

Congenital nephrotic syndrome and diffuse mesangial sclerosis in siblings

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Received for publication: 13/05/2010

Accepted in revised form: 10/08/2010

ABSTRACT

This is a rare renal disease characterised by steroid-resistant nephrotic syndrome in the first years of life with rapid progression to end-stage renal failure. Its occurrence is usually sporadic, and it has been associated with a mutation in the Wilms tumour (WT1) suppressor gene. Recently new gene defects causing isolated diffuse mesangial sclerosis, such as LAMB2 and PLCE1 mutations, have been described.

We describe the case of an infant with congenital nephrotic syndrome, whose renal biopsy revealed the presence of diffuse mesangial sclerosis. The parents were consanguineous and reported the death of a son at the age of six months with the same diagnosis. A search for mutations in exons 7, 8, 9 and 10 and surrounding regions of WT1 gene was negative.

We describe the clinical and pathological features of this rare condition and discuss the known gene mutations associated with familial forms of it.

Key-Words:

Congenital nephrotic syndrome; family diffuse mesangial sclerosis; genetic defect; infant.

INTRODUCTION

Diffuse mesangial sclerosis (DMS) is the second most frequent cause of primary congenital nephrotic syndrome. Initially described in its sporadic form, it was later associated with autosomal recessive inheritance occurring occasionally in siblings and monozygotic twins and in the presence of parental consanguinity¹⁻³.

The clinical picture is characterised by the presence of oedema and proteinuria usually appearing in the second or third year of life. However, it may also appear in the first three months of life, and be classified as congenital nephrotic syndrome. Evolution to end-stage renal failure (ESRF) is frequent, and renal transplantation is the only effective treatment as there are no reports of recurrence in the graft³.

In this case report, the development of nephrotic syndrome at the age of three months, the existence of DMS, the family background and laboratory exams suggest a rare case of familial isolated diffuse mesangial sclerosis, probably associated with an autosomal recessive gene not yet identified.

■ CASE REPORT

The patient was a Caucasian infant male born at the 37th week of gestation from a healthy mother. He was the second son of consanguineous young parents (second-degree cousins, sharing great-grandparents); his brother died at the age of six months from ESRF caused by DMS with nephrotic syndrome diagnosed when he was three months old. At that time the parents underwent genetic counselling and since it was considered to be the result of sporadic mutation, they were told the risk of having another child with this disease was similar to that of the general population, in spite of their consanguinity and the chance of having a child with an autosomal recessive disease was about 5%.

The birth was by spontaneous vaginal delivery. The Apgar scores were 7 and 9 at the first and fifth minute respectively, birth weight was 2680g (25-50th percentile), length was 49cm (25-50th percentile) and head circumference was 33cm (5th percentile). The neonatal period was uncomplicated and there were no signs of proteinuria in the first days of life.

At the age of three months the patient was brought to the Emergency Services with fever, cellulitis of the right lower limb, and peri-orbital and pretibial oedema.

Laboratory work-up revealed haemoglobin 10.8g/dL; leucocytes 15360/mm³; reactive C protein 5.42mg/dL; normal renal function and electrolytes; hypoalbuminaemia (1.6g/dL) with hypoproteinaemia (3.4g/dL), hypercholesterolaemia (250mg/dL) and hypertriglyceridaemia (460mg/dL). Urinary protein excretion was 214mg/m²/h. Serum immunoglobulin G (135mg/dL) and immunoglobulin A (23.0g/dL) levels were reduced; serum complement levels were normal. Antinuclear antibodies, anti-DNA antibodies, ANCA, and anti-GBM antibodies were negative, as were syphilis, toxoplasmosis, mononucleosis, herpes, cytomegalovirus, hepatitis and HIV serum markers.

An ultrasound scan showed a marked increase in echogenicity of the renal parenchyma and decreased corticomedullary differentiation.

Based on family history and clinical presentation, renal biopsy was performed. Light microscopy showed glomeruli with some capsular distension,

cell hypertrophy, and mesangial sclerosis, and tubules with moderate tubular dilatation. Immunofluorescence for IgG, IgA, IgM, C₃, and fibrinogen was negative. (Figs. 1, 2 and 3).

The karyotype was normal (46XY). A search for mutations in exons 7, 8, 9 and 10 and surrounding intronic regions of the WT1 gene was negative.

In the first days of admission, in spite of supportive treatment, the child underwent further clinical deterioration with development of generalised

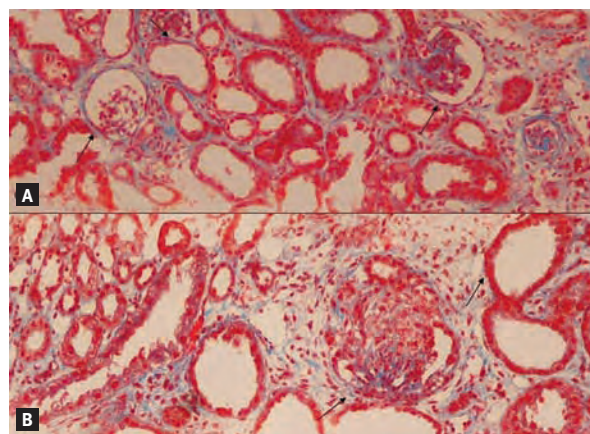


Figure 1

Three glomeruli showing capsular distension and mesangial sclerosis. Tubules show moderate dilatation. (A and B – Masson's trichrome method × 100).

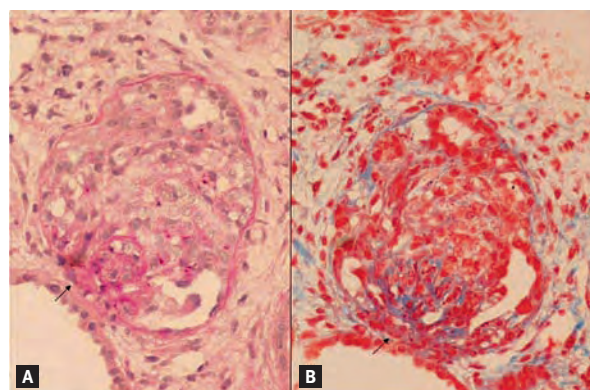


Figure 2

Glomeruli with moderate sclerosis and hypercellularity (A: Masson's trichrome method × 200; B: Methanamine silver nitrate × 200).

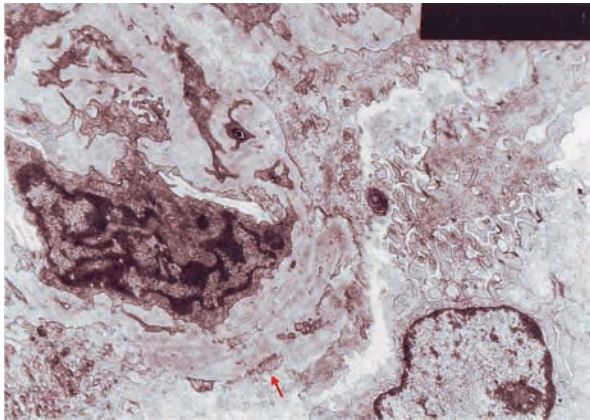


Figure 3

Electron micrograph showing a glomerulus with irregularity and thickening of the basement membrane and increased mesangial matrix.

oedema; on the fifteen day of admission we initiated treatment with indomethacin and captopril. Thereafter the patient remained haemodynamically stable with systolic and diastolic blood pressure at the 50th-95th percentile and serum albumin between 1.5g/dL and 2.5g/dL.

Serum creatinine and urea remained stable until the age of 4.5 months. By the age of six months a rapid deterioration of renal function occurred and peritoneal dialysis was required. At the age of two years and nine months the patient underwent deceased-donor kidney transplantation. He is now six years old and has good graft function with normal blood pressure and no proteinuria. His growth is normal as is his psychomotor development. He has a myopia-related visual deficit but ophthalmologic examination has shown no other abnormalities.

DISCUSSION

Diffuse mesangial sclerosis is a rare renal disease occurring either as an isolated abnormality or as part of other syndromes, such as the Denys-Drash syndrome (DDS). DDS is characterised by male pseudohermaphroditism and Wilms tumour and is associated with a mutation in the WT1 gene⁴. The detection of this mutation in some cases of isolated types of DMS suggests it could be a monosymptomatic type

of the syndrome⁵⁻⁷. However, DMS linked with WT1 mutations usually occurs sporadically or as an autosomal dominant trait, with autosomal recessive inheritance being quite exceptional.

In contrast, in line with most observations similar to this report, isolated DMS (IDMS) appears to be related to an autosomal recessive trait although a specific gene for the disease remains to be identified. A rare autosomal recessive syndrome, Pierson syndrome, was described recently. It is associated with LAMB2 mutations and children present with DMS and eye abnormalities (microcoria due to aplasia or atrophy of the dilator pupillae muscle, atrophy of the ciliary muscle, corneal and retinal changes). However, in these cases nephrotic syndrome is usually present in the neonatal period⁸.

In our patient, the karyotype was normal and there were no visible morphological abnormalities of the genitals, so we concluded this was IDMS. The parents' consanguinity and the fact that another son died at the age of six months from a similar pathology suggest a familial type of the disease with autosomal recessive inheritance.

A recessive mutation in the gene PLCE1/NPHS3 was recently identified as a novel cause of IDMS. Two affected individuals responded to immunosuppressive therapy, making this entity a molecular cause of nephrotic syndrome that may resolve after therapy⁹. In a cohort, PLCE1 mutation was the most common cause of IDMS. Mutations in PLCE1 may serve as a biomarker for selecting patients with IDMS who may benefit from treatment¹⁰.

Familial cases of congenital nephrotic syndrome in children with steroid-resistance and progression to end-stage renal failure have also been associated with podocin mutations. NPHS1 mutation is associated with nephrotic syndrome of Finnish type, and NPHS2 causes nephrotic syndrome with minimal glomerular changes or focal and segmental glomerulosclerosis^{11,12}.

As shown in this case study, the features of isolated DMS are similar to CNS of Finnish type but it differs in having an onset in the first days of life, a rapid progression to ESRF and a characteristic pattern of involvement of the glomeruli. In IDMS all the glomeruli are affected, showing obliterated capillaries

with fibrosis but without hypercellularity, giving a contracted appearance to the glomerular tuft. The glomerular basement membrane is thickened and the cortical tubules are atrophic with occasional cystic dilatations. There are usually no glomerular deposits of immunoglobulin or complement¹³.

In congenital nephrotic syndrome with DMS, steroid and immunosuppressive therapy are ineffective and therapy is aimed towards eventual kidney transplantation. The main therapeutic goals are appropriate nutrition, monitoring and treating oedema and hypertension, and preventing infections and thrombotic events, so that the child reaches a weight and a size that allows successful renal transplantation^{14,15}.

In spite of the controversy surrounding the use of the combination of indomethacin with an angiotensin conversion enzyme inhibitor in congenital nephrotic syndrome of the Finnish type¹⁴⁻¹⁶, the progressive clinical deterioration of our patient justified its use, and haemodynamic stability with significant improvement of the serum albumin was achieved.

Given its association with the mutation in the Wilms tumour (WT1) suppressor gene, children with DMS should always be investigated (karyotyping, checks for anomalies in gonad development and Wilms tumour) to exclude DDS. In fact, the presence of the WT1 mutation in female patients with nephrotic syndrome is common (21%) and frequently occurs in absence of any changes in genitalia^{6,17,18}. As mentioned previously, WT1 mutations tend to act dominantly, not recessively, and the history of parental consanguinity in our patient suggest that he is homozygous for a recessively acting gene mutation.

The clinical approach to a child with diffuse mesangial sclerosis must include consideration of the possibility of a familial type and guidance of the parents towards genetic counselling. Prenatal diagnosis of this disease is not possible at present, but it is important to alert the parents to the possibility of the disease in future pregnancies and to test subsequent offspring for proteinuria from birth.

In this patient, the absence of the WT1 gene mutation and the probable autosomal recessive inheritance suggest the existence of other mutation, as yet uncharacterised, associated with diffuse mesangial sclerosis. The new described cases of IDMS associated with

mutations on PLCE1 should be considered since the benefit of medical treatment on these patients.

Conflict of interest statement. None declared.

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