

# Diagnostic and Management Challenges in Congenital Nephrotic Syndrome

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**Abstract:** Congenital Nephrotic Syndrome (CNS) is defined as nephrotic range proteinuria, hypoalbuminaemia and edema in the first three months of life. CNS is most commonly genetic in cause, with international variance in the incidence of causative mutations. Initially defined by the histopathological appearance, increasingly sophisticated and accessible genetic analyses now provide a body of evidence to suggest that there is a disparity between the histological appearance, the genotype of individuals and the severity of the clinical disease. Through the evolution of management approaches CNS has changed from being an invariably fatal condition to one with appreciable ongoing morbidity and mortality but comparably good outcomes to other causes of paediatric end-stage renal disease, especially following transplantation. This review briefly summarises the more commonly recognised genetic mutations leading to CNS, addresses common management decisions, and concludes with potential therapies for the future.

**Keywords:** nephrectomy, genetics, infantile nephrotic syndrome

## Introduction

First described by Gautier and Miville in 1942, congenital nephrotic syndrome (CNS) is defined as the triad of nephrotic range proteinuria ( $>200\text{mg}/\text{mmol}$  creatinine), hypoalbuminaemia and clinically detectable edema, occurring in the first three months of life.<sup>1</sup> It is a separate entity from idiopathic childhood nephrotic syndrome. Congenital nephrotic syndrome is most frequently genetic in aetiology, with a minority being secondary to congenital infections such as syphilis or toxoplasmosis. Inheritance is autosomal recessive, with an incidence of 1–3 per 100,000 live births. Mutations in NPHS1 are the commonest cause and are particularly prevalent in Finland (“Finnish-type” CNS) where the incidence of CNS rises to 1 in 10,000.

CNS was historically defined by histopathological appearance, with five discrete patterns described; Finnish type, Diffuse mesangial sclerosis (DMS), Focal Segmental Glomerulosclerosis (FSGS), Membranous glomerulopathy and minimal change disease.<sup>2–7</sup> Emerging diagnostic and mechanistic tools challenge these distinctions.<sup>8</sup> The increasing range and accessibility of genetic analyses have demonstrated that the genotype-phenotype correlation is not as strict as once believed.

This review will discuss how the diagnostic pathway for children with CNS has changed and summarise some of the more frequently recognised genes in which mutations may cause a CNS phenotype. There remains a dichotomy in management

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between bilateral versus unilateral nephrectomy; the arguments for both are compared, with consideration of other management approaches. Common challenges in the management of these children are also briefly summarised, ending with novel approaches currently under investigation in the pre-clinical environment.

## Basic Pathophysiology

Filtration by the glomerulus is performed by a structural unit, the glomerular filtration unit (GFU), which constitutes the architectural arrangement of the capillary endothelium, the glomerular basement membrane (GBM), and the podocyte. Podocytes are highly differentiated cells comprising a cell body, major processes and foot processes. These foot processes are vital to the integrity of the slit diaphragm (SD), a highly specialised intercellular junction between podocytes. Disruption of these slit diaphragms is highly associated with proteinuria and glomerular disease. Almost exclusively, monogenic causes of congenital nephrotic syndrome are related to mutations within genes relevant to the podocyte and structural integrity of the GFU.

Though foot process effacement is typically associated with significant proteinuria, there are clinical situations where this association does not hold true. Effacement has been ascribed to the development of lamellipodia, thick protrusions from the foot process component of the podocyte.<sup>9,10</sup> Suvanto et al demonstrated reduced expression of slit diaphragm proteins in CNS kidneys compared to controls, though expression of cytosolic proteins was preserved.<sup>11</sup>

## Clinical Presentation

The diagnosis of CNS may be suspected antenatally, with placentomegaly being a commonly reported feature.<sup>12–14</sup> However, presentation is more typically in the neonatal or infant period. Infants may present with clinically evident edema, or more subtle features such as poor feeding and lethargy. There may be associated dysmorphic features or co-morbidities such as ocular abnormalities which may suggest the diagnosis. Common physical abnormalities associated with CNS are summarised in [Table 1](#).

Initial investigations aim to establish the likely diagnosis, exclude important secondary cause, and identify any complications that may require immediate management ([Table 2](#)).

The diagnosis of CNS is strongly suggested by the detection of massive nephrotic range proteinuria. Though classically nephrotic range is considered as >200mg/mmol, infants with CNS will often have proteinuria ten to a hundred-fold

greater. Thus, the measurement of a urinary protein: creatinine ratio on a single urine specimen can be indicative of the diagnosis.

Traditionally, the diagnosis was clinical. Persisting nephrotic range proteinuria presenting aged less than 3 months, and in the absence of an apparent secondary cause (i.e. congenital infection) would suggest the diagnosis. Histological confirmation either by percutaneous renal biopsy or by examination of nephrectomy material would then confer a confirmed diagnosis.

Histologically, Finnish-type NS is associated with expansion of the mesangial matrix and hypercellularity leading to progressive glomerulosclerosis. Microcystic dilatation of the proximal tubules is a classical feature. There is an absence of immune complex deposition on immunofluorescence.<sup>27</sup>

Conversely, diffuse mesangial sclerosis more typically demonstrates small condensed glomeruli with collagen deposition in the mesangium, a feature absent in the Finnish-type.<sup>28</sup> Immunofluorescence may demonstrate mesangial IgM and C3 deposition.

In membranous nephropathy, localised inflammation causes an increase in the thickness of the capillary membrane. Deposition of immune complexes with the associated inflammation leads to podocyte effacement.

FSGS shows sclerosis of segments of the glomerular tuft. These lesions are best demonstrated with PAS and silver-methenamine staining highlighting the increased collagen deposition. They will often abut normal glomeruli highlighting its focal nature.

However, the undertaking of percutaneous renal biopsy is not without risk. Though it can confirm the presence of histological features consistent with a diagnosis of CNS, the correlation between mutational analysis and histology is less definitive than originally believed. Unless there is significant diagnostic uncertainty, awaiting genetic analysis is often more prudent. Furthermore, nephrectomy often forms a part of the subsequent management, providing a wealth of histological tissue to support the diagnosis later on.

## Genetic Analyses

The advent of genetic mutational analysis has led to more specific diagnoses of CNS. It is increasingly recognised that the histological appearance may not correlate as readily with the genetic findings.<sup>5,15,16,19</sup>

The majority of cases of CNS are caused by mutations in four notable genes; NPHS1, NPHS2, WT1 and LAMB2.<sup>2,29</sup> However, as genetic assessment becomes more readily

**Table I** CNS Genotypes and Their Associated Features<sup>17–21,23–26</sup>

Gene	Protein	Main Site Affected	Associated Features	Notes	Ref
<i>NPHS1</i>	Nephrin	Slit diaphragm	Placentomegaly Flexion deformities secondary to placentomegaly Small for gestational age Splayed cranial sutures Small nose Low set ears Preterm	78% of all CNS cases due to Fin-major 16% of all CNS cases due to Fin-minor	[15,16]
<i>NPHS2</i>	Podocin	Slit diaphragm	Milder disease Often presents with edema and hypertension		[17,18]
<i>NPHS3</i>	PLCE1	Podocyte	Microcephaly Ocular abnormalities (cataract, myopia) Nystagmus Developmental Delay Muscular Dystrophy		[2]
<i>WT1</i>	WT1	Podocyte	Pseudohermaphroditism (46XY, phenotypic female) Gonadal Abnormalities Growth restriction Development of Wilms tumour Aniridia	Very large gene with many variants recognised Wide phenotypic variation	[19]
<i>LAMB2</i>	Beta2-Laminin	Glomerular basement membrane	Microcoria Cataract Lens abnormality Hypotonia Developmental Delay	Pierson Syndrome	[20]
<i>LMX1B</i>		Podocyte	Nail abnormalities Small/absent patellae Glaucoma Proteinuria may present at any age	Nail-patella syndrome	[21]
<i>ADCK4</i> <i>COQ2</i> <i>COQ6</i> <i>PDSS2</i>	Various	Mitochondria	Encephalopathy Seizures Ataxia Developmental delay	Co-enzyme Q10 pathway	[22]
<i>PODXL</i>	Podocalyxin	Podocyte	Renal malignancy Omphalocele Microcoria		[23]
<i>PMM2</i>	Phosphomannomutase-2	Impaired glycosylation	Hypotonia Developmental delay Strabismus Pericardial effusion Abnormal fat distribution Characteristic facies		[24]
<i>CD2AP</i>	CD2-associated protein	Podocyte	FSGS Hypertension	Unclear if truly associated with CNS	[25]

**Table 2** Preliminary Investigations Where CNS Suspected

Investigation	Possible Abnormality in CNS/Rationale
Blood tests	
Full Blood Count & film	Normal/anaemic
Urea & Electrolytes	Normal/renal dysfunction
Bone profile	Hypocalcaemia secondary to hypoalbuminaemia
Ionised calcium	Initially normal, may fall with loss of urinary Vitamin D binding proteins leading to reduced Ca absorption
Liver function tests	Defining characteristic hypoalbuminaemia <25g/l
Immune profiling (Complement, anti DS DNA, ANA, ANCA, Immunoglobulins, Hepatitis B & Varicella Serology)	Exclude immune-mediated disease potentially amenable to immunosuppressive therapy
Syphilis serology	Exclude a curable cause of CNS
Genetic mutational analysis	Recognised mutation may preclude requirement for biopsy, confirm diagnosis
Urine tests	
Dipstick and Microscopy	Massive Proteinuria
Urinary protein: creatinine ratio	Defining characteristic >200mg/mmol
Osmolality	High
Urinary electrolytes	Low urinary Na and high Urinary K may be indicative of fluid depletion
Imaging	
Renal USS	Normal or enlarged kidneys with increased cortical echogenicity

accessible and expansive, causative mutations in other genes are increasingly recognised e.g. PMM2, PODXL.<sup>23,24</sup> For example, a large UK paediatric cohort of steroid-resistant nephrotic syndrome, including CNS patients, had whole-exome sequencing undertaken, focussing on 53 genes recognised to associate with NS. Identified several novel likely pathogenic variants in NPHS1 and NPHS2.<sup>17</sup>

## NPHS1

NPHS1 encodes for the production of nephrin.<sup>16,30–32</sup> Nephrin is the major structural component of the slit diaphragm, being key to its integrity.<sup>31,33</sup> Mutation in NPHS1 leads to a loss of nephrin expression within the SD. This loss of interaction between the intracellular components of nephrin with podocin and other intra-podocyte processes leads to a reduction in actin polymerisation and corresponding change in foot process morphology and GBM functionality.<sup>16,34</sup> Fin-major (c.121delCT; p.L41fs) and Fin-minor (c.3325C>T; p.R1109X) mutations are the cause of 98% of the NPHS1 mutations seen in the Finnish population; however other mutations are more prevalent in other populations with multiple pathogenic mutations in the nephrin gene now identified.<sup>30,35</sup> Similar to other genetic diseases whereby mutation can affect protein

expression, the severity of the CNS may be associated with the impact on nephrin expression. Absence of nephrin leads to CNS, whilst altered (but not absent) expression is associated with a severe nephrosis presenting beyond infancy. Disruption of the nephrin signalling pathway, due to disease or injury, leads to changes in the actin cytoskeleton morphology with migration of healthy podocytes to cover areas where podocyte loss has occurred.<sup>36</sup> Deficiency in nephrin and neph1 leads to an upregulation of other intra-podocyte factors (podocin, NCK1/2 & CD2AP). Though the mechanism for this upregulation is not fully understood, it is felt to be in response to the failing SD and the resultant damage to the podocyte cytoskeleton.<sup>11</sup>

Typically, infants with NPHS1 mutation will be born in late prematurity (35–38 weeks' gestation).<sup>37</sup> Through their antenatal course, ultrasound scans may highlight a relatively large placenta and there may be a suggestion of crowding, restricting movement in utero. This can lead to flexion deformities of the elbows, hips and knees, and may also have an impact on respiratory development.<sup>13,14</sup> Infants can also present with a small nose and low set ears, and there is evidence of delayed ossification with gaping anterior and posterior fontanelles.

## NPHS2

NPHS2 encodes for podocin, a membranous protein which forms an anchoring hairpin structure between the plasma membrane and the internal actin cytoskeleton of the podocyte.<sup>38</sup> Podocin promotes the integration of nephrin in the lipid rafts of the SD (24), with loss of this signalling and integration leading to nephrotic syndrome. The phenotype tends to be less aggressive than those arising from NPHS1 mutations. In the main, these children present in early childhood but may avoid detection until early adulthood.

## WT1

The WT1 gene was initially identified in conjunction with WAGR syndrome (Wilm's tumour, Aniridia, Genitourinary malformation and mental Retardation).<sup>39,40</sup> Located on chromosome 11p13, WT1 is a tumour suppressor gene essential for normal gonadal and kidney development, and in later life promotes podocyte stabilisation. WT1 mutation may present with early onset NS in the context of Deny-Drash Syndrome (DDS) (with underlying diffuse mesangial sclerosis (DMS)) or later in life, e.g. Frasier syndrome. DDS associated with genotypical males (46XY) present with Wilm's tumour, pseudohermaphroditism (i.e. phenotypically female) and progressive glomerulopathy. Those of the female genotype (46XX) present with Wilm's tumour and glomerulopathy without the pseudohermaphroditism. There are other incomplete forms of the condition which present with DMS. In Frasier syndrome, the underlying pathological findings are more typically of FSGS. Though initially considered to contribute only 3% of CNS cases worldwide, finer tools for genetic diagnosis are suggesting a greater contribution. A recent UK registry review identified WT1 as the second commonest pathogenic genetic variant in children aged under 2 years.<sup>15</sup> Patients with WT1 mutation may have less symptomatic nephrosis in terms of oedema and hypoalbuminemia but are more likely to have progressive and rapid reduction in renal function. WT1 is a very large gene, partly explaining the very broad range of clinical findings associated with mutation.

## LAMB2

Unlike the aforementioned mutations which all impact the podocyte directly, the glomerular basement membrane is affected by mutations in LAMB2. This gene encodes for laminin- $\beta$ 2 a major structural protein providing anchoring within the GBM to podocytes. Being expressed in several systems, mutation in LAMB2 leads to Pierson syndrome,

comprising CNS, ocular manifestations and neurological defects in children.<sup>20</sup> The renal phenotype of this condition is variable from mild glomerulosclerosis to diffuse mesangial disease.<sup>41</sup>

## Secondary CNS

The development of nephrotic range proteinuria in infancy is rare, with most cases in the developed world resulting from genetic mutation leading to CNS. However, secondary NS with an antecedent infection should be considered and excluded.<sup>7,18,42</sup> Syphilis has seen a global resurgence<sup>43</sup> and is implicated in the development of CNS, with histological evidence of glomerular immune deposition which may demonstrate an antigen-dose effect.<sup>44</sup> Appropriate antibiotic therapy for syphilis may lead to resolution of the CNS (35).

Congenital toxoplasmosis infection has been identified as a cause of nephrotic syndrome.<sup>45</sup> Similarly, appropriate treatment should lead to resolution of the nephrosis.

Neonatal cytomegalovirus (CMV) infection has also been implicated in nephrotic syndrome, though whether this is causative remains controversial given that evidence of CMV infection is relatively common and CNS is very rare.<sup>18,46,47</sup> It is plausible that CMV infections represent a further "hit" in a complex multi-factorial condition.

The increasing availability of mutational analysis and technology that permits interrogation of multiple relevant genes on a single sample has altered the diagnostic pathway for infants with significant proteinuria. The ongoing identification of new mutations has progressed our understanding of the pathophysiology of podocytopathies, including CNS. Though individualised patient therapy based on mutational analysis is still outside the scope of most services, this may become an achievable goal in the future.<sup>8</sup>

## Management

The primary goal in the management of CNS in infancy and early life is optimisation of nutrition and minimisation of complications, to achieve an adequate weight and height for transplantation to proceed as soon as possible. Nutritional management in these children is extremely challenging, and mandates specialist dietetic input early on. These patients are at risk from several co-morbidities that may impact on their long-term functioning and quality of life. The low incidence of CNS has essentially precluded randomised controlled trials of management strategies though long-term registry data, particularly from Finland, has provided some reassuring outcome data that these children can have an excellent outlook.<sup>48–50</sup> The



management of complications can be broadly divided into those associated with the nephrotic state, those arising from impaired glomerular filtration rate (GFR), and those associated with co-morbidities, e.g. retinal detachment in Pierson syndrome. This review will focus on the former – the challenges of managing the nephrotic state and its complications in young infants.

## Managing Edema

The hallmark of CNS is significant protein loss. This leads to problematic edema, protein malnutrition, and complications relating to the wastage of specific proteins, e.g. immunoglobulins. What is the optimal strategy to reduce protein loss? The two predominant strategies in the last 25 years have been:

1. Early bilateral nephrectomy to minimise protein loss, optimisation of growth and renal replacement therapy
2. Medical management with non-steroidal anti-inflammatory (indomethacin) and angiotensin-converting enzyme inhibitor (ACEi) medication, sometimes with unilateral nephrectomy.

## Bilateral Nephrectomy

Due to the far higher incidence in Finland, many aspects of management have been heavily influenced by the strategies and outcomes reported there. The standard approach has been early bilateral nephrectomy to optimise growth and permit earlier transplantation. This achieves a rapid correction of protein deficiency, avoiding the requirement for long-term intravenous albumin administration, and with improvements in quality of life measures.<sup>3</sup> Unilateral nephrectomy may not be as impactful on protein loss leading to poorer growth, and ongoing intravenous albumin requirements. Uraemia and complications such as dyslipidaemia may also not be addressed by this less aggressive approach. There is a suggested distinction between children with “severe” protein loss, who should undergo bilateral nephrectomy, and less severe forms of the disease.<sup>3,51</sup> Outcomes showed good growth following nephrectomy and progression to transplantation. Finnish registry data on outcomes with end-stage renal disease (ESRD) demonstrate that these patients are not disadvantaged in terms of graft survival, overall mortality, or developmental attainment compared to other infants with ESRD of other causes.<sup>18,48,52</sup>

Subsequent work by Holmberg et al proposed bilateral nephrectomy as the best means of controlling protein deficit and attaining a stable nutritional platform from which to progress to renal transplantation.<sup>3</sup> Native nephrectomy prior to transplantation in a nephrotic patient is recommended to enable recovery of serum proteins which leads to a reduced complication rate including graft thrombosis and intravascular depletion. A recent cohort of nephrotic patients was described in this circumstance, of whom 3 had CNS, all undergoing bilateral nephrectomy; 2 synchronous and 1 staged prior to transplant. Within that cohort, unilateral nephrectomy was reported to effect a 40% reduction in proteinuria; this was a mixed cohort and therefore may not be generalisable to CNS.<sup>53</sup>

## Unilateral Nephrectomy

Unilateral nephrectomy is proposed as a less aggressive alternative to bilateral nephrectomy. Multiple case series have reported reductions in the burden of albumin infusion and a positive impact on growth. Additional short-term growth benefits seen after bilateral nephrectomy appear to diminish beyond a year postintervention.<sup>54,55</sup> Reported cohorts are heterogeneous and individual outcome data is often not presented. It would therefore be prudent in any future evaluation of management in nephrotic syndrome to include genetic variant data to enable distinctions to be made.<sup>56</sup> This has been replicated in more recent work.<sup>56–58</sup>

Dufek reported on a heterogeneous cohort of 80 patients, in whom just under half the patient cohort had nephrectomies performed to manage the gross proteinuria caused in this condition.<sup>57</sup> Initially, when reviewed at 12 months there was a weight advantage to those receiving nephrectomies consistent with the Finnish cohorts leading to beneficial growth and optimised conditions for transplantation. However, this advantage was lost over the subsequent 6 months, which adds weight to the argument for a more conservative approach. They also report no increase in the complications of CNS between conservative or nephrectomised patients. The cohort suggests poor correlation between genotype and phenotype in CNS, a familiar finding.<sup>4</sup>

It is accepted that transplantation in those under 2 yrs carries with it a significant increase in morbidity.<sup>49,59</sup> Dialysis carries with it its own independent morbidity.<sup>60,61</sup> It would appear pragmatic where there is not the increased risk of Wilm’s (WT1) that a management strategy of staged nephrectomy gives CNS patients the opportunity to be managed, potentially in their home

environment with domestic administration of albumin, allowing them to grow and avoid dialysis, and the possibility of pre-emptive transplantation.

As an increasing number of genes are implicated in the development of CNS it seems prudent to consider moderation of the Finnish approach and whether it is applicable to all CNS genotypes.

### Albumin Replacement and Medical Management

The development of edema is a core feature of the nephrotic syndrome. Whether the increased interstitial fluid is secondary to reduced oncotic pressure, hypotension, and renin-angiotensin-aldosterone activation – the “underfill” hypothesis, or sodium and water retention with intravascular expansion and overflow into the interstitium – the “overflow” hypothesis, the mainstay of early management is the infusion of human albumin solution with the co-administration of loop diuretics.<sup>42,57,58</sup>

The frequency of these infusions places a heavy burden on the family of the affected child, more so if delivery is required in an in-patient setting. Delivery of IV albumin by the family in the home setting can mitigate some of these quality of life issues, without an increase in adverse events.<sup>62–64</sup>

Deliberate reduction in renal blood flow using angiotensin-converting enzyme inhibitors (ACEi) and prostaglandin inhibitors (PGi) such as indomethacin leads to a reduced protein loss through reducing intraglomerular pressure, and may reduce the number of albumin infusions required.<sup>29,56,57,59,65–67</sup> There is some evidence to suggest the use of ACEi alone is ineffective at reducing the level of proteinuria.<sup>57,68</sup> Although the use of amiloride to limit sodium retention through ENaC activation seems similarly physiologically sound, it is not used routinely. Amiloride has been studied in conjunction with loop diuretics and has shown to have an additive effect.<sup>69,70</sup>

Medical management may also include trials of immunosuppressive therapy. The standard management of idiopathic nephrotic syndrome includes corticosteroids and often subsequently calcineurin inhibitors, e.g. cyclosporine.<sup>71</sup> Pre-clinical models investigating these medications demonstrate either observable beneficial effects on the podocyte or, in the case of rituximab, direct binding to the podocyte which may or may not be related to its therapeutic effect in other forms of nephrotic syndrome. Literature exists of infants with CNS trialled on corticosteroids, cyclosporin, or rituximab, in some circumstances with apparent benefit.<sup>72–75</sup> Limited patient numbers render it impossible to definitively confirm

a clinical effect, and all immunomodulatory therapy carries an adverse event profile. Pragmatically, if the diagnosis is unclear utilisation of immunotherapy until a genetic diagnosis is made is potentially justifiable but should be stopped if no clinical benefit is demonstrated.<sup>76</sup>

Overall, two main management strategies persist. Bilateral nephrectomy, especially in those with “severe” disease, or those with significant malignant risk, i.e. WT1 mutations, with early consideration of transplantation. Unilateral nephrectomy combined with medical anti-proteinuric strategies including ACEi and indomethacin, with optimised supportive renal care.

## Other Complications Arising from Proteinuria

### Nutrition and Growth

The development of protein malnutrition is intrinsic to CNS. Involvement of a specialist paediatric renal dietitian in the management of these patients is mandatory and should occur as soon as the diagnosis is suspected. A high calorific and protein content diet in combination with fluid and salt restriction are the cornerstones of the nutritional management.<sup>3,14,18,29,58</sup> Regular dietetic review as renal function declines and the degree of protein loss lessens is a cornerstone of management. Early consideration of supplemental feeding, i.e. nasogastric tube, gastrostomy to provide optimal nutrition from the earliest stages is vital. The primary endpoint for these patients is to achieve a height and weight at which they can be transplanted, minimising their morbidity and mortality.

### Vascular Access

Long-term central venous access is frequently essential for the secure regular delivery of IV albumin during the markedly proteinuric stage. The presence of a central venous catheter has associated risks including infection, bleeding, displacement and the need for anaesthesia for insertion and removal in children.<sup>77–79</sup> The most significant risk in this particular patient population is thrombosis – the combination of being relatively hypercoagulable secondary to proteinuria, and the presence of foreign material within the vessels provide a strong impetus to thrombus formation; an “aggravated” clot.<sup>80,81</sup> Anticoagulation therapy should be considered, either oral warfarin or subcutaneous low molecular weight heparin. The evidence base in preference for either therapy does not exist and may be guided by patient/family preference. Due to loss of anti-thrombin III in the urine, the dose required to achieve satisfactory

prophylactic anti-coagulant concentrations may be several-fold higher than in other patient populations.<sup>82</sup>

### Infective Risk

Several disease factors predispose these children to a higher risk of infective complications, including urinary loss of immunoglobulins, requirement for central venous catheter, and suboptimal nutrition. Administration of intravenous immunoglobulin in CNS is not recommended as intravascular persistence of the extraneous immunoglobulin is a matter of hours, providing no significant benefit.<sup>83</sup> Prophylaxis against encapsulated organisms is sometimes provided in the form of regular phenoxymethylpenicillin (“Penicillin V”) though the clinical benefit is uncertain.<sup>58,84</sup>

### Loss of Other Albumin-Bound Proteins

Urinary loss of thyroid-binding globulin leads to a functionally hypothyroid state requiring thyroxine replacement therapy.<sup>85</sup> Infantile hyperbilirubinaemia carries an increased risk of kernicterus due to a fractionally greater free bilirubin – such infants should be aggressively managed with phototherapy where the diagnosis is recognised early enough. Hyperlipidemia and hypercholesterolemia are common (22) – use of medication to lower such as statins do not yet have an established role in CNS.

## Transplantation

Transplantation is predominantly curative for the majority of cases of congenital nephrotic syndrome.<sup>3,29,48,49,51,57,58,86,87</sup>

Long-term graft survival is however dependent upon a number of pre and peri-transplant factors including adequate growth to accommodate a graft and very close monitoring and management in the early post-transplant phase, particularly graft vascular thrombus.

Living-related donation from a parent entails receiving a graft with heterozygosity for the causative mutation (if identified). Though there are theoretical concerns regarding this, in practice there is no evidence of poorer graft outcome, or the development of disease “recurrence” in patients receiving a living-related rather than deceased donor kidney.<sup>88</sup> More detailed donor genetic analysis is suggested in NPHS2 mutation, as the pR229Q variant is relatively common (~4% population) and is associated with adult onset NS in compound heterozygotes. In that circumstance, donation from an alternative donor should be considered.

Disease “recurrence” following transplant has been reported, though in truth it is the development of a different

pathophysiology. A subset of patients with Fin-major mutation who lack expression of normal nephrin develop an anti-nephrin antibody which may present with recurrence of proteinuria in the transplanted patient.<sup>89</sup> This process can be rapid post-transplant.<sup>90</sup> These patients typically respond to clearance of antibody with plasma exchange and anti-CD20 antibody (e.g. rituximab).

## Areas for Future Development

Previous podocyte models have been limited by the absence of a truly representative *in vitro* slit diaphragm. Novel techniques in three-dimensional cell cultures and “organoid” development hold promise for ongoing mechanistic investigation.<sup>91,92</sup>

As our understanding of the genetic permutations associated with CNS develops, translation into tailored treatments mirroring the developments in other genetic conditions like cystic fibrosis and juvenile idiopathic arthritis may occur. As an example, murine models of Pierson Syndrome showing disruption of the GBM have been shown to be amenable to treatment with intravenous human LM-521 leading to a reduction in GBM damage and subsequent protein loss.<sup>93</sup>

## Summary

The work carried out primarily by the Finnish group revolutionised the management of CNS in the 1980s and 1990s, changing it from a disease with little chance of survival beyond the first few weeks and months of life, to a chronic condition potentially curable through transplantation.

The evolution of next-generation genetic sequencing has led to clinically more meaningful stratification of CNS and opened the door to more moderate clinical approaches in patients with less severe nephrosis, reducing or halting the progression to ESRD.

Our understanding of the genetic basis of CNS alongside the creation of realistic facsimiles of the SD *in vitro* provide a research environment where targeted gene-specific therapies may transform management of this condition.

Management of CNS should be individualised. Both unilateral and bilateral nephrectomy offer benefits. Management of complications arising from proteinuria has very little evidence base to support and continues to be based on “best practice”.

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