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Case Report on Steroid - Resistant Nephrotic Syndrome in Children

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Abstract: ***Nephrotic syndrome (NS) is a glomerular disorder typically characterized by gross proteinuria, hypoalbuminemia, hyperlipidemia, and peripheral edema. We report the case of a 5 - year - old male child weighing 18 kg with a 1 - week history of swelling around the eyes and generalized body swelling. He had a history of upper respiratory tract infection two weeks before hospitalization, fever, cough and frequent urination and oliguria. Examination revealed bilateral pedal edema (pitting type). Laboratory investigations showed protein in urine, reduced serum albumin, reduced serum protein with elevated lipid levels. Calcium and magnesium serum levels slightlybelow normal range. It was also performed a kidney biopsy which further confirmed diagnosis of steroid - resistant nephrotic syndrome due to focal segmental glomerulosclerosis (FSGS). The patient was mainly treated with furosemide, prednisone, ramipril, intravenous albumin, omeprazole, ca gluconate 10% solution, kcl 7.5% solution, antibiotics. After8weeks on steroids, proteinuria, edema and hyperlipidemia persisted. Then biopsy was performed which resulted in FSGS (focal segmental glomerulosclerosis) and cyclosporine was added to the initial therapy. After three months of treatment with cyclosporine there was remission of the symptoms and improvement of laboratory findings.***

Keywords: steroid - resistant nephrotic syndrome, proteinuria, hyperlipidemia, edema and hypoalbuminemia, FSGS, prednisone, cyclosporine

1. Introduction

Primary nephrotic syndrome (PNS), also known as idiopathic nephrotic syndrome (INS), is associated with glomerular diseases intrinsic to the kidney and not related to systemic causes. The subcategories of INS are based on histological descriptions but clinical - pathological correlations have been made [1]. Nephrotic syndrome is a constellation of clinical findings that is the result of massive renal losses of protein. Thus, nephrotic syndrome is not a disease itself, but the manifestation of many different glomerular diseases. These diseases might be acute and transient, such as postinfectious glomerulonephritis, or chronic and progressive, such as focal segmental glomerulosclerosis (FSGS). Still other diseases might be relapsing and remitting, such as minimal change nephrotic syndrome (MCNS). [2]In order to establish the presence of nephrotic syndrome, laboratory tests should confirm (1) nephrotic - range proteinuria, (2) hypoalbuminemia, and (3) hyperlipidemia. [3]Diagnosis is generally based on clinical features and investigations including blood tests, urinalysis, renal imaging, and biopsy when indicated. [4]In patients who are initially or subsequently unresponsive to steroid treatment, kidney biopsy should be performed, because steroid unresponsiveness has a high correlation with prognostically unfavorable histology findings, such as those associated with FSGS or membranous glomerulonephritis (MGN). The incidence of idiopathic nephrotic syndrome (INS) is 1.15–16.9 per 100 000 children, varying by gender, ethnicity and region. The cause remains unknown but the pathogenesis of idiopathic NS is thought to involve immune dysregulation, systemic circulating factors, or inherited structural abnormalities of the podocyte. Genetic risk is more commonly described among children with steroid - resistant disease. The mainstay of therapy is prednisone for the vast majority of patients who are steroid responsive; however, the disease can run a frequently relapsing course, necessitating the need for alternative immunosuppressive agents. Infection and venous thromboembolism are the main complications of NS with also increased risk of acute kidney injury. Prognosis in terms of long - term kidney outcome overall is excellent for steroid - responsive disease, and steroid resistance is an important determinant of future risk of chronic or end - stage kidney disease ESKD. [5]

Clinical features

A 5 - year - old male weighing 18 kg presented with swelling on the face, (which started as periorbital, more prominent during the morning), and lower limbs. Frequent urination. The patient had decreased urine output (oligouria). The baby was delivered by C - section and was breastfed. Mother with urolitiasis. On examination pitting type of edema present over lower limbs and swelling over face. Based on these clinical presentations, nephrotic syndrome was suspected and specific laboratory testing was performed to establish diagnosis.

Laboratory finding

The urine dipstick indicated for proteinuria, with signs of microhaematuria. Blood testing showed hypoalbuminaemia and hypoproteinemia indicating nephrotic syndrome (NS). The lipid levels were markedly increased as outlined in the Table 1. HBsAG and Anti - HCV tests results negative. Protein electrophoresis test was performed and gamma - globulins a little bit low range 7.9% (11.1 - 18.8). ANA, Anti ds DNA, MPO, PR3 results negative. After unresponsive treatment with steroids (prednisone) for 6 weeks, it was indicated renal biopsy: focal segmental glomerulosclerosis (FSGS) found on histopathological examination.

Chest x - ray: bilateral hilar opacities: Renal ultrasound: bilateral renal stasis with bilateral renal piramids edema

Clinical course
After establishing diagnosis, supportive treatment included antibiotics iv, intravenous albumin, furosemide iv, prednisone p. o, ramipril p. o, ca gluconate 10% solution, kcl 7.5% solution. Peripheral edema and protein loss in the urine persisted. After persistence of hipoalbuminemia, proteinuria, and hypertriglyceridemia, it was prescribed cyclosporine in adition to prednisone. After 3 months of treatment, the peri - orbital edema and leg swelling reduced, and there was a concomitant increase in serum protein levels. The lipid levels also gradually decreased in due course of time without any medication.

2. Discussion

The hallmark of INS is massive proteinuria, leading to decreased circulating albumin levels. The initiating event that produces proteinuria remains unknown. However, strong evidence suggests that INS, at least in part, has an immune pathogenesis.

Steroid - resistant nephrotic syndrome:
Approximately 10% of patients overall with INS do not respond to an initial trial of steroids (2% of patients with MCNS do not respond to steroids). Additionally, about 1 - 3% of patients who initially do respond to steroids later become resistant to treatment ("late non - responders").

Most patients who do not achieve remission of proteinuria with steroids have kidney biopsy findings other than MCNS. The most common diagnosis in these patients is FSGS.

More than 60% of patients with nephrotic syndrome and FSGS who fail to achieve remission with any treatment progress to end - stage kidney disease (ESKD). In contrast, only 15% of patients with FSGS who achieve remission by any treatment progress to ESKD. Thus, patients with steroid - resistant INS have a good prognosis if remission of proteinuria can be achieved by medications other than corticosteroids. Failure to respond to treatment (ie, failure to achieve remission) and kidney insufficiency at presentation are predictors of poor outcome and progression to ESKD. [8]

Complications of INS include the following:
- Edema.
- Hyperlipidemia.
- Thrombosis (renal vein thrombosis, deep vein thrombosis, and pulmonary embolism are the most frequently encountered thromboembolic complications in children; other venous sites of thrombosis include the superior sagittal sinus, other cerebral venous sites, and the inferior vena cava).
- Infection (spontaneous bacterial peritonitis, sepsis, cellulitis).
- Acute kidney failure.
- Adverse effects of medications (steroids, diuretics, albumin, steroid - sparing agents).

The classical explanation for oedema formation is a decrease in plasma oncotic pressure, as a consequence of low serum albumin levels, causing an extravasation of plasma water into the interstitial space. The resulting contraction in plasma volume (PV) leads to stimulation of the reninangiotensin - aldosterone axis and anti - diuretic hormone secretion. The resultant retention of sodium and water by the renal tubules contributes to the extension and maintenance of oedema. A more recent theory of oedema formation posits that massive proteinuria leads to tubule - interstitial inflammation, release of local vasoconstrictors and inhibition of vasodilation. This leads to reduction in glomerular filtration rate and sodium and water retention.

INS is accompanied by disordered lipid metabolism. Apolipoprotein (apo) - B–containing lipoproteins are elevated, including very - low - density lipoprotein (VLDL), intermediate - density lipoprotein (IDL), low - density lipoproteins (LDL), with resultant increases in total cholesterol and LDL - cholesterol. Elevations in triglyceride levels occur with severe hypoalbuminemia. Also contributing to the dyslipidemia of INS are abnormalities in regulatory enzymes, such as lecithin - cholesterol *acyltransferase*, *lipoprotein lipase*, and cholesterol ester transfer protein [7]

Nephrotic syndrome is a hypercoagulable state; the increased risk of thrombosis can be attributed to two basic mechanisms:
1) Urine losses of antithrombotic proteins and
2) Increased synthesis of prothrombotic factors.

Abnormalities described in INS include decreased antithrombotic factors and increased synthesis of pro - thrombotic factors (6).

Risk of infection may be increased in INS because of low immunoglobulin IgG levels, which do not appear to be the result of urinary losses. Instead, low IgG levels seem to be the result of impaired synthesis, again pointing to a primary disorder in lymphocyte regulation in INS. The medications used to treat INS, such as corticosteroids and alkylating agents, further suppress the immune system and increase the risk of infection [9].

Acute kidney failure
Acute kidney failure may rarely result from complications of INS, from the underlying disease, or from drug therapy. In most cases, acute kidney failure is reversible with the remission of nephrotic syndrome, correction of intravascular volume contraction, or (in patients with acute interstitial nephritis) removal of the inciting agent. [10]

3. Conclusion

We have presented a case of steroid resistant NS in a 5year old child. First he was treated with prednisone, ramipril, furosemide, albumin iv for 6 weeks with not much benefit. Oedema, protein loss in the urine, hypoalbuminemia and dyslipidemia persisted. Since there wasn't a good response to the treatment, it was indicated a renal biopsy, which showed FSGS. Cyclosporine was added to the initial treatment, and after 3 months of using cyclosporinethere was remission of all the symptoms.

Take home messages/learning points

In order to establish the presence of nephrotic syndrome, laboratory tests should confirm nephrotic - range proteinuria, hypoalbuminemia, and hyperlipidemia.

A 3+ proteinuria on dipstick is highly suggestive of nephrotic syndrome to be confirmed by appropriate laboratory work - up.

Serologic testing for active infections should be done as the patients with NS are more prone to it.

Mantoux test [purified protein derivative (PPD)] should be performed prior to steroid treatment to rule out TB infection.

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Table 1: Laboratory parameters

Parameters	Result	References
Urine		
proteinuria	345.6 mg/dL	
Urine Protein 24h	3456 mg/24h	< 300 mg/24h
Erythrocyte andhemoglobin	10 u/L	<5
	serum	
Total protein	4g/dL	06-Aug
albumin	1.8g/dL	3.8 - 5.4
calcium	7.8mg/dL	8.8 - 10.8
magnesium	1.93 mg/dL	2.09 - 2.84
Serum lipid profile		
Total Cholesterol	323 mg/dL	< 170 mg/dL
Triglycerides	170 mg/dL	< 197 mg/dL