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SHORT REPORT

A boy with congenital analbuminemia and steroid-sensitive idiopathic nephrotic syndrome: an experiment of nature

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Abstract In this paper, a boy is reported with the association of congenital analbuminemia (CAA) and steroid-sensitive idiopathic nephrotic syndrome (INS), two conditions resulting independently in reduced colloid oncotic pressure. The unique occurrence helps confirm earlier reports that albumin is not the exclusive factor responsible for maintaining colloid oncotic pressure.

Keywords Congenital analbuminemia · Steroid-sensitive idiopathic nephrotic syndrome · Oncotic pressure · Albumin

Introduction

Congenital analbuminemia (CAA) is a rare autosomal recessive disorder [9] in which subjects have little or no circulating serum albumin due to defective albumin synthesis in the liver [23]. Fewer than 50 patients have been recorded so far in the continuously updated Register of Analbuminemia Cases [18]. Idiopathic nephrotic syndrome (INS) has a prevalence of 1 in 6,000 children and is characterized by hypoproteinemia, proteinuria, and edema. Approximately 90% of children with INS respond to steroids, and renal histology mainly shows minimal change nephropathy [19]. The underlying pathogenetic mechanism of INS is a defective glomerular permselectivity resulting in albuminuria and hypoalbuminemia (<2.5 g/dl), leading to the loss of serum oncotic pressure. We report a boy with the incidental association of CAA and steroid-sensitive INS.

Interest: no interest declared.

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Case report

The male patient was born at term (37 week gestation), but "small-for-gestational-age" with weight (2.2 kg) and length (44 cm) <3rd percentile. Pregnancy had been complicated by polyhydramnios. Mild peripheral edema was noted at three days of age. Further investigations revealed moderate hypoproteinemia (3.5 g/dl) and marked hypoalbuminemia (1.4 g/dl). At the age of nine months, the diagnosis of CAA was confirmed with serum albumin persistently below 0.2 g/dl; urinalysis and fecal concentration of alpha1-antitrypsin were normal, making urinary or enteral loss unlikely. At the age of four years, serum proteins (agarose gel electrophoresis) and lipids were as shown in Table 1: albumin was very low; alpha 1 globulins (main constituents: α1-lipoprotein, α1-glycoprotein, α1-antitrypsin), alpha 2 globulins (α2-macroglobulin, pre-β-lipoprotein, haptoglobin), and beta globulins (transferrin, β-lipoprotein, complement) were elevated; gamma globulins, IgG, IgA, IgM were normal; total and LDL cholesterol (enzymatic analysis) were markedly elevated, HDL cholesterol was just above reference range; lipoprotein(a) and triglycerides (turbidimetric analysis) were elevated; there was no proteinuria. The further clinical course was uneventful apart from recurrent mild upper respiratory tract infections associated twice with a febrile convulsion; an electroencephalogram was normal.

When the DNA sequence analysis of the human albumin gene became available, a C→T substitution at nucleotide

4446 was identified in the proband [4]. The mutation changes the codon CGA for Arg 114 to a stop codon TGA, resulting in premature termination and is responsible for the analbuminemic trait. The putative protein product, called Albumin Zurich, would have a length of 113 residues.

At the age of 5 years, he was admitted to our hospital because the parents had noticed swelling of the legs and a weight gain of 2 kg during the previous month. Clinical examination showed blood pressure in the upper normal range (110/70 mm Hg) and, apart from swelling of the legs and the face, no further abnormalities, in particular, no evidence of hypovolemia. Height and weight were 111 cm (50th percentile) and 23 kg (90th–97th percentile), respectively. On the assumption that the clinical condition was caused by the CAA, the patient was given immediately after admission (defined as day 0) a single dose of albumin intravenously (i.e., 100 ml of albumin 20%; purity of albumin ≥96%). Urine had been routinely collected before albumin was given, but the result was noticed only after the albumin infusion had been administered and unexpectedly revealed proteinuria (2+ on Combur Stix®, Roche, Basel, Switzerland). Combur Stix® is highly sensitive, but not specific for albumin, detecting also for other proteins. There was no hematuria. Further serum and urinary laboratory investigations were performed on day 1, i.e., after the albumin infusion (Table 1). Renal function, assessed as plasma creatinine (0.4 mg/dl; Jaffé method), and sodium were normal.

Serum albumin rose on day 1, i.e., 8 h after the albumin infusion, to a maximum concentration of 11.6 g/l and returned to baseline on day 10 with an estimated serum half-life (T1/2) of <5 days. Serum alpha 2 globulins and cholesterol showed a transient increase from baseline; in contrast, alpha 1 globulins, beta globulins and gamma globulins, and IgG were transiently decreased. Twenty-four-hour proteinuria on day 1 consisted mainly of albumin. On day 10, proteinuria persisted, but albuminuria was almost absent and the main urinary protein constituents

Table 1 Biochemical parameters in serum and urine

Date	Normal range (aged at 4 years)	Age 4 years	Age 5 years: INS			Age 11 years 2007
			Day 1*	Day 10	Day 37**	
Serum						
Total protein: g/l	60–80	**46*** **	**40**	**41**	**54**	**50**
Albumin: g/l	37–45	**2.6**	**11.6***	**2.4**	**2.6**	**1.1**
Alpha 1 globulins: g/l	1.2–2.8	**4.5**	1.8	**3.2**	**5.9**	**4.7**
Alpha 2 globulins: g/l	4.3–8.3	**13.9**	**15.0**	**19.1**	**19.0**	**16.6**
Beta globulins: g/l	4.9–8.1	**15.4**	**9.5**	**12.9**	**20.3**	**18**
Gamma globulins: g/l	4.9–10.5	9.6	**2.1**	**3.4**	6.3	9.7
Total IgG: g/l	6–12	8.0	**1.5**	**1.9**	**5.1**	8.9
IgG1	4–11			**1.1**		5.7
IgG2	0.85–4.1			1.1		2.7
IgG3	0.13–1.42			0.3		0.7
IgG4	0.03–1.89			0.2		0.6
IgA: g/l	0.5–2	1.9		1.6	**2.2**	**2.4**
IgM: g/l	0.5–1.5	1.1		0.9	1.5	1.0
Sodium: mmol/l	135–145	137	137	139	137	139
Cholesterol: mmol/l	1.6–4.9	**12.3**	**18.9**	**17.2**	**20.4**	**13.8**
HDL-cholesterol	1.0–1.3	1.6				1.1
LDL-cholesterol	2.9–4.9	**9.7**				**11**
Apo-lipoprotein A1: g/l	1.1–1.8					1.3
Apo-lipoprotein B: g/l	0.6–1.4					**2.8**
Lipoprotein (a): g/l	<0.56	**2.0**				**4.4**
Triglycerides: mmol/l	0.5–1.6	**2.2**	**4.0**	**3.7**		**3.6**
Urinary excretion: g/24 h						
Protein		0	**4.2**	**3.1**	0	0
Albumin		0	**3.0**	**0.1**	0	0
Alpha 1 globulins		0	**0.7**	**1.4**	0	0
Alpha 2 globulins		0	**0.1**	**0.5**	0	0
Beta globulins		0	**0.3**	**0.8**	0	0
Gamma globulins		0	**0.1**	**0.3**	0	0

*Day 1=*after* the administration of albumin 20 g i.v. on day 0; **Day 37=in remission; ***All results outside reference range in **bold**

(agarose gel electrophoresis) were alpha 1 and beta globulins. Qualitative sodium dodecyl sulfate polyacrylamide gel (SDS-PAGE) urinary electrophoresis on day 1 and day 10 revealed also transferrin, IgG, IgM, and complement C3.

The presumptive diagnosis was idiopathic nephrotic syndrome (INS). However, since hypoalbuminemia as a diagnostic hallmark of INS was difficult to interpret in the context of CAA, a renal biopsy was performed on day 5. Light microscopy showed 14 normally structured glomeruli and immunofluorescence was negative; electron microscopy revealed effacement of foot processes involving about 80% of the glomerular capillary circumferences, leading to the diagnosis of minimal change nephropathy (Fig. 1). On day 6, oral prednisone (40 mg per day) was started. On day 21, the patient came into remission (i.e., no proteinuria). On day 37, a detailed analysis of serum and urine was repeated (Table 1). Prednisone was continued for six weeks and was then switched to 25 mg on alternate days for a further six weeks. No relapse of the INS has occurred so far.

Currently, at the age of 11 years, the boy is healthy apart from occasional mild infections of the upper airways. Blood pressure (95/60 mm Hg), height (144.5 cm, 25th–50th percentile), and weight (40.8 kg; 75th centile) are normal, and there is no peripheral edema. The serum protein and lipid pattern is identical to the results obtained at 4 years of age; urinalysis shows no proteinuria (Table 1). X-rays of the hands and knees reveal normal osseous structure. The non-consanguineous Swiss parents, heterozygous for the C→T substitution at nucleotide 4446 [4], are healthy and have a slightly decreased serum albumin concentration (father: 32 g/dl; mother: 36 g/dl). Family history is negative for miscarriages or neonatal deaths.

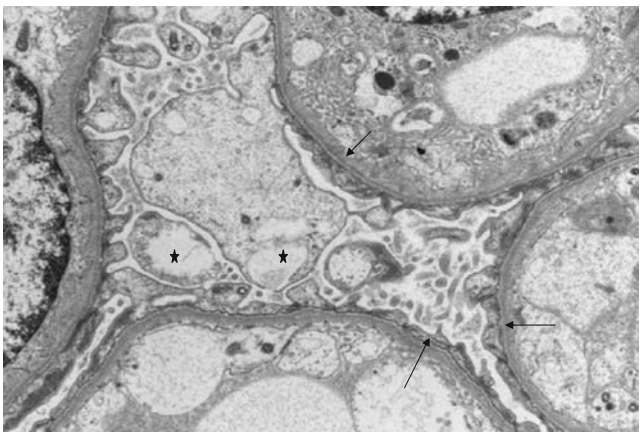

Fig. 1 Renal biopsy. Electron micrograph of a portion of a glomerulus with effacement of foot processes (*arrows*) and the vacuolization of podocytes (*asterisks*). (Uranyl acetate and lead citrate; ×7,500)

Discussion

This report describes a boy with CAA and steroid-sensitive INS, a unique association of two conditions resulting independently in reduced colloid oncotic blood pressure. CAA is a rare autosomal recessive disorder [4, 9, 18, 21], leading to defective albumin synthesis in the liver [23], with subsequent very low serum albumin concentration (<2 g/dl). If albumin is administered intravenously to patients with CAA, its biologic half-life is prolonged to 38–50 days (reference range: 16–20 days) [21, 23]; on the contrary, the half-life in our patient was very short (<5 days), raising the question of albuminuria.

Colloid oncotic blood pressure in healthy individuals is mainly maintained by serum albumin (normal range: 26–31 mm Hg) [12, 20]. The oncotic pressure in patients with CAA is persistently decreased to about half of its normal value [12, 16]. Marked edema, however, is absent, and only half of these patients present with mild peripheral edema, indicating the presence of edema-preventive measures (reviewed in 12, 16]). Increased concentrations of non-albumin proteins (mainly alpha 1, alpha 2, and beta globulins) [8, 12, 23] and lipoproteins [8, 12, 16, 21], and lowering in parallel of the interstitial oncotic pressure through washout of interstitial colloids and increased lymph drainage, mitigate the effect on the capillary oncotic pressure and the transcapillary oncotic gradient [8, 12, 16]. In addition, there is a reduction of the hydrostatic pressure gradient by lowering the capillary blood pressure and increasing the interstitial pressure [14]. Experimental data on the effect of hypoalbuminemia on the capillary permeability are controversial. Wraight [24] showed a decreased glomerular permeability to proteins in rats made acutely hypoalbuminemic after plasmapheresis, whereas Fujihara et al. [6] demonstrated enhanced glomerular permeability to macromolecules in the (chronic) analbuminemic Nagase rat. When our patient was in remission, he had no proteinuria, suggesting that permeability for macromolecules was not enhanced.

Children with INS present with marked edema, typically resulting in weight gain. Proteinuria mainly consists of albumin, but other proteins, including transferrin [3] and gamma globulins (IgG, subclasses) [1, 17], are also lost in the urine, though to a much lesser extent. Albuminuria and hypoalbuminemia result in the acute reduction of colloid oncotic pressure, with low values (≤12 mm Hg) [20] comparable to patients with CAA. This leads—at least in a subgroup of children with steroid-sensitive INS—to hypovolemia and secondary activation of the renin-angiotensin-aldosterone axis, the sympathetic nervous system, and vasopressin secretion with subsequent edema formation, consistent with the "underfilling" hypothesis (summarized in [20]). However, most studies from (mainly adult) patients

with the nephrotic syndrome have failed to find a consistent reduction in blood and plasma volume, suggesting primary renal sodium retention [14, 20]. In addition to renal molecular mechanisms, increased hydraulic conductivity due to the transconformation of endothelial intercellular junctions driving the leakage of fluid into the interstitium has been suggested [5]. Immune mechanisms related to the release of cytokines in INS, leading to generalized vascular hyperpermeability, have also been postulated [15]. The role of circulating vascular endothelial growth factor (VEGF) is, however, controversial [2, 22].

The defense mechanisms in nephrotic syndrome against edema formation are, at least partially, similar to CAA, i.e., lowering in parallel of the interstitial oncotic pressure through washout of interstitial colloids and increased lymph drainage, and reduction of the hydrostatic pressure gradient by lowering the capillary blood pressure and increasing the interstitial pressure [14, 20]. Additional defense mechanisms in children with INS and concomitant hypovolemia and hyponatremia (both not present in our patient) include unidentified endogenous osmoles [10, 13]. The colloid oncotic pressure in patients with CAA and INS is comparable. Whereas the low oncotic pressure state is a chronic condition in CAA, allowing for effective edema-preventive measures, the pressure changes occur very fast in INS and, thus, preclude successful defensive mechanisms.

The question, however, arises as to why this patient with INS and CAA did develop edema at all, as the CAA makes the usual cause for edema irrelevant. In fact, the clinical presentation of the INS, i.e., the extent of edema, in this patient was mild. We hypothesize that at least two mechanisms might have contributed.

Firstly, some of the serum proteins in patients with CAA compensating for the low albumin have a higher MW than albumin (MW 66 kD) [7], in particular, the main constituents of alpha 2 globulins (α2-macroglobulin: MW 725 kD; pre-β-lipoprotein: MW>3,000 kD; haptoglobin: MW 100 kD) [7], precluding major glomerular filtration. In fact, serum alpha 2 globulins were elevated during the INS, thereby, "defending" oncotic pressure. In contrast to alpha 2 globulins, two other non-albumin constituents maintaining oncotic pressure in CAA, i.e., alpha 1 and beta globulins, have MW comparable to albumin (α1-glycoprotein: MW 55 kD, α1-antitrypsin: MW 50 kD; transferrin: MW 77 kD) [7]. They were the main urinary protein constituents during the INS and their serum concentrations were decreased, leading to reduced oncotic pressure. Typically for minimal-change nephropathy, and often in contrast to focal segmental glomerulosclerosis, only a small amount of gamma globulins (≪1 g/d) was lost in the urine [1]. The main cause of hypogammaglobulinemia during a relapse of INS is not urinary loss, but a primary immunological mechanism, and low serum IgG persists for months after remission [11].

Secondly, the additional reduction of the colloid oncotic pressure, superimposed on an already low baseline oncotic pressure, might have exerted only a minor effect. As expected in INS, the serum cholesterol showed a transient increase beyond the highly elevated baseline concentration.

A few publications have reviewed the clinical presentation and long-term outcome of patients with CAA [8, 9, 12, 16, 21]. However, the follow-up data are incomplete and inconsistent in some cases. Thus, despite the very high serum concentrations of total and LDL cholesterol, the risk of progressive atherosclerosis and cardiovascular events is still not well defined; yet, an increased risk of atherosclerosis cannot be excluded [8, 9, 12, 16, 21]. Well-documented complications were lipodystrophy (mainly in adult females) and osteoporosis. Neonatal presentation occasionally included low birth weight ("small-for-gestational-age") and mild peripheral edema. Apart from recurrent mild respiratory infections, no additional clinical findings were observed in children. In contrast to the benign outcome after birth, the prenatal course of affected fetuses appears less favorable as maternal miscarriages and neonatal deaths were reported in family histories [12, 21].

We conclude that experiments of the nature—the unique association of congenital analbuminemia and idiopathic nephrotic syndrome—helps confirm that serum albumin is not the exclusive factor responsible for maintaining oncotic pressure. The precise information on the transient changes of various proteins in blood and urine might contribute to a better understanding of both conditions.

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