Congenital nephrotic syndrome

Hannu Jalanko

Abstract Congenital nephrotic syndrome (CNS) is a rare kidney disorder characterized by heavy proteinuria, hypoproteinemia, and edema starting soon after birth. The majority of cases are caused by genetic defects in the components of the glomerular filtration barrier, especially nephrin and podocin. CNS may also be a part of a more generalized syndrome or caused by a perinatal infection. Immunosuppressive medication is not helpful in the genetic forms of CNS, and kidney transplantation is the only curative therapy. Before the operation, management of these infants largely depends on the magnitude of proteinuria. In severe cases, daily albumin infusions are required to prevent life-threatening edema. The therapy also includes hypercaloric diet, thyroxin and mineral substitution, prevention of thrombotic episodes, and prompt management of infectious complications. The outcome of CNS patients without major extrarenal manifestations is comparable with other patient groups after kidney transplantation.

Keywords Proteinuria - Nephrotic syndrome - Nephrin - Podocin - Podocyte - Kidney transplantation

Introduction

Congenital nephrotic syndrome (CNS) is defined as heavy proteinuria starting within three months after birth. Nephrotic syndrome (NS) appearing later during the first year (4–12 months) is defined infantile, and NS manifesting thereafter is called childhood NS [1, 2]. These definitions have been used for decades in order to help the clinical diagnosis, although recent findings indicate that NS caused by a particular gene defect can manifest at various ages, questioning the rationale of the classification. Since the overall etiology, clinical features and management of CNS, however, are different from the more common forms of childhood NS, the terminology still seems warranted (Table 1).

Glomerular filtration barrier

The cardinal feature of CNS is the extensive leakage of plasma proteins into urine. In most cases, this is caused by mutations in genes encoding for structural or regulatory proteins of the kidney filtration barrier located in the glomerular capillary wall [3–5]. This filter is composed of three layers: fenestrated endothelium, glomerular basement membrane (GBM), and epithelial cell (podocyte) layer with distal foot processes and interposed slit diaphragms (SD) (Fig. 1). The barrier is an effective size- and charge-selective molecular sieve, and normally only water and small plasma solutes pass through it. The flux of albumin and larger plasma proteins is restricted by the GBM and especially SD, so that the protein content of the ultrafiltrate (primary urine) reaching the Bowman space is very low. The GBM’s role in glomerular permselectivity has been debated recently, but it is now known that proteinuria can be caused by a primary defect in either SD or GBM.

The GBM is a well-known protein network formed by type IV collagen, laminin, nidogen, and negatively charged proteoglycans. On the other hand, the precise molecular structure of the SD is still unresolved. Recently identified podocyte proteins, such as nephrin, Neph1, Neph2, FAT1,
also been reported [33]. CMV infection is common during the first weeks of life, and detection of this virus in an infant with NS does not exclude an underlining genetic defect. This should be searched especially if ganciclovir therapy is not helpful. In addition to infections, CNS has been associated with maternal systemic lupus erythematosus and more recently with neonatal alloimmunization against neutral endopeptidase present on podocytes [34].

Diagnosis of CNS

In severe forms of CNS, generalized edema, urinary protein $> 20$ g/L, and serum albumin level $< 10$ g/L can be detected in the newborn period. The amount of proteinuria, however, varies in different entities, and the clinical signs may not be evident during the first weeks of life. Also, the true magnitude of proteinuria may be detectable only after partial correction of hypoproteinemia by albumin infusions. Small amounts of red blood cells and leucocytes are often present in urine. Serum creatinine and urea levels are variable. Renal function remains quite normal for the first months in NPHS1, but in other forms, kidney failure may develop faster. Blood pressure values can be low due to hypoproteinemia or elevated if renal failure is already present.

In newborns, the placental weight $> 25\%$ of birth weight is present in NPHS1 but may be seen in other forms of CNS [14]. The kidneys may be of normal size or larger than normal in ultrasound scanning, and the renal cortex is often hyperechogenic. Search for possible nonrenal malformations is important, especially since they may give clues to the etiologic diagnosis. These include genital abnormalities (WT1), eye defects (LAMB2), and neurological disorders (Mowat–Galloway). Cardiac evaluation often reveals ventricular hypertrophy but no structural defects.

Renal biopsy does not reveal the etiology of CNS. As pointed out, the genetic defects may cause several types of glomerular lesions, such as mesangial expansion, FSGS, MCNS, and DMS, and the findings overlap in different entities. Also, the nonglomerular findings, such as tubular dilatations and interstitial fibrosis and inflammation, can be seen in all forms of proteinuric diseases. Thus, the indications for renal biopsy are not quite clear. The knowledge of severity of glomerular sclerosis and interstitial fibrosis may help in the assessment of treatment strategies. On the other hand, the lesions are focal, and the biopsy findings may be misleading. If immunohistochemistry for nephrin and podocin is available, analysis of their expression in a biopsy sample is useful. Total lack of either protein speaks for a severe disorder not responding to antiproteinuric therapy.

Genetic analysis is the method of choice for precise CNS diagnosis. The knowledge of etiology helps in assessing management and prognosis, in follow-up for possible associated symptoms, and in genetic counseling of the family. Analysis of NPHS1 and NPHS2 mutations is warranted in all CNS patients. These analyses are commercially available in Athena Diagnostics (www.athenadiagnostics.com). If no mutations are detected in these genes or if clinical findings speak for mutations in WT1 or LAMB2 gene, analysis of these genes can be obtained at research laboratories.

Prenatal diagnosis in families with a known risk for CNS should be based on genetic testing whenever possible. The results can be obtained fast if the mutations are known in advance. In case of no family history or if the mutations in the affected child were not identified, prenatal genetic testing is a challenge, since sequencing the NPHS1 (29 exons) and NPHS2 (eight exons) genes is time consuming and usually not possible within the short time frame available. NPHS1 especially can still be suspected prenatally based on elevated alpha-fetoprotein (AFP) levels in maternal serum and amniotic fluid. If the AFP concentration in amniotic fluid is very high and the ultrasound examination does not reveal fetal anencephaly or other malformations, NPHS1 is a probable diagnosis. However, heterozygous fetal carriers of NPHS1 gene mutations may have temporarily elevated AFP levels in amniotic fluid and maternal serum, and repeated measurement of amniotic fluid AFP before the 20th week of pregnancy is recommended in cases with high AFP levels [35].

CNS management

In contrast to most cases of childhood NS, therapy with steroids or other immunosuppressive drugs does not bring CNS into remission. The goals of therapy during the first months are to control edema and possible uremia, prevent and treat complications such as infections and thromboses, and provide optimal nutrition so that the child grows and develops as normally as possible (Table 2). In most cases, kidney transplantation is the only curative treatment.

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Congenital nephrotic syndrome, Finnish type

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Abstract
The congenital nephrotic syndrome of the Finnish type is a hereditary disease with autosomal recessive inheritance. The gene frequency is approximately 1/200 in Finland. The disease is caused by mutations in the gene for nephrin, which is a key component of the glomerular ultrafilter, the podocyte slit diaphragm. The first symptom is fetal proteinuria, which leads to a more than 10-fold increase of the alpha-fetoprotein concentration in amniotic fluid and a parallel but smaller rise in the maternal serum level. At birth, one notes a large placenta, whose weight exceeds by 25% the birth weight of the often-premature child. The nephrotic syndrome starts very early and is severe. Histologically, microcytic dilatations of the tubules are seen while glomeruli are only slightly modified. The nephrotic syndrome is resistant to corticosteroids and immnosuppressants. Infectious and nutritional complications are common, due to the massive protein loss. If the child survives, renal function deteriorates justifying initiation of dialysis/transplantation between the ages of 5 and 8 years. The disease does not recur in the graft.

Keywords
Congenital nephrotic syndrome of the Finnish type, autosomal recessive disease, renal failure, corticoresistance.

Disease name and synonyms
Congenital nephrotic syndrome of the Finnish type (CNF)

Definition
The term congenital nephrotic syndrome refers to disease which is present at birth or within the first 3 months of life. Later onset, between three months and 1 year of age, is called infantile nephrotic syndrome. Most of these children have a genetic basis for the renal disease and a poor outcome. The precise diagnosis of the glomerular lesion is based on clinical, laboratory and histological criteria. The congenital nephrotic syndrome of Finnish type (CNF) is an autosomal recessive disease responsible for severe nephrotic syndrome with proteinuria beginning in utero.

Incidence
CNF is most common in Finland, with an incidence of 1.2 per 10,000 live births [1,2]. It has, however, been described in various ethnic groups throughout the world [3,4].

Clinical description
Most infants with CNF are born prematurely (35-38 weeks), with a low birth weight for gestational age. The placenta is enlarged, being representing than 25% of the total birth weight.
Fetal distress is common and the cranial sutures are widely separated due to delayed ossification. Infants often have a small nose and low ears. Flexion deformities of the hips, knees and elbows are thought to be secondary to the large placenta.

Edema is present at birth or appears during the first week of life in half of the cases. Severe nephrotic syndrome with marked ascites is always present by 3 months. The proteinuria is highly selective early during the course of the disease and hematuria is uncommon, reflecting the lack of inflammation in the glomeruli. The urinary protein losses are accompanied by profound hypoalbuminemia and severe hypogammaglobulinemia due in part to loss of filtering selectivity as the disease progresses. As a result of these changes, nutritional status and growth are poor, and affected infants are highly susceptible to bacterial infections (peritonitis, respiratory infections) and to thromboembolic complications due to the severity of the nephrotic syndrome. Hypothyroidism due to urinary losses of thyroxine-binding proteins is also common. The blood urea nitrogen and creatinine concentrations are initially normal. Renal ultrasonography shows enlarged, hyperechogenic kidneys without normal corticomedullary differentiation.

End-stage renal failure invariably occurs between 3 and 8 years of age. Prolonged survival is possible with aggressive supportive treatment, including dialysis and renal transplantation.

**Histology**

Light microscopy studies of renal biopsy specimens obtained early during the course of the disease show mild mesangial hypercellularity and increased mesangial matrix in the glomeruli [3,5]. No immune deposits are detected by immunofluorescence studies. Over time, the mesangial matrix increases, accompanied by progressive glomerulosclerosis. Tubulointerstitial changes are prominent in CNF. Irregular microcystic dilatation of proximal tubules is the most striking feature; however, this change is not specific and is not seen in all patients [6]. Later, interstitial fibrosis, lymphocyte and plasma cell infiltrations, tubular atrophy, and periglomerular fibrosis develop in parallel with sclerosis of the glomeruli.

**Treatment**

The nephrotic syndrome in CNF is always resistant to corticosteroids and immunosuppressive drugs, since this is not an immune disease. Furthermore these drugs may be harmful due to the already high susceptibility to infection, as confirmed by a retrospective study on 21 infants with CNF, who suffered of (63 verified and 62 suspected) septic episodes over a mean follow-up period of 1 year [7]. Standard conservative treatment includes daily or every other day albumin infusion, gamma globulin replacement, nutrition with a high-protein, low-salt diet, vitamin supplement and thyroxine replacement, and prevention of infections and thrombotic complications. Nutrients are given by tube feeding or by parenteral alimentation.

However, the rate of intercurrent complications remains high; growth and development are usually retarded. As a result, some patients may require bilateral nephrectomy to prevent continued massive protein losses even before renal failure develops. Dialysis is then performed until the patient reaches a weight of 8-9 kg, at which time, renal transplantation can be considered [8,9]. No recurrence of the nephrotic syndrome has been observed after transplantation.

A possible medical alternative to nephrectomy has been described in two children. The combination of an angiotensin-converting enzyme inhibitor and indomethacin therapy, both of which should lower intraglomerular pressure, markedly reduced and led to striking improvement of nutritional status and growth [10].

**Etiology**

CNF is inherited as an autosomal recessive trait, with both sexes being equally involved. Heterozygous individuals have no manifestations of the disease. It has been advanced that proteinuria in CNF results from an inherited error in the structure of the glomerular capillary filter. The abnormal gene has been localized to the long arm of chromosome 19 in both Finnish and non-Finnish families [11-13]. The defective gene responsible for CNF, NPHS1 was recently cloned [14]. The gene encodes for a transmembrane protein, named nephrin, which is a member of the immunoglobulin family of cell-adhesion molecules. Nephrin is specifically located at the slit diaphragm of the glomerular podocytes; which could explain the absence of slit diaphragms and foot processes in patients with CNF who have a mutant nephrin protein [15,16].

In the original report, four different mutations in this gene were found to segregate with the disorder in affected Finnish families [14]. In another study, 32 novel mutations in the nephrin gene were discovered in patients elsewhere in Europe and North America, but no abnormalities were found in seven affected individuals (including the 5’ flanking region) [17]. These patients may have mutations elsewhere in the promoter, intron areas, or a gene encoding...
Fetal distress is common and the cranial sutures are widely separated due to delayed ossification. Infants often have a small nose and low ears. Flexion deformities of the hips, knees and elbows are thought to be secondary to the large placenta. Edema is present at birth or appears during the first week of life in half of the cases. Severe nephrotic syndrome with marked ascites is always present by 3 months. The proteinuria is highly selective early during the course of the disease and hematuria is uncommon, reflecting the lack of inflammation in the glomeruli. The urinary protein losses are accompanied by profound hypoalbuminemia and severe hypogammaglobulinemia due in part to loss of filtering selectivity as the disease progresses. As a result of these changes, nutritional status and growth are poor, and affected infants are highly susceptible to bacterial infections (peritonitis, respiratory infections) and to thromboembolic complications due to the severity of the nephrotic syndrome. Hypothyroidism due to urinary losses of thyroxine-binding proteins is also common. The blood urea nitrogen and creatinine concentrations are initially normal. Renal ultrasonography shows enlarged, hyperechogenic kidneys without normal corticomedullary differentiation. End-stage renal failure invariably occurs between 3 and 8 years of age. Prolonged survival is possible with aggressive supportive treatment, including dialysis and renal transplantation.

**Histology**

Light microscopy studies of renal biopsy specimens obtained early during the course of the disease show mild mesangial hypercellularity and increased mesangial matrix in the glomeruli [3,5]. No immune deposits are detected by immunofluorescence studies. Over time, the mesangial matrix increases, accompanied by progressive glomerulosclerosis. Tubulointerstitial changes are prominent in CNF. Irregular microcystic dilatation of proximal tubules is the most striking feature; however, this change is not specific and is not seen in all patients [6]. Later, interstitial fibrosis, lymphocyte and plasma cell infiltrations, tubular atrophy, and periglomerular fibrosis develop in parallel with sclerosis of the glomeruli.

**Treatment**

The nephrotic syndrome in CNF is always resistant to corticosteroids and immunosuppressive drugs, since this is not an immune disease. Furthermore these drugs may be harmful due to the already high susceptibility to infection, as confirmed by a retrospective study on 21 infants with CNF, who suffered of (63 verified and 62 suspected) septic episodes over a mean follow-up period of 1 year [7]. Standard conservative treatment includes daily or every other day albumin infusion, gamma globulin replacement, nutrition with a high-protein, low-salt diet, vitamin supplement and thyroxine replacement, and prevention of infections and thrombotic complications. Nutrients are given by tube feeding or by parenteral alimentation. However, the rate of intercurrent complications remains high; growth and development are usually retarded. As a result, some patients may require bilateral nephrectomy to prevent continued massive protein losses even before renal failure develops. Dialysis is then performed until the patient reaches a weight of 8-9 kg, at which time, renal transplantation can be considered [8,9]. No recurrence of the nephrotic syndrome has been observed after transplantation.

A possible medical alternative to nephrectomy has been described in two children. The combination of an angiotensin-converting enzyme inhibitor and indomethacin therapy, both of which should lower intraglomerular pressure, markedly reduced and led to striking improvement of nutritional status and growth [10].

**Etiology**

CNF is inherited as an autosomal recessive trait, with both sexes being equally involved. Heterozygous individuals have no manifestations of the disease. It has been advanced that proteinuria in CNF results from an inherited error in the structure of the glomerular capillary filter. The abnormal gene has been localized to the long arm of chromosome 19 in both Finnish and non-Finnish families [11-13]. The defective gene responsible for CNF, *NPHS1* was recently cloned [14]. The gene encodes for a transmembrane protein, named nephrin, which is a member of the immunoglobulin family of cell-adhesion molecules. Nephrin is specifically located at the slit diaphragm of the glomerular podocytes; which could explain the absence of slit diaphragms and foot processes in patients with CNF who have a mutant nephrin protein [15,16].

In the original report, four different mutations in this gene were found to segregate with the disorder in affected Finnish families [14]. In another study, 32 novel mutations in the nephrin gene were discovered in patients elsewhere in Europe and North America, but no abnormalities were found in seven affected individuals (including the 5’ flanking region) [17]. These patients may have mutations elsewhere in the promoter, intron areas, or a gene encoding
Nephrotic Syndrome, Type 1

http://www.cags.org.ae/FMPro?-DB=ctga.fp5&-Format=ctga/ctga_detail.html&-RecID=34351&-Find

Alternative Names
NPHS1
Finnish Congenital Nephrosis
CNF
Nephrotic Syndrome, Congenital

WHO International Classification of Diseases
Diseases of the genitourinary system > Glomerular diseases

OMIM Number
256300

Gene Map
Locus
19q13.1
Mode of Inheritance

Autosomal recessive

Description

Finnish congenital nephrosis is a very rare autosomal recessive form of nephrotic syndrome. It is seen more commonly in families of Finnish descent, with an incidence of 1:10,000 births, but can affect every race, with a considerably lower frequency. It is a distinct clinical entity involving massive proteinuria, prematurity, large placenta, hypoproteinemia and marked edema. The typical histological findings of Finnish congenital nephrosis kidneys are dilated proximal tubules, mesangial hypercellularity, and glomerular fibrosis and sclerosis. This progressive disease leads to death in the first two years of life; the only curative therapy is bilateral nephrectomy followed by renal transplantation.

Molecular Genetics

Finnish congenital nephrosis has been found to be caused by mutation in the NPHS1 gene, spanning 26 kb and contains 29 exons. The NPHS1 is mapped to chromosome 19q31.1 between marker D19S1175 and the APLP1 gene. NPHS1 encodes a podocyte-specific type I membrane protein, nephrin, which belongs to the large immunoglobulin (Ig)-like superfamily. The protein has 1,241 amino acid residues, and extracellular part consisting of eight Ig motifs followed by a fibronectin type III domain, a short transmembrane region and a cytoplasmic C-terminal part. Over 50 different mutations, including deletions, insertions, nonsense, missense, splice site and promoter mutations, have been identified both in Finnish and non-Finnish patients with congenital nephrotic syndrome.

Epidemiology in the Arab World

Jordan

Hamed and Shomaf (2001) reviewed the clinical characteristics, pathologic findings, and results of medical management in 30 infants who presented to Jordan University Hospital with congenital nephrotic syndrome in the years 1989 to 1999. Most patients (80%) had parents who were consanguineous. Most patients (80%) were born premature, with an average gestational age of 36 weeks. Most infants (77%) presented the nephrotic syndrome in the first three months of life and 26 (87%) had significant growth retardation. Twenty-five verified episodes of serious bacterial infections occurred in 18 patients. Antibiotic


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Gross proteinuria post transplant in a child with nephrotic syndrome of the Finnish type—mechanical vs immunological pathogenesis

Fleur Lorton1, Jérome Raynot1, Béatrice Letavernier1, Arnaud Isapof1, Hanna Debiec2, Monique Pressac3, Georges Deschênes1, Marion Lenoir4, Laurence Ross-Cerdan4, Christine Grapin5, Albert Bensman1 and Tim Ulinski1,6

1Department of Pediatric Nephrology and 2Department of Biochemistry, 3INSERM U489, 4Department of Radiology and 5Department of Pediatric Surgery, Hôpital Armand Trousseau, AP-HP and 6INSERM U515, Paris, France

Keywords: alloimmunization; nephrotic syndrome of the Finnish type; nutcracker syndrome; proteinuria; renal vein compression

Introduction

Nephrotic syndrome of the Finnish type (NSF) is an autosomal-recessive disorder, characterized by massive proteinuria in utero and nephrosis at birth. NSF is caused by mutations in the NPHS1 gene which codes for nephrin [1], a cell adhesion molecule specifically localized at the slit diaphragm of the glomerular basement membrane [2]. Mutations, such as Finmajor or Finminor result in a premature STOP codon and in nonsense mutation, respectively, responsible for the absence of the protein, and generally associated with a more severe phenotype [3]. Conservative treatment is based on supplementation of albumin, immunoglobulin, l-thyroxin and adequate nutrition. Renal transplantation (Tx) after bilateral nephrectomy is a successful long-term treatment option.

Nephrotic proteinuria may recur after Tx as a result of alloimmunization against normal nephrin in the kidney graft, requiring increased immunosuppression and plasma exchanges [4,5].

We report here a recurrence of massive proteinuria post transplant in a child with NSF, which occurred exclusively in night-time urine samples. This phenomenon cannot be explained by immunological mechanisms.

Case

We report a 17-month-old female of Portuguese origin with NSF. Sequencing of the 29 exons of the NPHS1 gene revealed a compound heterozygote state: a three base pair deletion (172delT) and a missense mutation (S366R) which have been described previously [6], confirming the diagnosis of NSF as well as a polymorphism (R408Q). Conservative treatment and nutritional supplementation were conducted, as reported by Holmberg et al. [7].

Haemodialysis was started after bilateral nephrectomy at the age of 10 months. Histological examination of the native kidneys showed a dilation of proximal tubules, partial glomerulosclerosis and interstitial hypercellularity.

At 17 months (weight 10 kg, length 76 cm), she received a living related transplant from her father. The transplant measured 11.5 x 5 cm without vascular anomalies. Implantation of the graft was performed through an extraperitoneal incision in the right iliac fossa. Surgery and the immediate post-Tx period were uneventful. Post-Tx urine production was prompt, serum creatinine levels decreased rapidly and reached 15 mmol/l on day 3 post Tx. Sonographic Doppler investigation was normal on days 1 and 11 post Tx. She received a standard immunosuppressive regimen including basiliximab induction, ciclosporin A, mycophenolate mofetil and prednisone.

On day 5 post Tx, proteinuria recurred (0.86 g/l) in the morning collection and reached 10 g/l on day 10 post Tx. Proteinuria almost disappeared after day-time (0.2 g/l). Serum creatinine (37 μmol/l) increased moderately between days 6 and 15 post Tx. Concomitant microscopic haematuria (10–50 x 10^3 red blood cells/ml) was present but remained stable over the first 2 weeks post Tx. Similar changes between gross proteinuria after night-time and almost normal proteinuria after daytime persisted for 11 days (Figure 1).

Electrophoresis of urinary proteins of night-time urine samples revealed glomerular proteinuria (albumin, α2 macroglobulin and haptoglobin) whereas merely physiological proteinuria was found in daytime urine samples.
Case Report

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Case Report

Congenital Nephrotic Syndrome in a Nigerian Infant

Adekamni2007 (condensed)

by A. Folashade Adekanmbi, Olusoga B. Ogunfowora, Tinuade A. Ogunlesi, Moji M. Ogundeyi, Adebiyi O. Olowu and S. Adetoun Sotimehin
Olabisi Onabanjo University Teaching Hospital Sagamu, Nigeria

Summary

Although nephrotic syndrome is common among African children, the congenital forms of it are rare. This report describes the clinical presentation of a 6-week-old Nigerian infant who presented with marked pedal oedema, heavy proteinuria and serum hypoproteinaemia leading to the diagnosis of congenital nephrotic syndrome. This case is being reported to create awareness about this condition and to highlight diagnostic and therapeutic challenges.

Introduction

Congenital nephrotic syndrome (CNS) is a clinically and genetically heterogeneous disease caused by mutation in the genes NPHS1, NPHS2 and WT1 [1]. It may be inherited, sporadic, acquired or occur as part of a general malformation syndrome [2]. Consanguinity and familial mode of inheritance have also been described [3]. This clinical condition can be diagnosed in utero in the presence of elevated maternal serum alpha fetoprotein [4]. It could present within the first month of life or as late as 1 year of life when it is referred as infantile nephrotic syndrome [5]. Although, the incidence is reported to be 1.2 : 10 000 in Finland, it is undetermined in various other ethnic groups across the world [6]. No sex pre-dilection is known.

The affected infants are usually low birth weight with large placenta and maternal toxæmia [7]. Hypothyroidism, pyloric stenosis and oesophageal reflux are associated clinical findings in CNS [6, 8] and it may also be complicated by electrolyte imbalance, renal failure, infections, thrombosis and growth retardation [6, 8, 9]. The condition is often unresponsive to conventional palliative therapies [6, 8–10], and dialysis and renal replacement therapy (RRT) are often required [6, 9, 11]. Unfortunately, the prognosis in CNS is reportedly poor with death occurring within few months of life or sometimes at about 5 years of age [2, 6, 8, 9]. Recurrence of proteinuria in transplanted kidneys had also been reported [12, 13].

This case is reported to create awareness about this clinical entity in this part of the world especially among preterm infants.

Case Report

C.P. was a 44-day-old female infant, first of a set of twins, who was referred to our hospital on account of vomiting, refusal of feeds and fever of 12 h duration. She was delivered at 30 weeks gestation to a severely pre-eclamptic, 34-year-old para 2 mother and a 55-year-old father, both of whom were from a riverine part of Nigeria but were not related. The infant’s birth weight was 1500 g but the Apgar scores were not known. She had a neonatal seizure at the age of 2 weeks, but further details of this were not presented by the referring physician. She was also transfused with sedimented cells at the 39th day of life for severe anaemia at the referral centre.

At presentation at our hospital, she was acutely ill-looking and febrile with a temperature of 39°C. She was severely pale but anicteric. There was bilateral pitting pedal oedema extending up to the pelvic region (Fig. 1). She weighed 1500 g. She was conscious but irritable with occipitofrontal circumference (OFC) of 33 cm (Fig. 2). There was generalized sutural separation with wide fontanelles but no ‘setting-sun’ appearance of the eyes.

She was dyspnoeic and tachypnoeic with a respiratory rate of 60 cycles per minute. The breath sounds were vesicular with no adventitious sounds. Her heart rate was 128 beats per minutes and heart sounds were normal. Abdominal examination revealed no ascites, but the right kidney was ballotable.

The results of laboratory investigations are shown in Table 1. Transfontanelle ultrasound scan revealed generalized ventriculomegaly (Fig. 3). Blood culture and cerebrospinal fluid culture yielded no growth.
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Case Report

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Congenital Nephrotic Syndrome

Radi M. A. Hamed

Department of Pediatrics, Jordan University Hospital

ABSTRACT. The congenital nephrotic syndrome (CNS) is an uncommon disorder with onset of the nephrotic syndrome usually in the first three months of life. Several different diseases may cause the syndrome. These may be inherited, sporadic, acquired or part of a general malformation syndrome. The clinical course is marked by failure to thrive, recurrent life threatening bacterial infections, and early death from sepsis and/or uremia. A characteristic phenotype may be seen in children with CNS. The majority of reported cases of CNS are of the Finnish type (CNF). Although the role of the glomerular basement membrane has been emphasized as the barrier for retaining plasma proteins, recent studies have clearly shown that the slit diaphragm is the structure most likely to be the barrier in the glomerular capillary wall. The gene (NPHS1) was shown to encode a novel protein that was termed nephrin, due to its specific location in the kidney filter barrier, where it seems to form a highly organized filter structure. Nephrin is a transmembrane protein that probably forms the main building block of an isoporous zipper-like slit diaphragm filter structure. Defects in nephrin lead to the abnormal or absent slit diaphragm resulting in massive proteinuria and renal failure.

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Introduction

The congenital nephrotic syndrome (CNS) is an uncommon disorder. The designation CNS identifies infants with onset of the nephrotic syndrome usually in the first three months of life, and is characterized by heavy proteinuria, hypoproteinemia, hyperlipidemia, and edema. Although uncommon, it continues to be a diagnostic and therapeutic challenge for the pediatrician. Several different diseases may cause the syndrome. These may be inherited, sporadic, acquired or part of a general malformation syndrome. Affected fetuses are commonly born prematurely and small for dates.

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glomeruli, thickening of the glomerular capsule and a moderate degree of interstitial inflammatory reaction.

In Mercury Intoxication, light microscopy reveals no abnormalities in the glomeruli.

C. Congenital Nephrosis Associated with Other Syndromes

1. Tricho-rhino-phalangeal syndrome type II (Langer-Giedion syndrome). 30
2. 46XY gonadal dysgenesis. 31 Reports of CNS and XY Gonadal dysgenesis in phenotypic females without genital ambiguity are extremely rare in the literature.
3. Denys-Drash syndrome 32,33 is a triad of nephropathy, male pseudohermaphroditism, and Wilms tumor. Patients with XY gonadal dysgenesis and renal disease have been reported with or without Wilms tumor. The genital malformations in XY gonadal dysgenesis are various. The external genitalia are often ambiguous.
4. Lipoprotein glomerulopathy. 34
5. Epidermolysis bullosa. 35
6. Diffuse mesangial sclerosis and bilateral cataract. 36
7. Nail-Patella Syndrome (Hereditary Onych-Osteodysplasia) 37 is an autosomal-dominant disease characterized by dystrophic nails, absence of one or both patellas, and an assortment of other skeletal abnormalities.
8. Lowe’s Syndrome (Oculo-Cerebro-Renal Syndrome) is a sex-linked recessive disease, characterized by congenital glaucoma, cataracts, growth retardation, mental deficiency, hypotonia, metabolic acidosis, generalized amino-aciduria, proteinuria, and rickets. 38 The metabolic abnormalities agree with the pathological changes in the kidney. It usually takes from a few months to a year to develop the characteristic renal symptoms and lesions, and they can be demonstrated in only a few before the age of three months. The renal lesions may be in the form of severe generalized and global glomerular changes of mesangial cellular proliferation, and a slightly increased amount of mesangial matrix.

D. Sporadic CNS of Childhood Type

a. Minimal change nephrotic syndrome (MCNS). The histology of MCNS is the same regardless of time of onset and shows adherence of the foot processes of podocytes on electron microscopy. Infants with MCNS can have a steroid-responsive or steroid-resistant disease. Unlike infants with other types of CNS, those with minimal changes may benefit from medical treatment; however the prognosis of these infants does not seem as good as the older children.

b. Mesangial proliferative glomerulonephritis (MesPGN). In infants, light microscopy shows prominent diffuse mesangial cellular proliferation and more or less increased amounts of mesangial matrix without segmental sclerosis. These changes including adherence of the foot processes of podocytes, are also seen by electron microscopy. Infants with MesPGN may be steroid-responsive but are more likely to be steroid-resistant.

c. Sporadic (non-familial) Focal Segmental Glomerulosclerosis (FSGS). Few cases of CNS have been reported as this type in the literature. 10

Discussion

Although uncommon, CNS continues to be a diagnostic and therapeutic challenge for the pediatrician. The nephritic syndrome presenting in children before the age of three months has been described well in the
Abstract  We reviewed the medical records of seven children with congenital nephrotic syndrome (CNS) treated by unilateral nephrectomy, captopril, and indomethacin since 1990. Clinical response to the treatment was analyzed using the Students’ t-test. After a median period of 54 months (range 36–88 months) follow-up, five patients were alive at a median age of 74 (range 43–88) months. Median (range) plasma albumin rose from 11 (6–17) g/l at the start of treatment to 18 (15–22) g/l and 21 (18–25) g/l after 6 and 12 months treatment, respectively ($P=0.001$ and $P=0.0006$). Albumin infusions per patient per month decreased from 7 (0–18) to 0 (0–30) in the 6 months post treatment ($P=0.017$). The median (range) height standard deviation scores at 12 months and 30 months from onset of treatment were $-1.56$ ($-2.96$ to $0.41$) and $-1.43$ ($-2.40$ to $0.90$), respectively. In conclusion, management of CNS with captopril and indomethacin therapy in combination with unilateral nephrectomy achieves significant improvements in plasma albumin and reduces the need for albumin infusions and time in hospital, while growth is maintained. Second nephrectomy, dialysis, and transplantation can be delayed until the 3rd year of life or longer.

Keywords  Congenital nephrotic syndrome · Captopril · Indomethacin · Unilateral nephrectomy · Management

Introduction

Congenital nephrotic syndrome (CNS) is difficult to treat because it does not respond to corticosteroids or immunosuppressive drugs. The infant typically requires prolonged hospital admissions and frequent albumin infusions. Recurrent infection, impaired growth and development, and fluid and electrolyte disturbance are common. The conventional approach in patients with Finnish type of CNS is intensive supportive treatment, early bilateral nephrectomy followed by dialysis, and transplantation when the infant reaches about 10 kg in weight [1]. However, dialysis and transplantation in infancy remain technically challenging, with mixed results [2, 3, 4, 5]. The North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) of renal transplantation in children with CNS demonstrated a higher rate of renal graft failure (33%) in these patients than in patients with other primary diseases (23.9%) [5]. Recipient age less than 2 years was a significant predictor of poor graft survival.

Angiotensin-converting enzyme inhibitors (ACEI) and prostaglandin inhibitors have been shown to reduce proteinuria [6, 7]. The effect of prostaglandin inhibitors is maximal within 1–3 days, while ACEI show an optimal effect after 4–8 weeks of treatment. A combination of these drugs was successfully used by Pomeranz et al. [8] in 1995 to reduce proteinuria in two children with CNS of the Finnish type. Good results with this regimen were also reported in children with the diffuse mesangial sclerosis (DMS) type of CNS [9]. Unilateral nephrectomy has also been reported as helpful in reducing proteinuria in children with CNS [10, 11].

Since 1990, we have treated infants with CNS by early unilateral nephrectomy, plus combined captopril and indomethacin therapy. We analyzed the clinical response of these children with regard to the patient’s general clinical condition and growth, requirement for albumin infusions and hospitalization, plasma albumin concentration, and renal function.

Patients and methods

The study patients comprised seven consecutive infants with CNS treated at Guy’s Hospital, London, since 1990. Five patients came from four Asian families, each with consanguineous parents (patients 1, 3, 6, 5, and 7). There were four males and three females, with a median gestational age of 36 weeks (range 33–40 weeks) and a median birth weight of 2.52 kg (range 1.51–3.30 kg). The diagnosis of CNS was based on the onset of generalized edema and ascites within the first 3 months of life, massive proteinuria, and hypoalbuminemia (<25 g/l). Congenital infection was excluded by

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serological tests in all children. Histological diagnosis was based on examination of open renal biopsy, or of nephrectomy specimen.

All patients received a high-calorie (130 kcal/kg per day) and high-protein (2–3 g/kg per day) diet, prophylactic phenoxymethylpenicillin, and furosemide. Additional treatment with spironolactone was used in patient 5. All patients received albumin infusions, which were given as a 20% solution at a dose of 1 g/kg ideal body weight over 4 h, followed by intravenous furosemide (0.5–1 mg/kg) when needed. The indications for albumin infusions were increasing edema and/or clinical evidence of hypovolemia. One infant (patient 4) received prednisolone as a 4-week course starting at the age of 6 weeks. Treatment with captopril and indomethacin was commenced at a median age of 2.3 months (range 0.2–5.2 months), and was given prior to unilateral nephrectomy in six children and 2 weeks after unilateral nephrectomy in one child (patient 2). Captopril was started at a low median dose of 0.3 (range 0.3–0.75) mg/kg per day divided in three doses and gradually increased to a maximum median dose of 3.4 (range 1.0–6.0) mg/kg per day. The initial median dose of indomethacin was 0.8 (range 0.3–1.2) mg/kg per day divided in two doses given to a maximum median dose of 2.8 (range 1.2–3.0) mg/kg per day.

Following captopril and indomethacin treatment, clinical symptoms persisted in five patients who continued to need frequent albumin infusions and inpatient care. For this reason, these patients underwent subsequent unilateral nephrectomy at a median age of 3.0 (range 2.3–6.2) months. Patient 2 underwent unilateral nephrectomy at the age of 2.1 months. Although her clinical condition improved after the procedure, she still needed albumin infusions every 2nd day. Captopril and indomethacin treatment was initiated at 2.3 months of age. Patient 4 responded very well to captopril and indomethacin treatment; he underwent subsequent unilateral nephrectomy at 31 months of age. Histological diagnosis was based on examination of open renal biopsy, or of nephrectomy specimen

We analyzed the clinical response after captopril, indomethacin, and unilateral nephrectomy with regard to the patient’s general clinical condition and growth, requirement for 20% albumin infusions and hospitalization, plasma albumin concentration, and glomerular filtration rate (GFR) calculated using the Schwartz formula corrected for infants [12]. Growth was assessed by height standard deviation scores. Statistical analysis was performed using the Students’ t-test. Data were expressed as median values and range.

**Results**

The median age at the time of diagnosis was 2.0 weeks (range 1.0–5.0 weeks) (Table 1). All patients presented with gross peripheral edema and ascites and had massive proteinuria, up to 40 g/24 h. The initial median plasma albumin was 11 g/l (range 6–17 g/l). Histology of the nephrectomy specimens in five children was compatible with CNS of the Finnish type, and histological diagnosis in one child was DMS. Patient 6 who was diagnosed at 3 weeks of age had histological changes that were not typical of either Finnish type or DMS type. Renal biopsy showed partial failure of the development of glomeruli and tubules, with slight tubular dilatation ascribed to hyaline cast formation.

Following captopril and indomethacin administration combined with unilateral nephrectomy, edema and ascites decreased significantly in all seven patients. Six months after treatment, only two patients had slight peripheral edema (patients 4 and 6). Diuretic requirement decreased in all patients and was stopped in two (patients 2 and 5). Spironolactone was stopped in patient 5.

Patients were followed for 36–88 months (median 54 months). Plasma albumin levels at diagnosis, start of treatment, and every 6 months from starting treatment are shown in Fig. 1. Compared with the level at the start of treatment (median 11 g/l, range 6–17 g/l), there was a significant increase at 6 months (median 18 g/l, range 15–22 g/l) and 12 months (median 21 g/l, range 18–25 g/l).

**Table 1** Clinical and laboratory findings in seven children with congenital nephrotic syndrome (CNS) treated with captopril, indomethacin and unilateral nephrectomy. (BW body weight, GA gestational age, DMS diffuse mesangial sclerosis, Rx age when treatment with captopril and indomethacin was started, UNx unilateral nephrectomy, BNx remnant nephrectomy, PD peritoneal dialysis, Tx transplantation, FU follow-up, GFR glomerular filtration rate)

<table>
<thead>
<tr>
<th>Patient</th>
<th>BW (g)</th>
<th>GA (weeks)</th>
<th>Age at diagnosis (weeks)</th>
<th>Age at Rx (months)</th>
<th>Age at UNx (months)</th>
<th>Age at BNx+PD (months)</th>
<th>Age at Tx (months)</th>
<th>Age at BN (months)</th>
<th>Development</th>
<th>Last FU</th>
<th>Last GFR</th>
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<td>Dead 58</td>
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<td>Normal</td>
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| Patient | First albumin (g/l) | Histology | Age at BN (months) | Age at Tx (months) | Age at UNx (months) | Age at BNx+PD (months) | Age at Rx (months) | Age at UNx (months) | Histology | First albumin (g/l) | Age at BN (months) | Age at Tx (months) | Age at UNx (months) | Age at BNx+PD (months) | Age at Rx (months) | Age at UNx (months) | Histology | First albumin (g/l) | Age at BN (months) | Age at Tx (months) | Age at UNx (months) | Age at BNx+PD (months) | Age at Rx (months) | Age at UNx (months) | Histology |
|---------|---------------------|-----------|---------------------|-------------------|---------------------|-----------------------|-------------------|-------------------|-----------|---------------------|---------------------|-------------------|---------------------|---------------------|-------------------|-------------------|-----------|---------------------|---------------------|-------------------|---------------------|---------------------|-------------------|-------------------|---------------------|-------------------|
| 1       | 10                  | Finnish  | 10                  | 11                | 12                  | 8                     | 6                 | 14                | Finnish   | 11                  | 10                  | 11                | 12                  | 8                    | 6                 | 14                | Finnish   | 11                  | 10                  | 11                | 12                  | 8                    | 6                 | 14                | Finnish   |
| 2       | 11                  | Finnish  | 11                  | 12                | 12                  | 8                     | 6                 | 14                | Atypical  | 14                  | 11                  | 12                | 12                  | 8                    | 6                 | 14                | Atypical  | 14                  | 11                  | 12                | 12                  | 8                    | 6                 | 14                | Atypical  |
| 3       | 12                  | Finnish  | 12                  | 12                | 12                  | 8                     | 6                 | 14                | Finnish   | 11                  | 12                  | 12                | 12                  | 8                    | 6                 | 14                | Finnish   | 11                  | 12                  | 12                | 12                  | 8                    | 6                 | 14                | Finnish   |
| 4       | 8                   | Finnish  | 8                   | 6                 | 8                   | 6                     | 6                 | 14                | Finnish   | 11                  | 8                   | 6                 | 6                    | 6                    | 6                 | 14                | Finnish   | 11                  | 8                   | 6                 | 6                    | 6                    | 6                 | 14                | Finnish   |
| 5       | 6                   | Finnish  | 6                   | 6                 | 6                   | 6                     | 6                 | 14                | Finnish   | 11                  | 6                   | 6                 | 6                    | 6                    | 6                 | 14                | Finnish   | 11                  | 6                   | 6                 | 6                    | 6                    | 6                 | 14                | Finnish   |
| 6       | 14                  | Atypical | 14                  | 14                | 14                  | 14                    | 14                | 14                | Finnish   | 11                  | 14                  | 14                | 14                    | 14                    | 14                | 14                | Finnish   | 11                  | 14                  | 14                | 14                    | 14                    | 14                | 14                | Finnish   |
| 7       | 17                  | Finnish  | 17                  | 17                | 17                  | 17                    | 17                | 17                | Finnish   | 11                  | 17                  | 17                | 17                    | 17                    | 17                | 17                | Finnish   | 11                  | 17                  | 17                | 17                    | 17                    | 17                | 17                | Finnish   |
| Fig. 1  | Individual plasma albumin levels before treatment with captopril, indomethacin, and unilateral nephrectomy (baseline) and every 6 months from starting treatment. *P=0.001 6 months post treatment vs. baseline, **P=0.0006 12 months post treatment vs. baseline
Congenital Nephrotic Syndrome with Adrenal Calcification and Cardiac Malformation

C.K. Indumathi, Chitra Dinakar, Sanjiv Lewin and Kishore D. Phadke

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Abstract. Congenital Nephrotic Syndrome (CNS) with adrenal calcification and CNS with congenital heart disease (CHD) have rarely been reported. However, CNS with both these rare associations has never been previously reported. Here we report a case of CNS with both rare associations, perhaps the first report from India to the best of our knowledge.

CASE REPORT

A four-month-old female, second baby born at term to a second-degree consanguineous couple, presented with the history of progressive abdominal distension of two months duration and symptoms of an acute lower respiratory tract infection. Birth weight was 2.8 Kg. Antenatal, natal and postnatal periods were uneventful.

On examination, she weighed 4.5 Kg. Head circumference was 36.5 cm. She had generalized edema, hypertension (B.P.110/70 mm of Hg), and bronchopneumonia with clinical evidence of patent ductus arteriosus in the form of bounding peripheral pulses and grade IV systolic mumur in the left second and third intercostals spaces. Abdominal examination revealed bilateral palpable kidneys and ascites. External genitalia were normal. There were no signs of intrauterine infections like rash, cataract, microphthalmia, microcornea, choreo-retinitis or hepatosplenomegaly.

Investigation reports were as follows: hemoglobin count 12 gms/dl, total leucocyte count-13,700/mm³ (Polymorphs-70 %, and Lymphocytes-30%), total protein 3.7gm /dl, Serum albumin-1.8 gm /dl, cholesterol-246mg/ dl, Blood Urea-11mg /dl, serum creatinine-0.7mg /dl. Urine analysis revealed protein (++++) RBC of 10-12/HPF and protein creatinine ratio of > 17.5. Serology for TORCH IgM, HBsAg, HIV ELISA and VDRL were negative. Echocardiogram was suggestive of patent ductus arteriosus with a left to right shunt. Abdominal X-ray revealed bilateral adrenal calcification. Abdominal ultrasonogram revealed bilateral symmetrical renomegaly (Right Kidney 8.1 X 3cm, Left Kidney 8.2 X 3.4 cm) with smooth contour. There was loss of corticomedullary differentiation with increased parenchymal echogenicity. There was no evidence of obstructive pathology. There was dense bilateral adrenal calcification measuring 1.8 X...
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Key words: Congenital nephrotic syndrome; Adrenal calcification; Congenital heart disease.

Congenital Nephrotic Syndrome (CNS) is a rare entity of massive proteinuria, severe hypoalbuminemia and oedema presenting within first three months of life. It could be primary as in the case of Finnish type of Nephrotic Syndrome or secondary to intrauterine infections. CNS is rarely associated with adrenal calcification or with congenital heart disease in isolation. The presence of all three associations complicates both the diagnosis and management. Such rare association of CNS with both adrenal calcification and congenital heart disease prompted this case.

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Fig. 1. CT Scan of the abdomen showing right adrenal calcification
1.5 cm. Adrenal glands were normal in size with no suggestion of cysts or tumors. CT Scan abdomen confirmed bilateral adrenal calcifications and renomegaly (Fig 1). Renal biopsy was consistent with a diagnosis of Finnish type of nephrotic syndrome with dilatation of proximal convoluted tubules and minimal proliferation of mesangial cells (Fig 2).

The baby was started on enalapril and indomethacin and discharged with counseling. However she was lost to follow up.

**DISCUSSION**

Congenital Nephrotic Syndrome generally presents with proteinuria, leading to clinical symptoms within first few days to weeks of life. An arbitrary age limit of 3 months has been adopted to separate this entity from the infantile variety manifesting later in first year of life. Finnish nephrotic syndrome has been considered as the prototype of CNS, the incidence being 1:8200 in Finnish population. This is inherited as an autosomal recessive disorder, caused by mutation in the NPHS1 gene located on chromosome 19. NPHS1 gene encodes a protein nephrin which plays an essential role in the normal function of the glomerular filtration barrier. Secondary causes of CNS include intrauterine infections like syphilis, cytomegalovirus, toxoplasmosis, hepatitis B and HIV infection. Nephrotic Syndrome in such cases is generally less severe and associated with other features of intrauterine infections.

Associated adrenal calcification has been reported earlier in a brief series. Adrenal calcification could be idiopathic, secondary to intrauterine infections, (especially toxoplasmosis and cytomegalovirus), Wolman disease, adrenal hemorrhage, adrenal tumours and neuroblastoma. In this case, TORCH IgM was negative.

CT abdomen ruled out neuroblastoma and adrenal tumours. Wolman disease was also ruled out by the absence of organomegaly and normal sized adrenals. The causal relationship between CNS and adrenal calcification is difficult to explain in the absence of intrauterine infections. It has been hypothesized that hypovolemia, secondary to severe hypoalbuminemia, could increase the risk of hemorrhagic infarction of the adrenals, subsequently leading to adrenal calcification.

Congenital heart disease has also been rarely reported in few cases of CNS. The Cardiac lesions described in these children were pulmonary stenosis and subaortic stenosis. However, patent ductus arteriosus has not been reported earlier.

Treatment of CNS is challenging as it responds poorly to corticosteroids and other immunosuppressants. Recurrent infections, impaired growth and development, fluid and electrolyte imbalance are common. Progressive renal failure develops in 1-2 years. Intensive supportive management consists of dialysis, prostaglandin inhibitors, angiotensin converting enzyme (ACE) inhibitors, intravenous albumin infusions, along with unilateral nephrectomy (to reduce proteinuria). This allows time for a possible renal transplantation later in the third year of life when transplantation is technically feasible. Recipient age less than two years is a significant predictor of poor graft survival. Unfortunately, the risk of recurrence of nephrosis following transplantation is 20%-25%.

Prenatal diagnosis of CNS is possible by estimation of high maternal serum alpha-fetoprotein (AFP). If the concentration of AFP is 2,50,000 to 5,00,000 micro gram/L and especially if there is another child with CNS in the family, it is highly suggestive of CNS. However analysis of NPHS 1 gene is now the method of choice for precise diagnosis of CNS.

The occurrence of these two unusual features viz., bilateral dense adrenal calcification with normal sized adrenal glands and congenital heart disease with CNS could be co-incidental or it could be a variant of Finnish nephrotic syndrome. Therefore, the major relevance of identifying this type of presentation of CNS is to consider it as a differential diagnosis to CNS secondary to intrauterine infection. In terms of prognosis, complications of CHD like congestive cardiac failure and infective endocarditis might adversely affect the outcome.

In conclusion, associated anomalies should be looked for in a child with congenital nephrotic syndrome.

**Acknowledgement**

We thank Dr. Kanishka Das, Dept. of Pediatric Surgery, for his valuable help in preparing the CT photograph and Dr. Usha kini, Dept.of pathology, for kindly providing renal biopsy photograph.

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Congenital nephrotic syndrome responsive to captopril and indometacin

P A J Heaton, O Smales, W Wong

Abstract
Two children with congenital nephrotic syndrome are described (one with Finnish-type nephrosis, the other with diffuse mesangial sclerosis). Both children have had a prolonged and sustained clinical response with good physical health and normal growth patterns using captopril and indometacin as their sole treatment. No adverse effects have been noted. We recommend a trial of indometacin and captopril treatment in cases of congenital nephrotic syndrome.

Keywords: congenital nephrotic syndrome; captopril; indometacin

Congenital nephrotic syndrome of the Finnish type and that caused by diffuse mesangial sclerosis are associated with profound growth failure and death from infection during infancy. Prolonged survival has been achieved by early aggressive medical management, nephrectomy, and renal replacement treatment with dialysis and transplantation. We report two children with congenital nephrotic syndrome in whom prolonged clinical control has resulted from treatment with captopril and indometacin.

Cases
CASE 1 (A WHITE GIRL)
Finnish-type nephrotic syndrome was diagnosed histologically in the patient’s brother who died at age 6 months. Raised amniotic fluid a fetoprotein concentrations and placental oedema were present, and heavy proteinuria was noted from birth. At age 8 months there was severe growth failure and anasarca. Indometacin 4 mg/kg/day and captopril 4.5 mg/kg/day were started. There was a rapid diminution of proteinuria and a corresponding rise in serum albumin concentrations. General health improved and no further albumin infusions have been given. At age 4 years she has normal growth (fig 1) and development, and intercurrent infections cause only mild transient oedema. Her sole medication remains indometacin 10 mg twice daily (now 1.5 mg/kg/day) and captopril (12.5 mg/kg/day).

CASE 2 (A MAORI GIRL)
This patient has healthy unrelated parents, and an uneventful obstetric and family history. She presented at age 10 weeks with pneumococcal meningitis and septicemia; in addition, proteinuria, hypoalbuminuria, hypomagnesemia, and coagulopathy were noted. Investigations for congenital infections were negative and karyotype was 46XX. Transfusion of albumin at 2 g/kg/day was required to maintain serum albumin above 15 g/litre. Indometacin and captopril were introduced at age 15 weeks and the dosage was increased from 1 mg/kg/day to 3 mg/kg/day of each drug as the proteinuria

Figure 1 Case 1: effect of treatment on weight.

Figure 2 Case 2: effect of treatment on serum albumin and urine protein concentrations.
Matrix deposition. The interstitial area shows fibrosis and an increased cellular infiltrate. This shows two glomeruli, one completely sclerosed and the other with increased mesangial matrix deposition. The interstitial area shows fibrosis and an increased cellular infiltrate.

Figure 3 Silver staining of a renal biopsy specimen taken at age 6 months from case 2. This shows two glomeruli, one completely sclerosed and the other with increased mesangial sclerosis.

Captopril and indometacin in congenital nephrotic syndrome

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The precise pharmacological actions of captopril and indometacin are unknown, but we speculate that activity is effected through microvascular pathophysiologic features shared by both Finnish-type congenital nephrotic syndrome and diffuse mesangial sclerosis.

Recently, the locus for Finnish-type congenital nephrotic syndrome was localized to chromosome 19q12–q13.1, through linkage analysis of Finnish families. As yet, our patient with a clinical picture resembling Finnish-type congenital nephrotic syndrome has not had DNA analysis carried out. Fuchshuber and colleagues recently confirmed the linkage of the Finnish-type congenital nephrotic syndrome locus to the same chromosome region as that of affected non-Finnish families, without evidence of dysequilibrium.3 Their results show that mutations in the same gene appear to be responsible for the disease in both Finnish and non-Finnish populations. This observation is of interest to us because a considerable number of children with congenital nephrotic syndrome in New Zealand are of Maori racial origin. We are presently undertaking further studies into the genetics of all children with congenital nephrotic children who are still alive in New Zealand.

Pneumococcal septicaemia may occasionally result in an acute glomerulonephritis or haemolytic uraemic syndrome. There were no clinical features in our second patient to indicate that she had either of these conditions. Her urine sediment at presentation showed no haematuria and her serum complement concentrations and blood smear were normal. Furthermore, the renal biopsy was performed at least six months after her acute illness, thus making it extremely unlikely that the diffuse mesangial sclerosis was the result of sepsis. All glomeruli in the biopsy showed varying degrees of mesangial sclerosis, a feature consistent with diffuse mesangial sclerosis.

We believe that this simple and inexpensive treatment has enabled our two patients to enjoy at least one and three years, respectively, of good health and normal growth, although the long term outcome remains unknown. We suggest that newly diagnosed cases of congenital nephrotic syndrome of the Finnish type or nephrotic syndrome as a result of diffuse mesangial sclerosis receive a trial of captopril (1–5 mg/kg/day) and indometacin (1–4 mg/kg/day).

Discussion

Pomeranz et al described two infants with Finnish congenital nephrotic syndrome who responded to treatment with captopril (to 5 mg/kg) and indometacin (to 1 mg/kg). One child remained well for at least 2½ years and the other developed renal failure after about 20 months of treatment. This latter child showed continued responsiveness to treatment, in that proteinuria increased then decreased in response to the cessation then reintroduction of the medication, which was brought about because of concerns regarding the possibility that it was contributing to the glomerular failure. So far, neither of our patients have shown significant reduction of glomerular filtration rate.

Birnbacher et al reported failure of any detectable response to treatment with captopril alone (0.15–2.5 mg/kg) in an infant with Finnish congenital nephrotic syndrome.3 However, Guez et al have documented one child who showed “adequate” clinical control using enalapril alone (0.75 mg/kg), having commenced treatment using captopril only (to 4.8 mg/kg/day).4 We are not aware of any reports of this mode of treatment being applied to the management of diffuse mesangial sclerosis.

Although Finnish-type congenital nephrotic syndrome and diffuse mesangial sclerosis result in a similar clinical presentation of severe and usually fatal nephrosis during infancy, the histopathological and molecular genetic features of each condition are distinct. We suggest that the precise pharmacological actions of captopril and indometacin are unknown, but we
Improved prenatal diagnosis of the congenital nephrotic syndrome of the Finnish type based on DNA analysis

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Improved prenatal diagnosis of the congenital nephrotic syndrome of the Finnish type based on DNA analysis. Haplotype analysis and a-fetoprotein quantitation comprise a prenatal diagnosis of congenital nephrosis. Congenital nephrotic syndrome of the Finnish type (CNF) is an autosomal recessive disease characterized by massive proteinuria and nephrotic syndrome from birth. Prenatal diagnosis of CNF has previously been based on the quantitation of a-fetoprotein (AFP) in the amniotic fluid and maternal serum, but an increased AFP is not specific for the disease. We have recently localized the CNF gene to the chromosome 19q13.1 region and observed a strong linkage disequilibrium to the genetic markers D19S610, D19S608, D19S224 and D19S220 in this chromosomal area. Four main CNF haplotypes have been observed in Finnish kindreds. In the present study, linkage and haplotype analyses have been applied to prenatal diagnosis of six families with a history of CNF. The results diminish the risk of false positive diagnosis and abortions of healthy fetuses in families at risk.

Congenital nephrotic syndrome of the Finnish type (CNF, NPHS1, MIM 256300) is inherited in an autosomal recessive manner [1]. Characteristic to CNF is massive proteinuria starting already in utero, a large placenta (over 25% of the child's birth weight) and nephrotic syndrome from birth [1, 2], and the incidence of CNF in Finland is 12.2 in 100,000 newborns [3]. Previously, all CNF patients died usually within the first year of life, but during the last decade CNF patients have been treated successfully with early intravenous albumin supplementation, nutritional support, aggressive treatment of complications and early renal transplantation after nephrectomy and dialysis [4, 5].

CNF can be reliably detected prenatally during the second trimester by elevated a-fetoprotein (AFP) levels in the amniotic fluid [6]. However, AFP values can be elevated also in other fetal abnormalities, mostly structural anomalies such as neural tube defects and abdominal wall defects. CNF is, especially in Finland, a likely cause for very high amniotic fluid AFP in pregnancies where ultrasound shows no fetal abnormalities.

We have localized the CNF gene to the chromosome 19q13.1 region by linkage analysis [7, 8]. The critical region is flanked by genetic markers D19S208 and D19S224, with a genetic distance of approximately 3 cm. A significant linkage disequilibrium has been found with several genetic markers, D19S610, D19S608, D19S224 and D19S220 on this chromosomal region [7, 8], and the markers with a significant association allowed us to construct four main haplotypes observed in Finnish kindreds comprising 90% of all observed CNF haplotypes. Using the haplotype analysis, we have been able to perform first trimester prenatal diagnosis by chorionic villus sampling in families with a known risk for CNF. Haplotype analysis can also be beneficial in cases with elevated amniotic fluid AFP without a family history of CNF. In the present study we have used this approach to carry out prenatal diagnoses in three Finnish families with an affected child, and in three families where the first pregnancy was terminated because of highly elevated AFP values in the amniotic fluid and, as subsequent renal histology revealed, typical CNF findings. In addition to these, we have analyzed the correlation between the CNF haplotype and the quantitated AFP from the maternal serum or the amniotic fluid in 18 cases.

Methods

Pedigrees and DNA samples

The families in this study consisted of three Finnish families with a child affected with CNF and three Finnish families where a pregnancy had been terminated on the basis of high AFP levels in the amniotic fluid (Figs. 1 and 2). The diagnosis of CNF in index cases was based on massive proteinuria, a large placenta, manifestation of nephrotic syndrome soon after birth, exclusion of other types of congenital nephrotic syndrome and typical findings in renal histology [9]. Haplotype analysis was also performed for eight families in which an elevation of amniotic fluid AFP raised a suspicion of CNF. Altogether in 18 cases in these families, AFP values were quantitated in the maternal serum or in the amniotic fluid (Table 1). Nine of the fetuses (cases no. 1, 2, 4, 5, 6, 9, 10, 12, 14 in Table 1) were aborted based on elevated AFP values in the
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CONGENITAL NEPHROTIC SYNDROME OF THE FINNISH TYPE

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SUMMARY

Congenital Nephrotic Syndrome of the Finish type (CNF) is a rare and severe disease. A neonate with CNF is described. The diagnosis carries a dramatically poorer prognosis than nephrotic syndrome diagnosed after one year. The clinical course is one of persistent oedema and recurrent infections leading to death. The gene for the Finish type has been mapped to the long arm of chromosome 19. Case reports show it to be responsive to captopril and indomethacin. It is uniformly resistant to steroids and immunosuppressive drugs.

Key words: Congenital nephrotic syndrome of the Finnish type (CNF), captopril, indomethacin

INTRODUCTION

Nephrotic syndrome is a clinical diagnosis defined by the presence of heavy albuminuria, hypoalbuminemia and oedema.1 It is classified as congenital if it presents at birth or appears during the first months of life.2 CNF is most frequent in Finland but has been reported in various ethnic groups worldwide.3,4 A diagnosis in this case was made on the basis of the clinical features, autopsy report and histological evaluation. To the best of our knowledge, this is the first report from Ghana.

CASE REPORT

A female was born at 38 weeks of gestation by spontaneous vaginal delivery weighing 2.6kg to non-consanguineous parents. The pregnancy was uneventful. Apgar scores were satisfactory at birth and child was breastfeeding well. She presented at 3 weeks of age with an 11 day history of periorbital oedema that appeared to improve by the end of each day. Her urine characteristics and output were said to be normal. There was an antecedent history of a pustular rash on the face that had resolved spontaneously. (Mother denied any history of renal disease in the family. This was her first child.

Clinical examination revealed a normal looking neonate with a purulent eye discharge affecting both eyes and generalized pitting oedema. She was not in respiratory distress. Her anterior fontanelle was large (6cm across). The cranial sutures were widened up to the occiput. Her head circumference was 35cm (50th centile) and body length 48cm (25th centile). She had significant ascites but no masses were felt on abdominal palpation. Blood pressure was not recorded due to the unavailability of an appropriate cuff size. A provisional diagnosis of a hypoproteinaemic state from sepsis or renal disease was made and urgent investigations requested.

Initial results revealed a normal complete blood count and ESR but abnormal blood chemistry and urinalysis. Serum sodium - 110mmol/L, potassium - 4.7mmol/L, urea - 6.9mmol/L, Total Protein - 17g/L, albumin 6g/L. Urinalysis gave a pH of 6.0 and microscopy showed amber colour, blood was positive (++), ketones – negative, glucose was positive (+) and protein was positive (+++). The specific gravity of the urine was 1.015, urobilinogen (normal) and bilirubin was negative. Urine microscopy showed 5 pus cells, 15 red blood cells, 3 epithelial cells per high power field and granular casts(+)

She was given two units of Fresh Frozen Plasma as a protein source due to the lack of albumin infusions in the hospital. An abdominal ultrasound showed a normal echo pattern and size of both kidneys. Liver and spleen size were normal.

Subsequent blood chemistry evaluations revealed deteriorating albumin, and sodium levels, as well as rising potassium. Creatinine levels crept up from an initial 183 µmol/L to 201 µmol/L on day 5 to 314 µmol/L on day 10 of admission. A single cholesterol estimation was recorded as 5.72 mmol/L on day 10 of admission. Retroviral screen was negative.

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Author for correspondence: Dr E. V. Badoe

Conflict of Interest: None

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sis of the consistent laboratory results of heavy proteinuria and hypoalbuminemia. She died that day.

**Autopsy findings**

Female infant showing marked generalized pitting oedema. The other major systems were normal except for the respiratory system which showed rubbery oedematous lungs. The genitourinary system revealed slightly oedematous kidneys. Cut surface of the kidneys were very pale with hemorrhagic rimming of the cortico-medullary junction. The cortex was of normal thickness. Ureters and pelvi-calyceal system were normal. The conclusion was that the findings were consistent with a nephrotic syndrome.

**Histology report of the kidneys**

In the renal tissue at low power, basophilic areas were evident, one of these in a subcapsular location. Cellular preservation was poor suggestive of a nephrogenic rest. The renal architecture was distorted due to the presence of ecstatic tubules with eosinophilic wispy material. Although the tubular basement membranes were not thickened Periodic Acid Schiff (PAS) stain suggested tubular casts.

Some of the glomeruli had a foetal appearance and others showed an apparent increase in cellularity and possibly an increase of eosinophilic material. Some of the glomeruli did show increased (PAS) and silver staining within the eosinophilic areas in the glomeruli suggestive of sclerosis. No vascular lesions were identified. It was concluded that the appearances in the appropriate clinical context was consistent with CNF.

**DISCUSSION**

The two main causes of congenital nephrotic syndrome is the Finnish type and diffuse mesangial sclerosis which are both inherited in autosomal recessive fashion. Both sexes are equally affected and are born early (at 35-38wks) and usually below gestational weight for age. The placenta is typically enlarged being more than 25% of the total birth weight. Classically the newborn has widely separated cranial sutures, with large posterior and anterior fontanelles which was present in our index case. There may be flexion deformities of the hips, knees and elbow.

Aggressive treatment is required including daily intravenous albumin, nutritional support via nasogastric tube feeding, prevention of infections (peritonitis, respiratory infections) and thrombi-embolic complications. In developed countries early bilateral nephrectomy to prevent massive protein loss, renal replacement treatment with dialysis and transplantation are further options.

Pomeranz et al described two infants with CNF who responded to treatment with captopril (5mg/kg) and indomethacin (4mg/kg). Subsequently, Heaton et al have also reported similar success. This combination therapy led to a decrease in protein excretion and improvement in nutritional status and growth.

**CONCLUSION**

An infant with CNF has been described. Treatment is highly specialized. In our setting, a trial of both angiotensin converting enzyme inhibition (captopril) and indomethacin could have prolonged life. CNF is a rare but devastating cause of nephrotic syndrome in children.

**ACKNOWLEDGEMENT**

We wish to thank Dr. Mark Taylor, Consultant Nephrologist and Dr. Rachel Brown, Consultant Paediatric Pathologist, all of the Birmingham Children’s Hospital, U.K for accepting and reviewing the histology slides. We are deeply grateful to Dr. Victoria Adabayeri, Paediatrician, Korle Bu Teaching Hospital who made this possible.

**REFERENCES**

Congenital nephrotic syndrome: Evolution of medical management and results of renal transplantation


We analyzed the clinical course, pathologic findings, and results of aggressive medical management and renal transplantation in 41 infants with onset of nephrotic syndrome in the first 3 months of life. All but one infant with congenital onset failed to thrive and had progressive renal insufficiency; 17 were given steroids or cytotoxic drugs or both, without benefit. Severe bacterial infections occurred in 85% of the infants, pyloric stenosis in 12%, gastroesophageal reflux in 8%, and thrombotic events in 10%. All children prior to the era of renal transplantation died before 4 years of age. The last 24 infants received aggressive medical management, which allowed renal transplantation in 17. Two-year patient and graft survival rates were 82% and 71%, respectively. There was no recurrence of the nephrotic syndrome in the children who underwent transplantation. All but one surviving infants has had normal or accelerated growth, although mean height for the group is 3.1 SD below the mean. School and social performance has been normal in 80%. Thus intensive medical therapy combined with renal transplantation offers a very good opportunity for survival with an acceptable quality of life for infants with congenital nephrotic syndrome. (J PEDIATR 105:549, 1984)


Congenital nephrotic syndrome is a rare and, until recently, lethal disorder characterized by heavy proteinuria, edema, and hypoalbuminemia occurring within the first 3 months of life. Congenital NS was initially reported from Finland, where kindred studies by Norio demonstrated an autosomal recessive inheritance. Familial and sporadic cases have been described in infants without a recognized Finnish background, suggesting that primary (idiopathic) congenital NS may not be a single entity. A strikingly uniform course of persistent NS associated with failure to thrive, frequent infections, declining renal function, and early death from sepsis or uremia has been described in most patients with congenital NS, regardless of ethnicity. Other causes of severe infantile proteinuria, including cytomegalovirus infection, congenital syphilis, toxoplasmosis, mercury intoxication, lupus erythematosus, nail-patella syndrome, and XY gonadal dysgenesis have variable outcomes, but Finnish and non-Finnish infants with idiopathic congenital NS appear to share the same dismal prognosis. All therapeutic attempts with adrenocorticosteroid and immunosuppressive drugs have failed. Renal transplantation, however, can provide a permanent cure and good quality of life for affected infants.

Since 1953, 41 children with the onset of nephrotic syndrome in the first 3 months of life have been observed at the University of Minnesota. We report our experience with these infants.
Renal biopsy tissue, nephrectomy specimens, or autopsy tissue, available from 39 patients, were reevaluated without knowledge of the clinical data. Immunofluorescent and electron microscopic findings were reviewed when available. The pathologic findings are detailed elsewhere and are only summarized here.

The management of each infant was supervised by one of us (R.L.V. or S.M.M.) and included a careful historical and laboratory evaluation at presentation. A renal biopsy was obtained in 38 infants. Prior to 1971 all 17 infants received diuretics, and most a trial of adrenocorticosteroid or immunosuppressive therapy. Since 1971, 24 infants have received medical therapy designed to make transplantation possible, including nutritional supplementation with a high-caloric (120 cal/kg/day), high-protein (3 to 4 gm/kg/day), low-sodium formula (PM 60/40, Ross Laboratories) via nasogastric tube or gastrostomy if needed; orally given diuretics and occasional intravenously administered albumin to allow sufficient fluid intake for caloric needs and to minimize edema; prophylactic penicillin to decrease *Streptococcus pneumoniae* infections; and low-dose aspirin and dipyridimole therapy for children with laboratory evidence of hypercoagulability or clinical manifestations of thrombosis.

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RESULTS

Clinical characteristics. Edema and proteinuria were detected within the first month of life in 31 (75%) children and in the first week of life in five (12%) of the 41 infants (Table I). The mean age at clinical diagnosis was 4 weeks (range 0 to 12 weeks). Microscopic hematuria (>2 RBC per high-power field) was noted in the first urinalysis in seven infants. All infants had heavy proteinuria (>50 mg/kg/day) in the initial urine specimen studied. In one child NS was detected by the finding of a low level of thyroxine in a cord blood screening program.

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**Table I. Clinical features in 41 patients with congenital nephrotic syndrome**

<table>
<thead>
<tr>
<th>Feature</th>
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<th>%</th>
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<tr>
<td>Positive family history</td>
<td>18</td>
<td>44</td>
</tr>
<tr>
<td>Finnish ancestry</td>
<td>9</td>
<td>22</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>41</td>
<td>100</td>
</tr>
<tr>
<td>Central nervous system delay</td>
<td>38</td>
<td>93</td>
</tr>
<tr>
<td>Seizures</td>
<td>12</td>
<td>30</td>
</tr>
<tr>
<td>Serious bacterial infections (67 episodes)</td>
<td>35</td>
<td>85</td>
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<tr>
<td>Meningitis</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Sepsis</td>
<td>13</td>
<td>32</td>
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<tr>
<td>Pneumonia</td>
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<tr>
<td>Peritonitis</td>
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<td>Urinary tract infection</td>
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<td>21/27</td>
<td>77</td>
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<tr>
<td>Short partial thromboplastin time</td>
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</tr>
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<td>24</td>
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*Mean age at onset 4 weeks (range 0 to 12 weeks).
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METHODS

The records and pathologic specimens of 41 infants with onset of edema, hypoalbuminemia, hyperlipidemia, and significant proteinuria within the first 3 months of life who were seen at the University of Minnesota from 1953-1982 were reviewed. The clinical features, family history, and laboratory data at the time of presentation and during the course of the disease were evaluated for each child in order to identify factors that might be predictive of the pathologic diagnosis or subsequent outcome.

The course and long-term results in those patients undergoing renal transplantation were reviewed. The results of renal transplantation in some of these children have been reported earlier.17-19 Patient survival and graft survival were analyzed by life table analysis.20 The graft was considered lost when a child returned to dialysis or died. Height was measured by standard methods21 and plotted on National Center for Health Statistics curves. Standard deviation scores were computed at time of transplantation and from the most recent height data using the formula: Observed height minus expected mean height for age divided by standard deviation in height for age.22 The SDS values for groups were analyzed using the Student t test for dependent means. Developmental assessment before and after transplantation utilized the Denver Developmental Screening Test as well as recent telephone interviews with the parents of surviving children. Developmental assessment in children older than 6 years was assessed by school performance and social activities.

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