Case Report

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

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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 × 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 × 103 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.

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Renal biopsy on day 12 did not reveal any histological alteration and no immune deposits on immunofluorescence (IF) investigation. No anti-nephrin antibodies were detected in the patient’s serum on indirect IF testing using normal human kidney as antigen.

Night-time proteinuria decreased progressively from day 15 post Tx, ranging from 0.25 to 0.5 g/l. Serum creatinine decreased to normal levels on day 16 and serum albumin was decreased from day 10 (35 g/l) to day 18 (32 g/l), but rapidly normalized thereafter (42 g/l). Three months post Tx, changes of proteinuria between night-time (≈60–90 mg/mmol creatinine) and daytime (≈10–20 mg/mmol creatinine) persisted, but to a much lesser degree; renal function as well as blood pressure were normal.

**Discussion**

Recurrence of nephrotic range proteinuria after renal Tx in children with the nephrotic syndrome of the Finnish type has been described in patients with mutations of the NPHS1 gene responsible for the absence of nephrin [4,5]. Our patient had mutations of the NPHS1 gene which were previously described [6]. These mutations are known not to cause premature stop codons or frameshifts responsible for complete absence of nephrin. However, these mutations might affect the folding and thereby the transport and addressing of the translated protein by the endoplasmatic reticulum, resulting in absence of nephrin in the glomerular basement membrane [6].

Generally, antibody production after exposure to a neoantigen (e.g. nephrin) occurs after more than 1 month, whereas proteinuria in our patient recurred after only 6 days post Tx. Further, the intermittent character of proteinuria in our patient makes immunological mechanisms extremely improbable.

Nevertheless, we searched for circulating anti-nephrin antibodies in the patient’s serum from post-Tx days 6, 8, 10 and 12 using indirect IF, which was negative. A difference between daytime and night-time urine samples has been evidenced from the fifth day post Tx. During the first post-operative days, the patient preferred a supine sleeping position due to pain at the site of transplantation. Once wound pain decreased, the patient preferred a ventral sleeping position especially on the side of her transplant.

We hypothesize that mechanical pressure on the transplant and, in particular, on the renal vein was increased during night-time due to her sleeping position, resulting in mild to moderate compression...
of the renal vein, despite an otherwise normal sonography (Figure 2). Complete renal vein compression would probably have caused macroscopic haematuria and renal failure. However, a moderate compression is comparable with the mechanism suspected for the proteinuria in ‘nutcracker syndrome’ (an entrapment of the left renal vein between the aorta and the superior mesenteric artery and subsequent compression of the renal vein) and orthostatic proteinuria as previously described [8–11]. Faizan et al. [12] described an adolescent patient with an asymptomatic proteinuria exclusively detected in night-time urine samples. A voluminous splenic cyst compressing the left renal vein was detected on CT scan. This compression was emphasized by her left lateral sleeping position [12]. Another clinical entity with a mechanical phenomenon responsible for proteinuria is the acute abdominal compartment syndrome with acute increase of intra-abdominal pressure due to surgery and/or trauma [13–15].

Reduction of night-time proteinuria after day 15 might be explained by resolution of moderate post-operative seroma, evidenced on sonography investigation on day one and considered as non-compressive by the examiner. Additional compression by very moderate post-operative venous lesion could not be evidenced by repeated Doppler investigations. These conditions could have ‘demasked’ moderate venous compression up to day 15 post Tx, followed by spontaneous resorption.

The diagnostic dilemma could not be firmly resolved by direct investigation of the renal vein, as Doppler examination in a child during a ventral sleeping position is technically impossible. Imaging studies using contrast medium such as arteriography and CT scan would represent a considerable risk for a recently transplanted child.

We believe that a mechanical pathogenesis of proteinuria post Tx should be considered once classical aetiologies are excluded by appropriate investigations. Recurrence of proteinuria has been reported in several cases of NSF without anti-nephrin antibodies on indirect IF examination [16,17]. Such cases suggest that (i) a renal biopsy with IF investigation is warranted because of the possibility of low serum antibody levels and false negative indirect IF due to the relatively high amount of potential nephrin binding sites and (ii) in case of negative direct and indirect IF examination, mechanical aetiologies should be investigated, in particular, if an adult kidney is transplanted to a relatively small child. Urine and blood samples concomitant with different positions of the patient may be an interesting diagnostic tool. Absence of diagnosis may lead to unjustified, aggressive immunosuppressive treatments and/or plasma exchange.

In conclusion, massive night-time proteinuria post Tx in a small child may mimic immunological mechanisms. The pathogenesis is presumably comparable with the mechanism of proteinuria in nutcracker syndrome.

Conflict of interest statement. None declared.

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Received for publication: 23.4.06  
Accepted in revised form: 5.7.06