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STEROID RESISTANT NEPHROTIC SYNDROME-A FORMIDABLE CHALLENGE : THE CYCLOSPORINE STORY

Paediatrics

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KEYWORDS

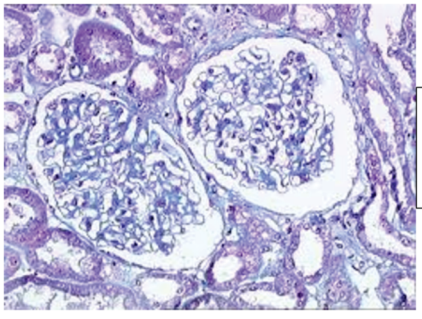
INTRODUCTION:
Nephrotic Syndrome is a primary glomerular disease and is a condition in which the glomeruli of the kidney leak protein from the blood into the urine. It results in hypoproteinemia and generalised oedema. The earliest recorded description of nephrotic syndrome was from the 15th century. Later, Volhard and Fahr [5] popularized the term nephrosis. It was used to describe a major classification of bilateral renal disease. Now, nephrotic syndrome is recognized as a common chronic illness in childhood. It is characterized by proteinuria defined by urine protein >3.5gm/24hrs or urine protein-creatinine ratio >2 mg protein per mg creatinine, edema, hyperlipidemia(>200mg/dl) and hypoalbuminemia. At the time of first presentation, ~80% of children achieve complete remission within 4 weeks of corticosteroid therapy and are classified as having steroid-sensitive nephrotic syndrome (SSNS). However, 60%–70% of the patients initially classified as steroid sensitive have >1 relapse. Among children who relapse, 30% will be further classified as having frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome. Steroid resistance, defined as the absence of remission despite 4 weeks of therapy with daily Prednisolone at a dose of 2 mg/kg/d, encompasses an even smaller proportion of patients. Steroid resistant nephrotic syndrome(SRNS) are at risk of progressive renal damage and are commonly genetic in origin. Children with steroid-resistant nephrotic syndrome (SRNS) may have minimal-change disease (MCD), mesangial proliferative glomerulonephritis (MesPGN), or focal segmental glomerulosclerosis (FSGS), although other histopathologic diagnoses also occur. Patients with steroid-resistant nephrotic syndrome (SRNS) represent a challenging subset of patients with nephrotic syndrome who often fail standard immunosuppression and have a higher likelihood of progressing to end-stage renal disease. Appropriate treatment of SRNS requires an adequate understanding of the historical treatment, renal histopathology, and genetics associated with the disease.

Table 1 Clinical definitions of nephrotic syndrome

Remission	Urine albumin nil or trace (or proteinuria <4 mg/m2/h) for 3 consecutive early morning specimens.
Relapse	Urine albumin 3+ or 4+ (or proteinuria >40 mg/m2/h) for 3 consecutive early morning specimens, after having been in remission previously.
Frequent relapses	Two or more relapses in initial 6-month period or more than 3 relapses in any 12 months.
Steroid dependence	Two consecutive relapses when on alternate day steroid therapy or within 14 days of its discontinuation.
Steroid resistance	Absence of remission despite therapy with daily prednisolone at a dose of 2 mg/kg/d for 4 weeks.

Abbreviations: d, day; h, hour.

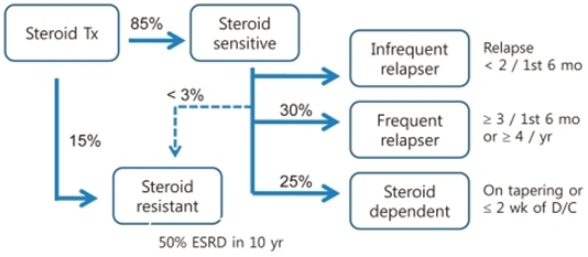
Case History:
A case of 15 month old female child presented with severe periorbital edema, abdominal distension and decreased urine output. Patient was admitted and routine investigations were sent in which Hb 10.3, TLC 5,700 Platelet 157000, Na/K/Cl 126/2/99 , CRP negative , serum creatinine 0.3, total proteins 3.3 with albumin 1.7 and urine routine had proteins +2 and no blood. Level 2 investigations were sent to workup for nephrotic syndrome in which serum Cholesterol 327.6 mg/dl, serum C3 178.3 mg/dl, serum Triglycerides 324.3 mg/dl and urine Albumin: Creatinine ratio 3324 mg/g creat with microalbumin spot urine was 595 mg/l. So the patient had severe anasarca, massive albuminuria, hypercholesterolemia, hypertriglyceridemia and hypertension with no hematuria confirming the diagnosis of Nephrotic syndrome. Child was started on tablet Prednisolone at 2mg/kg daily. Serial monitoring of patients urine proteins, weight, blood pressure, abdominal girth, input/output and urine albumin : creatinine ratio was done which increased to 25492 mg/g creat after starting steroids. Child's mother has dysmorphism in form of bilateral malformed ears, lower facial abnormality and retrognathia. Child also has bilateral microtia with retrognathia. BERA showed bilateral conductive hearing loss. On 6 weeks of Prednisolone, child showed partial response with slight decrease in urine albumin creatinine ratio to 18398.1 mg/g creat with persistent edema.USG guided renal biopsy was done. Light microscopy showed normal glomeruli with mild dilatation of tubules. Electron microscopy revealed foot process flattening with normal basement membrane thickness indicating minimal change NS (MCNS). Genetic testing was cost prohibitive. Cyclosporine was started and on day 7 of the same patient urine albumin creatinine ratio dropped to 11095.2 mg/g creat and serum albumin improved to 3.4. Steroids were tapered to alternate days, cyclosporine was continued and child was discharged to follow up. After one month patient followed up and investigations were done in which total proteins 6, serum albumin 4.0,serum creatinine 0.5, serum Cholesterol 163.7, serum Triglycerides 77.6, urine proteins absent and urine albumin : creatinine ratio was 1676 mg/g creat which confirmed the diagnosis.



DISCUSSION:
Child was classical case of Steroid Resistant Nephrotic Syndrome diagnosed at early age of 15 months.We clinically diagnosed our patient as Steroid resistant Nephrotic Syndrome based on response to Prednisolone and Cyclosporine. Also Renal biopsy helped in diagnosing the case.MCNS is most common in children and has a peak incidence at 2 to 6 years of age.It is also the most common cause of nephrotic syndrome of unclear cause (idiopathic) in children. Although the prognosis of SRNS is complicated and unfavorable, intensive treatment in the early stages of the disease may achieve remission in more than half of the patients.

CONCLUSION:

The optimal treatment of SRNS remains controversial. SRNS can be managed well with various immunosuppressant drugs such as Cyclosporine(CsA), Cyclophosphamide, Mycophenolic acid and Rituximab and steroids. Rituximab is a relatively new drug in the treatment of SRNS in children and certainly takes time to demonstrate its efficiency and long-term potential side effects. In our case, remission was achievable with CsA in many cases. CsA remains the primary cytotoxic treatment for childhood steroid-resistant nephrotic syndrome. Its use in combination with corticosteroids provides optimum efficiency without high risk of nephrotoxicity.



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