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Brief report

Adequate clinical control of congenital nephrotic syndrome by enalapril

Sophie Guez[1], Marisa Giani[1], Maria Luisa Melzi[1], Corinne Antignac[2], and Baroukh M. Assael[1]

[1] Department of Pediatrics, University of Milan, Milan, Italy
[2] INSERM U-423, Hôpital Necker-Enfants Malades, Paris, France

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Abstract. The combination of captopril and indomethacin has been shown to control nephrotic proteinuria in an infant with congenital nephrotic syndrome of the Finnish type. We report the satisfactory control of congenital nephrotic syndrome by enalapril, maintaining normal serum albumin levels without albumin infusions. The haplotype data of our patient were consistent with the diagnosis of a Finnish-type nephrotic syndrome. After 21 months, during which daily infusions of albumin allowed partial control of the symptoms, captopril treatment was started. No adverse effects were noted. Serum creatinine levels remained normal. Within 8 weeks, albumin infusions were completely stopped. After 1 month the treatment was changed to a single dose of enalapril (0.8 mg/kg per day). During the next 15 months, the serum protein concentration was maintained around 6.5–7 g/dl, although proteinuria persisted (0.3–0.5 g/day). Weight and length gain are now satisfactory. We conclude that enalapril may be safely used in infants with severe forms of congenital nephrotic syndrome and might allow the avoidance of aggressive treatments for prolonged periods.

Key words: Finnish-type nephrotic syndrome – Congenital nephrotic syndrome – Angiotensin converting enzyme inhibitors – Enalapril

Introduction

Finnish-type congenital nephrotic syndrome (CNF) is the most common of a variety of syndromes characterized by heavy proteinuria at birth or shortly thereafter. The diagnosis may be suspected antenatally from the presence of elevated amniotic fluid levels of alpha-fetoprotein and clinically in the presence of a heavy placenta weighing more than 25% of the baby's birth weight and massive proteinuria starting in utero or shortly after birth. The defective CNF locus has recently been located on chromosome 19q12-13.1 by linkage analysis in Finnish [1] and non-Finnish populations [2]; in informative families the disease may now be diagnosed antenatally.

The syndrome is characterized by unresponsiveness to steroids or to immuno-suppressive drugs. Renal function may deteriorate within the 2nd to 3rd year of life. Palliative interventions have included monolateral nephrectomy, to partially reduce proteinuria, and intensive treatment with daily infusion of high doses of human albumin. Dietary control of hypertriglyceridemia and supportive therapy with thyroid hormones are usually necessary. Generally, within the 2nd year of life such treatments are no longer sufficient and many affected children show inadequate somatic and intellectual development. At this point binephrectomy with subsequent dialysis are required [3, 4]. Renal transplantation is the only solution, although exceptionally the disease may reappear in some children after transplantation [5].

Pomeranz et al. [6] treated two such patients with indomethacin and captopril, the rationale being that the combined action of these drugs on glomerular hemodynamics may reduce proteinuria. Such an effect had been shown experimentally in diabetic microproteinuria and in some cases of idiopathic nephrotic syndrome [7–9]. The authors were successful in one patient. In the other, although proteinuria decreased, renal function deteriorated making hemodialysis necessary. To our knowledge, no other successful cases have been reported to date. We describe here a patient with congenital nephrotic syndrome whose haplotype was compatible with a Finnish type in whom enalapril alone allowed adequate clinical control.

Correspondence to: B. M. Assael, Clinica Pediatrica, Via Commenda 9, I-20122 Milan, Italy

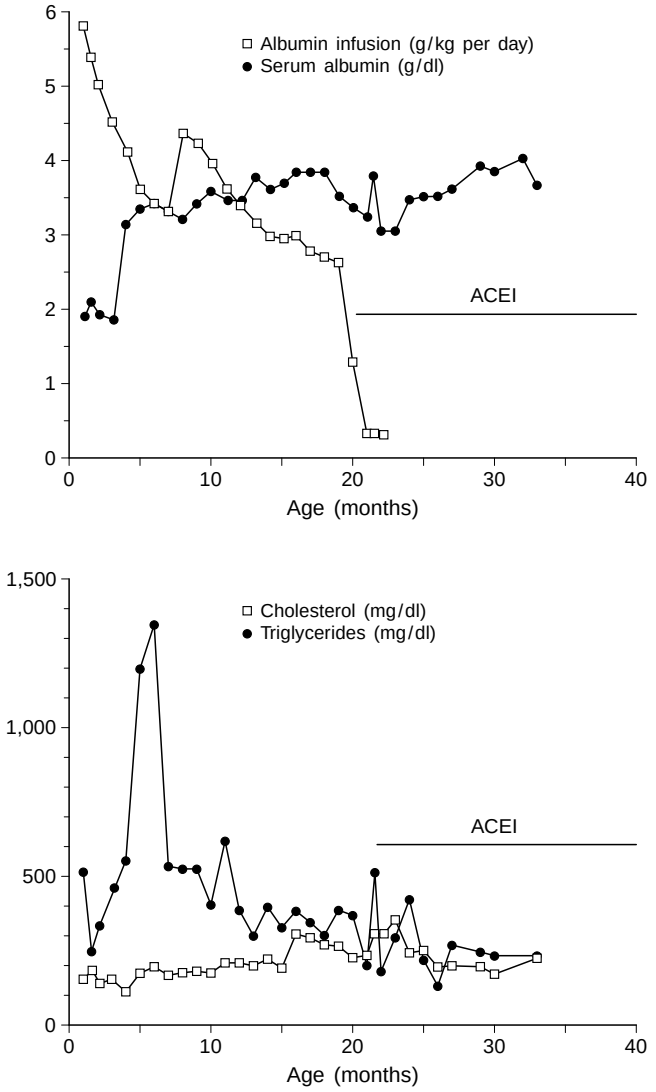

Fig. 1. Captopril-enalapril efficacy in congenital nephrotic syndrome of the Finnish type. Angiotensin converting enzyme inhibitor (*ACE-I*) was started at the age of 21 months. *Upper panel:* albumin infusion and serum albumin concentration. *Lower panel:* serum cholesterol and triglycerides concentrations

Case report

The patient is the second daughter of two related parents (first cousins) originating from Sicily (southern Italy). Several brothers of the father had died as neonates, although of unknown causes.

The child was born in September 1993, at 35 weeks' gestation; her birth weight was 2,330 g. The placenta weighed 1,030 g, approximately 45% of body weight. Heavy proteinuria was present from birth (3–6 g/day), associated with microhematuria, glycosuria, elevated calciuria, phosphaturia, and aminoaciduria. The plasma albumin concentration was as low as 1.5 g/dl. Calcium and phosphate supplementation were provided to correct hypocalcemia and hypophosphatemia. The serum creatinine concentration was moderately elevated (1.86 mg/dl) and slowly decreased in the first 4–5 months of life. The child was anemic (hemoglobin 5.8 g/dl, hematocrit 16.2%) and was transfused at 3 months of age. Serum albumin, cholesterol, and triglyceride concentrations in the first 34 months of life are shown in Fig. 1, during albumin infusion and angiotensin converting enzyme inhibiter (ACE-I) treatment. Renal ultrasound showed slightly enlarged hyperechogenic kidneys with poorly differentiated parenchyma.

Pathology. Renal biopsy was performed at the age of 2 months. Twenty-eight glomeruli were present; most glomeruli were normal, some had sclerosis. There was tubular microcystic dilatation. On electron microscopy, 2 glomeruli showed an irregular glomerular basement membrane, with a thickened internal lamina rara, abnormal architectural basal mesangial membrane, and fetal structured podocytes. No mesangial hypercellularity was present. This was consistent with the diagnosis of CNF.

Molecular genetics. We carried out molecular genetic studies of the family to ascertain whether the results would be consistent with the clinical and pathological diagnosis. The gene for CNF has been localized to chromosome 19q12-13.1 between markers D19S416 and D19S224 [10]. Four microsatellite markers located in the CNF region were tested for linkage in the family. Polymorphic microsatellite markers were analyzed by polymerase chain reaction. Details of the methods employed have been published previously [2]. The patient was homozygous for all the markers used, while the parents were heterozygous, and the unaffected sister did not share any haplotype with her affected sister. These haplotype data are consistent with the diagnosis of CNF.

Follow-up. In November 1993, we started daily human albumin infusions (4 g/kg per day), administered through a central venous line. The serum albumin concentration increased to an average level of 3.3–3.7 g/dl. This treatment was continued for 20 months and the maximum albumin dosage used was 24 g/day. The child also received an amino acid infusion (3–6 g/kg per day) until she was 16 months old. On an unrestricted diet her caloric intake was 100 kcal/kg per day and her protein intake was 2.4 g/kg per day. Extreme hypertriglyceridemia (plasma triglycerides reached a maximum level of 1,500 mg/dl) led us to start treating her with an oral hypolipemic drug (Genfibrosil). Erythropoietin was given to partially correct anemia from the 8th to the 11th month of life. She was also supplemented with thyroid hormones to correct a slight hypothyroidism. Overall this treatment was quite successful, although difficult to manage. Her general condition was satisfactory and she grew only slightly below the 3rd percentile. A Denver development test performed at the age of 18 months showed minimal retardation, which improved at a subsequent control 7 months later. During this period, massive proteinuria persisted and urinary protein excretion was about 10–12 g/day.

In June 1995, after an occlusion of the central catheter, we started treatment with captopril 3 mg three times a day (0.75 mg/kg per day), rapidly reaching a total daily dose of 4.8 mg/kg. After 1 month this was substituted by enalapril 0.75 mg/kg per day. Shortly after the beginning of this new treatment, albumin infusions were progressively tapered, the last being given 2 months later. During follow-up, which is now of 15 months' duration, serum albumin concentration was maintained at 3.8–4.0 g/dl. Urinary protein excretion gradually diminished, although proteinuria persisted around 300–500 mg/day. Serum creatinine concentration ranged between 0.5 and 0.7 mg/dl; the calculated creatinine clearance was 49–73 ml/min per 1.73 m^2. Serum lipid profile clearly improved: cholesterol decreased to 227 mg/dl and serum triglycerides to 155 mg/dl after 1 year of this treatment. Thyroid hormones were stopped. Moderate anemia persists (hemoglobin concentration 8.4–8.9 g/dl). The child is now growing along the 3rd percentile.

Discussion

Our patient presented some features which are not typically associated with CNF, such as good renal function in the first years of life and sclerosis and interstitial lesions at an age when mesangial hypercellularity is usually seen. The differential diagnosis of congenital nephrotic syndrome include various conditions [11], but early manifestations, high placental weight, familiarity (the parents were first

cousins), and haplotype analysis were present in our patient and were consistent with the diagnosis of CNF.

CNF has to date been considered an incurable disease, the goal of any treatment being to postpone renal transplantation to at least after the 1st year of life. Birnbacher et al. [12] treated one neonate with enalapril, but did not get any response in 8 weeks of treatment after reaching a total daily dose of 2.5 mg/kg. There are two reported cases, including the present, in which pharmacological treatment allowed good metabolic control, adequate growth and intellectual development, and no deterioration of renal function. In these cases however, captopril was used at higher dosages (up to 5 mg/kg per day), and in one [6] ACEI was combined with indomethacin.

The mechanism by which ACEI achieves this can only be speculated. Its ability to decrease proteinuria seems to be driven by an angiotensin-independent mechanism. ACEI increases the levels of bradykinin and stimulates the production of vasodilator prostaglandins. Bradykinin decreases the resistance of both afferent and efferent arterioles, increasing renal blood flow. This leads to a reduced axial protein concentration along the length of the glomerular capillary, with a beneficial effect on proteinuria. Reduction of proteinuria has been seen within 1 week to 1 month in children with glomerular diseases other than minimal change nephrotic syndrome and in diabetic adults [7, 8]. Indomethacin may potentiate the effect by selectively constricting the afferent glomerular artery. This effect is usually seen within 1–3 days and vanishes shortly after stopping the treatment [6], but the drug may also reduce glomerular filtration rate. We were able to avoid using indomethacin, since good results were achieved with enalapril alone.

It is still unclear which types of congenital nephrotic syndromes may react to ACEI. The gene mutation responsible for CNF has also not yet been identified and it is not known how many mutations account for the disease nor whether there is a correlation between genotypes and phenotypes. Some mutations might be milder or have some properties which favor the effect of ACEI. Since captopril has been associated with acute renal failure in the neonate [13], it is questionable whether ACEI should be tried soon after birth, before starting high-dose daily albumin infusions. Probably the optimal treatment would be to start infusion first and try enalapril after a month or more. Admittedly, this would still be an empirical approach, and more patients need to be studied. Although the value of medical treatment is not definitely established in CNF, and more generally in congenital nephrotic syndromes, we believe that it may be worth trying enalapril in any patient with congenital nephrotic syndrome before proceeding to nephrectomy.

We do not know how long enalapril will maintain its efficacy in our patient. The successful case described by Pomeranz et al. [6] was still on treatment at the age of 4 years (Bernheim J., personal communication). So far our patient has been treated for 1 year and has reached an age at which renal transplantation is far more successful than during the 1st year of life. Since all blood biochemistry is now normal we envisage continuation of this treatment as long as possible.

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