Microcephaly and congenital nephrotic syndrome owing to diffuse mesangial sclerosis: an autosomal recessive syndrome

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Abstract
Three sibs born to consanguineous parents had congenital nephrotic syndrome, microcephaly, and psychomotor retardation. Pathology of the kidneys showed diffuse mesangial sclerosis with deposits of IgG and C3 in the mesangium and glomerular basement membranes. All three children died before the age of 3 years. Of 19 published cases of children with the association of congenital nephrotic syndrome and microcephaly, only four had histological evidence of diffuse mesangial sclerosis, and two of their sibs probably had the same disease. The association of nephrotic syndrome owing to congenital diffuse mesangial sclerosis, microcephaly, and mental retardation appears to be a distinct syndrome with an autosomal recessive mode of inheritance.

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Congenital microcephaly is associated with a variety of pathological conditions, including chromosomal aberrations, metabolic diseases, intrauterine infections, postradiation injury, and chronic hypoxaemia.¹ In its isolated form, it is usually inherited in an autosomal recessive mode² and is accompanied by severe mental retardation. Occasionally it is inherited in an autosomal dominant mode, and in these patients the retardation is usually milder.¹⁻³

Nephrotic syndrome in the first year of life (congenital nephrotic syndrome) is rare. Infantile microcystic disease, or the Finnish type nephrotic syndrome, is the best documented form of the syndrome.⁴ Other known causes of congenital nephrotic syndrome are intrauterine infection,^{5,6} renal vein thrombosis,⁷ and mercury intoxication.⁸ Minimal change nephrotic syndrome, congenital focal glomerular sclerosis, membranous glomerulopathy, or diffuse mesangial sclerosis are uncommon causes of nephrotic syndrome in the first year of life.⁹⁻¹¹
The association of congenital nephrotic syndrome, microcephaly, and mental retardation has been reported in 19 children,¹²⁻²¹ but only six of them had diffuse mesangial sclerosis (table).¹⁸⁻²¹ We report a family with three microcephalic children who had severe psychomotor retardation and congenital nephrotic syndrome owing to diffuse mesangial sclerosis.

Case reports
The family was of Jewish North African origin. The pedigree is shown in fig 1. There were consanguineous marriages in generations III and IV-V. The father of the proband was the mother's uncle. Except for the proband and two of his sibs, there were no other family members with kidney disease or psychomotor retardation. The other five sibs, as well as the parents, were healthy and did not have microcephaly. The mother of the proband did not smoke and had not taken medication or alcohol

Clinical and pathological findings in the patients with congenital nephrotic syndrome owing to diffuse mesangial sclerosis and microcephaly

Case	Sex	Microcephaly	Onset of nephr syn	Kidney histology	Mental retardation	Neurological symptoms	Dysmorphic features	Age at death	Notes	Ref
1	F	+	1 d	Mesangial sclerosis	+	Seizures	No	3 mth		16
2	M	+	6 d	Diffuse mesangial sclerosis	?	Decreased vision & hearing	Wide set eyes; small nose	2 mth		19
3	F	+	6 d	Mesangial sclerosis		Hypertonic arms; seizures	Floppy ears; contractures of hands & feet	2 mth		20
4	M	+	12 d	—	NM	NM	Floppy ears; hypertelorism	1 mth	Sib of case 3	20
5	M	+	14 mth	Mesangial sclerosis	Severe	Seizures; hypertonic limbs; poor head control; no visual fixation	Micrognathia; large ears	18 mth		21
6	F	+	9 mth	—	Severe	Hypertonic limbs; seizures; poor vision & hearing	Large ears; small midface	3 y	Sib of case 5	21
7	M	+	1 mth	Diffuse messangial sclerosis. IgG and C3 deposit in the mesangium	Severe	Hypertonic limbs; poor head control; strabismus; poor vision & hearing	Large, low set, floppy ears; sparse, thin hair; micrognathia; bilateral undescended testes	2 y	Consanguinity	Present report
8	F	+	1 mth	Identical to case 7	Severe	Identical	Large, low set, floppy ears; sparse hair	15 mth	Sib of cases 7 & 9	Present report
9	M	+	1 y	—	Severe	Hypertonic limbs	?	3 y		Present report

NM = not mentioned.

Figure 1 Family pedigree.

during the pregnancies. Data regarding placental weight of the different pregnancies and alphafetoprotein measurements are not available.

CASE 1 (VI.8)

The boy was the term product of a normal pregnancy and delivery. Birth was 4400 g and marked microcephaly was noted.

During the first months of life, generalised oedema, recurrent vomiting, and psychomotor retardation were seen. On admission, at the age of 11 months, the patient had puffy eyes and mild pitting oedema of the ankles and sacrum. Blood pressure was 100/60 mmHg, pulse rate 110/minute, and respiratory rate 24/minute. Weight was 8000 g (3rd centile for his age), length 74 cm (60th centile for his age), and head circumference 40 cm (-5 SD below the mean for his age). The nose was small and the ears were large and low set, with unusually soft auricles. Strabismus, high arched palate, micrognathia, and sparse, thin hair were also present. Examination of the heart and lungs showed no abnormalities. There was no visceromegaly and the kidneys were not palpable. The scrotum was underdeveloped with bilateral undescended testes. The penis was normal. There was bilateral overlapping of the first toe by the second.

Neurological evaluation disclosed poor head control, inability to sit up or turn, and absence of interest in his surroundings. The anterior fontanelle was small and barely palpable. The cranial nerves were unremarkable. Motor examination showed muscle wasting without fasciculation and absence of purposeful movements. Strength was decreased mainly in the

proximal muscles, with a tendency to hypertonicity and scissoring of both legs. The fists were constantly clenched. Pain sensation was grossly intact and deep tendon reflexes were hyperactive with flexor plantar responses. The patient neither responded to noise nor followed objects with his eyes for more than a few seconds. Constant head rolling was present and he seldom smiled. Fundoscopic examination was normal.

Laboratory data showed haemoglobin 11.3 g/dl, white blood count 7×10^9 cells/l (45% neutrophils, 40% lymphocytes, 15% monocytes), platelets 460×10^9 /l, blood urea nitrogen 3.9 mmol/l, and creatinine $35.4 \mu\text{mol/l}$. Total serum protein measured 30 g/l, with albumin 19 g/l; C3 component of the complement was 1.3 g/l, C4 0.3 g/l, CH50 70%. Cholesterol was 0.65 mmol/l, triglycerides 0.75 mmol/l, and total lipids 4.6 mmol/l. IgG was 2.3 g/l (normal for age: 7.2 ± 2.7 g/l), IgA 0.6 g/l (normal: 0.7 ± 0.3 g/l), IgM 1.3 g/l (normal: 0.63 ± 0.3 g/l). Urine analysis showed 5 to 10 erythrocytes in high power field and granular casts. Daily urinary protein excretion was 3.8 to 4.8 g (mainly albumin). Creatinine clearance was 100 to 105 ml/min/1.73 m².

The following laboratory tests were normal: serum sodium, potassium, chloride, calcium, phosphorus, magnesium, bilirubin, aspartate aminotransferase (SGOT), lactate dehydrogenase (LDH), creatinine kinase (CK), uric acid, pH, lactate, pyruvate, T4, serology for rubella, toxoplasma, cytomegalovirus and syphilis, cerebrospinal fluid, electrocardiography, electroencephalography, and electromyography. The karyotype was of a normal male. Intravenous pyelography showed mild enlargement of both kidneys. Skull radiography disclosed a small cranium; the rest of the skeletal radiographic survey was normal. Bone age was 9 months. Cerebral CT scan showed a small posterior fossa with enlargement of the fourth ventricle and ambient cisterna compatible with cerebellar hypoplasia. There was also a mild degree of enlargement of the lateral and third ventricles (fig 2).

Percutaneous kidney biopsy showed hypercellularity of mesangial cells, an increase in PAS positive material in the mesangial matrix, and mild thickening of the capillary wall. Occasional segments showed obliteration of their normal structure. A few immature glomeruli were noted, as well as microcystic transformation of a few tubuli (fig 3). Electron microscopy of the glomeruli showed effacement of the epithelial foot processes and dilatation of the mesangium owing to hypercellularity and abundance of matrix. Electron dense deposits were present in the subendothelial region of the peripheral and axial glomerular basement membrane and in the mesangium. The lamina densa was irregular and sometimes thinner and sometimes thicker than usual (fig 4). Immunofluorescence staining showed massive deposits of IgG and C3 in the mesangium and glomerular basement membrane. These findings suggested the diagnosis of infantile diffuse mesangial sclerosis. The patient was discharged and was lost to detailed follow up. He

Figure 2 Cerebral CT scan showing enlargement of the fourth ventricle and cerebellar hypoplasia.

developed renal failure and died at the age of 2 years.

CASE 2 (VI.3)
The sister of case 1, born at term after an uneventful pregnancy and delivery, was examined at the age of 12 months. Head circumference was 39.5 cm (–5 SD below the mean for her age). There was poor head control and severe psychomotor retardation. Deep tendon reflexes were hyperactive and the limbs were

spastic. She could not turn and showed no interest in her surroundings or in social communication. Pitting oedema of the ankles and sacrum was present. She had strabismus, sparse hair, and large, low set, floppy ears, like her brother.

Laboratory tests showed hypoproteinaemia, hypoalbuminaemia, and hyperlipidaemia (total lipids were 1040 mg/dl). Urine analysis showed massive proteinuria, microscopic haematuria, and granular casts. Kidney biopsy showed similar changes to those seen in case 1. She was treated with 2 mg/kg/day of prednisone but without apparent effect. During the second year of life, rapid deterioration in kidney function occurred, and serum creatinine level reached 530 µmol/l. She died at the age of 15 months of *E coli* septicaemia. Necropsy could not be performed.

CASE 3 (VI.1)
This patient, the brother of patients 1 and 2, also had a “little head”, hypertonia of the limbs, severe psychomotor retardation, oedema, and proteinuria. His kidney function deteriorated gradually and he died before the age of 3 years. The clinical evaluation of this patient was performed at another hospital and kidney histology was not available.

Discussion
The characteristic features of congenital nephrotic syndrome associated with microcephaly are severe mental retardation, rapid deterioration of kidney function, unresponsiveness to medication, and usually fatal outcome before the age of 3 years. Nineteen cases of this association, first described by Galloway and Mowat,¹² have been reported.^{12–21} Additional findings include neurological abnormalities,

Figure 3 Light microscopy. (A) Matrix increase in glomerulus (arrows). (B) Focal increased cellularity in glomeruli. (C) Tubular dilatation. (D) Fetal glomeruli (H&E).

Figure 4 Electron microscopy of glomerular tuft showing subendothelial and paramesangial subendothelial deposits (arrow heads), increase in mesangial matrix (thick arrow), thinning of lamina densa (short thin arrows), and partial effacement of foot processes (long thin arrows).

such as abnormal muscle tone and seizures, and minor dysmorphic features, such as an unusually shaped head, low set, floppy ears, micrognathia, and, occasionally, hiatus hernia.¹²⁻¹⁴ Histology of the kidneys was reported in 12 of the 19 affected patients. However, some were evaluated by light microscopy only and in most cases immunofluorescence staining was not mentioned. Some patients underwent renal biopsy and in others tissue was obtained at necropsy. Thus, the available information on kidney histology is incomplete. If we divide the patients according to the classifications of Habib and Bois¹¹ and Kaplan *et al*,⁹ four had diffuse mesangial sclerosis,¹⁸⁻²¹ three microcystic dysplasia,^{12,14} three focal glomerulosclerosis,^{14,16,20} one had mesangial proliferation,²¹ and one a combination of microcystic dysplasia and focal glomerulosclerosis.¹⁴ Despite the variability in kidney histology, most patients had a similar clinical course of declining renal function and early death. Only two patients reached the age of 5 years.^{16,20} However, it is clear that, based on renal histology findings, these are different entities. A similar deteriorating clinical course was also noted in the patients with the "isolated" form of congenital nephrotic syndrome,²² without microcephaly.

Our patients' kidney histology showed diffuse mesangial sclerosis. Congenital nephrotic syndrome resulting from diffuse mesangial sclerosis has been reported in association with ocular abnormalities (nystagmus, cataract, or microphthalmia),^{23,24} male pseudohermaphroditism and Wilms's tumor (Drash syndrome),²⁵ or microcephaly.

Of special interest in our patients is the finding of IgG and C3 deposits in the mesangium and of IgG deposits along the basement

membrane. No immune complex deposits were mentioned in the other cases of congenital nephrotic syndrome and microcephaly, except for a patient with focal glomerulosclerosis reported by Roos *et al*,¹⁶ who showed deposits of IgM in the basal membrane of the capillary loops, and the patient with mesangial proliferation, reported by Cooperstone *et al*,²¹ who had segmental distribution of fine granular deposits of IgM.

In patients with "isolated" congenital nephrotic syndrome owing to diffuse mesangial sclerosis (without microcephaly), occasional deposits of immune complexes were noted. For example, of three sibs with diffuse mesangial sclerosis one had mesangial deposits of IgG, IgM, C3, and fibrinogen, while the other two, although they had a similar kidney disease, had no demonstrable deposits of immune complexes.¹⁰ This may have related to the stage of disease or to its differing pathogenesis.

No specific metabolic abnormalities were found in our patients or in those previously reported. The neurological abnormalities and the mental retardation are probably secondary to the severe microcephaly and the abnormal brain structure. The mental retardation in cases of severe microcephaly is negatively correlated with brain volume, especially in patients with autosomal recessive microcephaly.² Although brain histology was not available in our cases, brain CT scan suggested general atrophy, which was more pronounced in the subependymal zone, and cerebellar hypoplasia. In two previously reported patients with congenital nephrotic syndrome owing to diffuse mesangial sclerosis and microcephaly, the brain histology showed microgyria in the frontal, parietal, and occipital lobes²⁰ and pachygyria with neuronal ectopia.^{18,20} The association of congenital kidney disease and neural migration defect was also reported in two other male sibs with glomerular kidney disease causing proteinuria and hydrocephalus.²⁶ This may suggest a common insult during the first weeks of gestation affecting both the kidneys and the brain.

Four of the 19 previously reported children with congenital nephrotic syndrome and microcephaly had histological findings of diffuse mesangial sclerosis.¹⁸⁻²¹ Two sibs of these patients^{20,21} probably had the same kidney disease as well. Thus, two of the previously reported patients were sporadic cases, and the other four were pairs of brothers and sisters born to non-consanguineous parents.^{20,21} The fact that our three patients were sibs (two boys and a girl of a family of eight sibs) and that their parents were consanguineous, support the assumption of autosomal recessive inheritance of this syndrome.

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