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GENETIC RENAL DISEASE / ORIGINAL ARTICLE

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Another autosomal recessive form of focal glomerulosclerosis with neurological findings

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Abstract We report four patients in a consanguineous family with focal segmental glomerulosclerosis (FSGS), early onset nephrotic syndrome, eventual end-stage renal failure, psychomotor retardation, seizures and microcephaly or brain atrophy without hiatus hernia. Other characteristic dysmorphic features were convergent strabismus and narrow forehead. One patient had enamel hypoplasia of the upper incisors and deviation of bilateral thumbs to palm side. We could not detect an *NPHS2* mutation in this family. We propose that this may be another autosomal recessive syndrome with FSGS and neurological findings.

Keywords Familial · Focal segmental glomerulosclerosis · Nephrotic syndrome · Renal failure · Psychomotor retardation · NPHS2 · Galloway-Mowat syndrome

Introduction

In 1968, Galloway and Mowat described two infant siblings with a triad of abnormalities of early onset of nephrotic syndrome, congenital microcephaly associated with hypotonia, developmental delay and hiatus hernia [1]. The inheritance is autosomal recessive and the prognosis dismal. Since then, more than 20 additional cases with clinical features closely resembling those described by Galloway and Mowat have been reported [2–9], but few have had hiatus hernia. The age of onset of nephrotic syndrome has varied. Other minor abnormalities of eyes, ears and nervous system are documented with sufficient frequency to suggest the existence of a syndrome with a range of clinical manifestations [10]. Renal histopathological examinations of these patients consisted of microcystic disease, diffuse mesangial sclerosis and focal segmental glomerulosclerosis (FSGS). This syndrome and related disorders have clinical and histological heterogeneity.

In this report, we describe four patients in a consanguineous family who have FSGS, early onset nephrotic syndrome, end-stage renal failure, psychomotor retardation, seizures and microcephaly or brain atrophy, without hiatus hernia.

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Case report

Case 1

The patient was a 3-year 8-month-old girl with generalized edema, hypertension and oliguria. The parents were third cousins (Fig. 1). She had two brothers; one was healthy without any features and the other was the patient of case 2. Her mother was healthy except for asymptomatic proteinuria (1+ by dipstick), and the father was healthy. She was born of an uncomplicated full-term pregnancy and delivery with a birth weight of 2542 g and a placenta weight of 492 g. The neonatal period was unremarkable. Psychomotor retardation and mild hypotonia were first noticed at 4 months of age, head control at 7 months, rolling at 12 months, standing at 20 months and walking at 3 years. There was verbal retardation. Her height (80 cm) was –4.1 SD and her weight 11.1 kg (dry weight, 9.1 kg; –2.76 SD). Microcephaly was present (44 cm, –1.6 SD, corrected by her height). Other dysmorphic features included narrow forehead, convergent strabismus, enamel hypoplasia of the two upper central incisors and the deviation of bilateral thumbs to palm side. Her hearing was normal, and she had atopic dermatitis.

At 35 months of age, she had nephrotic range proteinuria of 6.6 g/day and microscopic hematuria, but no glucosuria. Serum total protein was 4.7 g/dl, albumin 2.3 g/dl, total cholesterol 442 mg/dl, urea nitrogen 6.6 mg/dl and serum creatinine 0.34 mg/dl. There was no generalized edema. Serum electrolyte concentrations and liver enzyme tests were normal. Serum IgG was low (378 mg/dl; normal 540–1340 mg/dl), while the IgE radioimmunosorbent test was high (1463 IU/ml; normal <400 IU/ml), but other immunoglobulins (IgA and IgM) were

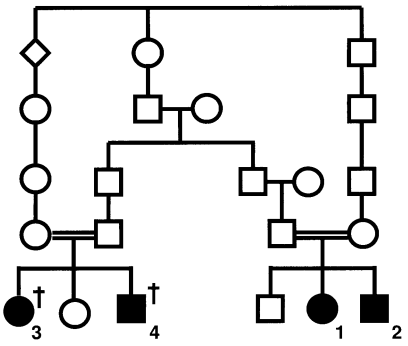

Fig. 1 Pedigree of a family with focal segmental glomerulosclerosis, early-onset nephrotic syndrome, eventual end-stage renal failure, psychomotor retardation, seizures and mild microcephaly without hiatus hernia. *Symbols are:* ○ unaffected females, □ unaffected males, ● affected females, ■ affected males. *Numbers 1–4* are cases 1–4, respectively. The parents of cases 1 and 2 were third cousins, and the parents of cases 3 and 4 were third cousins

within the normal range. Serum complement (C3, C4 and CH50), lactate, pyruvate, ammonia, serum and urinary amino acids were normal. Mild metabolic acidosis was present. Abdominal ultrasonography demonstrated increased echogenicity of the right renal parenchyma, and the ^{99m}Tc-diethylene tetramine pentaacetic acid renocintigram demonstrated prolonged peak time and delayed excretion of the right kidney, suggesting right renal dysfunction. Magnetic resonance imaging (MRI) of the brain and electroencephalography (EEG) were normal. Chromosomal analysis showed a normal female karyotype, 46XX. Muscle biopsy showed normal muscle with no findings of mitochondrial myopathy or muscular dystrophy. Light microscopic study of the kidney showed focal segmental glomerulosclerosis (Fig. 2). There was marked interstitial fibrosis and tubular atrophy and some tubules were dilated. Immunofluorescent microscopy revealed mesangial and peripheral deposits of IgM and fibrinogen, while IgG, IgA and C3 were negative. Electron microscopy showed focal foot process fusion without deposits. The ultrastructure of the glomerular basement membranes was intact.

The nephrotic syndrome was resistant to prednisolone and to the angiotensin converting enzyme inhibitor (ACE-I) enalapril. Her renal function deteriorated gradually. At 44 months of age, she was admitted to our hospital because of generalized edema, hypertension, oliguria, pulmonary edema and heart failure. Serum urea nitrogen was 158 mg/dl, serum creatinine concentration 7.5 mg/dl and serum potassium concentration 6.6 mEq/l. Continuous ambulatory peritoneal dialysis (CAPD) was started immediately. Secondary hyperparathyroidism and anemia were present (intact parathyroid hormone, 660 pg/ml; hemoglobin, 4.8 g/dl, respectively). Hypocalcemia was present (Ca, 5.2 mg/dl; albumin, 2.4 g/dl), and she experienced her first seizure. EEG revealed a central to parietal dominant single spike. Head computed tomography (CT) was normal. The seizures resolved with correction of the hypocalcemia.

Case 2

The patient was a 21-month-old boy who was a brother of the patient of case 1. He was born of an uncomplicated full-term pregnancy and delivery with a birth weight of 3626 g. At the age of 1 day, he was admitted to a neonatal intensive care unit due to neonatal pneumonia and wheezing. Psychomotor retardation was first noticed at 4 months of age, head control at 5 months, rolling at 9 months, and he still could not sit up without support at the age of 21 months. His height was 82.5 cm (mean) and his weight 11.5 kg (almost mean). Microcephaly was present (46 cm, –1.1 SD, corrected by his height). Characteristic dysmorphic features

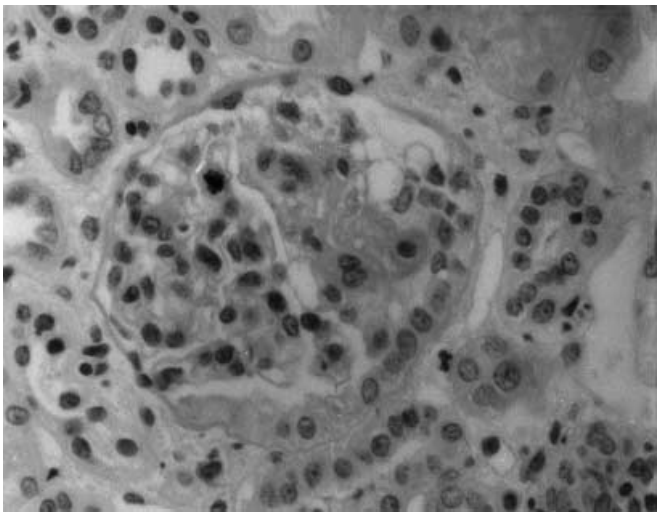

Fig. 2 Light microscopic study of the kidney of case 1 showed focal segmental glomerulosclerosis. Periodic acid-Schiff staining, ×420

included convergent strabismus and narrow forehead. Slight relaxation of the right diaphragm was present. Urinalysis showed proteinuria (1.8 g/day) without hematuria or glucosuria. Serum total protein was 4.0 g/dl, albumin 2.0 g/dl, and total cholesterol 360 mg/dl, indicating nephrotic syndrome. Urea nitrogen was 6.3 mg/dl and serum creatinine 0.27 mg/dl. Generalized edema was absent. Serum electrolytes and liver enzyme tests were normal. Metabolic acidosis was absent. He experienced his first seizure at the age of 11 months, and EEG demonstrated a central to parietal dominant single spike. MRI of the brain demonstrated atrophy in the frontal lobe of the brain and enlargement of the lateral ventricles. Renal biopsy was not done. His renal function deteriorated gradually, and uremia is now present at 35 months of age.

Case 3

The patient was a 4-year-old girl who was the paternal second cousin of those in cases 1 and 2. The parents were third cousins (Fig. 1). She had not experienced any seizures. Psychomotor retardation was present (sitting up at 18 months). Convergent strabismus was present. Nephrotic syndrome appeared at the age of 21 months. However, generalized edema was absent. Light microscopic study of the kidney showed focal segmental glomerulosclerosis. The nephrotic syndrome was resistant to prednisolone and her renal function deteriorated gradually. At 33 months of age, uremia was present and CAPD was introduced. However, she died of peritonitis at the age of 4 years.

Case 4

The patient was a 23-month-old boy who was the brother of the patient in case 3. Convergent strabismus was suspected. At the age of 2 months, he had severe convulsions and was diagnosed with West's syndrome by EEG. At the time, CT scan showed frontal lobe brain atrophy. His convulsions were difficult to control. Hypertension was present at the age of 3 months, and diuretic drugs and ACE-I were used. At the age of 11 months, urinalysis showed proteinuria with microscopic hematuria and hypoalbuminemia present, indicating nephrotic syndrome. Light microscopic study of the kidney showed focal segmental glomerulosclerosis. Focal monocyte infiltration in the interstitial area, tubular atrophy, and tubular dilatation were present. Immunofluorescent microscopy revealed segmental mesangial deposits of IgM and electron mi-

Table 1 Clinical findings in four patients (*F* female, *M* male, + positive, – negative, *y* year(s), *m* month(s), *FSGS* focal segmental glomerulosclerosis, *n.e.* not examined, *CAPD* continuous ambulatory peritoneal dialysis)

Case	Sex	Neurological findings			Renal findings			
		Seizure (onset)	Psychomotor retardation	Convergent strabismus	Onset of nephrosis	Histopathology	Uremia	Prognosis
1	F	+	+	+	2 years 10 months	FSGS	3 years 8 months	CAPD/alive
2	M	++ (11m)	++	+	1 year 1 month	n.e.	2 years 11 months	Alive
3	F	–	+	+	1 year 9 months	FSGS	2 years 9 months	CAPD/dead (4 years)
4	M	++ (2m)	++	Suspected	11 months	FSGS	1 year 10 months	Dead (1 year 10 months)

croscopy showed fusion of foot processes. His renal function deteriorated gradually. However, CAPD was not introduced. He died of uremia, pneumonia, disseminated intravascular coagulation syndrome and multiple organ failure at the age of 23 months.

Table 1 shows the clinical findings in the four cases.

Gene analysis

Genomic DNA was extracted from peripheral leukocytes from the patient in case 1 according to the standard method [11]. To amplify all exons of the *NPHS2* gene, eight pairs of oligonucleotide primers were synthesized based on flanking introns of the gene [12]. The amplified DNAs were sequenced using a DNA sequencer, GENESCAN model 373A and the *Taq* Dye Deoxy Terminator Cycle Sequencing Kit (Applied Biosystems). She had no mutation in the coding region of *NPHS2* gene (data not shown).

Discussion

We describe a consanguineous family with FSGS, early onset nephrotic syndrome, eventual end-stage renal failure, psychomotor retardation, seizures and microcephaly or brain atrophy without hiatus hernia. Convergent strabismus was present in three and suspected in one of four patients. There are few reports of convergent strabismus in Galloway-Mowat syndrome and related disorders. Other dysmorphic features included narrow forehead in two patients, and enamel hypoplasia of the primary upper incisors and deviation of bilateral thumbs to palm side in case 1. We consider that these minor anomalies are characteristic dysmorphic features in this family. Meyers et al. proposed that there may be at least three separate syndromes associated with nephrotic syndrome, microcephaly and developmental delay: Galloway-Mowat syndrome, a second syndrome of microcephaly, nephrotic syndrome and developmental delay (MNSDD), and a third syndrome of MNSDD with skeletal dysplasia [9]. The disorder in the present family differs from Galloway-Mowat syndrome in that there are no typical brain findings of Galloway-Mowat syndrome, namely mantle migration defects with gyral abnormalities, and developmental delay is not progressive in our patients [9, 13]. Children with MNSDD are more likely to have later onset of nephrotic syndrome and may respond to corticosteroid treatment whereas our patients never did. The disorder in this present family may be a possible fourth syndrome or another autosomal recessive syndrome.

Familial forms of FSGS that exhibit autosomal recessive or dominant modes of inheritance have been described [14–17]. The autosomal recessive form of FSGS is generally more severe, and patients present at an earlier age than those with the autosomal dominant form. The FSGS gene in one family with an autosomal dominant form maps to a region of chromosome 19q13, while in another family it does not link to this area but to chromosome 11q21-q22, indicating genetic heterogeneity [18–21]. Autosomal recessive and steroid resistant nephrotic syndrome, most of which are FSGS, maps to a region of chromosome 1q25-q31 [22]. *NPHS2*, encoding the glomerular protein podocin, is mutated in the autosomal recessive form [12]. The disorder in our family is inherited in an autosomal recessive manner. We analyzed all exons of the *NPHS2* gene for mutations in case 1, but could not detect a mutation in the coding region of the gene. Autosomal recessive forms of FSGS have genetic heterogeneity. Not only do our cases have steroid resistant nephrotic syndrome and FSGS, but also neurological findings. The disorder in our family may be a contiguous gene syndrome, or it may be an abnormality of a common factor or constituent that functions in the neurological and renal development during fetal and early infantile stages.

We propose that the disorder in the present family may be another autosomal recessive syndrome with FSGS and neurological findings.

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