

Nephrotic syndrome: Rare chronic kidney disease



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1. Introduction

The rare disease "nephrotic syndrome" refers to a kidney illness that causes your body to discharge an excessive amount of protein in urine. Nephrons, which are around a million filtering units, make up the kidneys. Each nephron consists of a tubule and a filter known as a glomerulus. The tubule replenishes the blood with necessary chemicals and eliminates surplus water and wastes, resulting in urine, while the glomerulus filters the blood. Damage to the glomeruli causes excessive amounts of protein to seep from the circulation into the urine, which is often the cause of nephrotic syndrome (1). The term "nephrotic-range proteinuria" refers to the loss of protein up to three grams or more through urine in a period of 24-hour or the presence of two grams of protein for every gram of urine creatinine in a single urine sample (2).

The English physician Richard Bright initially characterized nephrotic syndrome in his landmark 1827 publication "Reports of Medical Cases". Understanding the condition was made possible by Bright's documentation of the clinical signs of proteinuria, edema, and hypoalbuminemia in renal disease patients (3). Researchers like Friedrich Theodor von Frerichs and William Osler contributed to the understanding of the pathological alterations and clinical characteristics linked to nephrotic syndrome in the late 19th and early 20th centuries. Their work improved our understanding of the underlying causes of nephrotic syndrome and helped distinguish it from other kidney diseases (4).

2. Pathophysiology

Damage to the kidney's glomeruli, which are in charge of removing waste and surplus chemicals from the blood while holding onto vital proteins like albumin, is part of the pathophysiology of nephrotic syndrome. Proteinuria results from the glomeruli becoming too porous in this disease, which permits proteins like albumin to seep into the urine. Nephrotic syndrome in children can be caused by a number of underlying disorders, the most prevalent of which is minimal change disease. Additional reasons include membranous nephropathy, membranoproliferative glomerulonephritis, and focal segmental glomerulosclerosis. Its development may be influenced by immunological factors, genetic predisposition, infections, and environmental causes (5,6).

2.1 Characteristics of nephrotic syndrome

Nephrotic syndrome is a kidney disorder characterized by the following key features (7):

- **Heavy proteinuria:** The condition known as "heavy proteinuria" occurs when there is an excessively high level of protein in the urine, usually more than 3.5 grams per day.

- **Hypoalbuminemia:** Low albumin levels in the blood, often less than 3 grams per deciliter are known as hypoalbuminemia.
- **Edema:** Swelling brought on by fluid retention, especially in the legs, ankles, and eye area.
- **Hyperlipidemia:** Increased blood lipid (fat) levels, such as those of cholesterol and triglycerides, are known as hyperlipidemia.

2.2 Classification

Nephrotic syndrome can be categorized according to a number of factors, such as clinical presentation, histology, and etiology. Based on these variables, the following categorization of nephrotic syndrome exists (8).

2.2.1 Etiological classification

Nephrotic syndrome that develops without a known underlying cause is referred to as

- **Primary nephrotic syndrome:** The primary nephrotic syndrome including various conditions like focal segmental glomerulosclerosis (FSGS), membranous nephropathy and minimal change disease.
- **Secondary nephrotic syndrome:** An underlying systemic illness or condition causes the syndrome to develop in secondary nephrotic syndrome cases. Amyloidosis, diabetes mellitus, systemic lupus erythematosus (SLE), and certain infections are common secondary causes.

2.2.2 Histopathological classification

- **Minimal change disease (MCD):** Under optical microscopy, no alterations are observed in any Change Disease (MCD), however under electron microscopy, there is considerable podocyte foot process effacement.
- **Focal segmental glomerulosclerosis (FSGS):** FSGS causes nephrotic syndrome and proteinuria by sclerosis and scarring some but not all glomeruli.
- **Membranous nephropathy (MN):** The thickening of the glomerular basement membrane as a result of immune complex deposition is a characteristic of Membranous Nephropathy (MN).
- **Membranoproliferative glomerulonephritis (MPGN):** Thickening of the glomerular basement membrane as a result of both cellular proliferation and the deposition of immune complexes.

2.2.3 Clinical classification

- **Steroid-responsive nephrotic syndrome:** Nephrotic syndrome that responds effectively to corticosteroid therapy is known as "steroid-responsive nephrotic syndrome," which is usually observed in minimal change illness.
- **Steroid-resistant nephrotic syndrome:** Nephrotic syndrome, which can arise in FSGS and other disorders, that is unresponsive to corticosteroid treatment.
- **Relapsing nephrotic syndrome:** Nephrotic syndrome relapsing is characterized by intervals of remission followed by a return of symptoms.
- **Persistent nephrotic syndrome:** Nephrotic syndrome that remains untreated and does not go into remission is known as persistent nephrotic syndrome.

2.2.4 Genetic classification

Mutations in genes encoding proteins involved in podocyte organization and function are among the genetically based types of nephrotic syndrome. Examples include congenital nephrotic syndrome-related mutations in the NPHS1 and NPHS2 genes.

2.2.5 Age-related classification

Certain age groups are more likely to have certain kinds of nephrotic syndrome. For instance, membranous nephropathy is more common in adults, although minimum change disease is more frequently observed in children.

2.2.6 Health care professionals use various terms to understand nephrotic syndrome in children

- Congenital nephrotic syndrome is present within birth to 3 months
- Infantile nephrotic syndrome is present within 3 to 12 months
- Childhood nephrotic syndrome is present within 12 months or older

3. Incidence and prevalence

3.1 Incidence

Nephrotic syndrome is thought to affect 2–7 out of every 100,000 children globally each year. Although the occurrence in adults is less certain, it is often lower than in children.

3.2 Prevalence

Nephrotic syndrome is thought to affect around 16 out of every 100,000 children in Western nations. Adult prevalence is less certain and varies based on the demographic and underlying reason under investigation. Nephrotic syndrome affects less than 5 out of every 100,000 children worldwide on average each year. A significant chronic illness that affects children is nephrotic syndrome. Every year almost two to seven new instances out of every 100,000 children under the age of eighteen were affected by nephrotic syndrome (9-11).

Srivastava R N et al. (1975) studied and a major renal cause was found in 195 (96%), of which 77% were males, of the 206 Indian children with nephrotic syndrome analysed clinic-pathologically. Before the age of five, the condition manifested in 126 children (sixty-six boys and thirty girls). Three months to sixteen years following the beginning of nephrotic syndrome, renal biopsies were performed on 85 of the 150 patients (77%), and the results revealed mild abnormalities. The conditions that classified renal histological abnormalities in 45 instances were Membranous 3, focal segmental glomerulosclerosis 9, focal global glomerulosclerosis 2, advanced nonspecific 8, and moderate proliferative 9. Clearance of proteinuria with corticosteroid therapy was mostly limited to patients with mild or moderate renal histological alterations. According to our research, Indian children's idiopathic nephrotic syndrome pattern is comparable to that of Western nations (12).

4. Symptoms and diagnosis

4.1 Symptoms (7)

- Severe Swelling (Edema): Especially around the eyes, legs, and feet.
- Foamy Urine: Due to high levels of protein in the urine.
- Weight Gain: From fluid retention.
- Fatigue: Due to loss of protein and overall health decline.
- Loss of Appetite

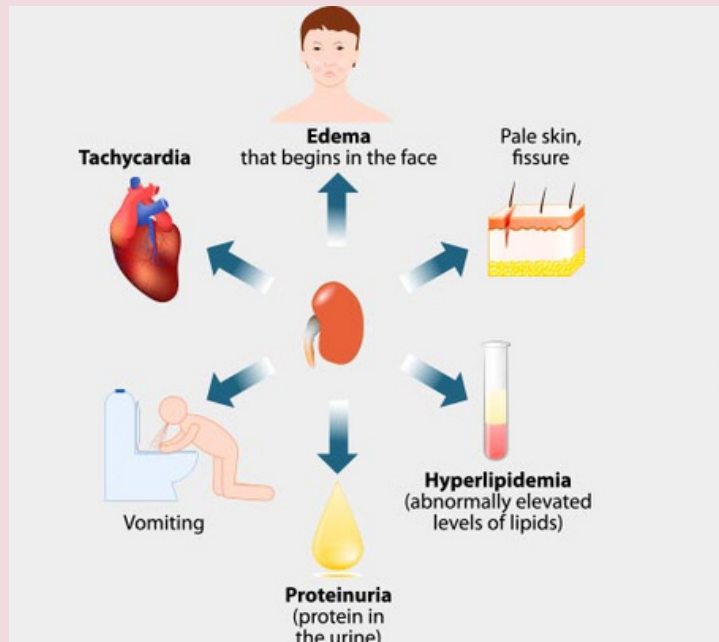


Figure1. Symptoms of nephrotic syndrome (7)

4.2 Diagnosis (7,13)

- Urine Tests: To detect high levels of protein and assess kidney function.
- Blood Tests: To check levels of albumin, cholesterol, and kidney function markers.
- Kidney Biopsy: Sometimes performed to determine the specific cause of nephrotic syndrome.

5. Treatment and management

Nephrotic syndrome treatment consists of treating the underlying cause, controlling symptoms, and preventing consequences. Common approaches include (7,13):

5.1 Medications

- Corticosteroids and Immunosuppressant: To reduce inflammation and immune response, particularly in primary nephrotic syndrome.
- Diuretics: To reduce fluid buildup and swelling.
- ACE Inhibitors or ARBs: To reduce blood pressure and protein loss in the urine.
- Statins: To manage high cholesterol levels

5.2 Dietary changes

- Low Sodium Diet: To reduce swelling.
- Low Protein Diet: Sometimes recommended to decrease protein loss through urine.
- Low Fat Diet: To manage cholesterol levels.

6. Complications

If not properly managed, nephrotic syndrome can lead to several complications, such as (7):

- Infections: Increased susceptibility due to loss of immunoglobulin in the urine.
- Blood Clots: Due to loss of proteins that prevent clotting.
- Chronic Kidney Disease: Potential progression to kidney failure.
- Acute Kidney Injury: Sudden decline in kidney function.

7. Prognosis

The prognosis for nephrotic syndrome varies depending on their cause and response to treatment. Some cases, particularly in children with minimal change disease, respond well to treatment and may go into remission. Other forms, such as FSGS or membranous nephropathy, may have a more chronic course and risk of progressing to chronic kidney disease. Regular follow-up with a healthcare provider is essential for monitoring and managing the condition effectively (11).

8. Future aspects

The future of nephrotic syndrome seems promising as researchers investigate new medicines, diagnostic tools, and approaches to customized care. The interdisciplinary nature of nephrology research and the cooperative efforts of clinicians, scientists, and industry partners in advancing the understanding and management of nephrotic syndrome are highlighted by future perspectives such as regulatory tolerance induction, precision medicine, biologic therapies, stem cell therapy, nanomedicine, biomarker discovery, artificial intelligence and machine learning, telemedicine, and remote monitoring. Sustained funding for research, innovation, and translational medicine is necessary to fully use these novel treatment approaches and enhance nephrotic syndrome patient outcomes.

9. Conclusion

In order to sum up, fighting orphan and rare diseases necessitates concerted efforts to overcome challenges and benefit from new advancements in collaboration and research. Important challenges involve the necessity for continuous cooperation and funding in addition to the developments in genomics and precision medicine. Limited resources and uneven access are further issues. It is essential that we put out a call to action for increased awareness and support, pleading with interested parties to demand improved funding for healthcare access, education, and research. Working together and prioritising the needs of persons with rare and orphan diseases can greatly enhance results and standard of life.

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