CASE REPORT

"A stitch in time saves nine": managing congenital nephrotic syndrome in resource-limited circumstances

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SUMMARY

We report a case of congenital nephrotic syndrome. Our patient presented with sepsis-like illness and acute kidney injury during the neonatal period. Subsequent urine analysis showed persistent heavy proteinuria with concomitant hypoalbuminaemia and clinical anasarca. Screening for congenital infections was negative. Diuresis was initially induced with daily albumin infusion. Subsequently, administration of furosemide combined with amiloride was adopted as albumin-sparing strategies. Both angiotensin-converting enzyme inhibitor and non-steroidal anti-inflammatory drugs were started after 4 weeks of life. Such treatment strategies resulted in a significant reduction in the need for albumin infusion, thus allowing better preservation of the venous estate and improving quality of life with a reduced need for inpatient care.

INTRODUCTION

Congenital nephrotic syndrome (CNS) is a rare disorder that presents with heavy proteinuria, hypoalbuminaemia and oedema in the first 3 months of life. Incidence is 0.5 per 100 000 live births.1 This disease is more prevalent in some parts of the world, owing to the genetic makeup of the population. Overall, disease outcomes in CNS are poor, with most children requiring kidney transplant. Herein, we discuss the challenges in the management of an infant with CNS and review the literature on conservative measures in the management.

CASE REPORT

A 3-week-old immigrant baby girl presented with sepsis-like illness. She had decreased physical activity and reduced oral intake. She was born full-term at 38 weeks with a birth weight of 2.5 kg. Antenatally, in-utero growth parameters were normal. Parents were non-consanguineous with no family history of concern. On clinical examination, she had no dysmorphic features. Her anterior fontanelle was sunken with dry mucous membrane. Her measured body weight was 2.2 kg. The cardiorespiratory and abdominal examinations were unremarkable. She had normal female genitalia. Her blood investigations showed hyponatremia and hypokalaemia (serum sodium of 129 mmol/L and potassium 2.9mmol/L) with elevated urea 5.2 mmol/L and creatinine 62 umol/L. Her haemoglobin measured 149 g/L, white cell counts $22.7x10^9$/L and platelet $527x10^9$/L. She had severe hypoalbuminemia with serum albumin of 8 g/L. Her corrected calcium 3.27 mmol/L, phosphate 1.5 mmol/L and magnesium 0.9 mmol/L. Venous blood gas revealed severe metabolic acidosis (pH 7.01, pCO_2 16.9mmHg, HCO_3 7.8mmol/L and base excess of -26mmol/L). Urinalysis showed heavy proteinuria (urine protein 4+). Urine protein:creatinine index was 10983 mg/mmol. Screening for congenital infections including toxoplasmosis, rubella, cytomegalovirus, herpes, hepatitis B and human immunodeficiency virus (HIV) were all negative. Karyotype was 46 XX. Soon after admission, we observed progressive generalised body swelling accentuated by crystalloids used during initial fluid resuscitation. Initially, she had to be given albumin infusion twice a day via a peripherally inserted central venous catheter to facilitate diuresis. Unfortunately, her condition was complicated with ESBL Klebsiella pneumoniae catheter-related blood stream infection. A combination of furosemide and amiloride to control the anasarca was instituted. Upon normalisation of her serum creatinine, both captopril and indomethacin were started.

These strategies allowed sustainable weaning measures of albumin infusions, with no resurgence of oedema. Her caloric intake was optimised to 130 kcal/kg/day. The albumin level remained stable in the range between 14 and 16 g/L. An increment of creatinine by 20% from her baseline was accepted. As expected, she required thyroxine and mineral supplements. Our management protocol allowed alleviation of fluid restriction and created room for optimisation of nutritional intake. It was also not necessary to maintain venous access constantly. She was discharged after 4 weeks of hospital stay. It was possible to continue the management on an outpatient basis without compromising her health. During clinic visits, she showed satisfactory weight gain as well as neurodevelopmental milestones.

DISCUSSION

Infants with CNS typically present with heavy proteinuria, hypoalbuminaemia and oedema. The degree of proteinuria, however, varies amongst individuals and the clinical signs may not be apparent during the first week of life. The true magnitude of proteinuria may be detectable only after partial correction of hypoalbuminaemia by albumin infusion.[2] Common causes of CNS are mutations in genes encoding structural or regulatory proteins of the kidney filtration barrier located in the glomerular capillary wall.[3]

This article was accepted: 22 November 2022
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This filter is made up of glomerular basement membrane (GBM), podocytes and slit diaphragm (SD). Defects in SD or GBM are known to cause proteinuria. Genetic mutations which have been linked to CNS are NPHS1, NPHS2, LAMB-2 and WT1. Non-genetic causes of CNS are infections namely toxoplasmosis, congenital syphilis, congenital rubella, HIV, and hepatitis B.2 These infants are at risk of several problems. Hypoalbuminaemia predisposes them to acute kidney injury, infections, thrombosis, and hyperlipidaemia.[4,5] These complications would result in multiple or even prolonged hospital stay, which have been shown to affect early childhood development.[6]

Our patient presented with sepsis-like illness and acute kidney injury. Infection is relatively more prevalent than CNS in this region of the world. Hence, this warranted extensive investigation to exclude infection as a non-genetic aetiology. At presentation, generalised body swelling was not evident albeit the heavy proteinuria and severe hypoalbuminaemia. Nevertheless, persistent laboratory markers coupled with progressive oedema in the first 3 months of life concurred with the diagnosis better. The severity of nephrosis in our patient contributed to the acute kidney injury.

Management of infants with CNS is highly individualised as these infants may demonstrate varying degrees of nephrosis.[2,3] Use of immunotherapy such as corticosteroids to induce remission is not recommended[7] in the management of CNS. Instead, management revolves around meticulous volume assessment and control of oedema, optimisation of growth and nutrition, antiproteinuric strategies, prevention of nephrosis-related complications such as infections and functional hypothyroidism, preservation of venous access and watchful surveillance of kidney function in anticipation of early needs for kidney replacement therapy.

Massive loss of albumin is commonly observed in infants with CNS. Decreasing the amount of protein leak could stabilise serum albumin level. Infusing albumin would raise the level but this effect remains transient with the ongoing urinary loss due to the defect in the kidney filtration barrier. Unfortunately, frequent albumin infusions also would translate to an increase in venous cannulation, risk of line-related infections and exhaustion of the venous estate with time! Antiproteinuric agent (angiotensin-converting enzyme inhibitors, ACEI or angiotensin II receptor blocker, ARB and non-steroidal anti-inflammatory drugs like Indomethacin) administration, however, produces a better sustained levels of albumin by modifying intraglomerular pressure, decreasing the glomerular filtration and subsequent resultant protein leak. Dufek et al[8] confirmed this finding in their studied population. Conventionally, albumin infusions would be coupled with diuretic therapy to achieve a desirable balance between oedema control and fluid intake; with careful consideration not to increase the infant's risk of acute kidney injury.

Frequent need for albumin infusion and long in-patient stay would culminate into a huge financial burden for the family. The existing healthcare system does not provide funded healthcare services to immigrants. The high medical cost incurred from our patient's in-patient care was indeed a significant financial burden to her family and we could have lost this child from continuation of medical care due to financial constraint. In our patient, we opted to intensify diuretic therapy as well as antiproteinuric strategies early. Early application of sequential blockade with a combination of furosemide and amiloride significantly reduced the need for albumin infusion. In addition, captopril and indomethacin were added successively once her creatinine recovered.

The European Reference Network for Kidney Diseases (ERKNet) and the European Society for Paediatric Nephrology (ESPN) Working Group (ERKNet-ESPN WG) recommended for amiloride, an epithelial sodium channel (ENaC) blocker over spironolactone, as a choice of potassium-sparing diuretic in addition to loop diuretic in infants with fluid overload. Experimental study has shown that the protein-rich urine of mice with nephrotic syndrome contains plasmin that activates the ENaC at the distal nephron.[9] Upregulation of the EnaC mediates sodium retention and contributes to oedema formation in children with nephrotic syndrome. Amiloride which directly blocks ENaC had been shown in vivo to reduce the absorption of sodium from the cortical collecting ducts in puromycin-aminonuclesiode (PAN) nephrotic mice hence reversing the positive sodium balance.[10]

Our patient responded well to this intensified management, allowing maximal fluid intake, calorie intake optimisation and early hospital discharge. In reality, the financial implications were more manageable by the family in addition to aid from the non-governmental organisations (NGOs). Early intensification of medical therapy avoided albumin infusions. It was also possible to find the 'balance point' between fluid intake and oedema control, allowing liberal nutritional support. This observation concurs with experience reported from highly specialised centres where prolonged conservative management has been effective.[7]

At the time of writing, our infant was in her 12th month of life. She was thriving and achieving neurodevelopmental milestones in the conservative management and continued to be managed on an outpatient basis. In the long run, our patient will still require dialysis support and even kidney transplantation. We hope the NGOs continue to help the family as kidney replacement therapy will pose a major financial constraint to the family since existing healthcare services do not support them like non-immigrant.

CONCLUSION

Managing an infant with CNS is challenging even in the most experienced centre. This is more pronounced in this region when the incidence of CNS is rare. We reflect upon the relevance of physiology in tailoring clinical decisions. Many medical comorbidities stem from the occurrence of severe oedema which is the hallmark of this disease. Early utilisation of an ENac Channel blocker in a sequential blockade strategy helped in managing oedema cost-effectively. This is even more relevant in our patient; when clinicians are at the crossroad trying to strike a balance between professional calling, humanity and governance.

CONFLICT OF INTEREST

None.

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