

ADVANCES IN THE PATHOGENESIS AND MANAGEMENT OF IDIOPATHIC STEROID RESISTANT NEPHROTIC SYNDROME IN CHILDREN

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Abstract : 20% children with idiopathic nephrotic syndrome are steroid resistant (SRNS) according to ISKDC report (1970); they are at the risk of developing ESRD, especially those with FSGS criteria; specific gene mutation could be likely mechanism. Clinically, hypertension, haematuria, elevated serum creatinine, massive proteinuria are some of the possible predictors of steroid resistance. Optimal approach to SRNS is uncertain; newer immunosuppressive agents may benefit a small proportion of these subjects.

INTRODUCTION

The idiopathic nephrotic syndrome (NS) of childhood is a heterogeneous disorder characterised by massive proteinuria, hypoalbuminaemia, hyperlipidaemia and oedema. Histological characteristics are non-specific and range from minimal change disease, focal and diffuse mesangial proliferation to focal and segmental glomerulosclerosis (FSGS). Immunofluorescence is usually negative and electron microscopy shows fusion of the epithelial cell foot processes¹. Over 80% of children presenting with an initial episode of NS respond to steroids (steroid sensitive), whilst the remaining 20% do not respond and are considered steroid resistant (SR)². On follow up, 50-60% of children in the steroid responsive group have frequent relapses or develop steroid dependent disease. This group of children together with those that are SR are at risk for extrarenal complications of NS, as well as progression to end-stage renal disease necessitating renal replacement therapy. In children with SRNS (particularly FSGS) who undergo transplantation, the overall risk for recurrence of the primary disease is about 25%¹. The aim of therapy is to control the nephrotic state and thus prevent complications and to especially try and halt or delay progression to end-stage renal disease. To date the plethora of agents in our therapeutic armamentarium has failed to produce a drug that is the panacea for this condition. Thus management of SRNS poses a major therapeutic challenge to the attending clinician.

MECHANISM OF STEROID RESISTANCE

Why some children develop resistance to steroids is not well understood [6]. There are certain clinical, laboratory, and histological characteristics that may predict the likelihood of steroid resistance (Table 1). Recent studies have shown that specific genetic mutations constitute a principle mechanism for steroid resistance. Mutations of *NPHS1*, *NPHS2*, *ACTN4* and *WT1* genes are responsible for severe forms of SRNS in childhood, progressing to end-stage renal failure³. Positional cloning has revealed defects in these 4 different genes as monogenic causes of SRNS in familial cases (Table 2)⁴.

Children presenting with NS in the first year of life are steroid

Table 1 Clinical, laboratory, and histological characteristics that may predict the likelihood of steroid resistance.

Clinical Characteristics	Laboratory
Hypertension (50-60% likelihood)	Selectivity index >0.2
Haematuria (30% likelihood)	Elevated plasma creatinine
Hypertension plus haematuria (20% likelihood)	Tubular proteinuria (Increase excretion of B ₂ -microglobulin, retinol-binding protein, lysozyme)
Black race	Massive proteinuria (>10g/day)
Age of first presentation in infancy, after 8 years or post puberty.	
Primary vs. secondary steroid resistance.	
Histology	
Tubulointerstitial disease on renal biopsy or collapsing FSGS and >50 percent of globally sclerosed glomeruli	
Non minimal change disease on histology.	

Table 2 Genetic mutations associated with SRNS in childhood.

GENE	TYPE OF NS
NPHS1	Recessive mutations, encoding nephrin, (OMIM No. 602716) causes congenital NS of the Finnish type.
NPHS2	Recessive mutations, encoding podocin (OMIM no. 604766), causes SRNS Type 1.
ACTN4	Mutations encoding actinin 4, (OMIM no. 604638), causes autosomal dominant form of SRNS. An additional locus for an autosomal dominant form of NS has been mapped to chromosome 11q21-q22 (OMIM no. 603965).
WT1	Mutations are associated with congenital NS and diffuse mesangial sclerosis in the Denys-Drash syndrome and Frasier syndrome.

resistant. Two thirds of NS manifesting in the first year of life can be explained by mutations in 4 genes only (*NPHS1*, *NPHS2*, *WT1*, or *LAMB2*)⁵. Interestingly, *NPHS1* mutations occur in congenital NS only. However there are likely to be additional

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unknown genes mutated in early-onset NS that have still not been detected. NS associated with syndromes in childhood are SR and progress to end stage renal disease. The *Denys-Drash syndrome* is characterised by early onset of NS progressing rapidly to end-stage renal disease, male pseudohermaphroditism, and Wilm's tumour⁶. The *Frasier syndrome* is characterised by the association of male pseudohermaphroditism and progressive glomerulopathy⁷.

CLINICAL PRESENTATION

The majority of patients present between 2-7 years of age. There is a preponderance of males with a ratio of males: females of 2:1. The disease is characterized by the sudden onset of oedema; anasarca may develop with ascites, pleural and pericardial effusions. Blood pressure is usually normal but is sometimes elevated. Abdominal pain is occasionally due to complications such as peritonitis, thrombosis, or rarely pancreatitis. Sometimes the rapid development of ascites with concomitant hypovolaemia leads to abdominal pain and malaise. In some patients oedema is minimal and the nephrotic state is only discovered during routine urine analysis. Macroscopic haematuria may occur in a few cases. Common complications of SRNS include the following: acute or chronic renal failure, growth retardation, increased susceptibility to infections as a result of secondary immunodeficiency from malnutrition, and arterial or venous thrombosis.

TREATMENT

Symptomatic treatment is similarly to that of children who are steroid sensitive. This includes dietary recommendations of no added salt and adequate intake of proteins and vitamins with reduced intake of foods high in cholesterol. Diuretics are used for the treatment of oedema. If there is anasarca, salt free albumin together with loop diuretics is given for control of oedema. Treatment includes prevention and appropriate treatment of infections and thromboembolic complications, and treatment of hypovolaemia, hypertension, and hyperlipidaemia. If the latter is not controlled by dietary restriction alone, lipid lowering agents are used.

Immunosuppressive Therapy

The optimal approach to SRNS is uncertain. Reports of the large number of agents used as specific therapy for SRNS bears testimony to the lack of a single effective agent for the treatment of this condition.

Alkylating Agents

Cyclophosphamide and chlorambucil have been used either alone, in combination with oral steroids or with high dose pulse steroids. These regimens have met with variable success rates of inducing remission ranging from 10% to 70%. Many patients exhibit features of steroid toxicity. The use of pulse dose cyclophosphamide over a few months induced remission in 25-60% of children with SRNS^{8,9,10}.

In a review of 223 children with SRNS, Bhimma et al¹⁰ showed distinct racial differences with respect to response to oral cyclophosphamide therapy in Indian and Black children. In this study, a total of 183(82.1%) underwent renal biopsy; 84(45.9%) were Indian and

99(54.1%) were black. Sixty-six (36.1%) had minimal change disease, 66(36.1%) FSGS, 15(8.2%) proliferative forms of NS, and 36(19.7%) had other forms of NS. Of the 50 children who were biopsied and treated with oral cyclophosphamide and corticosteroids only, 29(57%) achieved complete remission and 5(12%) partial remission, all were Indian. In view of the large number of Indian patients that responded to oral cyclophosphamide but the dismal response in black children, the authors recommend a trial of oral cyclophosphamide therapy in non-black children with SRNS before resorting to kidney biopsy¹⁰.

Cyclosporin

Initial studies evaluating the efficacy of cyclosporin in patients with SRNS showed a relatively small benefit. In eight uncontrolled studies involving 60 patients, complete remission was induced in only 12 (20%). In the study by the French Society of Pediatric Nephrology involving 65 children with SRNS, complete remission was observed in 42% of children (48% with minimal change disease and 32% with FSGS). Eight of the 27 responders became steroid-sensitive when they subsequently relapsed¹¹. Patients who respond to cyclosporin often relapse when the dose is tapered or discontinued. Many reports indicate that the prolonged use of cyclosporin is associated with chronic nephrotoxicity. The most prominent histological feature of chronic cyclosporin nephrotoxicity is the presence of *tubulointerstitial lesions*, characterised by striped interstitial fibrosis containing groups of atrophic tubules. *Cyclosporin associated arteriopathy* is rarely observed. Other side effects include elevation of blood pressure, hyperkalaemia, hypertrichosis, gum hypertrophy, and hypomagnesaemia.

Mycophenolate Mofetil

Mycophenolate Mofetil (MMF) is the prodrug of mycophenolic acid (MPA) which is formed by hydrolysis. MPA is a potent, selective, uncompetitive, and reversible inhibitor of inosine monophosphate dehydrogenase. The latter is an enzyme required for de novo purine synthesis. MPA inhibits B and T-lymphocyte proliferation, as these cells are critically dependant upon de novo purine synthesis for their proliferation whereas other cell types can utilize salvage pathways for purine synthesis.

MMF has been used in SRNS and FSGS. Although several reports of the use of MMF in steroid dependent NS have been published, a paucity of data exists concerning its use in SRNS. In a study by Mendizabal et al¹³, MMF was given to 5 children with SRNS. Only one achieved complete remission. Withdrawal of the drug led to relapse with one patient developing chronic renal failure¹³.

The advantage with the use of MMF is its benign side effect profile compared to prednisone and cyclosporin. Its use is not associated with nephrotoxicity, hepatotoxicity, neurotoxicity, hyperglycaemia or abnormalities of lipid metabolism.

Tacrolimus

Tacrolimus is a calcineurin inhibitor that is more potent in cytokine suppression than cyclosporine. The main mechanism of action of tacrolimus is through the inhibition of IL-2 dependant T-cell activation, a process occurring during the

early phase of T-cell activation. Tacrolimus also inhibits B-cell activation, in part through its action on T-cells and also directly by blocking TNF- α gene transcription by anti-Ig antibody. The drug only becomes active when complexed with a distinct endogenous intracellular receptor (cystocolic binding protein-FRBP₁₂) known as immunophilin. The immunophilin drug complex interferes with intracellular calcium-dependent signal transduction pathways, processes that are central to T-cell activation. The common biological target for the resulting complex is the calcium and calmodulin-dependent protein phosphatase, calcineurin. Case reports and single centre studies have shown tacrolimus to be effective in treating SR FSGS. In a prospective, open labeled study of 20 children with SR FSGS given tacrolimus (0.2-0.4mg/kg per day in 2 divided doses over 12 hours adjusted to achieve a trough level between 7-15ng/ml) for 12 months in combination with low dose steroids and angiotensin converting enzyme inhibitors, Bhimma et al showed tacrolimus to be a safe and effective agent in the management of SR FSGS. At the end of the treatment period of 12 months of tacrolimus therapy, 8(40%) children were in complete remission, 9(45%) children were in partial remission, and 3(15%) failed to respond. The average period of follow-up following cessation of tacrolimus treatment was 27.5 months (range 13.7-43.7). At last hospital follow-up 5 (25%) of children were in complete remission, 10 (50%) in partial remission and 2 (10%) in relapse. 3 children demised from dialysis related complications following cessation of tacrolimus treatment. Adverse events included sepsis (2), nausea (2) diarrhea (2), anaemia (4) and worsening of hypertension (4). None of the 14 children who underwent repeat biopsy after follow-up for 6-18 months post treatment showed evidence of calcineurin toxicity¹³.

In another prospective, open labelled study, Gulati et al treated 22 consecutive children with SRNS, 11 having FSGS, 9 minimal change disease and 2 diffuse mesangial hypercellularity. Tacrolimus was withdrawn in 3 children because of side effects. Of the remaining 19 children, complete remission was attained in 16(84%) children, 2(10.5%) attained partial remission and 1(4.5%) was non responsive¹⁴.

Both of these studies together with several other case reports an single centre studies have shown that tacrolimus is a safe and effective form of treatment in children with SRNS. Several patients included in the above studies were also cyclophosphamide and/or cyclosporine treatment failures and thus tacrolimus can be used as rescue therapy in these patients.

Monoclonal antibodies

The lack of efficacy and side effects of the various forms of immunosuppressive have lead to the consideration of the use of other, less typical, immunosuppressive drugs. Recently, several case reports have suggested that the monoclonal antibody *rituximab* could be an effective treatment for steroid-dependant nephrotic syndrome¹⁵. Rituximab has also been used in SRNS and a prospective multicentre, opened labelled study of 22 patients with severe steroid dependant or SRNS,

but cyclosporine sensitive disease, showed the drug to be effective in 19 of 22 patients.

The exact mechanism of action of rituximab in idiopathic NS is not known. The following effects have been found that may possible explain its efficacy viz. down regulation of α -cell receptors, shedding of CD 23 cells and apoptosis of CD20⁺ cells, general regulatory effects on the cell cycle, and increases in MHC II and adhesion molecules LFA-1 and LFA-3 (lymphocyte function – associated antigen).

The finding that rituximab is effective as rescue therapy in patients with decreased or complete cessation of therapy using other immunosuppressive agents, even when infused during a proteinuric phase (when significant amounts of CD20 antibody are likely to be lost in the urine) bears testimony to its efficacy. Its efficacy has been reported in idiopathic NS in several other case reports.

Other Agents

Other agents used in steroid dependent or SRNS include *inter alia* vincristine, azathioprine, sirolimus and mizoribine. Immunoglobulin transfusions have also been used with varying success.

CONCLUSION

Childhood SRNS poses a major challenge to the attending physician. Although specific genetic factors such as mutations in the *NPHS2* and other genes have been identified, suggesting a possible genetic basis for the SRNS in a subgroup of patients. However in the majority of patients the pathogenesis remains elusive. The large numbers of agents used in the treatment of this condition bears testimony to the lack of an optimal approach in managing this condition.

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