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Chapter

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 adrenocorticotropic 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 adrenocorticotropic 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 *(NPHS1)* gene leads to congenital nephrotic syndrome of the Finnish type (CNF) Mutation in podocin *(NPHS2)* gene results Autosomal recessive FSGS Mutation in *WT1* gene results Autosomal dominant diffuse mesangial Sclerosis (DMS) Mutation in laminin β_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 WT1 mutation with DMS Pierson syndrome Schimke immunoosseous dysplasia with FSGS due to mutation in SMARCAL1 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 *WT1* gene results autosomal dominant diffuse mesangial Sclerosis (DMS) Mutation in gene encoding transient receptor potential cation channel 6 *(TRPC6)* results Autosomal dominant FSGS Mutation in gene encoding CD2-associated protein *(CD2AP)* results autosomal dominant FSGS Mutation in gene encoding *α-actinin 4* leads to autosomal dominant FSGS Mutation in podocin*(NPHS2)* 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 α-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

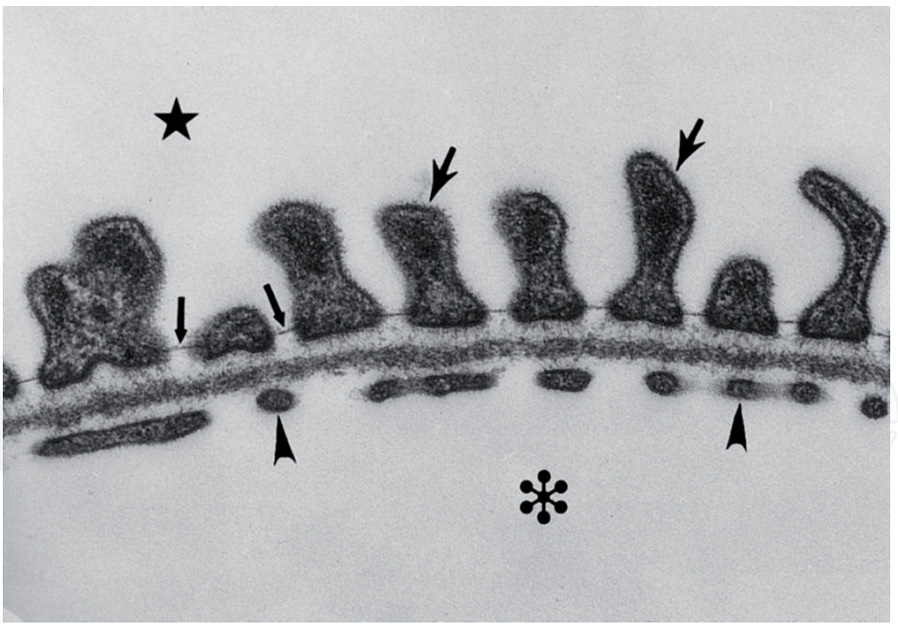

Figure 1.
Components of the glomerular filtration barrier (GFB) during normal glomerular filtration, electron micrographic view.

proteoglycan, resultant in these negatively charged heparin sulfate proteoglycan controlled from passage than positively charged molecules with same particles [15]. General healthy system, particle more than 42 Å in diameter is not capable to enter into the GFB [16]. This kind of restrictions based on mostly structural reliability of the podocyte bottom actions and opening diaphragms, by means of the charge of GBM. Loss of negative charge of the GBM occurs in nephrotic syndrome [17–19]. The confirmation, swelling and diffusion podocyte binds to bottom actions, dislocation of opening diaphragms, occurrence of filling junctions, vacuole formation, and deficiency of inclusion of podocytes from the GBM, these type of morphologic changes in podocytes that occur during progress of nephrotic syndrome [20–23]. Mutations in genes encoding some of the opening diaphragms proteins or their transcription factors can cause SRNS and/or FSGS. This mechanism of nephrotic syndrome is additional reinforced by recent observations in humans and experimental animals [4, 10, 11, 14, 24–26]. The subject of many recent reviews in the literature this type of result have been discussed [27–29]. In infants mutations in the gene encoding the opening diaphragms protein nephrin (NPHS1) mostly causes CNF. In addition, in children mutations in NPHS2 are estimated to be responsible for up to 25% of cases of sporadic familial and Steroid resistant nephrotic syndrome (SRNS) [10, 25]. Frasier syndrome and Denys rash syndrome in children occurs due to Mutations in the transcription factor suppressor gene WT1 [30–32]. Mutations in (1) CD2-associated protein (CD2AP); (2) the LIM-homeodomain protein (encoded by LMX1B), which leads to in nail-patella syndrome; (3) the actin-bundling protein α-actinin 4, which leads to adult-onset FSGS; which results in adult-onset FSGS; (4) laminin β2, which results in Pierson syndrome and (5) the chromatin regulator encoded by SMARCAL1. [25, 33–35].

3.2 Circulatory factors

Some of soluble mediators that may alter capillary wall permeability in nephrotic syndrome proved by investigational data to carry the existence [37–39] show to be true for this includes (1) scared decrease of proteinuria subsequent treatment with protein A immunoadsorption in of primary nephrotic syndromes [24], (2) progress of nephrotic syndrome in child babies born to mothers with nephrotic syndrome

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].

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

$$= \text{LpS}\,[(\text{Pcap} - \text{Pif}) - \text{s}(\pi\text{cap} - \pi\text{if})].$$

where:
Lp = the capillary permeability.
S = the surface area of the capillary wall.
Pcap = the capillary hydrostatic pressure.
Pif = the interstitial fluid hydrostatic fluid pressure.
s = the reflection coefficient for proteins (0 = complete permeability and 1 = complete impermeability).
πcap = the capillary oncotic pressure.
πif = the interstitial fluid oncotic pressure.

The formation of edema is prevented in healthy patients by a balance between forces favoring edema (capillary hydrostatic pressure [Pcap]) and those opposing it (capillary oncotic pressure [πcap]). 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 (πcap), which leads to relatively unopposed capillary hydrostatic pressure (Pcap) 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

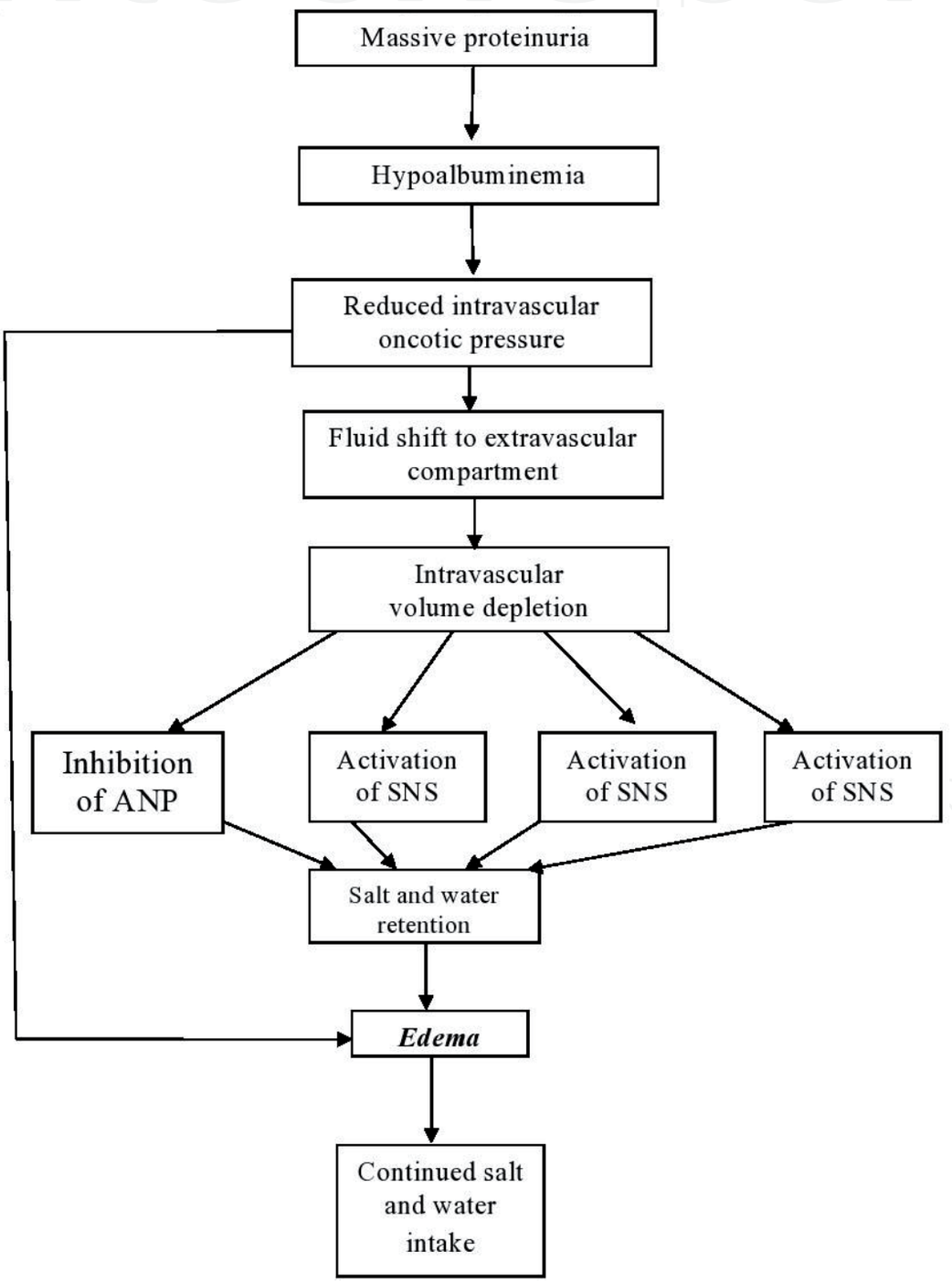

Figure 2.
Under fill hypothesis proposes the continuation of a reduced effective circulating blood volume in nephrotic syndrome. Pathophysiologic events leading to the formation of edema in nephrotic syndrome.

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 underfill 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 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 controversial. 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

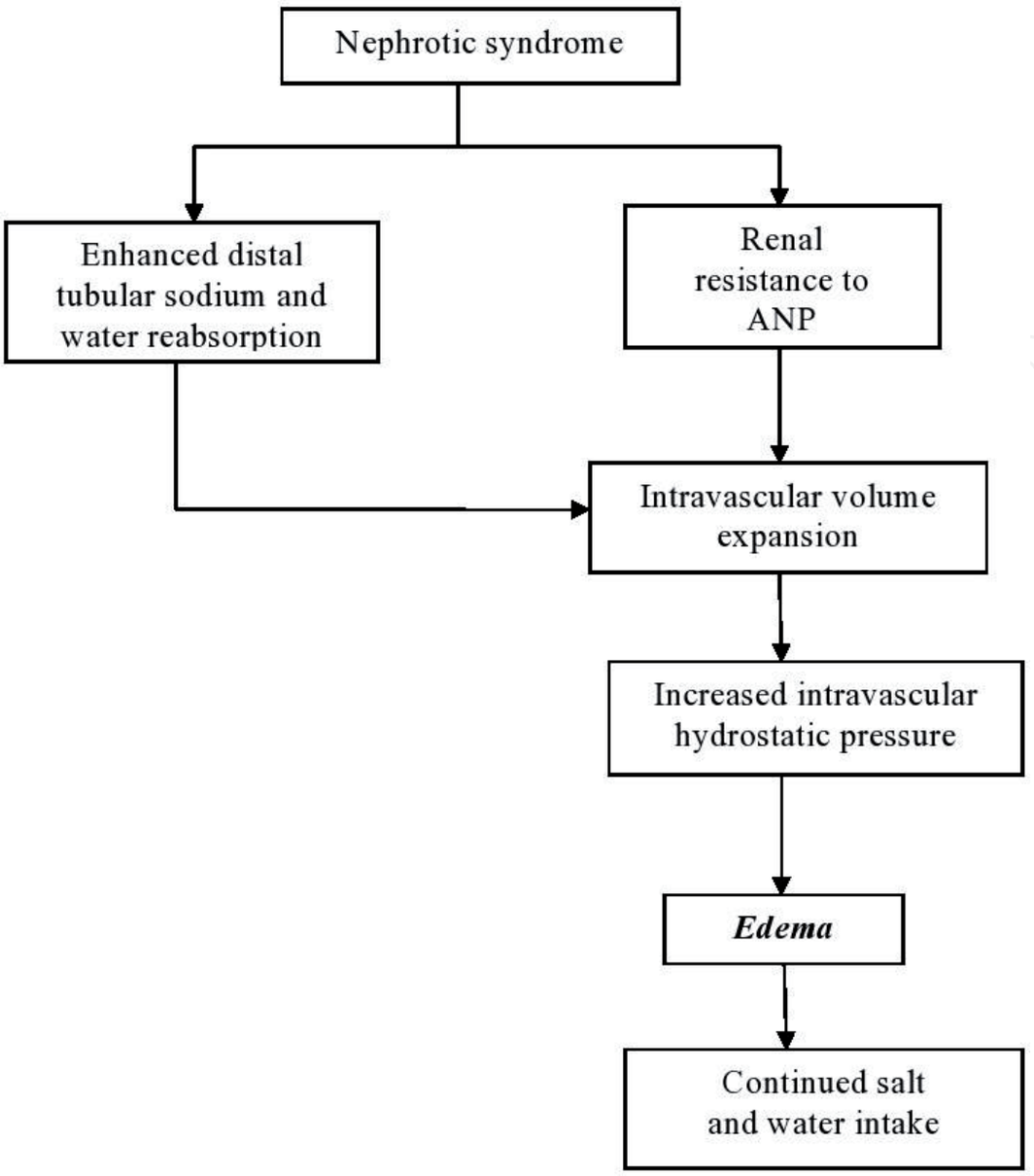

Figure 3.
Pathophysiologic events leading to the formation of edema in nephrotic syndrome according to the overfill hypothesis.

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

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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

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