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## ORIGINAL ARTICLE

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## Infantile nephrotic syndrome and congenital glaucoma

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**Abstract** A case of infantile nephrotic syndrome (NS) with advanced membranoproliferative glomerulonephritis (MPGN), type I, and bilateral congenital glaucoma, is presented. The patient also had persistent thrombocytopenia and subclinical hypothyroidism. The parents were second-degree cousins and the affected infant had a sibling who was born with congenital glaucoma. His mother had an aunt and uncle on the maternal side who were born with congenital glaucoma. In addition, there was a history of infantile death in five family members of unknown causes (pedigree). To the best of our knowledge, the association of congenital glaucoma and infantile NS due to MPGN has not been reported previously.

**Keywords** Infantile nephrotic syndrome · Congenital glaucoma · Thrombocytopenia

### Introduction

Congenital nephrotic syndrome (NS) presenting in the first 3 months of life [1] and infantile NS presenting during the 1st year of life [2] are usually secondary to microcystic disease (Finnish NS) or diffuse mesangial scler-

osis. However, other histopathological lesions can occur with infantile NS, including minimal change histopathology [3], and infrequently children presenting with infantile NS can go into complete remission [4]. However, membranoproliferative glomerulonephritis has not been reported as a cause of congenital or infantile NS [5–7].

Different associations between congenital/infantile NS and ocular lesions have been reported previously [8–10]. We report a case of infantile NS secondary to membranoproliferative glomerulonephritis (MPGN), type I, and congenital glaucoma.

### Case report

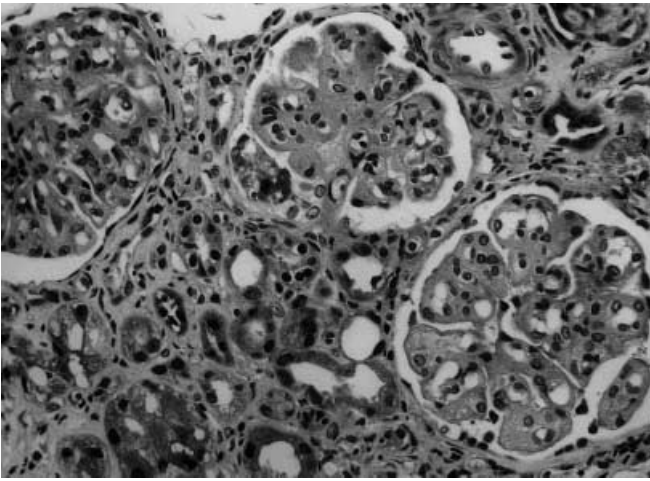
A full-term baby boy was born with bilateral congenital glaucoma and thrombocytopenia. The patient did not have any dysmorphic features, developmental delay or abnormal genitalia. He had a normal head circumference and the rest of the systemic examination was unremarkable. Intrauterine infection (TORCH syndrome) was excluded and bone marrow aspirate showed increased megakaryocytes, suggesting peripheral destruction of the platelet. He was diagnosed with isoimmune thrombocytopenia; however, his platelets remained low despite a slow improvement without specific treatment. At 8 months of age investigations showed a low serum albumin [20–22 g/dl (normal values: 35–50 g/dl)], normal serum creatinine [30  $\mu$ mol/l (normal values: 18–35  $\mu$ mol/l)], high serum cholesterol [7.23 mmol/l (normal <5.2 mmol/l)] and high triglycerides (TG) [13.39 mmol/l (normal <1.7 mmol/l)]. No records of his urine proteins were available and he was not reported to be edematous at that stage. At the age of 23 months, he presented with carpopedal spasm, tachypnea and irritability. He was found to be hypocalcemic with a total Ca of 0.52 mmol/l (normal: 2.1–2.6 mmol/l), hypertensive and in renal failure, with elevated serum creatinine (196  $\mu$ mol/l) and elevated blood urea nitrogen [11.3 mmol/l (normal 1.8–6.4 mmol/l)]. There was no evidence of hemolytic uremic syndrome (HUS) as there was no evidence of microangiopathic hemolytic anemia (normal blood film) or worsening of his thrombocytopenia. He was edematous with low serum albumin [22 g/dl (normal 35–50 g/dl)] and his urine was 4+ positive for protein. His urine continued to show a nephrotic range proteinuria with a high protein/creatinine ratio (2.4–5.3). His plasma C3 and C4 components of complement were normal. Renal biopsy contained 18 glomeruli, most of which revealed enlarged glomerular tufts filling the Bowman's space. Many of the glomeruli showed lobular patterns associated with markedly expanded mesangium due to increased mesangial matrix and mesangial hy-

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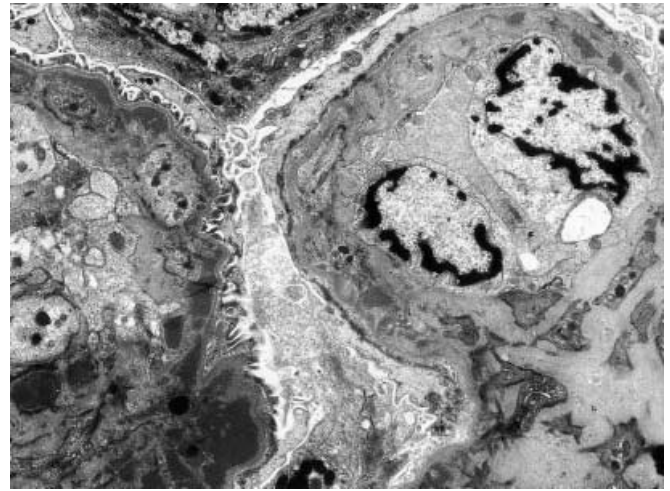
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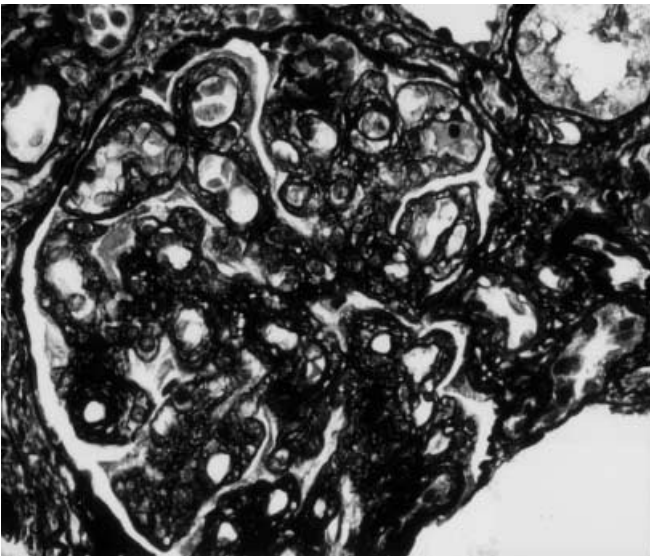
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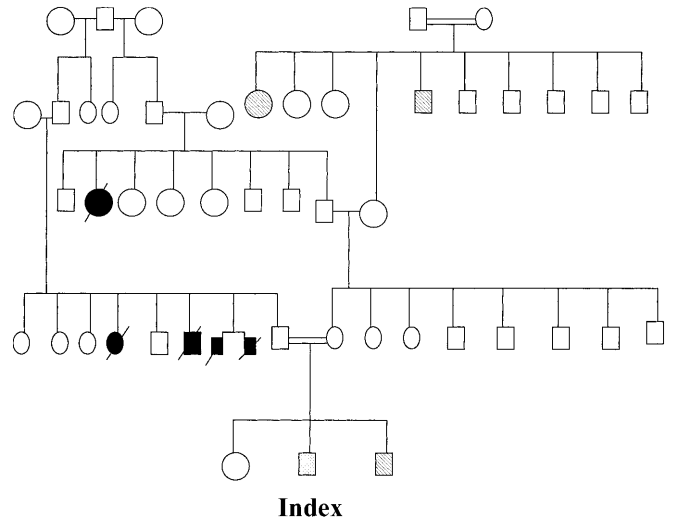
**Fig. 1** Photomicrograph from the renal biopsy showing three glomeruli, all of which reveal expanded mesangium and thickened capillary wall. Hematoxylin and eosin,  $\times 87$



**Fig. 3** Electron micrograph showing mesangial interposition and duplication of basement membranes. Several subendothelial electron-dense deposits are also seen.  $\times 2240$



**Fig. 2** A glomerulus after silver staining, showing prominent duplication of glomerular capillary basement membrane



**Fig. 4** Pedigree (open circles, open squares affected with congenital glaucoma, solid circles, solid squares patients who died in infancy, dotted square affected with congenital glaucoma and infantile NS)

percellularity (Fig. 1). The capillary walls were thickened and on silver stain revealed a prominent double contour of basement membrane (Fig. 2). There was focal tubular loss replaced by mild fibrosis. Occasional small blood vessels showed focal intimal thickening. Electron microscopic examination revealed numerous subendothelial electron-dense deposits with mesangial interposition and duplication of basement membranes and mesangial interposition. Marked mesangial expansion with obliteration of many of the capillaries was seen (Fig. 3). The renal biopsy was compatible with advanced membranoproliferative glomerulonephritis type I.

His kidneys had normal shape and size on ultrasound and there were no iliac horns on the X-rays. His thyroid function test showed high TSH and therefore he was started on thyroxin replacement therapy.

The parents were second-degree cousins and his younger sibling was born with bilateral congenital glaucoma, as was an aunt and uncle of his mother on the maternal side (Fig. 4). However,

they did not have other known ocular abnormalities or renal diseases. The affected sibling has not had thrombocytopenia or proteinuria so far (6 months old). There was a history of infantile deaths of unknown cause in five family members.

## Discussion

The association of membranoproliferative glomerulonephritis presenting in infancy and congenital glaucoma has not been reported before. Membranoproliferative glomerulonephritis usually presents in older children and young adults [5, 6], although it has been described in an infant aged 15 months [7]. Our case presented at 8 months of age. This is in contrast to mesangial prolif-

erative lesions, which have been reported previously as a cause of infantile NS [11, 12].

Infantile NS is associated with heterogeneous lesions including ocular anomalies. Congenital NS has been previously reported to be associated with diffuse mesangial sclerosis (DMS) and several other conditions such as strabismus, nystagmus and hypertelorism [13]; nystagmus and optic atrophy [14]; meiosis, nystagmus and cataract with peripheral neurological abnormalities [8]; and cataract [9] and congenital glaucoma [10]. In 1983, Schneller et al. reported four families with congenital NS, one of them presenting with the additional features of buphthalmus, and histologically it was very similar to diffuse mesangial sclerosis [15]. A few years later, they reported that another sibling of the same healthy Swiss couple, who were first-degree cousins, had congenital NS and congenital glaucoma. In both siblings, the nephrotic syndrome was diagnosed on the 1st day of life, as was the buphthalmus [10]. In the later paper they mentioned a communication from Dr. E. Monn about two daughters of a non-related Norwegian couple who had congenital NS one of them with buphthalmus, while the other one was noticed to have abnormal eyes with shallow chambers. Renal histopathology of the second Norwegian girl was similar to that of the Swiss girls, namely DMS. This association of congenital NS and buphthalmus can occur in congenital rubella [16], but we have excluded this possibility in our patient. The diagnosis of infantile NS as part of the Galloway syndrome was excluded as the patient had a normal head circumference and no evidence of developmental delay or hiatus hernia. The absence of iliac horns in the X-rays made the diagnosis of onycho-osteodysplasia (nail-patella syndrome) very unlikely. Similarly the diagnosis of Drash syndrome was very unlikely in the presence of normal genitalia.

The association of congenital or infantile NS and hypothyroidism has been reported previously [17–19]. The most likely cause of the thrombocytopenia in our case was chronic circulating antibodies, as the platelets showed a slow improvement over the years and the result of the bone marrow tests support this hypothesis. Chronic idiopathic thrombocytopenia has been reported in a patient with membranous glomerulonephritis [20, 21] and has been found to be associated with MPGN [22]. We have thought of the possibility of HUS as the cause of MPGN as it was reported previously [23, 24] or of the possibility that it occurred in association with the already existing glomerular diseases [25]. However, the absence of microangiopathic anemia and the absence of fibrin thrombus in the renal biopsy made this possibility very unlikely. The high values of lipids could be explained by the nephrotic syndrome [26] and in the later stages renal failure could worsen it [27].

The renal, ophthalmic, thyroid and platelet abnormalities found in this patient could represent a new syndrome caused by an inherited or mutated gene. However, the presence of several relatives with eye findings but no re-

nal diseases points to the possibility that glaucoma may not be linked to renal disease in this family.

We consider our case, infantile NS with MPGN, bilateral congenital glaucoma and thrombocytopenia, to be an association which has not been previously reported.

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## LITERATURE ABSTRACTS

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### Heat shock protein-70 repairs proximal tubule structure after renal ischemia

*Kidney Int* (2000) 58:2400–2407

**Background** Recent studies have suggested a role of heat shock protein (HSP)-70 in cytoskeletal repair during cellular recovery from renal ischemia. The aim of this study was to test the hypothesis that HSP-70 interacts in vitro with cytoskeletal elements obtained from rat renal cortex during early reflow after renal ischemia.

**Methods** Cellular proteins were fractionated into cytoskeletal pellets and noncytoskeletal supernatants by Triton X-100 extraction of rat renal cortex obtained after 15 minutes or 18 hours of reflow after 45 minutes of renal ischemia, or from controls. Aliquots of isolated pellets were coincubated with aliquots of isolated supernatants in different combinations. A repeat Triton extraction was performed, and differential distribution of Na, K-ATPase or HSP-70 was assessed by Western blots and densitometric analysis.

**Results** Coincubation of cytoskeletal pellets obtained during early reflow after renal ischemia (exhibiting severe injury of the cytoskeletal anchorage of Na,K-ATPase) and noncytoskeletal supernatant obtained during later reflow (showing high HSP expression) resulted in specific translocation of HSP-70 from the supernatant into the pellet, functionally associated with dose-dependent stabilization of Na,K-ATPase within this cytoskeletal fraction. These effects could be reproduced by incubation with purified HSP-70 and were abolished by the addition of anti-HSP-70 antibodies.

**Conclusion** These data support the hypothesis that HSP-70 interacts with cytoskeletal elements during the restoration of proximal tubule cell structure and polarity after renal ischemia. This experimental approach represents a new in vitro assay to study further the role of HSP in cellular repair.

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### Albuminuria in nondiabetic relatives of IDDM patients with and without diabetic nephropathy

*Kidney Int* (2000) 58:959–965

**Background** In non-insulin-dependent diabetes mellitus (NIDDM), there is a clustering of an elevated urinary albumin excretion rate (U-AER) in nondiabetic relatives of albuminuric patients. Whether this is also the case in insulin-dependent diabetes mellitus (IDDM) is unknown.

**Methods** Overnight U-AER was measured in 186 nondiabetic first-degree relatives of 80 IDDM patients with diabetic nephropathy (U-AER >200 µg/min or 300 mg/24 hours; DN+) and in 52 relatives of 25 IDDM patients without nephropathy (U-AER <20 µg/min; DN-). The two groups of relatives were comparable regarding gender distribution, age, obesity, blood pressure, prevalence of antihypertensive therapy, and smoking habits.

**Results** No difference was found in overnight U-AER between relatives of patients with DN+ and DN- [median (range), 3.4 (0.1 to 372) vs. 4.0 (0.2 to 62) µg/min, respectively, *P*=NS]. The proportion of relatives with a U-AER=10 µg/min was 12% in DN+ compared with 8% in DN- (*P*=NS). Among relatives of DN+, those with antihypertensive treatment (AHT+) had higher U-AER compared with those without [AHT+ vs. AHT-, 5.0 (0.5 to 372) vs. 3.4 (0.1 to 26.5) µg/min, *P*<0.01], a phenomenon that was not seen among relatives of DN-[AHT+ vs. AHT-, 3.6 (2.1 to 24.3) vs. 4.0 (0.2 to 61.5) µg/min, *P*=NS]. However, this analysis was impaired by the small number of relatives of DN- with hypertension (*n*=7).

**Conclusions** In IDDM, we found no clustering of elevated U-AER in nondiabetic relatives of patients with nephropathy. This is different from what has been reported in NIDDM, and suggests heterogeneity in the genesis of albuminuria in diabetes.