimated glomerular filtration rate. (B) Baseline urine suPAR/creatinine ratio from a 24-hour urine specimen in 173 NEPTUNE participants is plotted by diagnosis. Although membranous nephropathy (MN) participants had a statistically significantly greater median urine suPAR/creatinine ratio, as compared with focal and segmental glomerulosclerosis (FSGS) and immunoglobulin A nephropathy (IgAN) ($P=0.01$ and $P=0.02$, respectively), this difference did not persist after adjustment for differences in baseline urine protein. Adapted from Spinale JM, et al. *Kidney Int* 2015;87:564-74, with permission of International Society of Nephrology¹³.

Etiology

While the etiology of NS is not clear, conditions accompanying NS, such as leukemia/lymphoma and Kimura disease, suggest that the pathophysiology is immune-mediated.

1. Genetic causes of SRNS/congenital NS

Genetic causes need to be considered for patients with SRNS, congenital NS, family history of NS, and extrarenal involvement. Currently, there are 10 genes with names containing *NPHS* (auto-

Table 1. Causative genes of nephrotic syndrome/focal segmental glomerulosclerosis

Gene ID	MIM No.	Description	NPHS (AR)	FSGS (AD)	Characteristics
<i>NPHS1</i>	602716	nephrosis 1, congenital, Finnish type (nephrin)	NPHS1		
<i>EMP2</i>	602334	epithelial membrane protein 2	NPHS10		
<i>NPHS2</i>	604766	nephrosis 2, idiopathic, steroid-resistant (podocin)	NPHS2		
<i>PLCE1</i>	608414	phospholipase C, epsilon 1	NPHS3		
<i>WT1</i>	607102	Wilms tumor 1	NPHS4		
<i>LAMB2</i>	150325	laminin, beta 2 (laminin S)	NPHS5		
<i>PTPRO</i>	600579	protein tyrosine phosphatase, receptor type, O	NPHS6		
<i>DGKE</i>	601440	diacylglycerol kinase, epsilon 64 kDa	NPHS7		
<i>ARHGDI1A</i>	601925	Rho GDP dissociation inhibitor (GDI) alpha	NPHS8		
<i>ADCK4</i>	615567	aarF domain containing kinase 4	NPHS9		
<i>ACTN4</i>	604638	actinin, alpha 4		FSGS1	
<i>TRPC6</i>	603652	transient receptor potential cation channel, subfamily C, member 6		FSGS2	
<i>CD2AP</i>	604241	CD2-associated protein		FSGS3	
<i>APOA1</i>	107680	apolipoprotein A-I		FSGS4	
<i>INF2</i>	610982	inverted formin, FH2 and WH2 domain containing		FSGS5	
<i>MYO1E</i>	601479	myosin 1E		FSGS6	
<i>PAX2</i>	167409	paired box 2		FSGS7	
<i>ANLN</i>	616027	anillin, actin binding protein		FSGS8	
<i>CRB2</i>	609720	crumbs family member 2		FSGS9	
<i>COL4A3</i>	120070	collagen, type IV, alpha 3 (Goodpasture antigen)			
<i>COL4A4</i>	120131	collagen, type IV, alpha 4			
<i>COQ2</i>	609825	coenzyme Q2 4-hydroxybenzoate polyprenyltransferase			Early myoclonic epilepsy, HCMP
<i>COQ6</i>		coenzyme Q6 monooxygenase			Sensorineural deafness
<i>EXT1</i>	608177	exostosin glycosyltransferase 1			Multiple exostoses
<i>GATA3</i>	131320	GATA binding protein 3			HDR syndrome
<i>ITGA3</i>	605025	integrin, alpha 3 (antigen CD49C, alpha 3 subunit of VLA-3 receptor)			Interstitial lung disease and CNS
<i>LMX1B</i>	602575	LIM homeobox transcription factor 1, beta			Nail-patella syndrome
<i>MYH9</i>	160775	myosin, heavy chain 9, non-muscle			Fechtner syndrome
<i>PDSS2</i>	610564	prenyl (decaprenyl) diphosphate synthase, subunit 2			Leigh syndrome with CoQ10 deficiency
<i>SCARB2</i>	602257	scavenger receptor class B, member 2			Myoclonic epilepsy
<i>SMARCA1</i>	606622	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a-like 1			Schimke immuno-osseous dysplasia
<i>WDR73</i>	616144	WD repeat domain 73			Galloway-Mowat
<i>NEIL1</i>	608844	nei endonuclease VIII-like 1 (<i>Escherichia coli</i>)			Candidate?

MIM, Mendelian Inheritance in Man; HCMP, hypoparathyroidism, sensorineural deafness and renal disease; CNS, central nervous system; CoQ10, coenzyme Q10.

somal recessive nephrotic syndrome), and 9 with FSGS (autosomal dominant FSGS, Table 1). Recent studies reported that 20%–30% of childhood-onset SRNS or congenital NS cases involved genetic causes^{8,9)} (Fig. 2). While *NPHS2* is the most common causative gene for European SRNS/congenital NS, in Northeastern Asia, the *NPHS2* mutation is rare¹⁰⁾; otherwise, genetic distribution is similar, with *WT1* and *NPHS1* (encoding nephrin) being the most common.

2. Circulating factor for FSGS

For SRNS, especially with recurrence after KT, a circulating fac-

tor has been hypothesized¹¹⁾. Soluble urokinase receptor (suPAR) has recently been suggested as this factor¹²⁾. However, elevated suPAR did not induce proteinuria or FSGS in a recent study, and did not indicate FSGS clinically¹³⁾ (Fig. 3).

3. Angiopoietin-like 4 as a mediator of persistent proteinuria and hyperlipidemia

Circulating angiopoietin-like 4 (Angptl4) level rises in response to proteinuria and increased serum free-fatty acids, via peroxisome proliferator-activated receptors (PPAR) α and PPAR γ . It binds to $\alpha v \beta 5$ integrin on glomerular endothelial cells, leading to a

decrease in the severity of proteinuria¹⁴; in the circulation, Angptl4 inhibits lipoprotein lipase, leading to hyperlipidemia (Fig. 4). On the other hand, podocyte-producing hyposialylated Angptl4 is pro-proteinuric, suggesting the therapeutic potential of mutant Angptl4 as an antiproteinuric agent¹⁵.

4. Target antigen of membranous nephropathy

While membranous nephropathy (MN) accounts for only a small portion of pediatric NS, an interesting discovery is worth

mentioning. In addition to neutral endopeptidase of antenatal MN¹⁶, an M-type phospholipase A2 receptor on the basal surface of podocytes has recently been identified as a target antigen in idiopathic MN (IMN), with autoantibodies in the circulation of more than 70% of patients with IMN¹⁷. For some patients, a thrombospondin type-1 domain-containing 7A was identified as a target antigen in MN¹⁸.

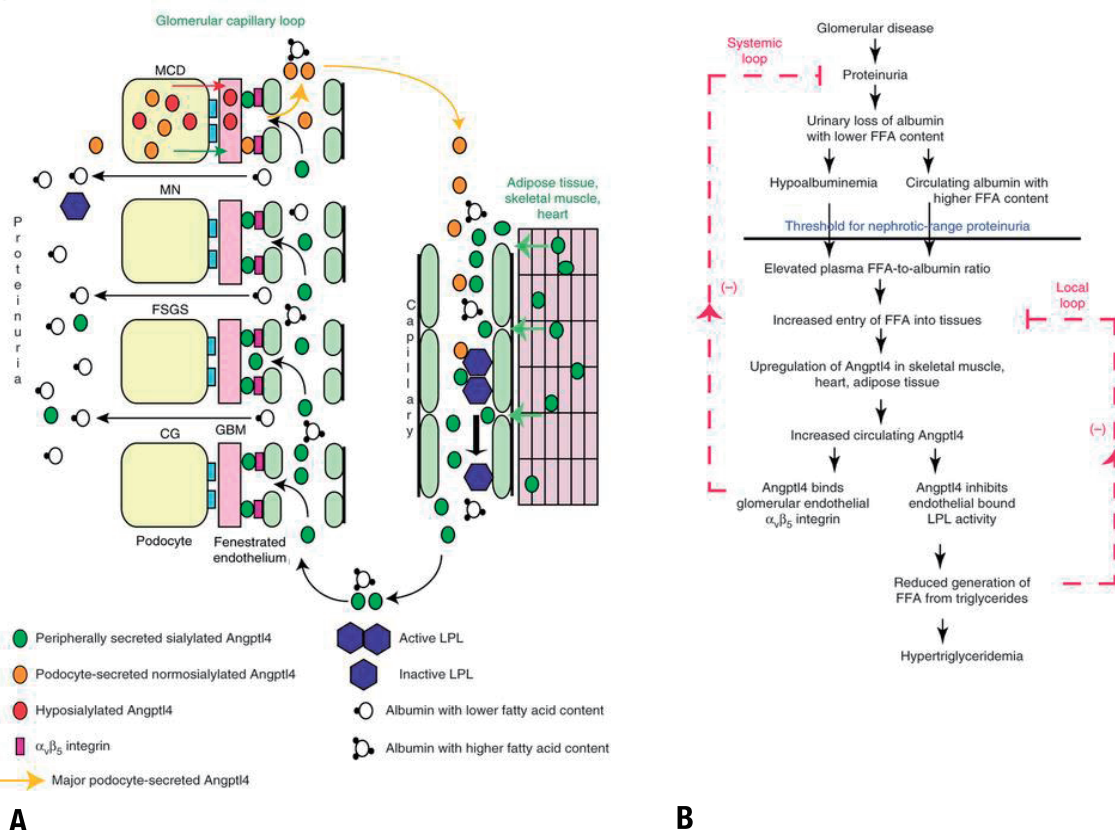


Fig. 4. Pathobiology of circulating Angptl4 in nephrotic syndrome. (A) Diagram representing the production of circulating Angptl4 protein and its biological effects. The circulating, normosialylated form of Angptl4 is secreted from peripheral organs (mostly skeletal muscle, heart, and adipose tissue) in minimal change disease (MCD), membranous nephropathy (MN), focal and segmental glomerulosclerosis (FSGS), and collapsing glomerulopathy (CG). In addition, podocytes in MCD secrete a hyposialylated form of the protein that remains restricted to the kidney and induces proteinuria and a normosialylated form that enters the circulation. Circulating Angptl4 binds to glomerular endothelial $\alpha_v\beta_5$ integrin to reduce proteinuria, or inactivates endothelium-bound lipoprotein lipase (LPL) in skeletal muscle, heart, and adipose tissue, to reduce the hydrolysis of plasma triglycerides to free fatty acids (FFA), resulting in hypertriglyceridemia. Some Angptl4 and LPL are lost in the urine. (B) Schematic illustration of negative feedback loops in the link between proteinuria, hypoalbuminemia, and hypertriglyceridemia that are mediated by Angptl4 and FFA (unesterified fatty acids with a free carboxylate group). Plasma FFAs are noncovalently bound to albumin, and because of the preferential loss of albumin with low FFA content during proteinuria, albumin with higher FFA content is retained in circulation. As glomerular disease progresses and proteinuria increases, hypoalbuminemia develops, and the combination of high albumin-FFA content and lower plasma albumin levels increases the plasma ratio of FFAs to albumin. This increased available FFA enters the skeletal muscle, heart, and adipose tissue to induce up-regulation of Angptl4, mediated at least in part by Ppar proteins. Angptl4 secreted from these organs participates in two feedback loops. In the systemic loop, it binds to glomerular endothelial $\alpha_v\beta_5$ integrin and reduces proteinuria. In a local loop, it inhibits LPL activity in the same organs from which it is secreted, to reduce the uptake of FFAs, thereby curtailing the stimulus for its own up-regulation. Adapted from Clement LC, et al. Nat Med 2014;20:37-46, with permission of Macmillan Publishers Limited¹⁵.

Diagnosis

1. Renal biopsy and diagnosis of FSGS

Pretreatment renal biopsy is necessary when the clinical profile of an NS patient is atypical. Therefore, if a patient is too young (<1 year) or too old (>12 years), has chronic infection, hypertension, azotemia, hematuria ($\geq 30\text{--}49$ red blood cells/high-power field)¹⁹, hypocomplementemia, or other findings implying another autoimmune disease, biopsy is indicated.

Diagnosis of FSGS on pathology may be missed due to sampling error; therefore, follow-up biopsy is required in some cases. On the other hand, diagnosis does not always imply primary FSGS, since FSGS may occur as a consequence of nephron mass reduction or renal damage. Secondary FSGS usually does not cause severe hypoalbuminemia, and electron microscopic examination often shows segmental foot process effacement, in contrast to the widespread foot process effacement in INS²⁰ (Fig. 5). This differentiation is necessary because immunosuppressive treatment is not effective for secondary FSGS.

2. Urinary marker of minimal change disease

Responsiveness to oral corticosteroid treatment is considered a clinical diagnosis of minimal change disease (MCD). Experimental models of NS have shown urinary CD80 levels are significantly elevated in MCD but not in others, and Ling et al. also reported similar findings in a clinical setting²¹.

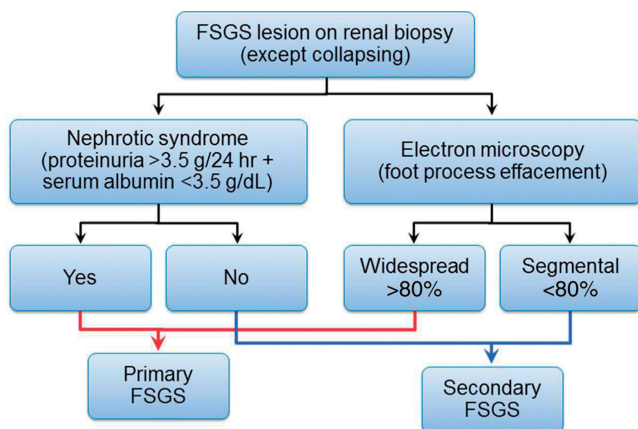


Fig. 5. Proposed diagram to differentiate between primary and secondary focal segmental glomerulosclerosis (FSGS) based on clinical presentation and electron microscopic examination (collapsing FSGS is excluded). Adapted from Sethi S, et al. *Nephrol Dial Transplant* 2015;30:375-84, with permission of European Renal Association - European Dialysis and Transplant Assoc²⁰.

Treatment

1. Duration of initial oral steroid treatment for steroid-sensitive NS

KDIGO (Kidney Disease: Improving Global Outcomes) published a guideline on glomerulonephritis in 2012 (<http://kdigo.org/home/glomerulonephritis-gn/>) including NS^{22,23}. It is recommended that oral corticosteroid therapy (prednisone, prednisolone, or deflazacort, 60 mg/m²/day or 2 mg/kg/day, up to 60 mg daily for 4–6 weeks; followed by 40 mg/m² or 1.5 mg/kg every other day) be given for at least 12 weeks, and continued for 2–5 months, with slow tapering. However, recent, large, randomized prospective studies state otherwise^{3,24,25} (Fig. 6); slow tapering did not reduce the relapse rate or incidence of frequent relapses²⁴⁻²⁶. Therefore, overtreatment with long-term steroids is not recommended, until novel biomarkers indicating otherwise become available.

2. Steroid-sparing calcineurin inhibitors

For frequently relapsing or steroid-dependent NS (SDNS) and SRNS, a calcineurin inhibitor (CNI) is recommended as a steroid-sparing agent^{22,23}.

3. Rituximab

Rituximab (RTX) is a monoclonal antibody against the CD20 antigen on B cells, developed as a chemotherapeutic agent for B-cell lymphoma. The efficacy of this agent in NS was discovered when a patient with recurrent FSGS after KT, who had concurrent posttransplant lymphoproliferative disease, responded to RTX²⁷. A few randomized, prospective trials on SDNS patients proved its efficacy, with a reduced relapse rate^{28,29}, and RTX is now considered a steroid- or CNI-sparing agent in SDNS³⁰, enabling im-

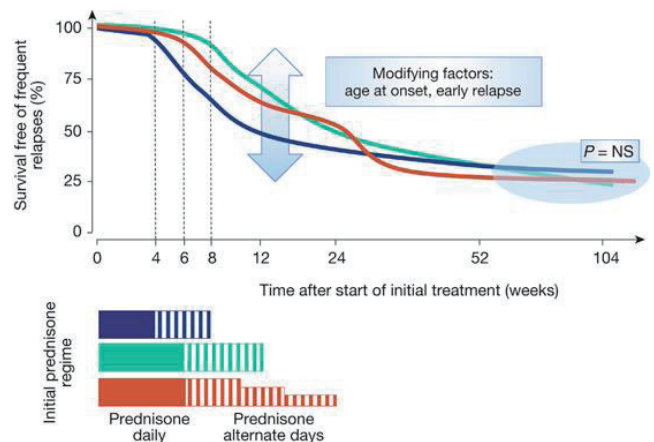


Fig. 6. Lack of effect of extending initial prednisone treatment on long-term freedom from frequent relapses. NS, not significant. Adapted from Hoyer PF. *Kidney Int* 2015;87:17-9, with permission of International Society of Nephrology³.

proved growth and reduction of obesity³¹). However, complications such as agranulocytosis (~10%) were reported³², and careful monitoring is therefore necessary after RTX treatment. RTX as an initial treatment of NS has not been reported.

While RTX treatment may maintain remission in the majority of SDNS patients, the effect often wanes over time, and many patients relapse 6 to 9 months after RTX treatment, with reappearance of CD19 (a marker of B cells)³³. Maintenance with mycophenolate mofetil or an additional cycle of RTX treatment were successful in a few studies^{30,34}. Notably, anti-RTX antibodies may emerge with repetitive treatment; therefore, if there is a severe infusion reaction and CD19 persists despite RTX treatment, the presence of anti-RTX antibody should be considered³⁵ (Fig. 7). In such cases, humanized anti-CD20 monoclonal antibody, such as ofatumumab can be considered, especially since ofatumumab was reported to be effective in RTX-resistant SRNS³⁶.

For SRNS, RTX is effective in about 20% of patients³⁷.

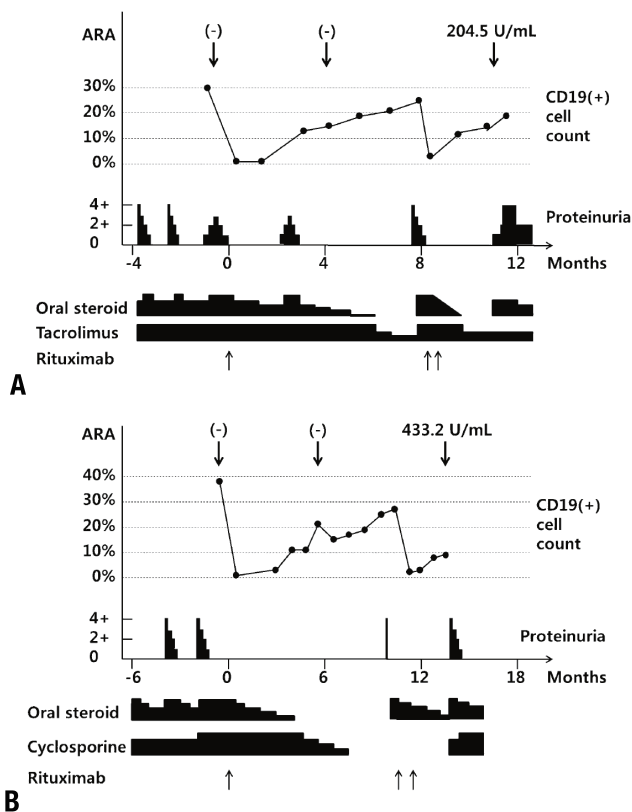


Fig. 7. Clinical courses of patients who developed antirituximab antibodies. Proteinuria (lower bar, 0–4+), CD19-positive B-cell count (%), and antirituximab antibody (ARA) titers at each point (down-pointing arrows), along the clinical course around rituximab treatments (up-pointing arrows below the graph). First treatment with rituximab was marked as month 0. Oral dosages of steroid and tacrolimus are represented as the height of the bar, below the graph. Adapted from Ahn YH, et al. *Pediatr Nephrol* 2014;29:1461-4, with permission of Springer International Publishing AG³⁵.

4. Galactose for SRNS

Galactose, a monosaccharide sugar, was shown to eliminate the proteinuric effect of FSGS-causing permeability factor (still of unknown identity) in an experimental model and some anecdotal cases³⁸. In a prospective clinical trial on pediatric SRNS, galactose was not effective after 16 weeks³⁹; however, reports from the Novel Therapies for Resistant Focal Segmental Glomerulosclerosis (FONT) trial (NCT00814255) state that some patients treated with oral galactose achieve a significant reduction in proteinuria during 24 weeks of therapy³⁷.

5. Relapse prevention

Upper respiratory infection triggers relapse of NS, accounting for approximately 2/3 of relapses⁴⁰. Three prospective studies showed a significant reduction in relapse rate with daily dosing of corticosteroids (conversion of alternate-day dosing to daily dosing or prednisolone of 0.5 mg/kg) for 5 to 7 days⁴¹⁻⁴³, during common viral infections. Supplementation with zinc (10 mg/day, the recommended dietary allowance) reduced relapses by 20%⁴⁴.

6. Vaccination and supplements

NS patients are prone to infections caused by encapsulated bacteria, such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and group B streptococcus. Therefore vaccination is necessary; 23-valent pneumococcal polysaccharide vaccine is indicated in NS patients older than 2 years, with boosting every 5 years⁴⁵. For those who had 13-valent pneumococcal vaccination, an interval greater than 8 weeks is required before 23-valent vaccination. Vitamin D or thyroid hormone replacement should be considered, as well as medication for dyslipidemia, if prolonged⁴⁵.

7. Dietary modification

Gluten-free and dairy-free (milk protein-free) diets were effective in some patients in small studies^{46,47}, suggesting that modification of gut microbiota with a diet may help control immune-mediated diseases such as NS⁴⁸.

Prognosis

1. Status in 10 years: frequently relapsing NS

In a long-term follow-up study of frequently relapsing nephrotic syndrome for more than 10 years, half of the patients had frequent relapses, and one-fifth were disease-free, with no relapse for 2 years. However, mortality or loss of kidney function was not identified⁴⁹.

2. Steroid toxicity, quality of life

Adverse effects of long-term steroid treatment include short stature, osteoporosis, obesity, cataracts, hypertension, diabetes

mellitus, and behavioral disturbances. Growth and bone mineral density were both negatively associated with the cumulative dose of glucocorticoid, and final height was significantly shorter in patients receiving >0.2 mg/kg/day doses of glucocorticoids⁵⁰.

Long-term morbidity of pediatric NS, especially SDNS or SRNS, affects quality of life significantly, with impaired peer relationships, social functioning, and school performance, especially in those with longer disease duration⁵¹.

Conclusions

While NS is decreasing in Korea, the morbidity of difficult-to-treat NS is significant. Efforts to minimize toxicity showed that treatment with glucocorticosteroids prolonged beyond an initial 2–3 months was not effective in reducing frequent relapses. For SDNS, RTX, a monoclonal antibody against the CD20 antigen on B cells, was proven as effective, and short-term, daily low-dose steroid reduced relapses during upper respiratory infections. Steroid resistance or congenital NS are indications for genetic study and renal biopsy, since the number of genes involved in NS is increasing.

Conflict of interest

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

Acknowledgments

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