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Congenital Nephrotic Syndrome: Etiology, Clinical Presentation, and a Comparison of Optimal Treatment Strategies – A Literature Review

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Abstract

Introduction: Congenital nephrotic syndrome is a rare condition with symptom onset occurring within the first three months of life. It affects approximately 1 to 3 per 100,000 live births. It has a varied etiology on a genetic, non-genetic, and infectious basis. While management primarily relies on symptomatic care, advances in modern medicine have significantly improved long-term outcomes, slowly ensuring affected children normal functioning in the future.

Aim: The primary aim of this literature review is to synthesize current knowledge regarding the etiology and clinical presentation of CNS, and to compare the efficacy of evolving therapeutic methods, contrasting conservative medical management with radical surgical and renal replacement strategies.

Materials and methods: This study is a narrative literature review based on the analysis of scientific articles concerning congenital nephrotic syndrome (CNS). The reviewed studies included neonates and infants with CNS, focusing on genetic causes, medical and surgical management (nephrectomy), and kidney transplantation outcomes. Clinical guidelines, literature reviews, meta-analyses, cohort studies, and case reports published between 2001 and 2026 were analyzed.

Conclusions: Congenital nephrotic syndrome (CNS) lacks a universal treatment protocol, demanding a strictly personalized, multidisciplinary approach tailored to the unique clinical, metabolic, and genetic profile of each infant. Early prenatal detection is critical for planned delivery in tertiary centers and immediate postnatal stabilization. While contemporary management remains purely symptomatic and supportive, optimizing long-term outcomes requires expanded multicenter registries and a decisive shift in research toward causal, gene- and molecular-targeted therapies.

Keywords: Congenital Nephrotic Syndrome; NPHS1 Gene; Nephrin; Glomerular Filtration Barrier; Bilateral Nephrectomy; Kidney Transplantation; Pediatric Nephrology.

1. INTRODUCTION

Congenital nephrotic syndrome (CNS) is a rare and life-threatening renal disorder defined by the manifestation of massive proteinuria, profound hypoalbuminemia, and generalized edema within the first 90 days of life. This condition arises from the severe structural disruption of the glomerular filtration barrier, leading to an uncontrolled and continuous loss of essential plasma proteins into the urine.

Historically regarded as fatal in infancy, CNS has seen significant improvements in survival due to modern advancements in pediatric nephrology and intensive supportive care. As medicine continues to progress, clinicians and researchers are actively seeking the most effective and safest therapeutic solutions. The primary clinical challenge lies in finding a balance between eliminating life-threatening complications and minimizing the invasiveness and morbidity associated with early surgical and dialytic interventions.

Understanding CNS is complicated by its diverse underlying causes and wide spectrum of disease. While most cases stem from monogenic structural mutations affecting key podocyte and glomerular basement membrane components, a subset develops secondary to non-genetic factors, such as congenital infections or maternal alloimmunization, which require entirely different therapeutic approaches. Moreover, the clinical presentation spans from early intrauterine markers to severe, multisystem postnatal complications involving nutrition, hemostasis, and immunity.

The aim of this review is to provide a comprehensive analysis of the current state of knowledge regarding congenital nephrotic syndrome. This paper examines the diverse genetic and non-genetic etiology of the disorder, details its wide prenatal and postnatal clinical manifestations, and provides a comparative analysis of contemporary treatment strategies, contrasting conservative nephron-sparing approaches with aggressive surgical and renal replacement protocols.

2. GENETIC ETIOLOGY

2.1. Monogenic cause of disease

In contrast to idiopathic forms of nephrotic syndrome, CNS has a monogenic etiology in the majority of cases [2, 4, 9]. Rapid diagnostics based on molecular testing are crucial, as they allow for establishing a precise prognosis and facilitate the early planning of radical renal replacement therapy [20, 24]. The genetic etiology of CNS stems from abnormalities in the

structure and function of the glomerular filtration barrier. Most commonly, the defect involves the glomerular basement membrane and the structure of podocytes [5, 11, 20]. The vast majority of both isolated and syndromic cases are associated with mutations in genes such as *NPHS1*, *NPHS2*, *WT1*, and *LAMB2* [5, 9, 22]. Both global guidelines and multicenter observations across various populations (including in Japan and China) confirm that *NPHS1* gene mutations are one of the most common causes of the disease in this youngest age group [10, 14, 23]

2.2 Glomerular filtration barrier

The glomerular filtration barrier (GFB) is a highly specialized, three-layered biological filter in the renal corpuscle that separates the lumen of glomerular capillaries from the urinary space of Bowman's capsule [7, 11]. The primary function of the barrier is considered to be the selective ultrafiltration of plasma [11], namely retaining formed blood elements and high-molecular-weight proteins (predominantly albumin) within the bloodstream, while allowing the free passage of water, electrolytes, and low-molecular-weight metabolites into the primary urine [7, 11]. Structurally, the barrier consists of three closely cooperating layers: the fenestrated endothelium of glomerular capillaries, the acellular glomerular basement membrane (GBM), and the outer layer of podocyte foot processes. Between the podocyte foot processes spans the slit diaphragm, whose main component is nephrin, encoded by the *NPHS1* gene. [2, 11].

2.3 NPHS1- gene encoding nephrine

The *NPHS1* gene is located on the long arm of chromosome 19, responsible for the production of the transmembrane protein nephrin [2, 8, 21]. This glycoprotein consists of a large extracellular domain, a single transmembrane segment, and a relatively short cytoplasmic tail within the cell interior [2, 7, 23]. The extracellular domains of nephrin form a dense molecular sieve that mechanically blocks protein leakage, while its cytoplasmic domain transmits signals that stabilize the actin cytoskeleton and promote podocyte survival [7, 8]. The absence or dysfunction of nephrin resulting from genetic mutations (including recurrent deletions, nonsense mutations, or missense mutations) disrupts the architecture of the slit diaphragm, leading to a breakdown in the overall barrier selectivity and the development of massive proteinuria in congenital nephrotic syndrome [2, 5].

Mutations in the *NPHS1* gene are the most common cause of congenital nephrotic syndrome (CNS) and are directly responsible for classic congenital nephrotic syndrome of the Finnish type (CNF) [8, 17, 22].

2.4 Other genes mutations

Not only are *NPHS1* gene mutations responsible for CNS, but defects in other genes can also cause GFB insufficiency. Other genes most commonly implicated in the disease include *NPHS2*, *WT1*, and *LAMB2* [5, 9, 22].

The *NPHS2* gene encodes podocin—an integral membrane protein specifically localized within lipid microdomains (lipid rafts) of the podocyte foot process membrane [2, 7, 9]. Podocin functions as a scaffold protein that interacts directly with the cytoplasmic tail of nephrin and the CD2AP protein, enabling proper anchoring and stabilization of the slit diaphragm [2, 7, 10]. Mutations in this gene lead to protein misfolding, its retention in the endoplasmic reticulum, and premature degradation, which prevents podocin from reaching the plasma membrane [2, 9, 20]. The molecular consequence of the absence of functional podocin is the disruption of the nephrin complex, collapse of the podocyte actin cytoskeleton, and generalized effacement of foot processes [2, 7, 16]. These mutations are inherited in an autosomal recessive manner and are responsible for steroid-resistant nephrotic syndrome (SRNS) and early infantile forms of CNS [2, 9, 13].

The *WT1* gene encodes a zinc-finger transcription factor essential for urogenital system development and the direct regulation of podocyte gene expression, including nephrin (*NPHS1*) [5, 7, 20]. Dominant mutations in this gene (mostly *de novo*) lead to arrested podocyte differentiation, loss of cellular markers, and severe dysfunction of the filtration barrier [7, 20, 22]. Missense variants in exons 8–9 cause Denys-Drash syndrome (DDS), characterized by early-onset CNS manifesting with diffuse mesangial sclerosis (DMS), gonadal dysgenesis (in XY individuals), and a high risk of Wilms tumor [5, 9, 22]. In turn, mutations in intron 9 that alter the ratio of KTS isoforms result in Frasier syndrome (FS), which is marked by later-onset nephrotic syndrome (FSGS), gonadal dysgenesis, and a predisposition to gonadoblastoma [5, 7, 20].

The *LAMB2* gene encodes the laminin $\beta 2$ chain, a crucial component of the laminin-521 ($\alpha 5\beta 2\gamma 1$) heterotrimer—the primary matrix protein of the mature glomerular basement membrane (GBM) [7, 11, 20].

Laminin-521 forms the scaffold of the GBM and is responsible for directly linking the basement membrane to integrins ($\alpha 3\beta 1$) and dystroglycans on the podocyte surface, thereby ensuring the mechanical stability of the entire glomerulus [7, 11, 20].

Mutations in the *LAMB2* gene are inherited in an autosomal recessive manner and encompass deletions, nonsense mutations, or splice-site defects, which result in the complete absence or loss of function of the $\beta 2$ chain [9, 11, 20]. The lack of laminin-521 leads to structural disorganization of the GBM, abnormal thickening, and loss of permselectivity, secondarily causing podocyte foot process effacement [7, 11, 20].

The classic manifestation of severe, inactivating *LAMB2* mutations is Pierson syndrome, which presents as congenital nephrotic syndrome (histologically presenting as DMS or microcystic tubular dilatation) associated with severe ocular anomalies (microcoria, cataracts) and neurodevelopmental delay [5, 9, 20].

Milder missense mutations in the *LAMB2* gene can lead to isolated, non-syndromic nephrotic syndrome characterized by a milder clinical course and a later age of onset [5, 10, 20].

3. NON-GENETIC ETIOLOGY

Although congenital nephrotic syndrome (CNS) is overwhelmingly of genetic origin, in a subset of patients (approx. 10–15%), the disease is caused by secondary, non-genetic factors [5, 9].

3.1. Congenital infections

Congenital infections constitute the most common non-genetic cause of CNS [5, 7]. These infections are mostly classified within the so-called TORCH complex, which includes pathogens transmitted transplacentally from the mother to the developing fetus [7, 10]. Congenital syphilis (caused by *Treponema pallidum*) is of particular clinical importance within this group. Nephrotic syndrome in the course of congenital syphilis develops as a result of the deposition of circulating immune complexes (antigen-antibody) in the glomerular basement membrane (GBM) [7, 9]. Histopathologically, this most commonly leads to the development of secondary membranous nephropathy or proliferative glomerulonephritis [7]. Identifying this etiology is of crucial importance, as the implementation of appropriate antibiotic therapy (e.g., crystalline penicillin) leads to the complete and permanent resolution of proteinuria and full recovery of renal function [5, 7, 9]. Other infectious agents that can cause secondary damage to the filtration barrier in neonates include cytomegalovirus (CMV), rubella virus, HIV, and the protozoan *Toxoplasma gondii* [7, 9, 20].

Given the potential reversibility of these conditions, global guidelines (including ERKNet-ESPN recommendations) categorically advise that TORCH infections must be urgently

excluded in every neonate newly diagnosed with massive proteinuria [5, 20]. Rapid recognition of an infection facilitates the immediate implementation of targeted antimicrobial therapy, allowing the patient to avoid toxic, ineffective immunosuppression and, in the longer term, unnecessary nephrectomy and dialysis [5, 7, 12].

3.2. Alloimmune pathomechanism

A rarer, non-genetic cause of CNS is the alloimmune pathomechanism, resulting from the transplacental transfer of maternal IgG antibodies targeting fetal glomerular antigens, such as neutral endopeptidase [5, 7]. This occurs when a mother deficient in this protein develops antibodies during a previous pregnancy, which in a subsequent pregnancy attack fetal podocytes and destroy the filtration barrier [5, 7].

Importantly, this form of nephrotic syndrome is transient and reversible symptoms resolve with the natural clearance of maternal antibodies, and this process can be supported by supportive therapy or plasmapheresis [5, 7].

4. CLINICAL PRESENTATION

4.1 Prenatal clinical presentation

The manifestation of congenital nephrotic syndrome begins in utero, driven by early breakdown of the glomerular filtration barrier and massive intrauterine fetal proteinuria [8, 20, 22].

The primary prenatal biochemical sign is a pronounced elevation of α -fetoprotein (AFP) in both maternal serum (MSAFP) and amniotic fluid (AFAFP), typically detected during routine second-trimester screening [2, 8, 24]. Synthesized by the fetal liver, AFP leaks across the disrupted filtration barrier in massive quantities into fetal urine, entering the amniotic cavity and then maternal circulation [8, 20, 22].

A characteristic sign, particularly in CNS caused by NPHS1 and WT1 mutations, is placental hypertrophy [8, 17, 22]. In such cases, the placental weight exceeds even 25–40% of the neonate's total birth weight [8, 17].

4.2 Postnatal clinical presentation

4.2.a Classical disease manifestation

Postnatally, the disease manifests within the first 90 days of life. The classic triad of symptoms comprises massive nephrotic-range proteinuria, profound hypoalbuminemia, and generalized edema [6, 13, 21]. Fluid accumulation in the peritoneal cavity (massive ascites) and pleural

spaces exerts pressure on the diaphragm and reduces lung compliance, leading to early respiratory failure in neonates [12, 13, 22].

4.2.b Metabolic, digestive, and nutritional consequences

Edema of the gastrointestinal wall leads to severe impairment of digestion and absorption, recurrent diarrhea, and intolerance to enteral feeding [3, 14]. In combination with the persistent loss of amino acids and transport proteins, this causes profound protein-energy malnutrition, muscle atrophy, and severe failure to thrive [10, 15, 17].

4.2.c Infectious and immunological complications

Uncontrolled urinary loss of immunoglobulins (especially IgG) and complement cascade factors leads to severe acquired hypogammaglobulinemia [6, 10]. Infants with CNS exhibit extreme susceptibility to invasive bacterial infections caused by encapsulated microorganisms, manifesting as spontaneous bacterial peritonitis, sepsis, pneumonia, and catheter-related bloodstream infections [6, 14, 15]. These infections, alongside cardiovascular complications, remain a leading cause of early infant mortality prior to the implementation of definitive renal replacement therapy [6, 15, 17].

4.2.d Prothrombotic State and Hemostatic Imbalance

Renal wasting of antithrombin III alongside proteins C and S, compounded by hepatic overproduction of fibrinogen and reactive thrombocytosis, creates a severe hypercoagulable state [10, 13, 20]. This markedly elevates the incidence of life-threatening thromboembolic events, such as renal vein thrombosis, sagittal sinus thrombosis, and pulmonary embolism, further aggravated by hemoconcentration and indwelling central venous catheters [13, 18, 20].

4.2.e Endocrine and Electrolyte Disturbances

Massive proteinuria causes marked urinary wasting of carrier proteins, leading to secondary hypothyroidism from the loss of thyroxine-binding globulin (TBG) [2, 6, 20]. Furthermore, loss of vitamin D-binding protein (DBP) leads to severe hypocalcemia, secondary hyperparathyroidism, and early metabolic bone disease, mandating co-supplementation with levothyroxine, vitamin D analogues, and calcium from early infancy [10, 16, 20].

5. TYPES OF TREATMENT

5.1 Non-aggressive treatment approach

The non-aggressive, or conservative, approach aims to prolong the function of the child's native kidneys for as long as possible and avoid complications associated with early nephrectomy and dialysis in neonates with very low body weight [1, 4, 16]. The primary therapeutic goal is not the immediate surgical removal of the source of protein loss, but rather the pharmacological reduction of proteinuria to a level that permits proper somatic and neuromotor development [4, 19, 23]. This strategy employs combination antiproteinuric pharmacotherapy based on glomerular hemodynamic modulation [4, 16]. The administration of angiotensin-converting enzyme inhibitors (ACEi, e.g., enalapril, captopril) or angiotensin II receptor blockers (ARBs) induces dilation of the glomerular efferent arteriole, which lowers intraglomerular pressure and decreases hyperfiltration [4, 19]. Concomitant introduction of nonsteroidal anti-inflammatory drugs (predominantly indomethacin) inhibits the renal synthesis of vasodilatory prostaglandins, leading to constriction of the afferent arteriole and a reduction in glomerular filtration rate (GFR) [4, 16, 19]. The synergistic action of both drug classes enables a reduction in proteinuria by up to 50–70%, which drastically curtails albumin loss and stabilizes its plasma concentration [1, 4, 19].

In this paradigm, decompressive nephrectomy is deferred until the natural onset of end-stage kidney disease or is performed simultaneously with kidney transplantation [4, 23, 25]. This strategy frequently allows children to completely bypass peritoneal dialysis, facilitating pre-emptive kidney transplantation once an optimal body weight (>9–10 kg) is reached [4, 16, 25].

5.2 Aggressive treatment approach

The aggressive approach, derived from the classic Finnish protocol, represents a structured management paradigm oriented toward the rapid surgical eradication of proteinuria and early preparation for definitive kidney transplantation [8, 17, 18]. During the initial months of life, therapy centers on intensive supportive replacement, consisting of daily intravenous infusions of 20% albumin co-administered with furosemide via a central venous catheter, aggressive high-calorie and high-protein nutrition delivered via nasogastric tube or gastrostomy, continuous thromboprophylaxis, and regular substitution of levothyroxine and vitamin D [3, 12, 18]. The cornerstone of this strategy is elective bilateral (or staged unilateral) decompressive nephrectomy, performed once the infant reaches a body weight of 7–9 kg, typically between 6 and 9 months of age [12, 17, 22]. Surgical removal of the native kidneys immediately arrests

massive urinary protein leakage, resolves generalized edema, and eliminates the life-threatening risks of severe infection and thromboembolism [17, 18, 22]. Following surgery, the anephric patient is promptly initiated on automated peritoneal dialysis (APD), which maintains metabolic homeostasis and facilitates continuous somatic growth until a body weight exceeding 9–10 kg is attained, allowing for successful kidney transplantation with long-term graft survival rates exceeding 85–90% [8, 12, 18, 25].

Discussion

The indisputably heterogeneous etiology and multifaceted clinical manifestation of congenital nephrotic syndrome (CNS) represent established realities that continue to be the subject of active scientific investigation. Unraveling the complex genetic landscape and identifying potentially reversible secondary causes remain essential for accurate diagnostic stratification and long-term prognostication. However, the true axis of contemporary debate centers on the choice of therapeutic strategy.

Proponents of the aggressive paradigm argue that prompt surgical intervention is essential to eradicate the profound systemic hazards associated with massive proteinuria. Uncontrolled urinary wasting of albumin, immunoglobulins, and anticoagulant factors places infants at constant risk of life-threatening sepsis, severe malnutrition, and devastating thromboembolism. Early bilateral nephrectomy eliminates these protein-losing complications immediately, reversing gastrointestinal edema and providing metabolic stability that facilitates catch-up growth under maintenance automated peritoneal dialysis (APD). Nevertheless, this radical strategy carries substantial iatrogenic morbidity. The necessity of daily central venous access prior to nephrectomy presents high rates of line-related sepsis and vascular thrombosis, while chronic APD in low-weight infants is frequently complicated by bacterial peritonitis, peritoneal leaks, and the total loss of residual diuresis, necessitating strict fluid restrictions.

In response to these procedural risks, the non-aggressive approach has gained widespread support as a viable and less invasive alternative. By utilizing combination therapy with ACE inhibitors/ARBs and NSAIDs (specifically indomethacin), this strategy exploits glomerular hemodynamics to reduce intraglomerular pressure and decrease protein leakage by up to 50–70%. The major clinical advantage of this model is the preservation of native urine output and the potential to avoid or significantly shorten the duration of peritoneal dialysis. In favorable cases, conservative management stabilizes plasma albumin sufficiently to facilitate outpatient care and allows the child to progress directly to pre-emptive kidney transplantation once

optimal somatic growth is achieved. Despite these benefits, conservative therapy is not without significant challenges: prolonged pharmacological exposure risks acute kidney injury, hyperkalemia, and NSAID-related gastrointestinal toxicity. Furthermore, infants with severe truncating NPHS1 mutations frequently show poor responsiveness to antiproteinuric regimens, necessitating late conversion to surgical nephrectomy.

Emerging international consensus, including guidance from the ERKNet-ESPN working groups, suggests that these two therapeutic strategies should not be viewed as mutually exclusive dogmas, but rather as complementary elements of an individualized, risk-stratified algorithm. Clinical and genetic factors—including the specific underlying gene variant, baseline GFR, nutritional trajectory, and frequency of severe infectious or thrombotic episodes—must dictate management. A conservative, nephron-sparing regimen is increasingly advocated as the preferred first-line strategy in hemodynamically stable infants, reserving radical early nephrectomy as an indispensable rescue intervention for patients with refractory, life-threatening protein wasting or severe failure to thrive.

Conclusions

Congenital nephrotic syndrome is a complex, life-threatening disorder without a single, universally standardized treatment protocol. Because clinical manifestations, disease severity, and rates of progression differ drastically among individual neonates—ranging from relatively stable cases manageable with pharmacotherapy to fulminant, treatment-refractory failure to thrive—management demands a strictly personalized, case-by-case approach. The choice between conservative, nephron-sparing strategies and radical surgical intervention must be continually adjusted to each patient's specific metabolic, clinical, and genetic profile.

The complex multi-system sequelae of massive urinary protein loss demand coordinated collaboration among pediatric nephrologists, clinical geneticists, dietitians, pediatric endocrinologists, and surgeons to balance nutrition, hormonal homeostasis, and thromboprophylaxis..

Prenatal diagnostics play a fundamental, critical role in the clinical management and prognosis of congenital nephrotic syndrome. The detection of key intrauterine markers during routine second-trimester screening—most notably a marked elevation of α -fetoprotein (AFP) in maternal serum and amniotic fluid, alongside pronounced placental hypertrophy—serves as an indispensable early warning signal.

As the core extracellular backbone of the slit diaphragm, nephrin directly orchestrates actin cytoskeleton remodeling, cell polarity, and podocyte survival via complex downstream signaling cascades. The structural absence or dysfunction of nephrin precipitates immediate foot process effacement, irreversible loss of glomerular permselectivity, and massive proteinuria. Elucidating the master regulatory role of the nephrin complex within the GFB defines a critical blueprint for future translational therapies—ranging from pharmacological chaperone stabilization to targeted gene editing

Precise determination of the underlying etiology—specifically differentiating between genetic and non-genetic causes—is paramount, as it directly dictates both the patient's prognosis and the entire therapeutic pathway. Identifying secondary, non-genetic forms resulting from congenital infections or maternal alloimmunization offers a favorable prognosis with the potential for complete functional recovery under targeted, non-invasive therapies, effectively sparing the infant from unnecessary dialysis or nephrectomy. Conversely, establishing a monogenic etiology confirms an irreversible structural defect, directing clinical efforts toward aggressive or nephron-sparing supportive regimens, organ preservation, and early preparation for renal replacement therapy and definitive kidney transplantation.

Kidney transplantation remains the definitive, life-saving therapeutic milestone for children with monogenic CNS who progress to end-stage kidney disease. Modern pediatric renal replacement and surgical protocols demonstrate excellent long-term patient and graft survival rates that are fully comparable to infants transplanted for other congenital nephropathies. Importantly, monogenic forms carry a remarkably low risk of primary disease recurrence

Despite the relative rarity of CNS, there is an imperative need for expanded, high-quality research. Establishing international patient registries, conducting multicenter clinical trials, and performing comprehensive meta-analyses are essential to generate high-level, evidence-based recommendations for this vulnerable population. Most importantly, contemporary management remains entirely symptomatic and supportive, oriented around fluid-electrolyte balance, infection control, and organ replacement. Future scientific efforts must urgently pivot toward causal, etiological therapies—such as targeted molecular chaperones, RNA-based interventions, and gene-editing technologies—capable of directly restoring the structural and functional integrity of the glomerular filtration barrier.

AUTHOR'S CONTRIBUTION

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Artificial Intelligence use declaration

AI tools were used only to refine the language and improve text readability. The authors retain full accountability for the academic integrity of the work. The conceptual design, literature review, data analysis, and final drafting were executed solely by the authors.

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