Case report: A toddler with anasarca caused by congenital nephrotic syndrome

Tumelo M. Satekge1, Olivia Kiabilua1, Gertruida van Biljon2, Komala Pillay3, Tahir S. Pillay1,4

1 Department of Chemical Pathology, Faculty of Health Sciences, University of Pretoria and NHLS Tshwane Academic Division, Pretoria, South Africa
2 Department of Paediatrics, University of Pretoria and Steve Biko Academic Hospital, South Africa
3 Division of Anatomical Pathology, University of Cape Town and Red Cross Children’s Hospital and NHLS, South Africa
4 Division of Chemical Pathology, University of Cape Town, South Africa

INFO

Corresponding author:
Prof. Tahir S. Pillay
Department of Chemical Pathology
Faculty of Health Sciences
University of Pretoria
Arcadia, Pretoria, 0007
South Africa
Phone: 012-319-2114
E-mail: tspillay@gmail.com

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ABSTRACT

Congenital nephrotic syndrome is a rare inherited disorder arising from defects in the proteins of the cells in the glomerular basement membrane and develops either in utero or at birth. The clinical presentation is the result of massive protein loss in the urine with associated compensatory mechanisms.

Here we present a clinical case of a female toddler with a history of anasarca (severe generalised oedema) from birth and who presents with the classical biochemical laboratory findings of nephrotic syndrome, together with the more pronounced features that arise from protein loss including abnormal thyroid function testing and a marked hypercholesterolaemia. Renal biopsy indicated congenital nephrotic syndrome of the Finnish type. This clinical-diagnostic case report represents an example of the broad spectrum of pathophysiological findings of a severe congenital nephrotic syndrome.

TS, OK and TSP conceived the idea and wrote and edited the manuscript. GvB was the paediatrician managing the patient and contributed to the manuscript. KP was the anatomical pathologist who analysed the biopsies and contributed to the manuscript.
**INTRODUCTION**

**Congenital nephrotic syndrome (CNS)**

CNS manifests normally at birth to 3 months of life and is associated with inherited defects in one of the three components of the glomerular basement barrier namely fenestrated endothelium, glomerular basement membrane and podocytes (1-3). Mutations in podocytes lead to congenital nephrotic syndrome of the Finnish type (CNS-F) where podocyte foot processes form filtration slits covered by the slit diaphragm (1-4). The responsible NPHS1 gene was the first described and encodes for nephrin, a type-1 transmembrane protein of the immunoglobulin superfamily and is a pivotal component of the slit diaphragm. Almost 50 mutations so far have been described in the NPHS1 gene and the autosomal recessive gene maps to 19q13.1 (4, 5).

CNS-F presents with massive non-selective proteinuria in utero allowing for prenatal screening (1). Other features include premature birth (35 – 38 weeks) with low birth weight and neonatal edema as they were present in this case. Other mutations may occur in podocin (NPHS2) and is associated with autosomal recessive, steroid-resistant focal segmental glomerulosclerosis (FSGS). Autosomal dominant FSGS can result from TRCP6 and CD2AP mutations causing defects in the podocyte. Also, mutations in Wilms’ tumor suppressor gene can occur in the Denys-Drash syndrome (glomerulopathy in combination with Wilms’ tumor and male pseudohermaphroditism). Although the common histological finding is mesangial sclerosis, this diagnosis was excluded by the absence of ambiguous genitalia and abdominal mass (2, 4).

**CASE REPORT**

**Clinical features**

A 15-month-old first-born female toddler presented with a history of generalised body swelling since birth and neurodevelopmental delay. The first presentation was at 2 weeks after full-term normal vaginal delivery with low birthweight of 2.3 kg. The mother was HIV-positive during pregnancy and received anti-retroviral drugs. She reported unsatisfactory growth of the new-born with motor and speech delay. The child was fed breast milk until 4 months and afterwards with infant formula. On examination, she was below the 3rd percentile for height and weight (weight 6.5 kg; length 64 cm and head circumference 44.5 cm). Despite having Harrison’s sulci, the child was un-distressed with no dysmorphic features. There were generalised edema and hypoplastic teeth. Central nervous system examination revealed delayed social and motor milestones with no smile, reaching or sitting and decreased tone and muscle power with normal reflexes. Based on these clinical presentations, congenital nephrotic syndrome was suspected and specific laboratory testing was performed and renal biopsy was done for immuno-histochemical work-up to establish diagnosis.

**Laboratory findings**

The urine dipstick resulted with 3+ for proteinuria, no signs of haematuria. Blood testing showed a significant depressed C3 level of 0.638 g/L (reference interval 0.9-1.8 g/L) and hypoalbuminaemia of 2.0 g/L (reference interval 27-43 g/L) indicating nephrotic syndrome (NS). Whole blood count revealed anaemia with haemoglobin of 8.0 g/L and there was thrombocytosis with 656 x 10⁹/L. Plasmatic coagulation tests were found within normal ranges, as well as liver enzymes and renal function testing and electrolytes. Total- and LDL cholesterol levels were markedly increased; TSH and PTH were also significantly elevated together with hypocalcaemia and hyperphosphatemia as outlined in Table 1. Serologic testing for active infections including hepatitis, toxoplasmosis, anti-streptolysin-O titer, cytomegalovirus and syphilis gave negative results, HIV-antibody ELISA was negative and HIV-RNA was not detectable.
**Histological and immunochemical findings**

A renal biopsy showed mesangial hypercellularity, focal microcystic dilatations of the tubules and a mild interstitial inflammatory infiltrate (Figure 1A). 4+ foot process effacement and increased tubular lipid droplets were visualised on electron microscopy. Immunofluorescence displayed focal 1+ IgM mesangial positivity.

**Clinical course**

After establishing diagnosis, optimal supportive treatment including Enalapril p.o., intravenous albumin, furosemide, low salt intake, high caloric- and protein diet were given along with calcitriol and thyroxine. Poor compliance to thyroxine contributed to neurodevelopment delay. Treatment was not effective and was hampered by persistent proteinuria.

Unilateral nephrectomy was performed showing massive lymphoplasmocytic inflammatory infiltrates, focal segmental glomerulosclerosis with microcystic tubular dilatation, hypertensive vascular changes and ascending pyelonephritis (Figure 1B). Unfortunately, renal function dramatically deteriorated with volume overload, subsequent bacterial peritonitis and the patient died from septic shock.

![Renal biopsy histology showing mesangial hypercellularity and focal microcystic dilatations of tubules](image)
DISCUSSION

Generalised edema can result from renal disease, liver disease, allergic reactions, cardiac disease, malnutrition or protein-losing enteropathy. In children, the most common cause is renal disease. First, evaluation can commence with simple tests such as urine dipstick and urine microscopy to identify proteinuria and casts. In our case, edema is a hallmark of NS but the pathogenesis is not fully understood (6, 7). Selective loss of albumin leads to hypoalbuminemia and decreased capillary oncotic pressure resulting in net fluid flux outwards and renal losses not compensated with increased albumin production in the liver. Sequestration of fluid in the interstitium triggers renal sodium reabsorption and fluid retention to maintain intravascular volume and blood pressure balanced (the “underfill” hypothesis) (6, 7).

In NS associated with glomerulonephritis the extent of proteinuria is variable and a reduction in GFR is common. Intravascular fluid volume is typically normal or expanded because of inappropriately stimulated sodium and fluid retention together with decreased GFR results in an “overfill” state. Distinguishing between these two
states is critical to the management of edema in NS. Protein loss in the urine leads to further complications including hypogammaglobulinaemia.

In NS, there is increased risk of thromboembolism owing to increased pro-coagulants and decreased anticoagulants (urinary loss of antithrombin III, plasminogen and protein S) (8). In our patient, we found thrombocytosis which is one of the prothrombotic factors in NS; however the rest of the coagulation profile was unremarkable and there were no clinical signs of a thromboembolic state. As part of nephrotic syndrome workup to exclude secondary causes, relevant infections particularly in the presence of pre-natal HIV exposure were sought and testing was found negative for all pathogens tested.

The markedly elevated total and LDL cholesterol is probably due to over-compensated lipoprotein synthesis for reduced plasma oncotic pressure due to depleted albumin (9). This is associated with an increased risk of cardiovascular events (9). The hypothyroid state in the nephrotic syndrome could also be a contributory factor to the hypercholesterolemia. The elevation of Apo B containing lipoproteins is a prominent feature in nephrotic syndrome and in severe cases is accompanied by hypertriglyceridaemia (9). Thyroid hormone alterations in Congenital Nephrotic syndrome of the Finnish type (CNS-F) without renal impairment are well documented (10). Thyroid binding globulin is lost with proteinuria leading to low total T4 and T3. Correspondingly, free thyroid hormones are expected to be normal or even elevated with normal TSH. In severe CNS-F, as in this case, FT4 is lost in urine proportionally with massive proteinuria without commensurate compensation by the thyroid gland. This in turn stimulates the hypothalamic-pituitary axis as demonstrated by high elevated TSH (10). Low FT3 in this case can be explained by the catabolic nature of NS as a non-thyroidal illness characterised by impaired peripheral conversion of T4 to T3.

There was persistent hypocalcaemia with no other overt signs of rickets. She had poor neurodevelopment including motor milestones, Harrison sulci and hypoplastic teeth. Vitamin D-binding protein loss is a likely cause for calcidiol depletion owing to its greater affinity for 25OHD$_3$. However, 1,25(OH)$_2$D$_3$ and 24,25(OH)$_2$D$_3$ can also be low in patients with nephrotic syndrome without renal impairment (11). This can be explained by depletion of the precursor in the form of 25-OHD$_3$ and to a lesser extent to loss of binding protein in severe cases. Tubular damage as a result of exceeded reabsorption of filtered protein can lead to destabilisation of 1α-hydroxylase resulting in low calcitriol level (11). It has been hypothesized that corrected total calcium overestimates hypocalcaemia; this was also evident in our case (Table 1). Ionised calcium and vitamin D metabolites were unfortunately not measured. Depleted total calcium was associated with an elevated PTH on more than two occasions (Table 1) indicative of secondary hyperparathyroidism leading to bone demineralization (11).

The histology was typical of CNS-F where immunofluorescence did not detect immune deposits. Microcystic changes of proximal and distal tubules are common findings in CNS of Finnish type, but it may also be present in other histological subtypes of NS. Mostly, CNS-F shows slower progression even with marked proteinuria and renal function tests can be normal early on. If signs of deterioration are present despite optimal supportive treatment, bilateral nephrectomy, dialysis and subsequent transplantation should be the definitive approach to prevent further severe deterioration by reversing the biochemical abnormalities and hormonal disturbances with minimal risk of recurrence after surgery (12). However, in our case a rapid dramatic deterioration occurred with septic shock leading to fatal outcome.
| Table 1 | Laboratory testing |
|---------|---------------------|
|         | Result              | Reference interval |
| **Urine** |                     |                    |
| Protein | 4.9 g/L              |                     |
| Creatinine | 0.6 mmol/L        |                     |
| Protein/creatinine ration | 8.17               | <0.015 g/mmol       |
| **Urea and electrolytes** |                   |                    |
| Sodium | 141                  | 136-145 mmol/L      |
| Potassium | 5.2                  | 3.4-4.7 mmol/L      |
| Chloride | 112                 | 98-107 mmol/L       |
| Urea | 27.0                 | 1.1-5.0 mmol/L      |
| Creatinine | 124                 | 15-31 umol/L        |
| Bicarbonate | 13                  | 23-29               |
| Anion gap | 21                   | 9-16                |
| **Liver function tests** |                   |                    |
| Total protein | 26                   | 48-70 g/L           |
| Albumin | <10                  | 27-43 g/L           |
| Total Bilirubin | 6                    | 6-21 mmol/L         |
| Direct Bilirubin | 1                    | 0-6 mmol/L          |
| Alanine transaminase (ALT) | 11                 | 2-25 U/L            |
| Aspartate transaminase (AST) | 28                 | 0-49 U/L            |
| GGT | 129                  | 15-132 U/L          |
| ALP | 191                  | 48-406 U/L          |
| Calcium | 1.66                 | 2.12-2.59 mmol/L    |
| Corrected calcium | 2.39                | 2.19-2.64 mmol/L (low albumin) |
| Magnesium | 0.92                 | 0.7-0.99 mmol/L     |
| Phosphate | 2.13                 | 1.10-1.95 mmol/L    |
A toddler with anasarca caused by congenital nephrotic syndrome

TAKE HOME MESSAGES / LEARNING POINTS

• Anasarca in neonates requires a systemic approach to rapidly establish the correct diagnosis. Bedside testing with urine dipstick is an essential screening tool to guide further investigations; a 3+ proteinuria on dipstick is highly suggestive of nephrotic syndrome to be confirmed by appropriate laboratory work-up.

• Nephrotic syndrome is characterised by proteinuria, edema, hyperlipidaemia, hypoproteinaemia and may be associated with coagulopathy. Early diagnosis will necessitate aggressive supportive treatment in preparation for definitive treatment with surgery for restoration of growth and development.

• Always exclude secondary causes of congenital nephrotic syndrome because they tend to occur more frequent than primary causes showing better treatment response.

• Various mutations in CNS have been described; CNS-F resulting from nephrin gene mutations is not uncommon worldwide and affects both sexes equally. Genetic counselling and antenatal screening for congenital nephrotic syndrome - Finnish type with

|     |     |     |
|-----|-----|-----|
| TSH | >100 | 0.95-6.52mIU/L |
| FT4 | 5.8  | 7.6-16.1pmol/L  |
| FT3 | 2.9  | 4.5-10.5pmol/L  |
| PTH | 103.4| 1.3-9.3pmol/L  |

| Lipids       |     |     |
|-------------|-----|-----|
| Total Cholesterol | 13.36 mmol/L |
| Triglycerides   | 6.55 mmol/L  |
| LDL-Cholesterol  | 9.19 mmol/L  |
| HDL-Cholesterol  | 0.68 mmol/L  |

| Complete blood count |     |     |
|----------------------|-----|-----|
| WBC                  | 20.56 | 6-18x10⁹L |
| Hb                   | 8.0  | 10.7-13g/L |
| MCV                  | 93.3 | 70-86fl |
| Haematocrit          | 0.255| 0.32-0.420|
| Platelet             | 656  | 180-440x10⁹L |
| Iron                 | 4.9  | 9.0-21.5 umol/L |
| Transferrin          | <0.70 | 1.49-3.82 g/L |
| Ferritin             | 34   | 36-84 ug/L |

TSH: Thyroid Stimulating Hormone; FT4: Free Thyroxine; FT3: Free Triiodothyronine; PTH: Parathormone; WBC: White Blood Cells; Hb: Haemoglobin; MCV: Mean Corpuscular Volume; Platelet: Platelet Count; Iron: Iron Level; Transferrin: Transferrin Level; Ferritin: Ferritin Level.
haplotype analysis is often required and should therefore be considered early on.

- In congenital nephrotic syndrome, thyroid hormones and Vitamin D status must be evaluated.
- Renal biopsy is mandatory in CNS to further differentiate and support diagnosis and to better estimate the severity of clinical progression regarding renal failure.

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