Therapy-resistant anaemia in congenital nephrotic syndrome of the Finnish type—implication of EPO, transferrin and transcobalamin losses

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Abstract

Congenital nephrotic syndrome of the Finnish type (CNF) is due to NPHS1 mutation and is responsible for a variety of urinary protein losses. We report the case of a 4-month-old girl with a particularly severe form (proteinuria ~150 g/l) of CNF. She developed severe non-regenerative anaemia requiring bi-monthly blood transfusions despite daily EPO (600 UI/kg) and iron supplementation. Epoetin pharmacokinetics revealed a urinary loss of 27% of the given dose within the first 24 h after IV injection. However, plasma levels remained increased after 24 h (228 UI/l). Plasma transferrin and transcobalamin levels were undetectable. Atransferrinaemia and atranscobalaminaemia seem to be responsible for disturbed erythropoiesis.

Keywords: congenital nephrotic syndrome of the Finnish type; erythropoietin; transferrin; transcobalamin

Introduction

Congenital nephrotic syndrome of the Finnish type (CNF) is a rare autosomal recessive disease due to mutations in the
NPHS1 gene encoding nephrin [1,2]. No clear evidence was found for the genotype/phenotype correlation in NPHS1 mutations. Traditional therapy of CNF included intravenous albumin infusion (up to 6 g/kg/day), high-energy diet, multivitamin and oligoelement preparations (above all magnesium and calcium). Nephrectomy and dialysis are usually performed shortly before the child reaches the weight for renal transplantation. ACE inhibitors and indometacin have allowed for the avoidance of surgery and dialysis for several years, but the efficacy has not been demonstrated for patients with Fin-major and Fin-minor mutations.

Case report

The patient was born at 37-week gestational age, female, of French origin, with a birth weight of 2870 g. Antenatal sonographies were normal. There was no history of kidney disease or consanguinity. CNF was diagnosed at birth by major oedema, and massive proteinuria detected in the first urine sample. Serum albumin was 19 g/l and serum creatinine 72 µmol/l on her first day of life. There was no materno-foetal infection.

Continuous albumin infusion was started on Day 1 by 2 g/kg/day and progressively increased to 4 g/kg/day. Immunoglobulin substitution was started by 1 g/kg twice a week, and coumadine was administered for anticoagulation. The renal biopsy showed normal glomeruli and tubular dilatations. Genetic investigation revealed a composite heterozygote anomaly in the NPHS1 gene: one deletion in exon 16, and one nonsense mutation in exon 7.

Glomerular filtration rate increased (serum creatinine: 14 µmol/l on Day 20). Albuminæmia decreased progressively and proteinuria increased to ~150 g/l, requiring high IV albumin (10 g/kg/day) to maintain serum levels ≥20 g/l. An attempt to discontinue IV albumin for 4 h failed completely with reappearance of oedema and serum albumin levels <10 g/dl. Hypothyroidism due to a urinary loss of thyroxin-binding globulin required oral L-thyroxin treatment. Massive proteinuria did not decrease under ACE inhibitor therapy.

The patient rapidly developed non-generative anaemia despite iron and vitamin B12 supplementation. Serum transferrin and transcobalamin were undetectable, and epoetin was <2 UI/l (Table 1). Urine samples revealed a significant loss of transcobalamin, transferrin and erythropoietin. She was started on subcutaneous EPO 100 UI/kg/week, but anaemia persisted, requiring bi-monthly blood transfusions. The EPO dose was increased to 600 UI/kg/day (~40-fold increase compared to the initial EPO dose) and switched to IV injections. A pharmacokinetic profile of EPO plasma and urine levels was performed in order to investigate the low efficacy of epoetin treatment.

Methods

The patient received a single dose of intravenous epoetin at 600 UI/kg (4000 UI). Blood samples were obtained for pharmacological analysis (1 ml/sample; total drawn per patient during study: 4 ml) before infusion and 12, 24 and 36 h after EPO infusion. At the same time, urine samples were collected at hours 0, 1/2, 1, 2, 3, 4, 5, 6, 12, 18 and 24. The 24-h amount of urine excretion was calculated in order to obtain the total rate of urinary erythropoietin excretion.

The EPO level in each sample was measured by an enzyme-linked immunoabsorbant assay. The ELISA used quantifies epoetin as well as endogenous EPO.

EPO—pharmacokinetics

Urinary epoetin pharmacokinetics is described in Figure 1. The urinary loss of 27% of the given dose was observed within the first 24 h following IV injection. The urinary concentration peak was found at 3 h (194 × 10^3 UI/g creatinine).

Plasma EPO levels remained increased 24 h (228 UI/l) after injection, but decreased drastically after 7 days (1.6 UI/l), which resulted in inappropriately low plasma EPO considering haematocrit of 20%.

Discussion

Anaemia in patients with nephrotic syndrome has been described before [3,4]. In these patients, EPO losses have been identified and treated by substitution with usual doses of epoetin [4–6]. Our patient had an exceptionally severe phenotype requiring extremely high amounts.
of IV albumin. Despite increasing doses of epoetin, transfusion requirements remained identical. While the patient received daily epoetin, levels in our patient were supra-physiological. However, anaemia persisted, suggesting the loss of other plasma proteins such as transferrin (80 kDa) and/or transcobalamin (43 kDa) to be responsible for the disturbed erythropoiesis.

Atransferrinaemia has been reported as a cause of severe non-regenerative anaemia [7]. Transferrin levels were undetectable in our patient. Erythropoietic cells are dependent on iron availability that requires transferrin for iron transport into the cell via a specific transferrin receptor on the cell surface. If transferrin is absent, iron supplementation is inefficient.

Transferrin substitution is possible using fresh frozen plasma in patients with congenital atransferrinaemia [7]. In cases of severe nephrotic syndrome, such a supplementation is not reasonable. The only treatment option is repeated blood transfusions.

The soluble transferrin receptor (sTFR) has been shown to be upregulated in nephrotic children with hypotransferrinaemia [8], but presumably upregulation of sTFR can only counterbalance hypotransferrinaemia but not atransferrinaemia as detected in our patient.

Similar to transferrin, there is a massive loss of transcobalamin, a plasma protein essential for the transport and cellular uptake of vitamin B12. The serum transcobalamin level is known to reflect vitamin B12 absorption better than does the serum vitamin B12 level [9].

Repeated blood transfusions encounter a risk for immunization. Therefore, we decided to perform bilateral nephrectomy when the patient reached a body weight of 7 kg resulting in normalization of transferrin and transcobalamin levels and blood cell count under a standard epoetin substitution of 150 UI/kg/week.

The severity of the phenotype might be due to the particular genotype (c2212+delTG in exon 16 of the NPHS1 gene). However, Fin-major and Fin-minor mutations have been shown to cause the absence of nephrin, but not therapy-resistant anaemia. Another hypothesis is that the patient carries a second genetic anomaly of the glomerular filtration barrier. However, search for mutations of NPHS2 and WT-1 revealed normal genes.

Classically, transferrin deficiency causes microcytic, whereas transcobalamin deficiency causes macrocytic anaemia. Our patient had both transferrin and transcobalamin deficiencies and as a result of both, anaemia was normocytic.

A correlation between anaemia and total protein concentration was made in very low birth weight infants [10]. This setting could also be applicable for proteinuric children. Subsequent hypoproteinaemia might concern ion transporters but also globin synthesis, which may play a part in EPO-resistant anaemia.

The use of darbepoetin alpha (molecular weight 37 kDa) instead of epoetin beta (34 kDa) might be discussed in our patient. However, the difference in molecular weight is probably not high enough to significantly reduce its leakage.

**Conclusion**

EPO-resistant normocytic anaemia in our patient with CNF seems to be due to the massive loss of transferrin and transcobalamin in the urine. The benefit–risk ratio of very early bilateral nephrectomy or repeated blood transfusions has to be carefully evaluated in such patients.

**Conflict of interest statements.** None declared.

**References**