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# Nephrotic syndrome in pediatrics

**ABSTRACT**

Nephrotic syndrome is a glomerulopathy caused by renal diseases that increase the permeability of the glomerular filtration barrier; minimal change disease is the cause most associated with the development of nephrotic syndrome in pediatrics. The clinical manifestations that characterize this syndrome are: proteinuria in nephrotic range, hypoalbuminemia, edema in areas of decline and alterations in the lipid profile. The diagnosis is made by clinical findings and other studies including urinalysis, urinary proteins as initial tests, serum albumin levels and sometimes alterations in the lipid profile, in few cases renal biopsy is required to confirm the diagnosis. Most patients respond to first line medical treatment with disease remission and symptomatology control.

**Keywords:** proteinuria; edema; steroids; hypoalbuminemia.

## INTRODUCTION

Nephrotic syndrome (NS) has been known throughout history as the most frequent primary glomerulopathy in the pediatric population (1); this syndrome encompasses several diseases characterized by an alteration in the glomerular filtration barrier (2). NS is classified according to its causes in primary, secondary or congenital; the bibliographic review emphasizes in primary NS, which represents more than 90% of all the diagnosed cases.

Currently, proteinuria in the nephrotic range, hypoalbuminemia, edema and alterations in the lipid profile, especially hyperlipidemia, are recognized as the main clinical manifestations that characterize this syndrome.

The aim of the literature review is to provide recent and updated information on the most important aspects of NS in the pediatric age group, in order to provide health professionals in primary care with basic knowledge of the pathology and thus establish a diagnosis and, therefore, timely and appropriate management of patients.

## METHOD

To prepare this literature review article, we searched 25 different bibliographic references, which contain updated data and information on the topic of interest, the references used were published between 2013 and 2019. The main databases and sources used for the information search were: Scielo, Uptodate, elsevier and PubMed.

## EPIDEMIOLOGY

NS is caused by renal disease and is one of the most frequent primary glomerulopathies in the pediatric population. With a reported incidence in children under 16 years of age of 2-7 new cases per 100,000 children per year (1). The most frequent age of onset is 2-8 years and generally presents after 2 years of age, with the maximum age at 3-5 years, nevertheless according to the literature approximately 1 to 6% of the patients evolve to the pathology before the year of age this secondary to congenital NS (3). In the pediatric age it is twice as frequent in the male sex (1, 3).

## CLASSIFICATION

According to the different laboratory findings and associated clinical features, NS is classified into three subgroups: primary or idiopathic, secondary and congenital or infantile NS.

Primary NS is defined by the absence of an identifiable systemic disease or etiologic drug associated to the glomerular alteration, it is the most frequent in general and represents >90% of the cases of ages between 1-10 years (2). Minimal change disease (MCD) is the most frequent histologic alteration in patients with primary NS, present in >85% of all diagnosed cases (1).

The definitive cause of SCD is not clearly defined but there is evidence suggesting a primary immunologic disorder that generates dysfunction in the glomerular podocytes causing alterations in the permeability of the glomerular barrier (4). A multivariate analysis demonstrated that the findings in the clinical presentation of the primary SN accurately differentiate children with MCD from those with other glomerular pathologies (1,2).

NS secondary to systemic diseases or any identifiable process causing glomerular injury such as: infections (human immunodeficiency virus, syphilis, hepatitis B, toxoplasmosis, endocarditis, infectious mononucleosis), drugs (interferon, lithium, captopril), immunological disorders (systemic lupus erythematosus, vasculitis), associated with cancer (lymphoma, leukemia, solid tumors) (5).

Congenital NS occurs in patients under one year of age, of which up to 85% of children present clinical manifestations in the first 3 months of life, usually associated with genetic mutations that make them

resistant to the usual pharmacological treatment and therefore have a worse prognosis in the short and long term (1, 2).

## PATOGENIA

NS is a manifestation of renal diseases that deteriorate and increase the permeability of the glomerular filtration barrier (3). The glomerular filtration barrier is formed by three components: fenestrated endothelial cells, glomerular basement membrane and podocytes with their podocyte processes (6). These components act as a barrier to glomerular filtration by the mechanism of charge and size selectivity, thus preventing the passage of proteins and macromolecules from the capillaries to the urinary space.

An alteration or injury in any of the components that form part of the glomerular filtration barrier generates an increase in the permeability of this barrier, which results in protein loss through urine (4,6).

## CLINICAL MANIFESTATIONS

The loss of protein in urine causes a series of alterations that constitute the clinical and laboratory features of NS. It usually presents commonly with four clinical manifestations, of which the first two are essential to make the diagnosis (7,8).

The characteristic clinical manifestations are:

- Proteinuria in nephrotic range (>50 mg/kg/d)
- Hypoalbuminemia (serum albumin < 3g/dL)
- Edemas
- Hyperlipidemia

The first clinical manifestation is usually the appearance of edema; in children it usually follows a precipitating event such as an upper respiratory tract infection or an insect bite. The first site where edema usually appears is at the periorbital level (2). Often periorbital edema goes unnoticed and is misdiagnosed as an allergic reaction (9). The distribution of edema is dependent on severity, so it is normal that periorbital edema decreases as the hours of the day go by and edema increases in the region of the lower extremities and in the sacral area with scrotal edema in boys or vulvar edema in girls (2,9). In severe forms there may be generalized edema with anasarca and pleural effusions, manifesting clinically with abdominal distension and abdominal pain or respiratory distress.

Hypoalbuminemia appears when the capacity of hepatic synthesis is surpassed by urinary losses of albumin (10,8). This alteration increases the decrease of capillary oncotic pressure contributing to the appearance of edema and loss of liquid in third spaces, hypoalbuminemia is an indispensable laboratory criterion for the diagnosis of NS and is present in all cases (11).

Hyperlipidemia with increased concentrations of total cholesterol, LDL cholesterol and less frequently elevated serum triglyceride levels are secondary to increased hepatic lipid synthesis and decreased lipid catabolism (8, 12). In adults hyperlipidemia usually implies an increased cardiovascular risk although the implications in children are not as serious especially in those cases that respond to steroid therapy.

Other less frequent manifestations and signs are: hematuria (25%), arterial hypertension (20%) and renal failure (3%), which are associated with underlying renal lesion and more severe disease, in fact the presence of these alterations are usually an indication to perform a renal biopsy and to think of other more serious etiological causes (1,2).

## COMPLICATIONS

They result from abnormalities directly related to the disease and secondary to pharmacological therapy (13). The most frequent complications directly associated with the pathophysiology of the SN are:

- Infections
- Thromboembolism

- Renal insufficiency
- Anasarca
- Hypovolemia

Patients with NS have an increased risk of infections due to several factors: IgG hypoglobulinemia (urinary leakage), impaired ability to produce antibodies and decreased complement levels (urinary leakage) in addition to immunosuppression due to drug therapy in this case mainly due to the use of corticosteroids (13).

They have a significantly higher risk of infections by encapsulated bacteria, especially pneumococcal disease. The infections that most commonly affect them are: spontaneous bacterial peritonitis, pneumonia, cellulitis, meningitis and sepsis (3).

These patients present a hypercoagulable state secondary to urinary losses of antithrombotic factors (antithrombin II, protein S, plasminogen), hemoconcentration and platelet activation. With a reported incidence of thromboembolic complications (pulmonary thromboembolism, renal vein thrombosis) in 23% of all cases (13).

Despite an apparent increase in total body water in children due to the presence of edema, patients have a decrease in effective circulating volume (ECV), secondary to hypoalbuminemia, which is usually aggravated by the presence of diarrhea (infectious complications) and the use of diuretics (edema management) (14).

Signs and symptoms that these patients with decreased ECV may present are: tachycardia, findings of severe vasoconstriction such as: cold extremities, weak pulse, slow capillary filling, oliguria and abdominal pain (13,15).

Renal failure can occur as a consequence of several mechanisms (16); hypovolemia due to decreased ECV that can lead to acute tubular necrosis or be secondary to an infectious process, pharmacological nephrotoxicity due to the use of Cyclosporine or Tacrolimus, especially in patients with a diagnosis of steroid-dependent NS (13).

## DIAGNOSIS

Clinical and laboratory findings are used to confirm the diagnosis of NS. In the specific case of MCD which is the main cause of idiopathic SN; the following clinical criteria are used for a presumptive diagnosis of MCD:

- Age < 10 years,
- Absence of hypertension
- Absence of hematuria
- Normal full levels
- Normal renal function tests

In almost all patients with a presumptive diagnosis of MCD, treatment with steroids is initiated without the need to perform a renal biopsy (1,17).

Among the studies performed is urinalysis and urinary protein analysis; it is usually the initial and most important test to evaluate these patients. The findings found in the urinalysis are: proteinuria in the nephrotic range >50 mg/kg/day in a 24 hr urine sample; however, this collection technique is difficult to achieve in children, so a random urine sample can be used as an alternative to measure the protein/creatinine ratio, which a value>3mg is indicative of proteinuria in the nephrotic range (18). Urinary sediment is usually inactive in cases of idiopathic NS, with the presence of hyaline casts and oval bodies only.

Serum albumin concentration is typically <3 g/dL, serum complement concentration is usually normal as are total globulins (12).

The alteration in the lipid profile with hyperlipidemia, especially elevation of LDL cholesterol and less frequent elevation of triglyceride levels (19). Cholesterol elevation is inversely correlated with serum albumin concentration.

## TREATMENT

The objective of pharmacological treatment is to achieve the induction of remission of the disease in order to obtain symptomatic improvement, i.e., proteinuria in physiological range, disappearance of edema and normalization of albumin levels, and also to prevent complications (20). In order to understand the management and response to NS treatment, important concepts must be clear; they are described in **Table 1.**

| **Table 1.** Concepts in Nephrotic Syndrome | |
|---|---|
| corticosensitive SN | No proteinuria and normalizes albumin in response to treatment (8 weeks). |
| corticoresistant SN | Clinical and/or biochemical NS persists despite 8 weeks of treatment. |
| corticodependent SN | >2 relapses on alternate-day prednisone tapering or relapse within 2 wk after withdrawal |
| Relapse | Proteinuria in dipstick >2+ in 5 consecutive days |
| Infrequent relapses | < 2 relapses in 6 months after initial manifestation or <3 in one year |
| Frequent relapses | >2 relapses in 6 months or >3 relapses in one year |
| Referral | Negative proteinuria/diagnoses on test strip for five consecutive days |
| Complete referral | Proteinuria disappears and serum albumin normalizes. |
| Partial remission | Normalization of albuminemia (> 3g/l) with persistence of proteinuria in the NON nephrotic range. |
| **Source**: data and information taken from the Spanish association of pediatrics AEP, protocols- pediatric nephrotic syndrome, 2014. | |

The basis of pharmacological treatment is corticosteroids, indicated in the first manifestation in all patients (12), most children with idiopathic NS respond to steroid therapy, although there are variations in dosage and duration in most cases the initial course of corticosteroids is given for at least two or three months (21).

Corticosteroid therapy is initiated with prednisone at a dose of 2 mg/kg or 60 mg/$m^2$ on continuous days in a single daily dose (maximum dose, 60 mg/d) for 4-6 weeks, then continued with prednisone every other day at a dose of 1.5 mg/kg or 40 mg/m? for 4-6 weeks (maximum dose 40 mg/d) (22,23). When there is a state of remission, prednisone is progressively withdrawn. Several studies have shown that prolongation of the initial treatment for periods varying between 3 and 7 months significantly reduces the number of relapses per patient per year (22,23).

The majority of children presenting with idiopathic SN respond to steroid therapy. However, approximately 10-20% of patients do not respond to initial steroid treatment with resistance to this therapy (24).

In this case of resistance, relapses or side effects to first line therapy; the pharmacological management provided is with immunosuppressive therapy; cyclophosphamide is usually the first pharmacological choice, followed by mycophenolate and reserving cyclosporine and tacrolimus as the last line due to their nephrotoxic effects (24).

## FORECAST

The long-term prognosis of these patients is conditioned above all by the response to corticoids (12), therefore conditioned to an early and opportune diagnosis. Patients sensitive to first line therapy with steroids >90% of the cases evolve towards resolution of their disease with preservation of renal function, however a high percentage between 50% of the cases have frequent relapses in the course of the disease with greater risk of suffering chronic renal disease in the long term (25).

## CONCLUSION

NS is the most common primary glomerulopathy affecting the pediatric population, most cases are initially seen in primary care services.

The initial clinical manifestation of patients is usually edema, especially at the periorbital level, which is frequently misdiagnosed as an allergic reaction, hence the importance for the treating physician to have knowledge of the main clinical characteristics and laboratory alterations such as proteinuria in the nephrotic range, hypoalbuminemia and alteration of the lipid profile; characteristics that lead to the diagnosis of NS.

The first line treatment is steroids, most patients have an initial response to this treatment, which is the most important prognostic factor in the long term, emphasizing the importance of assertive diagnosis and proper management to improve the prognosis and preservation of renal function of patients.

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