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Congenital Nephrotic Syndrome in a Nigerian Child

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Summary

Adedoyin OT, Adesiyun OO, Mark F, Anigilaje EA, Adeniyi A. Congenital Nephrotic Syndrome in a Nigerian Child. *Nigerian Journal of Paediatrics* 2006;33:109 We report a six-week-old Nigerian male term infant with biochemical findings and clinical course in keeping with nephrotic syndrome (NS), prompting a probable diagnosis of congenital nephrotic syndrome. He presented to our facility on account of three weeks' history of generalized body swelling and one-week history of recurring convulsions and scalp alopecia. The birth weight was 2.4 kg but the placental weight could not be ascertained. He developed recurrence of oedema once and also developed clinical features suggestive of severe sepsis, which were adequately managed before his death at home. Renal biopsy could not be done before death.

Introduction

CONGENITAL nephrotic syndrome is a heterogeneous collection of primary and secondary diseases that may share only the fact that onset occurs in the first three months of life.[1] It is therefore one of the three known varieties of nephrotic syndrome. The others include primary and secondary nephrotic syndrome. It presents within the first year of life with massive proteinuria, anasarca, hypoproteinaemia and hypercholestrolemia.[2] It is sometimes associated with congenital infection and may be inherited in an autosomal recessive fashion. It is an uncommon disease in Africa, particularly West Africa. Most times, when an infant presents with oedema, other common causes such as protein energy malnutrition are first considered. We therefore report a case of congenital nephrotic syndrome that presented in our hospital at six weeks of age.

Case report

A six-week-old term male infant was referred from a mission hospital in a neighbouring state on account of three weeks' history of generalized body swelling and one-week history of recurring convulsions and scalp alopecia before presentation. The swelling started on the face and later involved the lower limbs. There was no history of oliguria. Excessively large placenta could not be ascertained and there was no antenatal maternal illness. The birth weight was 2.4kg. Convulsions of which he had multiple episodes, were noticed a week before presentation. Initially, the convulsions were focal but later became generalized. They were not associated with loss of consciousness or fever. Hair loss on the scalp was also noticed a week before presentation; it was preceded by a rash over the same site. The child was the third of three children. There was no similar history in the other siblings.

The main findings on examination included puffy face, pallor, skullcap alopecia and bilateral pitting pedal oedema which extended up to the knees. His weight and length at presentation were 3kg and 44cm respectively, while his surface area was 0.2 m^2. No dysmorphic feature was observed, and ascites was absent. There was however, a grade 3/6 pansystolic murmur loudest at the apex. He was conscious but there was reduced tone in all the limbs.

Some of the investigations carried out included random blood sugar (RBS) of 1.8mmol/l, urinalysis protein 3+, blood 2+, serum protein 40g/l, and serum albumin of 10g/l. The serum cholesterol was elevated with a value of 10.8 mmol/l. The 24-hour urine protein was 2g/24 hours. Serum electrolytes and urea analysis revealed sodium of 130mmol/l, potassium of 3.6mmol/l, urea of 6.4mmol/l, creatinine of 49mmol/l, calcium of 1.90mmol/l and phosphate of 1.1mmol/l. The cerebrospinal fluid analysis was not suggestive of meningitis. Abdominal ultrasound done on two occasions was normal with no evidence of ascites. The full report indicated that both kidneys were normal in position, size and outline. Their measurements were 41mm and 43.5 mm in bipolar lengths on the right and left, respectively. The corticomedullary differentiation was normal bilaterally. No intra-abdominal mass lesion was seen. The full blood count (FBC) showed a packed cell

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volume (PCV) of 23 percent, white blood cells (WBC) of 26.8 x 10^9/l, with neutrophils 54 percent, lymphocytes 46 percent, while the platelet count was 10.8 x 10^9/l. Urine microscopy and culture were normal and no organism was isolated from a blood culture. An assessment of congenital nephrotic syndrome with hypoglycaemia was made. The hypoglycaemia and anaemia were corrected and he was commenced on parenteral frusemide 1mg/kg four times daily and syrup spironolactone 2mg/kg two times daily. The clinical condition improved within two weeks of admission including the disappearance of cardiac murmur, resolution of oedema, and absence of convulsion, although the urinalysis still showed 2+ of protein but no blood. He was discharged after two weeks of admission.

During one of the follow up visits to the clinic, he was noticed to have marked facial and leg swelling. The urinalysis showed 2+ of protein with no blood. The serum electrolytes and urea were within normal ranges. A repeat of the 24-hour urine protein showed 2.5g/24 hours. He received IV frusemide 1mg/kg/dose 6hourly, spironolactone 1mg/kg dose 12 hourly, and lisinopril 2.5mg daily and was also commenced on prednisolone 40mg/m^2 in three divided doses (2.5mg tds). The frusemide was later changed to oral hydrochlorothiazide 2mg/kg/dose eight hourly following the marked regression of the body swelling. Two weeks after commencement of the prednisolone, he developed high-grade intermittent fever (peak of 40°C) and carpopedal spasms. The former prompted the immediate discontinuation of steroids as the fever might have been a sign of infection which was predisposed to, by the steroid. The FBC revealed an elevated WBC of 32 x 10^9/l with differentials of neutrophils, 87 percent, lymphocytes six percent and PCV of 23, suggesting the presence of bacterial infection; the neutrophils also showed marked toxic granulation. There was no malaria parasite in the peripheral blood film and no organism was isolated from blood culture. The serum calcium was 1.38mmol/l. He received parenteral ceftriaxone for 10 days, while intravenous calcium gluconate and oral calcium lactate were also given. By the 20th day of admission, there was remarkable improvement as evidenced by the resolution of the body swelling, fever and spasms. However, the proteinuria persisted at between 2+ and 3+ indicating that the steroid and lisinopril were not effective. He was discharged by the 26th day. When the patient was not brought for follow-up, our inquiry revealed that the child had died at home.

Discussion

This case is the first known to us of congenital nephrotic syndrome in our centre in over 25 years of its existence. This case did not respond to steroids, a phenomenon that has been confirmed by previous studies. He had a recurrence of oedema, which was complicated by a severe infection from which he recovered. The infection might have been predisposed to, by the steroid or as a result of the NS. Such children are usually susceptible to infection due to loss of immunoglobulin in the urine, among other causes. The carpopedal spasms were the aftermath of frusemide usage as it causes increased excretion of calcium in the urine resulting in hypocalcemia which occurred in this child. The systolic murmur which occurred at the first admission was probably haemic as it disappeared shortly after blood transfusion. The convulsion most likely resulted from hypoglycaemia; it resolved after correcting the latter. The scalp alopecia which followed a rash on the scalp was an isolated event rather than part of a syndromic complex. This is further strengthened by the absence of any dysmorphic feature. The oedema also subsided before the child was discharged home. However, shortly after discharge from the hospital, we got the information that the child had died at home due to unknown cause. It is possible that the child died from infection or uraemia due to the unresolved NS; this is in view of the persistent proteinuria which probably indicated the progression of the disease process.

This case report notwithstanding, congenital NS remains an uncommon occurrence in African children although one case had been reported in a five-month-old Sudanese boy.[3,4] The latter case neither had features typical of the Finnish type nor of other hereditary diseases. The most striking changes were in the glomerular basement membranes, which showed patchy thinning, thick segments with reduplication and occasional low spikes. Congenital nephrotic syndrome though rare, should still be considered in the differential diagnosis of infants aged less than three months who present with oedema; such an infant should be evaluated for proteinuria, hypoalbuminaemia and hyperlipidaemia.

We could not carry out a renal biopsy in our patient because he was not clinically stable. However, the clinical configuration aligned perfectly with NS. It would have been more instructive had a biopsy been carried out to ascertain the histological characteristics. We indeed planned for it, but the child died at home shortly after recovery from a relapse.

Congenital nephrotic syndrome (CNS) is defined as proteinuria leading to clinical symptoms soon after birth. An arbitrary age limit of three months has been adopted to separate CNS from infantile NS, which manifests later in the first year of life.[5-6] The most common type of CNS is the congenital NS of the Finnish type (CNF) with a clinical onset invariably

before one month of age. The other early onset nephroses have a more widespread age of onset from the first days of life to several months of age. CNS and early onset NS can be classified into three main categories; primary NS, NS associated with malformation syndromes and secondary or acquired NS. The primary NS comprises CNF, diffuse mesangial sclerosis, minimal change NS, focal and segmental glomerulosclerosis (FSGS), and membranous glomerulopathy. The malformation syndrome consists of Denys-Drash syndrome, CNS with brain malformations and some other syndromes. The secondary NS are those CNS due to congenital syphilis, toxoplasmosis, rubella, cytomegalovirus, hepatitis, malaria and SLE

Congenital NS of the Finnish type, is the most common single type of CNS and is considered the prototype of CNS. Hallman *et al* first described it in 1956.[7] This autosomal recessive disease is common in the Finnish population, the incidence in Finland being 1:8200 live births.[8] It is inherited as an autosomal recessive trait.[9] The gene for CNF has been localized to chromosome 19q13.1 and recently isolated and named NPHS1.[10] The NPHS1 gene encodes a transmembrane protein called nephrin, which appears to be expressed solely in glomerular podocytes. Familial cases of CNF without evidence of Finnish ancestry have been reported worldwide. The incidence outside Finland is unknown. Mutations in the NPHS1 gene have been shown to be responsible for many non–Finnish cases. Genetic analysis in seven European and North African CNS families have shown clear linkage to the chromosomal region19q12q13.1[4] and recent results have also demonstrated a variety of insertions, deletions, splice mutations and point mutations in the NPHS1 gene in non-Finnish CNS patients.[11]

The diagnostic criteria for CNF include high a-fetoprotein concentration in maternal serum and amniotic fluid, placenta greater than 25 percent of birth weight, severe proteinuria of intrauterine onset; serum albumin < 10g/l at presentation, urinary protein > 20g/l when serum albumin is corrected to > 15g/l, exclusion of other types of CNS, normal glomerular filtration rate during the first six months of life, positive family history and mutation in the NPHS1 gene.[11] The basic problem in CNF is severe loss of protein most of which is albumin,[7] beginning *in utero*. All the signs and symptoms are believed to be secondary to this protein deficiency. The children are often born prematurely, on average at the thirty sixth week. Birth weight is below the fifth percentile in one third of the cases, but birth length is within the normal range. Oedema and abdominal distension are present immediately after birth in 25 percent of the children, while the remaining children develop NS within the first few weeks of life; more than 90 percent within the first week. In contrast to most other CNS, the protein loss in CNF always leads to severe hypoalbuminaemia and serum albumin concentration is usually less than 10g/l at presentation. In addition to albumin, many other proteins are lost in the urine; such proteins include immunoglobulin G, transferrin, apoproteins, lipoprotein lipase, antithrombin III (AT III), ceruloplasmin, vitamin D binding protein and thyroid binding globulin. The serum levels of these and their ligands are low in the serum leading to secondary metabolic disturbances. The low thyroxine concentration leads to an increase in thyroid stimulating hormone, while urinary excretion of plasminogen and AT III leads to compensatory protein synthesis, resulting in increasing levels of macroglobulins, fibrinogen, thromboplastin and factors II, V, VII, X and XII, contributing to coagulopathy.[6, 12]

Low serum albumin and post heparin plasma lipoprotein lipase (LPL) activities and high free fatty acid concentration leads to hypertriglyceridaemia. These lipid abnormalities and arteriolar changes seen already during the first year of life may lead to an increased risk of arteriosclerosis.[13] During the first two months, the kidney size as determined by renal ultrasound is normal in most patients. The corticomedullary differentiation is also preserved. The striking lesion by light microscopy is microcystic dilatation of the proximal tubule, more prominent in the cortex than the medulla. The dilated tubules have flattened epithelial cells and intact basement membranes. These characteristic changes can be minimal early in the disease and may not be specific since they have been noted in other forms of nephrotic syndrome. Likewise, the glomeruli, which are the sources of the proteinuria, may initially appear quite normal by light microscopy and show only spreading and fusion of the epithelial cell foot processes by electron microscopy. Later on, the more mature glomeruli show mesangial hypercellularity with an increase in matrix. Most glomeruli are immature with pallisading of epithelial cells around a contracted tuft within a dilated urinary space. Immunofluorescent studies are generally negative. Later biopsies may show progressive tubular atrophy, interstitial fibrosis and glomerular obliteration with segmental IgM and IgG deposition.

Steroids and cytotoxic drugs are ineffective in treatment. In fact, since infection is such a major complication, it is probably in the child's best interest that immunosuppressive therapy is not used. This was confirmed in our patient as our 'steroid trial' never benefited the child, rather it probably predisposed to the infection. The immediate cause of death is usually infection, not uraemia. Meticulous supportive

therapy such as albumin substitution since the albuminuria could lead to protein malnutrition, is essential. Vigorous specific therapy of infection rather than prophylactic antibiotic therapy is preferred. Practically all patients fail to thrive and remain in poor general condition throughout the disease. Growth is meager, bone age is severely retarded and motor development is poor. Even with successful therapies, uremia eventually ensues in practically all cases. Successful renal transplantation is the ultimate therapy.[1] Some centres have adopted the routine of performing unilateral nephrectomy to reduce the protein losses. However, unilateral nephrectomy does not eliminate the need for nutritional support and albumin substitution.[14]

There are major differences between CNF, which is the prototype of CNS, and other infantile NS cases. In CNF, proteinuria always starts *in utero*, amniotic fluid a-fetoprotein is always increased, placental birth weight is >25 percent of birth weight, proteinuria is severe and the affected children are born prematurely. They also have normal GFR during the first 6-12 months, there is mutation of the NPHS1 gene and there is radial dilation of the proximal tubules after 3-8 months. In the other types of infantile CNS, the proteinuria may start at birth but mostly later, during the first year of life, amniotic fluid a-fetoprotein is usually normal, placental weight is normal, birth weight is normal, proteinuria is less severe, and there is end-stage renal disease usually within months after presentation of nephrosis. There is also essential sclerosis contracting the glomerular tufts, tubular atrophy and interstitial fibrosis and there is a mutation of the WT1 gene in Denys–Drash syndrome.[11]

It was unlikely that the proteinuria in our patient started at birth. It is therefore not likely that he had CNS of the Finnish type but rather, other primary CNS apart from CNF.

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