Introduction

The nephrotic syndrome (NS) is characterised by a triad of massive proteinuria (> 40mg/m² per hour or 50mg/kg per day), hypoalbuminemia (≤2.5mg/dL), and hyperlipidemia (serum cholesterol >200mg/dL or 6.5mmol/L). (1, 2) Other supporting characteristics include the presence of edema and a raised β2 globulin on serum electrophoresis, although these are not essential for the diagnosis. In physicians managing young children in whom 24 hour urine collections are difficult, the Children's Nephrotic Syndrome Study Group Consensus Conference recommended the use of the protein: creatinine ratio on a spot early morning sample of urine with a urine protein: creatinine (Up/Ucr) ratio ≥2.0. (2)

NS may be classified according to etiology (primary or secondary), age of onset (congenital, infantile, acquired or late onset NS), or histopathology (e.g. minimal change disease, mesangial hypercellularity, focal segmental glomerulosclerosis [FSGS], membranous, membranoproliferative). However the most useful classification for management purposes is to define the disease according to its response to steroids (steroid sensitive or resistant with steroid sensitive disease being further classified into frequent relapses and steroid dependent NS) as patients who are steroid sensitive have an excellent prognosis with preservation of kidney function whilst those that are steroid resistant are more prone to complications with a high risk of having deterioration of kidney function and progression to end-stage kidney disease needing renal replacement therapy. More recently single gene mutations affecting podocyte differentiation and function have been described in steroid resistant disease, predicting unresponsiveness to immunosuppressive therapy. (3)

Congenital nephrotic syndrome (CNS) is a rare form of nephrotic syndrome (NS) that presents at birth or within the first three months of life. It is due in most cases to genetic defects in the components of the glomerular basement membrane or may also present as part of a more generalised syndrome. (4) NS presenting after three months up to one year of age is called infantile NS. The precise diagnosis of the glomerular lesion is based on clinical, laboratory and histological criteria (5) (Table 1).

Genetic forms of Congenital Nephrotic syndrome

Nephrin gene (NPHS1) mutations: Nephrin gene codes for nephrin, a 1241-residue trans-membrane adhesion protein of the immunoglobulin superfamily and is synthesized almost exclusively by glomerular podocytes. (5) The protein is a key component of the podocyte slit diaphragm. NPHS1 mutations account for most (nearly 90%) patients responsible for the Finnish-type of congenital NS. In Finland two founder

Table 1: The etiology of congenital Nephrotic Syndrome (CNS)

<table>
<thead>
<tr>
<th>Primary CNS</th>
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<tbody>
<tr>
<td>Nephrin gene mutations</td>
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<tr>
<td>Podocin gene mutations (NPHS2)</td>
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<tr>
<td>WT1 gene mutations (Denys-Drash, isolated CNS)</td>
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<tr>
<td>LamB2 gene mutations (Pierson syndrome, isolated CNS)</td>
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<tr>
<td>PLCE1 gene mutations</td>
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<tr>
<td>LMX1B mutations (nail-patella syndrome)</td>
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<tr>
<td>Lam B3 gene mutations (Herlitz junctional epidermolysis bullosa, mitochondrial myopathies)</td>
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<tr>
<td>CNS with or without brain and other malformations (no gene defect identified as yet)</td>
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<table>
<thead>
<tr>
<th>Secondary CNS</th>
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<tr>
<td>Congenital syphilis</td>
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<tr>
<td>Toxoplasmosis, malaria</td>
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<tr>
<td>Cytomegalovirus, rubella, hepatitis B, HIV</td>
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<tr>
<td>Maternal systemic lupus erythematosus</td>
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<td>Neonatal autoantibodies against neutral endopeptidase</td>
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<tr>
<td>Maternal steroid-chlorpheniramine treatment</td>
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mutations (Fin-major and Fin-minor) are detected in almost all cases of CNS. (6-8) Close to 100 mutations in the NPHS1 gene have been identified and has been described in various ethnic groups throughout the world. (9-11) Since nephrin is specifically located at the slit diaphragm of the glomerular podocytes, this could explain the absence of slit diaphragms and foot processes in patients with NPHS1 mutations. (12,13) Although NPSH1 mutations account for the majority of Finnish type CNS, no abnormalities were found in seven affected individuals from Europe and North America (including the five flanking region). (14) It is postulated that these patients may have mutations elsewhere in the promoter or in the intron areas or in a gene encoding another protein that interacts with nephrin. (15) Also two siblings with a mild form of CNS of the Finnish type with intermittent proteinuria were found to be compound heterozygotes for two novel non-conserved misuse mutations. (16)

Children with CNS due to NPHS1 mutations show little phenotype variation. (7) There is often a history of premature birth with a low birth weight for gestational age. The placenta in almost all cases is over 25% of the newborn weight. Fetal distress with meconium stained liquor is common but major respiratory problems are rare. Extra-renal malformations include:

- Widely separated cranial sutures due to delayed ossification
- Small nose and low set ears
- Flexion deformities of the hips, knees, and elbows secondary to the large placenta
- Minor functional disorders such as muscular hypertrophy and cardiac hypertrophy

Proteinuria begins in utero and is detectable in the first urine sample at birth. Heavy proteinuria (up to 100g/L) results in oliguria and severe edema if not treated. Hematuria is uncommon but may develop in some cases. Severe urinary protein losses are accompanied by severe hypogammaglobulinaemia. As a result of this these patients have severe malnutrition, poor statural growth and are highly susceptible to bacterial infections (peritonitis, respiration infections, etc.). Hypothyroidism from loss of thyroxin binding protein in the urine develops as the disease progresses. These patients are also prone to thromboembolic complications due to the severity of the NS.

Laboratory findings of hypoalbuminaemia, hypogammaglobulinaemia, and hyperlipidemia with massive proteinuria are typical. The blood urea and serum creatinine are initially normal or low corrected for gestational age due to the state of inanition. Sonography shows enlarged kidneys with increased echogenicity and loss of cortico-medullary differentiation[5].

Podocin gene: Podocin gene (NPHS2) mutations are more common in childhood steroid resistant NS [autosomal recessive focal segmental glomerulosclerosis (FSGS)] but also found in some cases of CNS. (7,17-21) NPHS2 encodes an integral membrane protein called podocin that is found exclusively in glomerular podocytes. Since podocin is a podocyte-adapter protein required for proper targeting of nephrin in the slit diaphragms, nephrin expression may also be distorted in CNS due to NPHS2 mutations. (22) It is responsible for half of the CNS cases in European families and has been found in Japan and elsewhere. (5,23)

A triallelic abnormality with NPHS1, and NPHS2 mutations (homozygotes mutations in one gene and heterozygous mutations in the other) has also been reported in some patients with CNS. (17,24,25) These findings demonstrate the genetic heterogeneity of CNS and the absence of clear genotype/phenotype correlations. The clinical findings in patients with CNS due to NPHS2 mutations are more variable than those with NPHS1 mutations. Some individuals have milder disease and only presents in adolescents or young adulthood. Patients presenting with CNS develop end-stage kidney disease after a few years. (23) These patients do not have major extra-renal manifestations although minor cardiac abnormalities have been reported. (5) The histopathological findings are usually that of FSGS.

Other genetic forms: Some of the other genetic forms of CNS include mutations in the Wilm’s tumour suppressor genes [WT1, laminin-β2 gene LAMB2 and phospholipase epsilon gene (PLCE1)]. Wilm’s tumour suppressor gene (WT1) encodes for a transcription factor WT1, which plays a crucial role in the embryonic development of the kidney and genitalia. WT1 mutations can cause isolated CNS or several types of developmental syndromes (Denys-Drash, Frasier, and WAGR syndromes). Patients usually have moderate proteinuria and histopathology findings are that of diffuse mesangial sclerosis of the glomeruli. (23,26) Laminin-2 LAMB2 is a component of the glomerular basements membrane, where it is crucial for the network structure and anchoring of the glomerular basement membrane to the podocyte foot processes. LAMB2 mutations with CNS and distinct ocular anomalies with microcoria as the leading clinical features have been reported as Pierson Syndrome. However, CNS patients with LAMB2 mutations without eye involvement have also been reported. (27) The Galloway-Mowat Syndrome is CNS associated with central nervous system abnormalities (microcephaly, psychomotor retardation and brain anomalies). (28) Other extra-renal manifestations include hiatus hernia, short stature, diaphragmatic defects and dysmorphic features. (29) The syndrome appears to be transmitted as an autosomal recessive trait and NS presents early with a mean age of 3 months (range 0-34 months), is severe, and steroid resistant. Kidney biopsy shows variable histopathology including minimal change, FSGS or diffuse meningeal sclerosis. The underlying genetic defect is unknown. (5) CNS has been reported with other extra renal defects including CNS associated mitochondrial cytopathy (30), nail-patella syndrome (31), congenital disorders of glycosylation type 1 (32), Herlitz junctional epidermolysis bullosa (33) and CNS caused by PLCE1 mutations. (34)
Non genetics forms of Congenital Nephrotic syndrome

Whilst genetic forms of CNS are most common in developed countries, in developing countries, non-genetic form of CNS, usually due to infections, are most prevalent.

- Congenital syphilis causes a nephritic or nephrotic syndrome in newborns. Patients present with proteinuria and hematuria but severe NS is rare. Histopathology shows a mixed pattern with membranous nephropathy and mesangial proliferation. Antimicrobial treatment (penicillin is the drug of choice) leads to complete resolution of all renal lesions. (5,35)
- Congenital toxoplasmosis presents with proteinuria at birth or during the first three months and leads to CNS. Associated ocular and neurological abnormalities are common. (36) Histopathology shows mesangial proliferation with or without FSGS. Treatment of toxoplasmosis in combination with steroids usually leads to remission of proteinuria.
- Congenital cytomegalovirus infections can present with CNS. Extra renal manifestations such as hepatitis, neurological abnormalities and respiratory involvement are common. Important to note is that cytomegalovirus is common during the first months of life, and detection of the virus in patients with CNS does not exclude an underlying genetic defect, particularly when there is no response to antiviral treatment. Treatment with gancyclovir and/or valgancyclovir leads to disease remission. (37)
- CNS has also been reported in association with other congenital infections such as human immunodeficiency virus, hepatitis B virus, and rubella.
- Non-infectious causes of CNS has been reported in association with maternal systemic lupus erythematosus and neonatal alloimmunisation against neutral endopeptidase present on podocytes. (38)

Diagnosis of Congenital Nephrotic Syndrome

CNS in its most severe form presents with anarsaca, severe proteinuria (>20 g/L), and severe hypoalbuminemia (<10 g/L) in the newborn period. Depending on the etiology (genetic forms of CNS being most severe), the degree of proteinuria is variable and hence clinical sign of NS may only present after a few weeks of life. (5) Also the true magnitude of proteinuria may only be apparent after partial correction of hypoalbuminemia with albumin infusions. Microscopic hematuria and leucocyturia are often present. Blood pressure may be low due to the hypoproteinemia or elevated if severe chronic kidney disease is already present. An increased placental weight (usually >25% of birth weight) suggests NPHS1 mutations but may be seen in other forms of CNS. (7) Presence of extra-renal malformations may point to syndromic forms of CNS. These include genital abnormalities (WT1), eye defects (LAMB2), and neurological disorders (Mowat Galloway). Cardiac ventricular hypertrophy without structural defects is common. (5) At the time of diagnosis blood urea and serum creatinine are usually normal but kidney failure invariable develops, varying in time, depending on etiology.

Kidney biopsy on light microscopy shows mild mesangial hypercellularity and increased mesangial matrix in the glomeruli early in the course of the disease. Tubulointerstitial changes are also prominent. Irregular dilatation of proximal tubules is the most prominent finding. These changes however may not be seen in all patients. Later in the course of the disease, interstitial fibrosis, lymphocytic and plasma cell infiltration, tubular atrophy and periglomerular fibrosis develop parallel with an increase in mesangial matrix accompanied by progressive glomerulosclerosis. (9,39) No immune deposits are detected by immunofluorescence studies. Electron microscopy shows effacement of the foot processes and disappearance of the filamentous image of the slit diaphragms. (7)

Unfortunately kidney biopsy may not reveal the diagnosis of CNS as lesions may be focal and biopsy findings may therefore be misleading. Genetic forms of CNS may cause several histopathological patterns of glomerular lesions, including mesangial expansion, minimal change disease, FSGS, and diffuse mesangial sclerosis. There may overlap of these different entities. (5) Tubular dilatation and interstitial fibrosis and inflammation are also seen in other forms of proteinuric disease. The lack of nephrin and podocin on immunohistochemistry suggests a severe form of CNS that is unlikely to respond to anti-proteinuric therapy.

Prenatal diagnosis in families with a known risk for CNS should be based on genetic testing whenever possible. Elevated alpha fetoprotein in maternal serum and aminotonic fluid in the absence of foetal anencephaly or other malformations is strongly suggestive of NPHS1 mutations. However heterozygous cases of NPHS1 mutations may have temporary elevations in alpha fetoprotein. A therefore repeated measurement of aminotic alpha fetoprotein before the twentieth month of pregnancy is recommended in cases with high alpha fetoprotein. (40)

Management

The main aim is to control edema and possible uremia, prevent and treat complications such as infections and thrombosis as well as providing adequate nutrition to ensure optimal growth of the child. In many cases the ultimate curative therapy is kidney transplantation. (5) (Table 2)

Control edema

Symptomatic control of edema is achieved by parental albumin infusions using 20% albumin (5-20 mg/kg/day) given over 6 hours with intravenous furosemide (0.5 - 1 mg/kg given half way through and at the end of the albumin infusion) is helpful to control life threatening edema, protein malnutrition, reduced growth, and secondary complications such as thrombosis. (5) Thiazide diuretics and aldosterone antagonists are used as adjunctive for control of edema. Reduction of protein excretion includes administration of angiotensin converting enzymes inhibitors and indomethacin. Patients with severe NPHS1 and NPHS2
mutations inhibiting nephrin and podocin expression (stop codons, deletions, missense mutations) do no respond to this treatment.

As this disease progresses, loss of thyroxin binding globulin and thyroxin lead to a rise in thyroid-stimulating hormone. This necessitates thyroxin substitution stating with 6.25 - 12.5 ug/kg, the dose adjusted according to thyroid stimulation hormone levels.

Anti-coagulation therapy using aspirin and dipyridamole is indicated as urinary protein losses result in imbalance of plasma coagulation factor levels, predisposing to hypercoagulability and risk for thrombosis. Finnish patients with \textit{NPHS1} mutations have also been successfully treated with warfarin from 3-4 weeks of age. Before surgical or vascular procedures, warfarin is stopped, and antithrombin III (50 iu/kg) is given to temporarily correct the deficiency. (5)

Urinary losses of gammaglobulins and complement predispose patients with CNS to bacterial infections. Prophylactic antibodies treatment has not shown to be helpful and may induce resistant bacterial strains. (5) A high index of suspicion for infections is needed as symptoms are vague and often masked by signs of focal infection occurring at the same time. Parenteral antibodies should be commenced promptly if sepsis is suspected providing broad spectrum cover. Prophylactic use of immunoglobulin infusions does not reduce the incidence of bacterial infections but has been used as adjunctive treatment with antibodies to control sepsis. (5) Response to treatment is favourable in most cases if commenced early.

\textbf{Nutrition}

A high energy (130 kcal/kg per day) and high protein (3-4 g/kg per day) diet is indicated. Breast milk and milk formulas are first used with excess protein given as casein based protein products. Glucose polymers are given to increase energy intake, and a mixture of rapeseed and sunflower oil is given to balance lipid levels. (29) Vitamin D supplementation is used starting with 400 iu/day) and adjusted to maintain 25-OH vitamin D levels between 30-100 ng/L. Alphacalcidol is indicated for secondary hyperparathyroidism to present renal osteodystrophy.

Multivitamin preparations are given according to recommended dietary allowances for healthy children of the same age. Supplemental magnesium (50 mg/ day) and calcium (500-1000 mg/day) may be required to maintain normal serum levels. Fluid intake is adjusted to 100-130 mls/kg per day. Most patients may require supplemental feeding via a nasogastric tube or stomach peg to ensure adequate energy intake.

Unilateral nephrectomy to reduce protein losses has been done in some centres as a temporizing procedure to decrease the frequency of albumin infusions whilst ensuring adequate kidney function, so that kidney transplantation can be postponed to an older age. (41) In other centres bilateral nephrectomy and peritoneal dialysis are postponed early to avoid complications. Kidney transplantation is the only definitive treatment for children with severe CNS unresponsive to medical therapy. This is feasible when the child weighs more than 9 kg and the extra-peritoneal placement of the graft is possible. (5)

An alternate option is to perform early, pre-emptive kidney transplantation with an intra-peritoneal placement of the kidney graft and the native kidney removed at the time of the transplant being done. (5)

The use of adult size kidneys in a small recipient is surgically demanding and increases the risk for thrombotic and ureteral complications compared with older recipients. Adequate hydration post-transplant (3000 mls/m2 per day) is necessary to maintain

\begin{table}
\centering
\caption{CNS management of infants with heavy proteinuria}
\begin{tabular}{|l|}
\hline
Protein substitution parenterally (20% albumin infusions, 3-4 g/kg per day of albumin) \\
\hline
\textbf{Nutrition} \\
Hypercaloric diet (130 kcal/kg per day) \\
Protein Supplementation (Rapeseed/sun flower oil) \\
A, D, E and water soluble vitamins \\
Calcium and magnesium supplementation \\
\hline
\textbf{Medication} \\
Anti-proteinuric drugs (angiotensin converting enzyme inhibitors, indomethacin) \\
Thyroxin supplementation \\
Anticoagulation (warfarin, aspirin, anti-thrombin III-infusion) \\
Parenteral antibodies when bacterial infection suspected \\
\hline
Adapted with permission from: Jalanko H \cite{5}. Congenital nephrotic syndrome in Pediatric Nephrology 2009; 24(11): 2121-8.
\end{tabular}
\end{table}
adequate aortic and renal artery perfusion and avoid low flow rates resulting in thrombotic complications and graft loss. (42) The use of immunosuppressant therapy must be optimised to prevent rejection but avoid over suppression with its complication of sepsis and malignancy.

Recurrence of NS in the graft is rare but has occurred in some NPHS1 children who developed anti-nephron antibodies after transplantation. Treatment of recurrence with cyclophosphamide and plasmapheresis is helpful. (43) Patients’ survival at 5 years post-transplant is over 90% and graft survival over 80% in this group of patients. Chronic allograft nephropathy is a major problem with most patients needing second kidney transplantation in adulthood. (44,45)

Conclusion

The diagnosis of CNS requires a high index of suspicion especially in any neonate presenting with oedema. When possible, genetic testing should be performed early to prognostic on response to therapy and long term outcome. Management of this condition requires a dedicate team of experts to ensure a favourable outcome. Kidney transplantation is the treatment of choice, especially in those patients that do not respond to anti-proteinuric treatment.

References


From: Departments of *Paediatrics & Child Health and **Anatomical Pathology, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, KwaZulu-Natal and **National Health Laboratory Service, South Africa.

Address for Correspondence Rajendra Bhimma, Department of Paediatrics and Child Health, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Private Bag 7, Congella 4013, South Africa.

Email: bhimma@ukzn.ac.za.

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