


LETTER TO THE EDITOR

Spontaneous remission in a child with an NPHS1-based congenital nephrotic syndrome

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Congenital nephrotic syndrome (CNS) refers to disease presenting within the first 3 months of life. Mutations in five different genes (NPHS1, NPHS2, PLCE1, WT1 and LAMB2) are responsible for >80% of cases [1]. The disease is classically considered as irreversible, progressing in early infancy to end-stage renal disease (ESRD). Although some NPHS1 mutations have been associated with a more favorable evolution [2], only anecdotal cases of spontaneous remission have been reported.

We present an 11-day-old male term neonate who was admitted in hospital with a generalized seizure. Pregnancy ultrasounds were normal; no polyhydramnios or placental edema was reported. Nuclear magnetic resonance imaging diagnosed a cerebral venous sinus thrombosis. Physical examination showed palpebral and lower limb edema. Laboratory tests showed albumin 0.5 g/dL, total proteins 3.2 g/dL, creatinine <0.15 mg/dL, calcium 6.7 mg/dL and total cholesterol 230 mg/dL, with a urinary protein:creatinine ratio of 36.1 mg/mg. An etiological study ruled out a congenital infection. The genetic study showed a compound heterozygous for two different sequence variants in exons 9 and 27 (NM_004646.4:c.1048T>C:p.Ser350Pro; M_004646.4:c.3478C>T:p.Arg1160Ter) of the NPHS1 gene, inherited from both parents. Anticoagulant, antiproteinuric and diuretic treatment was started. Edema was partially controlled and no albumin infusions were required. After 6 months, a progressive increase in serum albumin with a parallel decrease

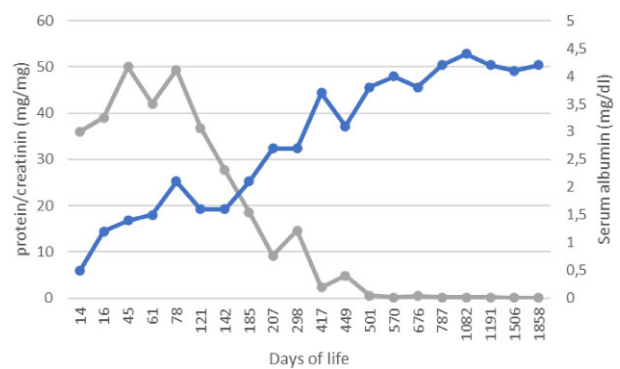


FIGURE 1: Albumin and proteinuria evolution. Blue line shows the progression of serum albumin and grey line the progression of proteinuria.

in proteinuria was observed until normalization at 18 months (Figure 1). Antiproteinuric treatment was withdrawn at 2 years of age.

Initial coagulation studies identified a factor XII deficiency (43%) that continued 1 year later (44%). A familial deficiency was suspected, but the genetic study is not yet available. Anticoagulant treatment was maintained for 3 years and it was replaced by antiplatelet therapy for one more year.

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Table 1. Clinical and genetic features of published patients with spontaneous remission and proven NPHS1 mutation

Reference	Age at onset	Mutation in NPHS1	Clinical course	Treatment
Wong et al. [5]	No data	c.2131C>A(p.Arg711ser) homozygous missense mutation	Renal survival of 30 years No data about proteinuria	No data
Li et al. [7]	1 month and 20 days	c.3312-23C>T intron 25 c.2207T>C exon 16 c.928G>A in exon 8	Remission	Glucocorticoids (maintains)
Kozziel et al. [6]	No data	c.3478 C>T in exon 27 homozygous missense mutation	Remission at 11 years of age 5 years of age	No data
Our case	11 days	c.1048T>C(p.Ser350Pro) in exon 9 c.3478C>T(p.Arg1160Ter) in exon 27	Remission at 6 months	Supportive

At present, he is 5 years old and serum protein, albumin and cholesterol are normal with no proteinuria (urinary protein:creatinine ratio 0.11 mg/mg).

CNS is a rare kidney disorder usually caused by genetic defects in the components of the glomerular filtration barrier. Immunosuppressive medication is not helpful and these children usually progress rapidly to ESRD. Spontaneous resolution was reported anecdotally in the 1980s–1990s, most of the patients with no genetics studies [3, 4]. Data available in five patients with a proven NPHS1 mutation are shown in Table 1.

NPHS1 mutation patients appear to behave distinctly in some ethnic groups, such as the Maori population, which displays a clear improved renal survival (median 30 years versus 0.7 years in non-Maories) [5]. Nevertheless, all patients remained with proteinuria and continued antiproteinurics. The most prevalent alteration was a homozygous missense mutation in exon 16, but other alterations in exon 19 and exon 27 were also described. One of the mutations in our patient is in exon 27 (p.Arg1160Ter), although different from those described in the study. A previous report also showed that this mutation can produce a severe clinical picture in some patients but an atypical milder phenotype in others [6].

Factor XII deficiency is usually an asymptomatic disorder, only associated with an increased risk of hemorrhage in its most severe forms. In adults, there are registered cases of thrombosis only if another thrombotic risk factor is present; no cases have been described in children. Our patient had only a partial deficit and it is difficult to accept it as the cause of the cerebral thrombosis. No studies linking factor XII deficiency and nephrotic syndrome have been published.

In conclusion, although the clinical presentation and the genetic study correspond with a classic CNS, clinical evolution has been surprising, with complete remission. We do not know the role played by the factor XII deficiency, if any. The use of genomic approaches will perhaps allow us in the future to identify the most favorable mutations in this severe disease.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

PATIENT CONSENT

The patient's family gave informed consent to publish this case.

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