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Research Article

NEPHROTIC SYNDROME IN PAEDIATRICS

Praneeth Chandaluri [1]* and Ramesh Ganpisetti[2]

Department of Pharmacy Practice, Malla Reddy Hospital, Hyderabad, Telangana, India-500055

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ABSTRACT

Childhood nephrotic syndrome is not a disease in itself; rather, it is a group of symptoms that indicate kidney damage, particularly damage to the glomeruli, the tiny units within the kidney where blood is filtered result in the release of too much protein from the body into the urine. When the kidneys are damaged, the protein albumin, normally found in the blood will leak into the urine. Proteins are large, complex molecules that perform a number of important functions in the body. The two types of childhood nephrotic syndrome are **Primary**—the most common type of childhood nephrotic syndrome, which begins in the kidneys and affects only the kidneys. **Secondary**—the syndrome is caused by other diseases. Common primary causes of nephrotic syndrome include kidney diseases such as minimal-change nephropathy, membranous nephropathy, and focal glomerulosclerosis. Secondary causes include systemic diseases such as diabetes mellitus, lupus erythematosus, amyloidosis. Characteristic findings: Proteinuria, Hypoalbuminemia. Treatment includes Prednisone 2 mg/kg per day for 4-6 weeks, followed by 1.5 mg/kg per day on alternating days for other 4-6 weeks, 95% of patients with MCD will go into remission following 8 weeks of corticosteroid treatment. Remission defined as 3 consecutive days with no or trace protein on urinalysis. Confirms diagnosis of MCD. Lower rates of remission seen in patients treated for 12 week. Complications are an acute renal failure, Usually reversible with restoration of intravascular volume Thrombosis. Secondary to urinary losses of antithrombin III and protein. Infection, usually staphylococcal or streptococcal.

INTRODUCTION

Childhood nephrotic syndrome is not a disease in itself; rather, it is a group of symptoms that indicate kidney damage—particularly damage to the glomeruli, the tiny units within the kidney where blood is filtered result in the release of too much protein from the body into the urine .When the kidneys are damaged, the protein albumin, normally found in the blood, will leak into the urine. Proteins are large, complex molecules that perform a number of important functions in the body. The two types of childhood nephrotic syndrome are primary—the most common type of childhood nephrotic syndrome, which begins in the kidneys and affects only the kidneys secondary — the syndrome is caused by other diseases[1-7].

A health care provider may refer a child with nephrotic syndrome to a nephrologist—a doctor who specializes in treating kidney disease. A child should see a pediatric nephrologist, who has special training to take care of kidney problems in children, if possible. However, in many parts of the country, pediatric nephrologists are in short supply, so the child may need to travel. If traveling is not possible, some nephrologists who treat adults can also treat children.

Epidemiology

In the United States, the incidence of 2.7 cases per 100,000 children per year. Cumulative prevalence of 16 per 100,000 children. More common in boys than girls in younger age groups, but once adolescence is reached there is no significant difference between genders. Most commonly seen at ages 3 to 5. Increased incidence and more severe disease seen in African American and Hispanic populations[8-10].

Etiology

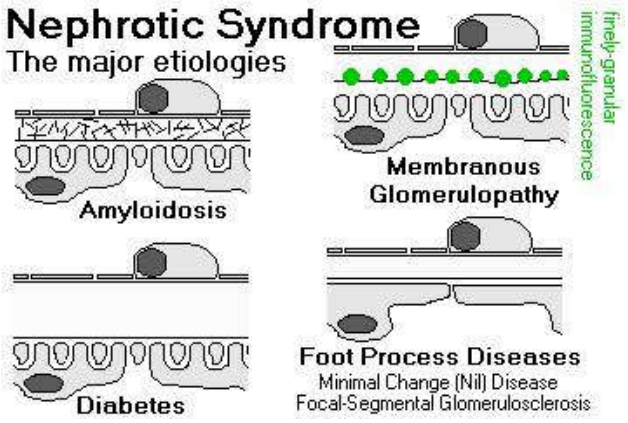
Common primary causes of nephrotic syndrome include kidney diseases such as minimal-change nephropathy, membranous nephropathy, and focal glomerulosclerosis. Secondary causes include systemic diseases such as diabetes mellitus, lupus erythematosus, and amyloidosis[11-13]. Congenital and hereditary focal glomerulosclerosis may result from mutations of genes that code for podocyte proteins, including nephrin, podocin, or the cation channel 6 protein. Nephrotic syndrome can result from drugs of abuse, such as heroin.

The proposed mechanisms of membranous nephropathy are as follows:

1. Immune complex deposition from the circulation

Corresponding author: **Praneeth Chandaluri*
Department of Pharmacy Practice, Malla Reddy Hospital, Hyderabad, Telangana, India-500055

2. In-situ formation of immune complexes through the reaction of circulating autoantibodies to a native antigen
3. In-situ formation of immune complexes with a non-native (extrinsic) antigen that is bound to the podocytes or glomerular basement membrane.



The first mechanism could explain the secondary membranous nephropathy of systemic lupus erythematosus.

The second mechanism appears to explain 70% of idiopathic membranous nephropathy. M-type phospholipase A2 receptor (PLA2R) antibodies are found in about 70% of patients who have idiopathic membranous glomerular nephropathy.[14] These IgG antibodies are found both circulating in the plasma and deposited on the glomerular basement membranes.

The third mechanism may explain the rare occurrence of nephrotic syndrome in subjects treated with enzyme replacement therapy for genetic enzyme deficiency diseases such as Pompe or Fabry disease[15, 16] This may result from alloantibodies to the infused enzyme that are deposited on the glomerular basement membrane, with ensuing secondary membranous nephropathy.

Nephrotic-range proteinuria occurring in the third trimester of pregnancy is the classical finding of preeclampsia. It may occur de novo or it may be superimposed on another chronic kidney disease. In the latter case, the patient will have had existing proteinuria that worsened during pregnancy.

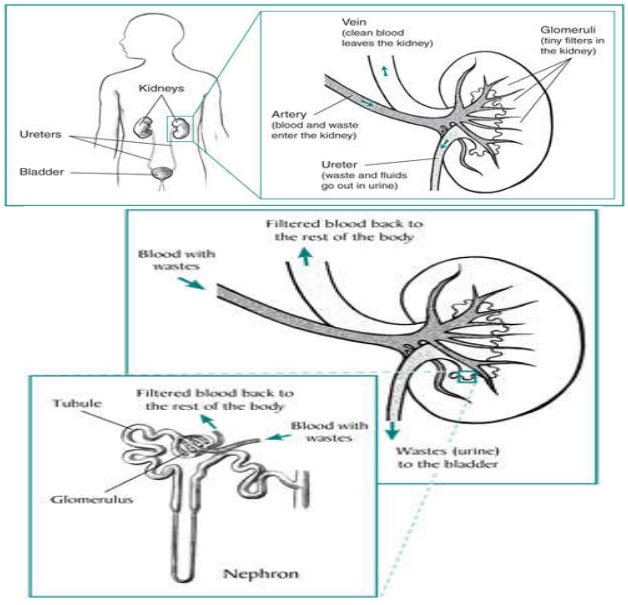
Medication can cause nephrotic syndrome. This includes the very infrequent occurrence of minimal-change nephropathy with use of nonsteroidal anti-inflammatory drugs (NSAIDs), and the occurrence of membranous nephropathy with the use of gold and penicillamine, which are older drugs used for rheumatic diseases. Focal glomerulosclerosis can occur in association with intravenous bisphosphonates. Lithium and interferon therapy have been associated with focal glomerulosclerosis of the collapsing type.

Nephrotic-range proteinuria could occur with the use of anticancer agents, such as bevacizumab, that inhibit vascular endothelial growth factor (VEGF).[17] However, the clinical picture of this complication is of a thrombotic microangiopathy rather than of nephrotic syndrome per se.

The association of membranous nephropathy with cancer is a clinical dilemma. This association presumably results from immune complex injury to the glomeruli caused by cancer antigens. While about 6000 new cases of membranous nephropathy occur each year in the United States, 1.5 million new cases of non-skin cancer are diagnosed. Therefore, from the oncologist's standpoint, the problem of paraneoplastic membranous nephropathy is trivial. However, a carefully performed analysis from France suggested that the cancer rate is approximately 10-fold higher in persons with membranous nephropathy than in the general population, especially in individuals over age 65 years.[18] In that study, 50% of membranous nephropathy cases were diagnosed before the diagnosis of cancer. Thus, in some patients with membranous nephropathy, one should consider the possibility of a cancer.

Pathophysiology

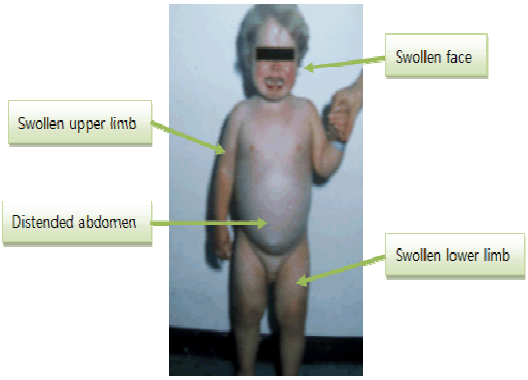
- Normally, the glomerular filtration barrier is composed of 3 layers, listed from capillary side to bowman's space side:
- Fenestrated endothelium, Glomerular basement membrane, Negatively charged to prevent the passage of large anionic molecules (such as albumin)[19-20].
- Visceral glomerular epithelium, also known as podocytes, Podocytes contain foot processes, which create a barrier. Small pores between adjacent foot processes are bridged by slit diaphragms, Podocytes affect the structure and function of both the, glomerular basement membrane and the endothelial cells.
- Size discrimination is accomplished by the pores in the glomerular, basement membrane and podocytes which have a radius of approximately 40 to 45 amperes.
- In nephrotic syndrome, the normal glomerular filtration process in interrupted, resulting in protein passing through the filtration barrier and severe-range proteinuria.
- Commonly a defect in the podocytes and/or glomerular basement membrane.
- Recent experiments have implicated T-Cells in the damage to podocytes leading to 2 common types of nephrotic syndrome (minimal change disease and focal segmental glomerulosclerosis).
- Exact pathology varies depending on the specific type of nephritic syndrome[21-23].



Signs and Symptoms

The signs and symptoms of childhood nephrotic syndrome may include;

- edema—swelling, most often in the legs, feet, or ankles and less often in the hands or face
- albuminuria—when a child's urine has high levels of albumin
- hypoalbuminemia—when a child's blood has low levels of albumin
- hyperlipidemia—when a child's blood cholesterol and fat levels are higher than normal, In addition, some children with nephrotic syndrome may have blood in their urine, symptoms of infection, such as fever, lethargy, irritability, or abdominal pain, loss of appetite, diarrhea, high blood pressure.



Types of Nephrotic Syndrome

Minimal change disease

Most common pathology found in childhood nephritic syndrome (77-85% of cases).Usually idiopathic, though an association with Hodgkin lymphoma has been studied in adult cases, As the name implies, light microscopy renal biopsy samples shows no change On electron microscopy, effacement of the foot processes can be seen Immunofluorescent staining for immune complexes is negative Foot process effacement seen in minimal change disease[24-25].

Focal segmental glomerulo sclerosis Accounts for 10-15% of cases

1. More common in adults Light microscopy of renal biopsy sample shows scarring, or sclerosis, of portions of selected glomeruli which can progress into global glomerular sclerosis and tubular atrophy Like minimal change disease, will see effacement of foot processes on EM and in most cases, negative immunofluorescence (no immune complex or antibody deposition) Also usually idiopathic but can be associated with HIV or sickle cell disease Potentially on a spectrum with minimal change disease as opposed to being completely separate entities.
2. The two share pathologic findings and occasionally respond similarly to treatment Typical H&E stain of FSGS Membranoproliferative glomerulonephritis More commonly presents as nephritic syndrome involves immune complex deposition.

Granular Pattern Seen on Immune Fluorescence Staining on Light Microscopy, Can See Thickened Basement Membrane

1. Membranous glomerulonephritis Accounts for just 2-4% of cases in children, but the most common type in adults Like a membranoproliferative disease, can see thickened basement membrane and granular pattern on immunofluorescence.
2. On electron microscopy, characteristic "spike and dome" appearance seen, with membrane deposition growing around subepithelial immune complex deposition. Can be a primary disease, or due to several other causes[26-30].

Classification

Primary Nephrotic Syndrome

Not due to any identifiable systemic disease.

Secondary Nephrotic Syndrome

Caused by identifiable systemic disease Infections, Hepatitis B and C, HIV, malaria, syphilis Drugs.

Non-steroidal anti-inflammatory drugs, heroin lithium Malignancies, Lymphoma, leukemia, Auto-immune, SLE, Endocrine, Diabetes mellitus, Congenital nephrotic syndrome, Finnish type (CNF), Most common congenital nephrotic syndrome, with an incidence of 1 per 8,200 in Finland Not only seen in Finland, it is especially prominent in Mennonites in Pennsylvania Genetic mutation in the NPHS1 gene which codes for the protein nephrin or NPHS2, which codes for the protein podocin Massive proteinuria starts in fetal life, and prematurity usually complicates pregnancies Treatment is aimed at supporting the patient's growth until a transplant is available Other genetic mutations that lead to nephrotic syndrome lead to an FSGS type pathology and include the following genes[31-35]:

CD2AP, TRPC6, WT1, ACTIN4, tRNA(leu), COQ2.

Primary Childhood Nephrotic Syndrome

Health care providers treat idiopathic childhood nephrotic syndrome with several types of medications that control the immune system, remove extra fluid, and lower blood pressure.

Control the immune system. Corticosteroids are a group of medications that reduce the activity of the immune system, decrease the amount of albumin lost in the urine, and decrease swelling. Health care providers commonly use prednisone or a related corticosteroid to treat idiopathic childhood nephrotic syndrome. About 90 percent of children achieve remission with daily corticosteroids for 6 weeks and then a slightly smaller dose every other day for 6 weeks.2 Remission is a period when the child is symptom-free.

Many children relapse after initial therapy, and health care providers treat them with a shorter course of corticosteroids until the disease goes into remission again. Children may have multiple relapses; however, they most often recover without long-term kidney damage.

When a child has frequent relapses or does not respond to treatment, a health care provider may prescribe other medications that reduce the activity of the immune system. These medications prevent the body from making antibodies

that can damage kidney tissues. They include cyclophosphamide, mycophenolate (CellCept, Myfortic), cyclosporine, tacrolimus (Hecoria, Prograf).

A health care provider may use these other immune system medications with corticosteroids or in place of corticosteroids.

Remove extra fluid. A health care provider may prescribe a diuretic, a medication that helps the kidneys remove extra fluid from the blood. Removing the extra fluid can often help to lower blood pressure.

Lower blood pressure. Some children with childhood nephrotic syndrome develop high blood pressure and may need to take additional medications to lower their blood pressure. Two types of blood pressure-lowering medications, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers, have the additional benefit of slowing the progression of kidney disease. Many children with nephrotic syndrome require two or more medications to control their blood pressure.

Secondary Childhood Nephrotic Syndrome

Health care providers treat secondary childhood nephrotic syndrome by treating the underlying cause of the primary illness. For example, a health care provider may treat children by prescribing antibiotics for an infection adjusting medications to treat lupus, HIV, or diabetes changing or stopping medications that are known to cause secondary childhood nephrotic syndrome, While treating the underlying cause, the health care provider will also treat the child to improve or restore kidney function with the same medications used to treat primary childhood nephrotic syndrome. Caretakers should make sure that children take all prescribed medications and follow the treatment plan recommended by their health care provider.

Congenital Nephrotic Syndrome

Researchers have found that medications are not effective in treating congenital nephrotic syndrome and that most children will need a kidney transplant by the time they are 2 or 3 years old. A kidney transplant is a surgery to place a healthy kidney from someone who has just died or a living donor, most often a family member, into a person's body to take over the job of the failing kidney[36-42]. To keep the child healthy until the transplant, the health care provider may recommend the following: albumin injections to make up for the albumin lost in urine diuretics to help remove extra fluid that causes swelling antibiotics to treat the first signs of infection growth hormones to promote growth and help bones manure removal of one or both kidneys to decrease the loss of albumin in the urinedialysis to artificially filter wastes from the blood if the kidneys fail.

Clinical Presentation

Characteristic findings

- Proteinuria
- Hypoalbuminemia

Secondary to proteinuria

- Generalized edema
- Due to a decrease in plasma oncotic pressure which follows massive albumin urinary losses.
- Begins in areas with low resistance, which can be seen in minimal change disease's characteristic eyelid swelling, or "puffy eyes"

Can also lead to scrotal or vulvar edema

- Hyperlipidemia
- Likely due to increased hepatic production of very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and low-density lipoprotein (LDL) in response to hypoproteinemia.

Diagnostic criteria (must see both)

- Serum albumin below 3 g/dL
- Urine protein excretion greater than 50 mg/kg per day Or, greater than 3.5g of protein in a 24-hr urine sample.

WORK-UP

In the absence of identifiable systemic disease, the vast majority of patients that meet diagnostic criteria for nephrotic syndrome have minimal change disease and will be treated accordingly other diagnostic tests, mostly aimed at identifying pathologic processes other than minimal change disease, include[46-50]:

Urinalysis

Hematuria can occasionally be seen in FSGS but is usually a sign of nephritic syndrome.

Protein to creatinine ration from first void of morning UPr/Cr greater than 3.0 is consistent with nephrotic syndrome. Serum studies including electrolytes, creatinine, BUN, lipid panel, albumin, and complement levels. Also, ANA for patients over ten years old, and hepatitis b/c and HIV testing. Renal biopsy if strong suspicion of pathology other than minimal change disease.

When to biopsy

Patients that meet all of the following criteria can be treated empirically without renal biopsy (other patients could benefit from biopsy):

Between ages of 1 and 10 None of the following present: hypertension, gross hematuria, elevated creatinine, Normal complement levels.

Treatment

1. Prednisone 2 mg/kg per day for 4-6 weeks, followed by 1.5 mg/kg per day on alternating days for another 4-6 week, 95% of patients with MCD will go into remission following 8 weeks of corticosteroid treatment
2. Remission defined as 3 consecutive days with no or trace protein on urinalysis. Confirms diagnosis of MCD. Lower rates of remission seen in patients treated for 12 week
3. If recurrent relapses despite adequate steroid therapy, consider cyclophosphamide, 2 mg/kg per day, for 8-12 weeks. Cyclosporine can also be used instead of or the following cyclophosphamide

4. Loop diuretics, such as furosemide 2 mg/kg per day, can be used to treat fluid overload and edema
5. Prophylactic penicillin can be used to prevent streptococcal or staphylococcal infection secondary to decreased complement levels.
6. Pneumococcal vaccination should be given.

Complications

Acute renal failure, Usually reversible with restoration of intravascular volume Thrombosis

Secondary to urinary losses of antithrombin III and protein S, Infection, Usually staphylococcal or streptococcal, The complications of childhood nephrotic syndrome may include

Infection. When the kidneys are damaged, a child is more likely to develop infections because the body loses proteins that normally protect against infection. Health care providers will prescribe medications to treat infections. Children with childhood nephrotic syndrome should receive the pneumococcal vaccine and yearly flu shots to prevent those infections. Children should also receive age-appropriate vaccinations, although a health care provider may delay certain live vaccines while a child is taking certain medications[51,52].

Blood clots. Blood clots can block the flow of blood and oxygen through a blood vessel anywhere in the body. A child is more likely to develop clots when he or she loses proteins through the urine. The health care provider will treat blood clots with blood-thinning medications[53,54].

High blood cholesterol. When albumin leaks into the urine, the albumin levels in the blood drop. The liver makes more albumin to make up for the low levels in the blood. At the same time, the liver makes more cholesterol. Sometimes children may need treatment with medications to lower blood cholesterol levels[55].

Eating, Diet, and Nutrition

Children who have nephrotic syndrome may need to make changes to their diet, such as limiting the amount of sodium, often from salt, they take in each day reducing a amount of liquids they drink each day eating a diet low in saturated fat and cholesterol to help control elevated cholesterol levels

Parents or caretakers should talk with the child's health care provider before making any changes to the child's diet.

Points to Remember

- Childhood nephrotic syndrome is not a disease in itself; rather, it is a group of symptoms that
- indicate kidney damage—particularly damage to the glomeruli, the tiny units within the kidney where blood is filtered result in the release of too much protein from the body into the urine
- The two types of childhood nephrotic syndrome are primary—the most common type of childhood nephrotic syndrome, which begins in the kidneys and affects only the kidneys secondary—the syndrome is caused by other diseases
- The signs and symptoms of childhood nephrotic syndrome may include
- edema—swelling, most often in the legs, feet, or ankles and less often in the hands or face albuminuria—when a child's urine has high levels of albumin hypoalbuminemia—when a child's blood has low levels of albumin hyperlipidemia—when a child's blood cholesterol and fat levels are higher than normal
- A health care provider may order urine tests to help determine if a child has kidney damage from childhood nephrotic syndrome.
- Health care providers will decide how to treat childhood nephrotic syndrome based on the type: primary childhood nephrotic syndrome: medications secondary childhood nephrotic syndrome: treat the underlying illness or disease congenital nephrotic syndrome: medications, surgery to remove one or both kidneys, or transplantation[56,57].

Prognosis

For patients with minimal change pathology, the prognosis is very good, with most patients going into remission following corticosteroid treatment. For patients with focalsegmental glomerulosclerosis, the prognosis is grave. Generally, will progress to end-stage renal disease requiring dialysis and kidney transplant.

CONCLUSION

The nephrotic syndrome produces a wide range of clinical risks, irrespective of cause. In many cases, these may persist for months or even years. Hence, a wide range of protective strategies need to be implemented to protect patients from potentially serious complications while specific attempts are made to reduce or abolish proteinuria. Thrombo-embolism represents the highest life-threatening risk to such patients and, despite difficulties in implementation and monitoring, anticoagulation must be considered in the persistently nephrotic patient. With safer therapies for dyslipidaemia, osteopenia and reduction in proteinuria, it would also seem appropriate to include these agents in the therapeutic regimen.

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