

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.  
For more information visit [www.intechopen.com](http://www.intechopen.com)



# Causes and Pathophysiology of Nephrotic Syndrome in Childhood

*Nagaraju Vallepu, Saikiran Velpula, Bharath Kumar Dasari, Manish Kumar Thimmaraju, Sridhar Babu Gummadi, Neeraja Yelugam and Supraja Jannu*

## Abstract

Nephrotic syndrome is a general type of kidney disease seen in children. In the past, Roelans is credited with the first clinical description of nephrotic syndrome in the late fifteenth century. Nephrotic syndrome is appropriate to excessive hypoalbuminemia, edema, and proteinuria may be hyperlipidemia also present in some cases. Periorbital swelling with or without edema of the body is observed in first starting little period of life, frequently show in children with this condition. Nephrotic syndrome starts develops due functional and structural changes in the GFB, consequential difficulty to control protein in the urine. Nephrotic syndrome possibly causes due to some of glomerular diseases and systemic diseases, but significantly the mostly in childhood is unknown nephrotic syndrome. The first significant improvement with introduction of sulfonamides and then penicillin was seen in 1939. The beginning of adrenocorticotrophic hormone and cortisone greater decrease in mortality (to 9%), in the 1950s it was noted to happen in association with spectacular declaration of proteinuria. Etiology of nephrotic syndrome is also age reliant. Most cases reported in the first 3 months of life are referred to as congenital nephrotic syndrome (CNS) and are due to genetic diseases.

**Keywords:** nephrotic syndrome, hypoalbuminemia, proteinuria, glomerular filtration barrier, congenital nephrotic syndrome

## 1. Introduction

Nephrotic syndrome is a general type of kidney disease seen in children. Historically, Roelans is credited with the first clinical description of nephrotic syndrome in the late fifteenth century. Nephrotic syndrome is appropriate to excessive hypoalbuminemia, proteinuria, and edema, although additional clinical hyperlipidemia is also usually present. The beginning of adrenocorticotrophic hormone and cortisone in the 1950s contributed to an even greater decrease in mortality (to 9%), which was noted to occur in association with dramatic resolution of proteinuria.

2. Causes

The childhood nephrotic syndrome is principally idiopathic or primary, though a limited number of cases are secondary to glomerular and inclusive diseases and other infectious agents. Age reliant is also the etiology factor of nephrotic syndrome. Maximum cases presenting in the first 3 months of lifespan are mentioned as CNS (congenital nephrotic syndrome) and are caused by genetic diseases. While in the remaining of the first year of lifecycle (3–12 months) there has been no effective study of the etiology of nephrotic syndrome reported cases, there are a number of stats shows that up to 40% of reported cases meanwhile this time may also be due to genetic factors [1]. At the time of first year and in the first decade of life, maximum presenting cases are due to primary or idiopathic nephrotic syndrome, at the time of first 10 years of lifecycle the number of secondary nephrotic syndrome cases increases.

2.1 Inborn nephrotic syndrome

Congenital nephrotic syndrome is the type of nephrotic syndrome which occurs in first 3 months of life and is due to genetic causes mostly by alterations in the gene encrypting nephrin, a podocyte opening diaphragm protein. For the first time, these mutations were expressed in the Finnish, from then the name congenital nephrotic syndrome of the Finnish type (CNF) [1]. Though the incidence of CNF is high in Finland it also occurs in other populations also. Congenital nephrotic syndrome is not either equivalent with CNF, reason is that alterations in other genes encrypting podocyte opening diaphragm proteins, early-onset nephrotic syndrome can also be caused by proteins such as podocin. Upto 40% of all cases of nephrotic syndrome occurring in the first 3 months of life are due to alterations in a sequence of podocin gene [2] in the earliest 3 months of life. Nephrotic syndrome may also be part of multisystemic syndromes such as nail-patella syndrome, Pierson syndrome, Denys-Drash syndrome, and others or a sequence of congenital infections such as cytomegalovirus and syphilis (**Table 1**).

Genetic	Mutation in nephrin ( <i>NPHS1</i> ) gene leads to congenital nephrotic syndrome of the Finnish type (CNF) Mutation in podocin ( <i>NPHS2</i> ) gene results Autosomal recessive FSGS Mutation in <i>WT1</i> gene results Autosomal dominant diffuse mesangial Sclerosis (DMS) Mutation in laminin $\beta_2$ gene leads Congenital nephrotic syndrome
Syndromes	Nail-patella syndrome due to mutation in LIM homeodomain protein (LMX1B) Jeune's syndrome Galloway Mowat syndrome Denys-Drash syndrome due to <i>WT1</i> mutation with DMS Pierson syndrome Schimke immunoosseous dysplasia with FSGS due to mutation in <i>SMARCA1</i> Cockayne syndrome
Idiopathic	Nonsyndromic DMS Minimal change nephrotic syndrome FSGS
Infections	Congenital toxoplasmosis Congenital cytomegalovirus (CMV) infection Congenital syphilis

**Table 1.**  
*Causative factors of congenital nephrotic syndrome (CNS) in 0–3 months of age.*

2.2 Nephrotic syndrome after infancy

Above the infancy and above the first year of life, maximum of the nephrotic syndrome cases are idiopathic. MCNS (Minimal-Change Nephrotic Syndrome) is the most usual deviation, and is responsible for more than 80% of all cases [3]. Focal segmental glomerulosclerosis (FSGS), Membranoproliferative glomerulonephritis (MPGN), and mesangial multiply glomerulonephritis are the other less common histopathologic types in this age group (**Table 2**). For a few cases in this age group genetic disease is also responsible. 10–25% of all cases of familial and sporadic SRNS were caused by

Idiopathic	C1q nephropathy IgM nephropathy Membranous nephropathy (MN) Membranoproliferative glomerulonephritis (MPGN) Minimal change nephrotic syndrome (MCNS) Focal segmental glomerulosclerosis (FSGS) Mesangial proliferative glomerulonephritis
Hereditary	Mutation in <i>WT1</i> gene results autosomal dominant diffuse mesangial Sclerosis (DMS) Mutation in gene encoding transient receptor potential cation channel 6 ( <i>TRPC6</i> ) results Autosomal dominant FSGS Mutation in gene encoding CD2-associated protein ( <i>CD2AP</i> ) results autosomal dominant FSGS Mutation in gene encoding $\alpha$ -actinin 4 leads to autosomal dominant FSGS Mutation in podocin( <i>NPHS2</i> ) gene results autosomal recessive FSGS
Drugs	NSAIDs Penicillamine ACEIs Pamidronate Gold Lithium Mercury Interferon Heroin
Metabolic diseases	Glutaric acidemia Mitochondrial cytopathies Glycogen storage disease Fabry's disease
General diseases	Systemic lupus erythematosus Sarcoidosis Diabetes mellitus Henoch-Schönlein purpura
Blood and oncologic diseases	Lymphoma (Hodgkin's most likely can lead to minimal change) Leukemia Sickle cell disease
Infections	HIV Malaria Filariasis Schistosomiasis Hepatitis B and C
Others	Food allergies Obesity (usually with FSGS) Bee stings (MCNS) Pregnancy Oligomeganephronia

**Table 2.**  
*Causative factors of nephrotic syndrome above 3 months of life.*

mutations in NPHS2, inherited in an autosomal genetic mode, because it was exposed in one series. Beginning of nephrotic syndrome in untimely childhood, not response to steroid treatment, strong findings of focal segmental glomerulosclerosis (FSGS) on histopathology renal biopsy, progress to ESRD in 5 years of finding, and comprehensively decreases the risk of disease recurrence following renal transplantation are by the phenotype typically associated with NPHS2 mutations [4, 5]. Additional genetic factors consists autosomal dominant transmitted causes such as  $\alpha$ -actinin 4, mutations in the Wilms' tumor suppressor gene (WT1), TRPC6 and CD2AP [6–10]. Individually from those in WT1, maximum of these mutations go to result in adult-onset disease. To a number of systemic diseases in children, nephrotic syndrome may also be secondary. Pediatric diseases such as Henoch-Schönlein purpura; diabetes mellitus; systemic lupus erythematosus, especially membranous (WHO Class V) SLE; and sarcoidosis may all exist with nephrotic syndrome. Infective factors can also cause nephrotic syndrome and can be bacterial, viral, or parasitic. Despite it is not so far fully known how these factors cause nephrotic syndrome, it is maybe due to an bizarre immune response to them in the majority of the reported cases, occurring in the progression and aggregation of immune complexes in the glomerulus. The interpretation of these factors as a cause of nephrotic syndrome turn to parallel their prevalence in demanding regions of the world. For example, in Hong Kong and countries in Africa, hepatitis B and C are important causes of nephrotic syndrome [11, 12]. In areas where malaria is endemic, Malaria, particularly quartan malaria, is also an important cause. Eighteen nephrotic syndrome in both adults and children can be caused by Human immunodeficiency virus (HIV). despite the renal abrasion linked with HIV can be changeable, FSGS is the most common histologic finding affiliated with HIV is, particularly the breakdown is different. Despite the result of treatment of the underlying infection on the nephropathy is not well known, but there are details that hepatitis B-associated nephrotic syndrome may be cooperative to treatment of the hepatitis [13]. A list of infective factors associated with nephrotic syndrome is shown in **Table 2**. Drugs such as angiotensin converting enzyme inhibitors (ACEIs), penicillamine, gold, nonsteroidal antiinflammatory drugs (NSAIDs), sickle cell disease, bee stings, lymphoma, leukemia, and various types of food allergies are the other less common causes of nephrotic syndrome. Moreover, in children with obesity the nephrotic syndrome is being seen further recurrently. The histologic scrape most frequently occurs in this setting is FSGS.

### 3. Mechanism of nephrotic syndrome

The development of massive proteinuria is the central abnormality in all cases of nephrotic syndrome. Some of the literature shows the evidence in that nephrotic syndrome may be a significance of glomerular defect, circulating factors, and defect in immunological system.

#### 3.1 Glomerular defect

The most important possible functions of the kidney is the filtration of blood and blood products at glomeruli, which permits the fluid and dirty products while retaining the greater part of blood proteins and all blood cells within the vasculature. These types of process of filtration is made potential by the (GFB), which is made up of specific glomerular epithelial cells (podocytes), endothelial cells, and GBM these distal bottom actions are attached to the GBM (**Figure 1**) [14]. Adjacent podocyte bottom actions are associated to each one other by networks of specific cell-cell junctions called as opening diaphragms. Additionally, the GBM (glomerular basement membrane) has a plentiful supplies of negatively charged molecules of heparin sulfate





who actually transferred a soluble factor to their fetuses in utero [39], (3) decrease of repeated disease induced by treatment with protein A immunoadsorption due to presumed removal of circulating factors in the reappearance of FSGS in transplanted kidneys in patients with primary FSGS [40], and (4) FSGS recurrence in transplanted kidney patients serum injected in to the experimental animals leads to causing of enhanced glomerular permeability [32] serum of children with FSGS and recognized as components of apolipoproteins, from the suggestive of that an imbalance involving serum permeability factors and permeability inhibitors may have a pathogenic role in FSGS. Moreover, inhibitors of glomerular permeability have also been isolated [33].

### 3.3 Defect in immunological system

For more than 30 years nephrotic syndrome may be because of abnormalities of the immune system has existed. Both the humoral and cellular immune responses are abnormal during relapse of nephrotic syndrome. Still, have a thought that relationship between the nephrotic syndrome and T lymphocyte function was first proposed by Shalhoub and his colleagues and concluded that abnormalities in cellular immune responses [36] proves for this includes (1) sensitivity of most forms of primary nephrotic syndrome to mycophenolate mofetil, corticosteroids, calcineurin inhibitors, and alkylating agents, these drugs all are inhibitors of T lymphocyte purpose, (2) mostly measles and malaria, diseases well-known to slow down the cell-mediated immunity following remission of nephrotic syndrome, and (3) detection of Minimal-Change Nephrotic Syndrome (MCNS) as a paraneoplastic manifestation of lymphoreticular malignancies and other Hodgkin's disease. Latest reported cases have also suggested and vital role of the cell-mediated immune system in nephrotic syndrome, collectively with depressed cell-mediated immunity during relapses of MCNS alterations in T cell subsets during relapses and increased cell surface expression of IL-2 receptors on T cells, reflective of T cell activation [34, 41]. Additionally, a number of cytokines, released in part by T lymphocytes, have been recommended to be erratically changed throughout nephrotic syndrome (NS) [42, 43].

## 4. Pathophysiology

In children with nephrotic syndrome facial or general edema, is the basic symptom due to accumulation of fluid in the interstitial compartment. In nephrotic syndrome the edema is usually causes disproportionate proteinuria, which leads to retention of sodium and water, hypoalbuminemia to recompense for intravascular volume depletion. The pathogenesis of edema can be well explained by analysis of the classic Starling equation, which explains the regulation of fluid movement across capillary walls [44].

Net filtration =  $L_p S (\Delta \text{hydraulic pressure} - \Delta \text{oncotic pressure})$ .

$$= L_p S [(P_{cap} - P_{if}) - s(\pi_{cap} - \pi_{if})].$$

where:

$L_p$  = the capillary permeability.

$S$  = the surface area of the capillary wall.

$P_{cap}$  = the capillary hydrostatic pressure.

$P_{if}$  = the interstitial fluid hydrostatic fluid pressure.

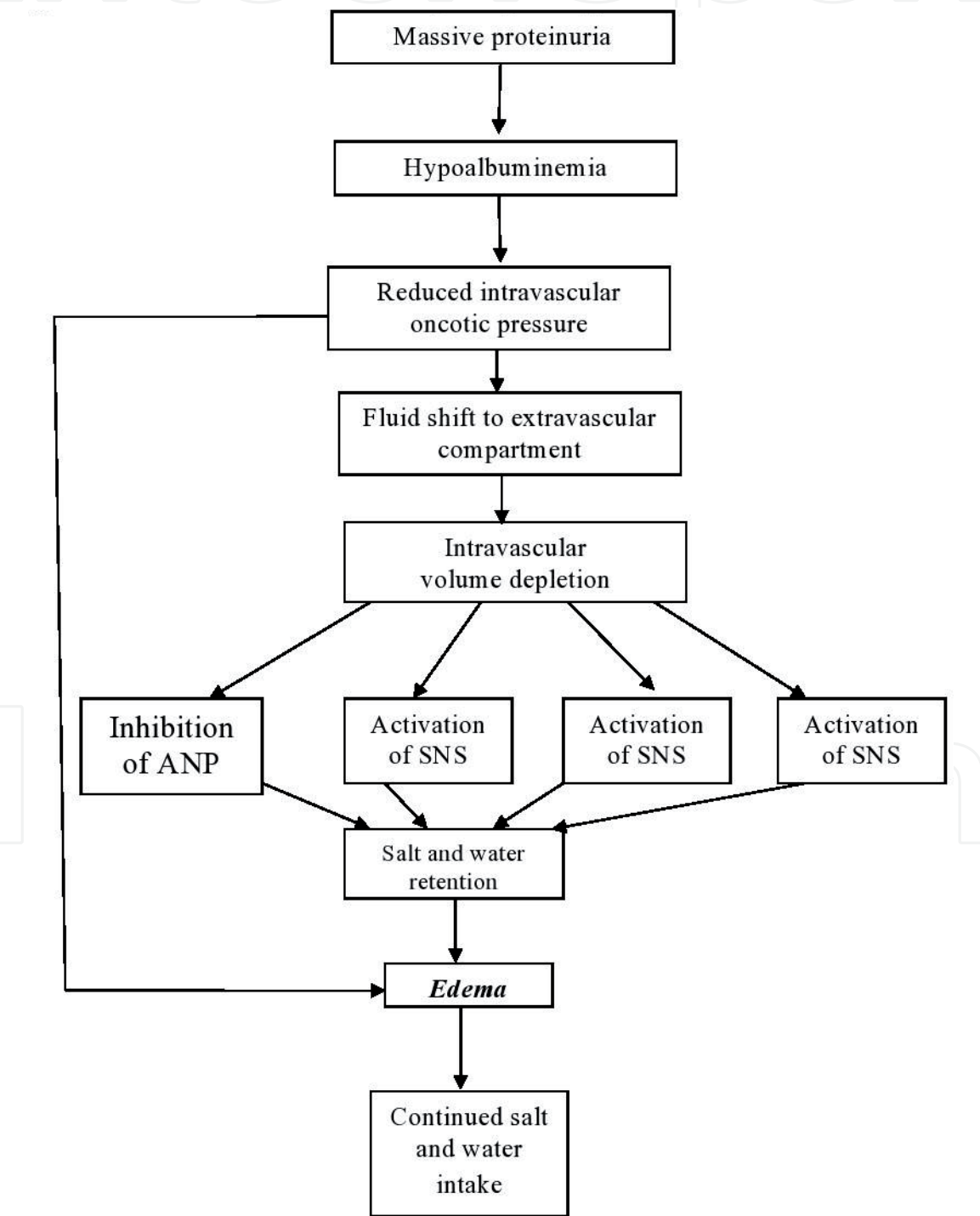
$s$  = the reflection coefficient for proteins (0 = complete permeability and

1 = complete impermeability).

$\pi_{cap}$  = the capillary oncotic pressure.

$\pi_{if}$  = the interstitial fluid oncotic pressure.

The formation of edema is prevented in healthy patients by a balance between forces favoring edema (capillary hydrostatic pressure [ $P_{cap}$ ]) and those opposing it (capillary oncotic pressure [ $\pi_{cap}$ ]). The slight tendency toward fluid accumulation is counterbalanced by the lymphatics in the interstitial space. In nephrotic patients hypoalbuminemia results when the liver fails to synthesize the loss of albumin through urine. The hypoalbuminemia results leads to low down capillary oncotic pressure ( $\pi_{cap}$ ), which leads to relatively unopposed capillary hydrostatic pressure ( $P_{cap}$ ) and subsequent edema formation. Relative intravascular volume reduction is due to edema formation the intravascular volume which triggers neurohumoral compensatory mechanisms. Which includes sympathetic nervous system (SNS), arginine vasopressin (AVP), and the renin angiotensin aldosterone system (RAAS), with



**Figure 2.**  
*Under fill hypothesis proposes the continuation of a reduced effective circulating blood volume in nephrotic syndrome. Pathophysiologic events leading to the formation of edema in nephrotic syndrome.*



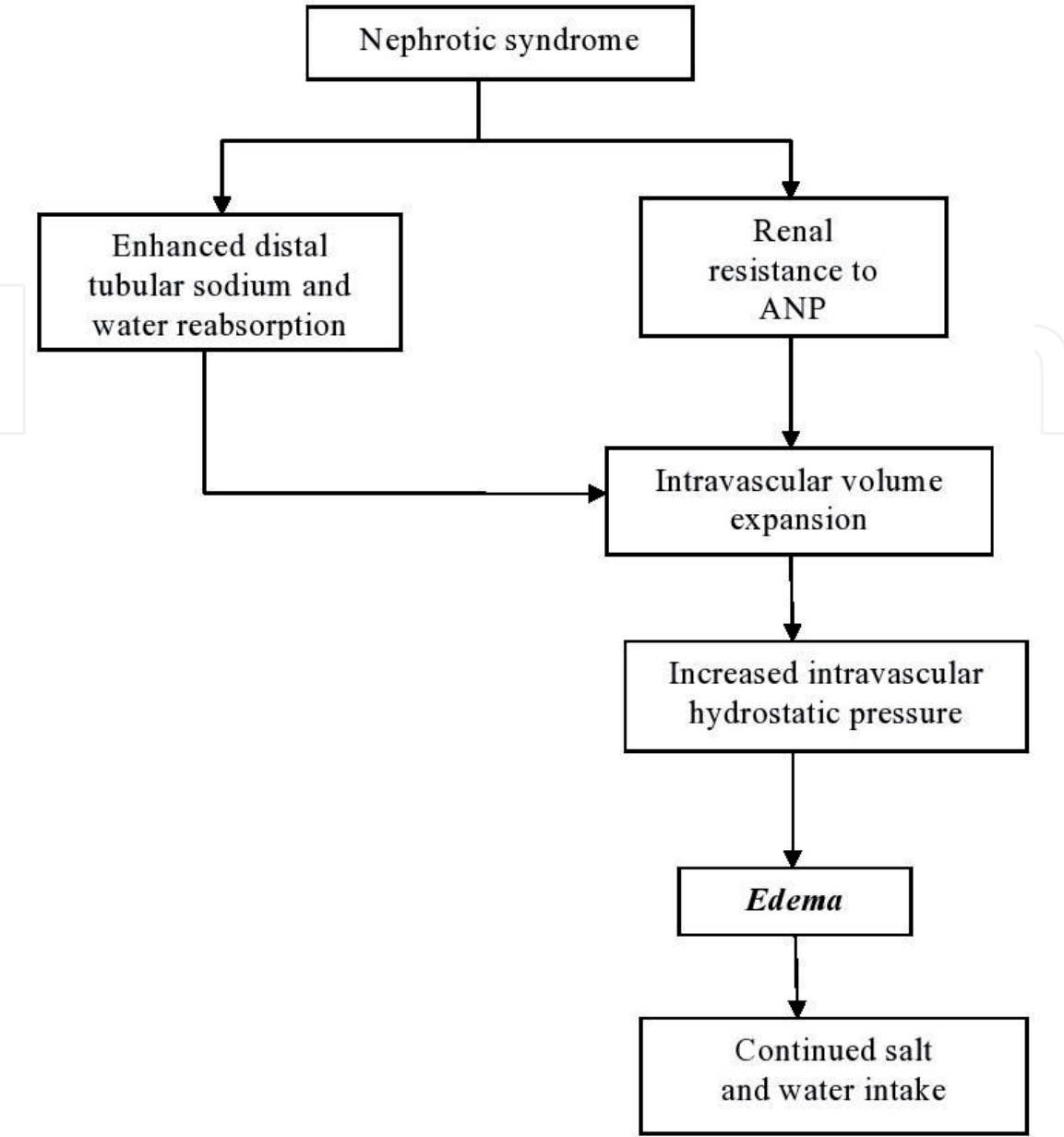
the net causes being sodium and water retention by the kidney. In the background of nephrotic syndrome, aortic arch, left ventricle, mechanoreceptors in the carotid sinus, and afferent arterioles in the glomeruli detect reduced pressure distension. This produce (1) SNS outflow increases from the central nervous system, (2) RAAS activation, and (3) nonosmotic release of AVP from the hypothalamus. These three changes lead to peripheral vasoconstriction (increased SNS and angiotensin II), sodium retention (angiotensin II, aldosterone, and increased SNS), and water retention.

As a result of these mechanisms, it is greatly accepted that patients with nephrotic syndrome have an excess of total body water and sodium. The condition of their intravascular volume is to some amount controvertible. Intravascular state in nephrotic is demonstrated by the following hypothesis: so-called overfill hypothesis and under-fill hypothesis. The continuation of a reduced effective circulating blood volume in nephrotic syndrome is explained by underfill hypothesis (**Figure 2**). Due to activation of the RAAS with resultant of reduction in urinary sodium excretion and elevation of aldosterone levels, is most expectedly promoted by findings of low urine sodium in the presence of edema. The low urinary sodium [45] is due to reduction of atrial natriuretic peptide (ANP). Evidence, additionally for the underfill hypothesis includes betterment in sodium excretion with albumin infusion or head-out water immersion, and reduced cardiac output and increased vascular evaluated. It is possible that the overfilled state may be major in the chronic phase during which patients may have long-lasting sodium retention due to unrelenting low-grade hypoalbuminemia. But the underfilled state may be major in the acute setting in which excessive proteinuria causes rapid development of hypoalbuminemia and a gradual drop in plasma oncotic pressure.

Supposed to be intravascularly volume-expanded as different to degree-constricted, founding whether a child is underfilled versus overfilled can be clinically important in the edema in children with nephrotic syndrome may be different. Depends upon the below urinary estimations comparison with elevated plasma vasopressin, renin, norepinephrine, aldosterone levels they are Single group has support to estimate the relative urinary potassium excretion [ $UK/(UK + UNa \text{ and})$ ] absolute excretion of sodium (FENa) to elucidate the distinction. Nephrotic patients who are with high urinary potassium excretion ( $>60\%$ ) and a low FENa ( $<1\%$ ) would be probable to have a low intravascular load [46].

## 5. Conclusion

Causes of nephrotic syndrome are also age reliant. The majority of the cases reported in the first 3 months of life is referred to as congenital nephrotic syndrome (CNS) and are because of genetic diseases. While there has been no efficient study of the etiology of nephrotic syndrome presenting in the rest of the first year of life (3–12 months), there are data telling that up to 40% of cases during this time may also be due to genetic causes. While it is extensively accepted that patients with nephrotic syndrome have an excess of total body sodium and water as a result of these remunerative mechanisms, the status of their intravascular volume is to some extent controvertial. Nephrotic syndrome was a variety of disease processes with heavy proteinuria and hypoalbuminemia at its main symptoms. Although ongoing research hard work in the mechanism of disease, first-line therapy has stay over relatively unaffected for decades, and corticosteroids drugs are the basis of treatment Most children have MCNS, which come through a good prognosis; renal failure is uncommon in patients with MCNS. The manner of patients with nephrotic syndrome is changeable, but most patients will have periods of relapse and remission. Guidelines published by the American Academy of Pediatrics and the KDIGO can guide the pediatrician in the treatment of MCNS. There are alternative to corticosteroid therapy that has had



**Figure 3.**  
*Pathophysiologic events leading to the formation of edema in nephrotic syndrome according to the overfill hypothesis.*

success in induction and/or maintenance of reduction, although findings are conflicting, necessitating additional multicenter trials to contrast these medications head to head. Hypotheses concerning the mechanisms of proteinuria and the possible association of glomerular structure to the nephrotic syndrome are discussed (**Figure 3**).

**Conflict of interest**

None declared.

**Notes/Thanks/Other declarations**

I am very much thankful to Dr. Manish Kumar Thimmaraju for his guidance, kind help and constant encouragement during progress of my work. I am also very thankful to my colleagues for the completion of this work.

Abbreviations

NS	nephrotic syndrome
CNS	congenital nephrotic syndrome
CNF	congenital nephrotic syndrome of the Finnish type
ESRD	end-stage renal disease
GBM	glomerular basement membrane
SRNS	steroid-resistant nephrotic syndrome
MPGN	membranoproliferative glomerulonephritis
FSGS	focal segmental glomerulosclerosis
MCNS	minimal-change nephrotic syndrome
RAAS	renin angiotensin aldosterone system
SNS	sympathetic nervous system
AVP	arginine vasopressin
GFB	glomerular filtration barrier
SRNS	steroid resistant nephrotic syndrome

Author details

Nagaraju Vallepu<sup>1\*</sup>, Saikiran Velpula<sup>1</sup>, Bharath Kumar Dasari<sup>1</sup>,  
Manish Kumar Thimmaraju<sup>2</sup>, Sridhar Babu Gummadi<sup>3</sup>, Neeraja Yelugam<sup>1</sup>  
and Supraja Jannu<sup>1</sup>

1 Department of Pharmacy Practice, Balaji Institute of Pharmaceutical Sciences,  
Warangal, Telangana, India

2 Department of Pharmaceutical Analysis, Balaji Institute of Pharmaceutical  
Sciences, Warangal, Telangana, India

3 Sri Shivani College of Pharmacy, Warangal, Telangana, India

\*Address all correspondence to: vallepunagaraju99@gmail.com

IntechOpen

© 2019 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

## References

- [1] Cattran DC, Feehally J, Cook HT, Liu ZH, Fervenza FC, Mezzano SA, et al. Kidney disease: Improving global outcomes (KDIGO) glomerulonephritis work group. KDIGO clinical practice guideline for glomerulonephritis. *Kidney International Supplements*. 2012;**2**:139-274. DOI: 10.1038/kisup.2012.9
- [2] Arneil GC. The nephrotic syndrome. *Pediatric Clinics of North America*. 1971;**18**(2):547-559
- [3] Arneil GC, Lam CN. Long-term assessment of steroid therapy in childhood nephrosis. *Lancet*. 1966;**2**(7468):819-821
- [4] Lenkkeri U et al. Structure of the gene for congenital nephritic syndrome of the Finnish type (NPHS1) and characterization of mutations. *American Journal of Human Genetics*. 1999;**64**(1):51-61
- [5] Hinkes B et al. Genetic causes of nephrotic syndrome in the first year of life. *American Pediatric Nephrology Meeting*. Marburg; 2006
- [6] Eddy AA, Symons JM. Nephrotic syndrome in childhood. *Lancet*. 2003;**362**(9384):629-639
- [7] Gipson DS, Troost JP, Lafayette RA, et al. Complete remission in the nephrotic syndrome study network. *Clinical Journal of the American Society of Nephrology*. 2016;**11**:81-89
- [8] Ruf RG et al. Patients with mutations in NPHS2 (podocin) do not respond to standard steroid treatment of nephrotic syndrome. *Journal of the American Society of Nephrology*. 2004;**15**(3):722-732
- [9] Weber S et al. NPHS2 mutation analysis shows genetic heterogeneity of steroid-resistant nephrotic syndrome and low post-transplant recurrence. *Kidney International*. 2004;**66**(2):571-579
- [10] Nash MA et al. The nephrotic syndrome. In: Edelmann CMJ, editor. *Pediatric Kidney Disease*. Boston: Little, Brown, and Company; 1992
- [11] Srivastava T, Simon SD, Alon US. High incidence of focal segmental glomerulosclerosis in nephrotic syndrome of childhood. *Pediatric Nephrology*. 1999;**13**(1):13-18
- [12] Ravani P, Rossi R, Bonanni A, et al. Rituximab in children with steroid-dependent nephrotic syndrome: A multicenter, open-label, noninferiority, randomized controlled trial. *Journal of the American Society of Nephrology*. 2015;**26**:2259-2266
- [13] Coulthard MG. Oedema in kwashiorkor is caused by hypoalbuminaemia. *Paediatrics and International Child Health*. 2015;**35**:83-89
- [14] Hogg RJ et al. Evaluation and management of proteinuria and nephrotic syndrome in children: Recommendations from a pediatric nephrology panel established at the National Kidney Foundation conference on proteinuria, albuminuria, risk, assessment, detection, and elimination (PARADE). *Pediatrics*. 2000;**105**(6):1242-1249
- [15] McEnery PT, Strife CF. Nephrotic syndrome in childhood. Management and treatment in patients with minimal change disease, mesangial proliferation, or focal glomerulosclerosis. *Pediatric Clinics of North America*. 1982;**29**(4):875-894
- [16] Bonilla-Felix M et al. Changing patterns in the histopathology of



idiopathic nephrotic syndrome in children. *Kidney International*. 1999;**55**(5):1885-1890

[17] Wong SN, Yu EC, Chan KW. Hepatitis B virus associated membranous glomerulonephritis in children—Experience in Hong Kong. *Clinical Nephrology*. 1993;**40**(3):142-147

[18] Bhimma R et al. Treatment of hepatitis B virus-associated nephropathy in black children. *Pediatric Nephrology*. 2002;**17**(6):393-399

[19] Filler G et al. Is there really an increase in non-minimal change nephrotic syndrome in children? *American Journal of Kidney Diseases*. 2003;**42**(6):1107-1113

[20] Smoyer WE, Mundel P. Regulation of podocyte structure during the development of nephrotic syndrome. *Journal of Molecular Medicine*. 1998;**76**(3-4):172-183

[21] White RH, Glasgow EF, Mills RJ. Clinicopathological study of nephrotic syndrome in childhood. *Lancet*. 1970;**1**(7661):1353-1359

[22] Brenner BM, Hostetter TH, Humes HD. Glomerular permselectivity: Barrier function based on discrimination of molecular size and charge. *The American Journal of Physiology*. 1978;**234**(6):F455-F460

[23] Kitano Y, Yoshikawa N, Nakamura H. Glomerular anionic sites in minimal change nephrotic syndrome and focal segmental glomerulosclerosis. *Clinical Nephrology*. 1993;**40**(4):199-204

[24] Carrie BJ, Salyer WR, Myers BD. Minimal change nephropathy: An electrochemical disorder of the glomerular membrane. *The American Journal of Medicine*. 1981;**70**(2):262-268

[25] Van den Born J et al. A monoclonal antibody against GBM heparin sulfate induces an acute selective proteinuria in rats. *Kidney International*. 1992;**41**(1):115-123

[26] ISKDC. Nephrotic syndrome in children: Prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. *Kidney International*. 1978;**13**:159-165

[27] Shih NY et al. Congenital nephrotic syndrome in mice lacking CD2-associated protein. *Science*. 1999;**286**(5438):312-315

[28] Kaplan JM et al. Mutations in ACTN4, encoding alpha-actinin-4, cause familial focal segmental glomerulosclerosis. *Nature Genetics*. 2000;**24**(3):251-256

[29] Ruf RG et al. Prevalence of WT1 mutations in a large cohort of patients with steroid-resistant and steroid-sensitive nephrotic syndrome. *Kidney International*. 2004;**66**(2):564-570

[30] Winn MP et al. A mutation in the TRPC6 cation channel causes familial focal segmental glomerulosclerosis. *Science*. 2005;**308**(5729):1801-1804

[31] Mucha B et al. Members of the APN study group. Mutations in the Wilms' tumor 1 gene cause isolated steroid resistant nephritic syndrome and occur in exons 8 and 9. *Pediatric Research*. 2006;**59**(2):325-331

[32] Boute N et al. NPHS2, encoding the glomerular protein podocin, is mutated in autosomal recessive steroid-resistant nephrotic syndrome. *Nature Genetics*. 2000;**24**:349-354

[33] Barisoni L, Mundel P. Podocyte biology and the emerging understanding of podocyte diseases. *American Journal of Nephrology*. 2003;**23**(5):353-360

- [34] Benzing T. Signaling at the slit diaphragm. *Journal of the American Society of Nephrology*. 2004;**15**(6):1382-1391
- [35] Tryggvason K, Patrakka J, Wartiovaara J. Hereditary proteinuria syndromes and mechanisms of proteinuria. *The New England Journal of Medicine*. 2006;**354**(13):1387-1401
- [36] Barbaux S et al. Donor splice-site mutations in WT1 are responsible for Frasier syndrome. *Nature Genetics*. 1997;**17**(4):467-470
- [37] Morello R, Lee B. Insight into podocyte differentiation from the study of human genetic disease: Nail-patella syndrome and transcriptional regulation in podocytes. *Pediatric Research*. 2002;**51**(5):551-558
- [38] Boerkoel CF et al. Mutant chromatin remodeling protein SMARCA1 causes Schimke immuno-osseous dysplasia. *Nature Genetics*. 2002;**30**(2):215-220
- [39] Zenker M et al. Human laminin beta2 deficiency causes congenital nephrosis with mesangial sclerosis and distinct eye abnormalities. *Human Molecular Genetics*. 2004;**13**(21):2625-2632
- [40] Shalhoub RJ. Pathogenesis of lipoid nephrosis: A disorder of T-cell function. *Lancet*. 1974;**2**(7880):556-560
- [41] Kemper MJ, Wolf G, Muller-Wiefel DE. Transmission of glomerular permeability factor from a mother to her child. *The New England Journal of Medicine*. 2001;**344**(5):386-387
- [42] Meyrier A. Mechanisms of disease: Focal segmental glomerulosclerosis. *Nature Clinical Practice Nephrology*. 2005;**1**(1):44-54
- [43] Dantal J et al. Effect of plasma protein adsorption on protein excretion in kidney-transplant recipients with recurrent nephrotic syndrome. *The New England Journal of Medicine*. 1994;**330**(1):7-14
- [44] Savin VJ et al. Circulating factor associated with increased glomerular permeability to albumin in recurrent focal segmental glomerulosclerosis. *The New England Journal of Medicine*. 1996;**334**(14):878-883
- [45] Candiano G et al. Inhibition of renal permeability towards albumin: A new function of apolipoproteins with possible pathogenetic relevance in focal glomerulosclerosis. *Electrophoresis*. 2001;**22**(9):1819-1825
- [46] Topaloglu R et al. T-cell subsets, interleukin-2 receptor expression and production of interleukin-2 in minimal change nephrotic syndrome. *Pediatric Nephrology*. 1994;**8**(6):649-652