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Evidence Update

A Brief Overview of the management of Steroid-Sensitive Nephrotic Syndrome in Children

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Abstract

Management of steroid sensitive nephrotic syndrome (SSNS) in the paediatric age group poses many challenges, which are not limited to steroid toxicity and suboptimal control of proteinuria but also include obtaining long term remission and improving quality of life. Though steroids are the mainstay of treatment for SSNS, various other immunosuppressant medications have been used to achieve remission in frequently relapsing and steroid dependent nephrotic syndrome patients. Selection of these medications should be done carefully, weighing their toxicity profiles and relative effectiveness. This clinical update discusses the disease SSNS and the different treatment strategies that have been evaluated along with their therapeutic outcomes

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Introduction

Nephrotic syndrome is characterized by proteinuria (>40mg/m^2 per hour), hypoalbuminaemia (≤3.0g/l), hypercholesterolaemia (serum cholesterol >200mg/dl) and generalized body oedema [1]. Ninety percent of children with idiopathic nephrotic syndrome in childhood are steroid sensitive and have a good prognosis. However, 70-80% of them relapse during the course of the illness and a significant proportion of them end up being steroid dependent, only going on to complete remission by the early second decade of life. Approximately 10-20% of children either present with or subsequently develop steroid resistant nephrotic syndrome over the course of their disease [2].

Although steroids are the mainstay of therapy for children with SSNS, management often becomes complicated, either due to steroid related side effects or inadequate control of proteinuria, necessitating second line therapy in children with frequently relapsing and steroid dependent nephrotic syndrome (SDNS). Alkylating agents and calcineurin inhibitors are recognized second line therapies. The clinical management of severe SDNS is often complicated by inadequate disease control, adverse effects on

growth and therapy related side effects, such as changes in appearance, renal toxicity and hypertension.

Pathogenesis

Structural and functional defects of podocytes are implicated in the pathogenesis of nephrotic syndrome. These defects result in increased glomerular permeability to albumin and other plasma proteins including immunoglobulin. Primary renal sodium retention and decreased oncotic pressure from hypoalbuminemia lead to increased movement of fluid from the intravascular space into the interstitial space, resulting in oedema. Thromboembolism in nephrotic syndrome is due to a multifaceted pathophysiology, including genetic factors such as concurrent thrombogenic mutations, shift in the hemostatic balance toward a prothrombotic milieu and environmental and acquired thromboembolism risk factors (inflammation, medications and central venous catheters).

Genetics

It has been well established that the clinical behavior of nephrotic syndrome is partly influenced by genetic factors. To date 53 genes have been described which are implicated in structural and functional defects in the podocyte [3]. The most recent advance in children with more difficult to control nephrotic syndrome is the identification of a single gene mutation that leads to steroid resistance [4]. Conversely, certain genes are linked with steroid and cyclosporine sensitivity [5].

Clinical presentation and evaluation

Most children present with body oedema and proteinuria. Ascites, hypertension and exertional dyspnea secondary to pleural effusion are also presenting features. Rarely thrombotic and infective complications could be the presenting feature.

A detailed evaluation is required for any child with relapse before commencement of corticosteroids. The height, weight and blood pressure should be recorded. Regular weight and fluid balance records help to monitor the decrease or increase of oedema. Physical examination must be focused on identifying complications (infections, hypovolaemia, thrombosis, hypertension and renal dysfunction) and underlying systemic disorders (systemic lupus erythematosus, Henoch-Schonlein purpura, other vasculitic disorders etc.).

Diagnosis

Diagnosis of nephrotic syndrome requires demonstration of nephrotic range proteinuria (>40mg/m^2 per hour), hypoalbuminemia (≤3.0g/L), hypercholesterolemia (serum cholesterol >200mg/dl) and body oedema. A single, first morning urine sample which is used to quantify protein excretion by estimation of the urine protein/creatinine ratio, is preferred over 24 hour-urine collections which are often unreliable and cumbersome in the paediatric age group [6]. A urine protein/creatinine ratio of ≥300 mg/mmol indicates 'nephrotic-range' proteinuria or dip-stick proteinuria of 3+ [7].

A relapse is defined as >2+ proteinuria for 3 consecutive days or any amount of proteinuria associated with oedema.

Diagnosis of SDNS is made clinically. International Study for Kidney Diseases in Children (ISKDC) defines frequently relapsing nephrotic syndrome (FRNS) [8] as two or more relapses in the first 6-months or four or more relapses in any 12-month period. Steroid dependent nephrotic syndrome (SDNS) is defined as two consecutive relapses occurring while on steroid treatment or within 14 days of discontinuing steroid therapy.

A pretreatment renal biopsy is necessary in children with atypical features of nephrotic syndrome. These atypical features include hypertension, azotaemia, hypocomplementaemia, haematuria (≥30 red blood cells/high-power field), specific age groups (<1 year and >12 years) and the presence of other findings implying another autoimmune disease [9].

Management

Drug Therapy

Steroids are the mainstay of therapy in children with SSNS. However, most children with frequently relapsing and SDNS require second line therapies following steroid toxicity and inadequate disease control. A recent systematic review of children with relapsing SSNS showed that oral cyclophosphamide significantly reduced the risk of relapse compared to long term low dose prednisolone [10].

Steroids are recommended as first line therapy in steroid sensitive nephrotic syndrome including its variants; minimal change disease and focal segmental glomerulosclerosis, to reduce proteinuria and induce remission. The initial dose is 60mg/m^2/day for 28 days. This is followed by a gradual dose reduction of 10mg/m^2 every two weeks, given on alternate days, for a further 12 weeks Relapses are treated with oral prednisolone 60mg/m^2/day till remission followed by gradual reduction in the dose over several weeks. The risk of frequently relapsing nephrotic syndrome is significantly lower with prolonged duration of prednisone therapy compared with treatment with prednisolone for two months [11]. The risk of relapse by 12 to 24 months was significantly less in children treated with a prolonged course of prednisolone compared to a short course [12,13,14]. Serious adverse events (growth retardation, hypertension, cataracts/glaucoma, psychological disorders, osteoporosis, infections and features of Cushing's syndrome) were not significantly different between these regimens [11]. Intravenous steroid therapy is recommended when absorption of oral prednisolone seems unreliable. Viral upper respiratory tract infections frequently precipitate relapses of nephrotic syndrome in children and prescribing prednisolone daily for 5-7 consecutive days at the dose of 1mg/kg (maximum-20mg) significantly reduces the risk of relapse in children with frequently relapsing or steroid-dependent nephrotic syndrome [15].

Levamisole and cyclophosphamide, either by oral or intravenous route, substantially reduces the number of relapses in children with frequently relapsing and steroid

dependent nephrotic syndrome. No difference in efficacy was noted between intravenous and oral cyclophosphamide although more short term and long-term side effects were noted with intravenous therapy (eg. haemorrhagic cystitis). Kidney Disease Improving Global Outcomes (KDIGO) 2012 guidelines recommend an 8–12 weeks course of oral cyclophosphamide (2-3mg/kg/day) for steroid dependent nephrotic syndrome [16]. Gonadal toxicity and neutropaenia are clinically important adverse effects of cyclophosphamide which need close supervision.

Though there are variations in practice, levamisole is commonly administered on alternate days at a dose of 2.5mg/kg. Safety data is not available for it to be used daily or for it to be continued for more than two years. Clinically important side effects of levamisole include neutropaenia and disseminated vasculitis [17].

A calcineurin inhibitor, cyclosporine (3-5mg/kg/day), is equally or more effective compared with cyclophosphamide during therapy, especially with severe SDNA. However, the risk of having a relapse is greater with withdrawal of cyclosporine while in remission compared to that following completion of a course of cyclophosphamide. Children should be evaluated for renal toxicity and hypertension regularly while they are on cyclosporine and the dose should be adjusted according to the drug level in the blood (Target C-0 level; 50-150ng/ml for maintenance and 100–200ng/ml for induction). Tacrolimus, also a calcineurin inhibitor, has shown similar efficacy with a different profile of side effects. It increases the risk of hyperglycemia but causes fewer changes to the external appearance.

Mycophenolatemofetil (MMF), an anti-proliferative agent is also used as an optional therapy for severe SDNS. MMF is a prodrug of mycophenolic acid (MPA), an inhibitor of inosine-5'-monophosphate dehydrogenase. MPA depletes guanosine nucleotides preferentially in T and B lymphocytes thus inhibiting their proliferation. Therefore, it suppresses both cell-mediated immune responses and antibody formation. MMF is rapidly metabolized in the liver to MPA once it is taken orally [18]. The recommended dose is 300-600mg/m^2/ twice daily, initially for one to two years. It is associated with gastrointestinal side effects and blood dyscrasias. There are, however, insufficient data on long term use of MMF to date. The author's experience in using mycophenolate sodium in SDNS is encouraging.

Recent reviews have suggested rituximab as a promising treatment for relapses in children with severe steroid and cyclosporine dependent nephrotic syndrome [19]. However, most children are likely to relapse by one year following commencement of therapy. Repeated courses of rituximab and adjunct immunosuppressive therapies may be required in these children [20,21]. Rituximab treatment leads to B cell depletion, caused by antibody-dependent cellular cytotoxicity, B cell apoptosis or phagocytosis, suppressing interactions between B cells and T cells, which may prevent relapses in patients with nephrotic syndrome. Rituximab may also improve the function of regulatory T cells [22,23] which are usually impaired in minimal change nephrotic

syndrome [24]. Rituximab is given as 750mg/m^2 body surface area by the intravenous route in two doses, two weeks apart. After that it can be repeated every 6 months if disease control is not optimal. Bronchospasm, hypotension, fever, skin rash and arthralgia are reported side effects of rituximab. Heart failure, herpes, cytomegalovirus and other severe infections and uncontrolled heart disease are contraindications for treatment.

Supportive Therapy

Hypovolaemia is common, not always easy to recognize, and is a major contributor to morbidity and mortality. If the child is having features of hypovolaemia (oliguria/UOP <0.5ml/kg/hr or raised haematocrit, 20% above baseline) without evidence of shock, an infusion of human albumin should be considered. Intravenous human albumin 20% (0.5 to 1g/kg=2.5 to 5.0 ml/kg) is infused over a minimum of 4 hours to prevent flash pulmonary oedema.

Acute tubular necrosis is another complication of nephrotic syndrome. The management is more difficult in the oedematous child with erratic enteral absorption of oral prednisolone. This may require institution of parental immunosuppressants and renal replacement therapy until recovery of renal function occurs [25,26,27].

Routine immunization against varicella infection is recommended in children with nephrotic syndrome [28] during remission as it can be associated with a complicated course whilst steroids are being prescribed. Parenteral acyclovir therapy should be considered for varicella infection in children who are on immune-suppressants. Data support the use of acyclovir prophylaxis as an adjunctive measure to VZIG for the prevention of potentially serious varicella infection in children receiving steroids [29].

Primary peritonitis is a recognized complication of nephrotic syndrome as well as a putative presenting feature [30]. Pneumococcal vaccine is currently indicated for all children with nephrotic syndrome to prevent peritonitis. Penicillin prophylaxis should be prescribed to reduce the risk during a relapse.

Salt restriction is an essential primary step in controlling oedema. Water restriction is usually not indicated in the management of nephrotic syndrome as they are more vulnerable to become hypovolemic. If oedema is severe, diuretics can be used cautiously after clinically determining that the vascular volume is normal, and the nephrotic state is neither acute nor rapidly changing.

Nutritional status is not much affected in steroid sensitive nephrotic syndrome as the course of disease is generally short. However, in children who relapse frequently and are steroid dependent on going dietary monitoring to maintain adequate growth and prevent obesity is required.

A balanced diet, adequate in energy (recommended dietary allowances for the chronological age) is adequate for most patient with a protein intake matched for the chronological age (required nutrient intake). During a relapse, hyperlipidaemia is invariably present and advice on general healthy eating and use of mono and polyunsaturated oils with reduction in saturated and trans fat intake is advised.

Nephrotic patients are at risk of deprived bone growth and reduction in bone density due to prolonged corticosteroid therapy. Moreover, during a relapse, vitamin D binding proteins are lost in the urine. Calcium and Vitamin D supplements are advocated during a relapse and while on high prednisolone doses.

Conclusion

Steroid sensitive nephrotic syndrome is the commonest chronic glomerular disease in childhood with good long-term prognosis. Steroids are the mainstay of therapy but a significant proportion of children with relapsing disease need second line medications to control the disease optimally. A multitude of factors need to be considered when selecting a second line therapy for a patient as disease behavior is unique for each individual.

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