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## Respiratory chain deficiency presenting as congenital nephrotic syndrome

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**Abstract** Nephrotic syndrome (NS) in infancy includes NS of Finnish type (mutation of the nephrin gene), diffuse mesangial sclerosis (idiopathic or linked to *WT1* mutation), idiopathic NS, most often steroid resistant, and NS related to infections during pregnancy (virus, syphilis, toxoplasmosis). Later in life, NS has a large variety of etiologies. It has been described in association with neuromuscular symptoms, deafness, and diabetes in a few children and adults with respiratory chain (RC) disorders. To date, however, NS has never been observed in neo-

nates with RC disorders. Here, we report RC deficiency in one infant with certain congenital NS and two siblings with acute neonatal cardiac and renal disease with probable NS. Although clinical and histopathological presentations were initially close to congenital NS of Finnish type, clinical outcome was atypical and nephrin mutation was excluded. Mitochondrial RC complex II+V deficiency was identified in the three patients. Based on these observations, we suggest that RC disorders should be considered in patients with congenital NS.

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### Introduction

Several diseases are known to account for congenital nephrotic syndrome (NS) in infancy [1, 2, 3]. These include congenital NS of Finnish type [4], diffuse mesangial sclerosis [5], idiopathic NS, most often steroid resistant [6], and NS related to infections during pregnancy. Familial proteinuria/NS with focal glomerulosclerosis occurs later in life [7, 8].

Genetic defects of oxidative phosphorylation have been reported in late-onset NS in children and adults with multiple organ involvement [9, 10, 11, 12, 13, 14, 15]. Delayed-onset NS has occasionally been the first manifestation of the disease and the 3243 MELAS mitochondrial (mt) DNA mutation has been detected in most cases [1, 16, 17, 18, 19, 20, 21]. To date, however, respiratory chain (RC) deficiency has never been described as a cause for congenital NS, although secondary mitochondrial dysfunction has been documented in NS of Finnish type.

Here we report mitochondrial RC deficiency (complex II+V) in one patient with congenital NS and two patients with severe congenital renal and cardiac disease and probable NS.

## Case reports

### Case 1

A boy was born to unrelated parents after a term pregnancy with intrauterine growth retardation and acute fetal distress at birth (birth weight 2,130 g, birth length 49 cm). During pregnancy, serology for rubella, toxoplasmosis, syphilis, hepatitis B and C, and HIV excluded any infections. The placental weight was 800 g. Moderate diffuse edema was noted at birth and NS with hypoproteinemia (28–30 g/l), hypoalbuminemia (10–12 g/l), and proteinuria between 6 and 8 g/24 h was found at the age of 15 days. No renal insufficiency (serum creatinine=49  $\mu\text{mol/l}$ ) was observed and hematuria was in the normal range for newborns. Ultrasound examination revealed hyperechoic kidneys without corticomedullary differentiation, and a slightly increased size (+1 SDS).

Medical treatment with spironolactone (6 mg/kg per day), a high-protein diet, 20% human albumin infusion (1/week), acetylsalicylic acid (50 mg per day), and captopril (0.1 mg/kg per day), followed by indomethacin because of neutropenia, allowed uneventful evolution. At the age of 15 months, chronic renal insufficiency appeared (creatinine clearance=42 ml/min per 1.73 m<sup>2</sup>). Terminal renal insufficiency, severe hypertension, and the need for peritoneal dialysis occurred at 22 months of age. Bilateral nephrectomy was performed at 18 and 22 months.

At the age of 20 months, the child was admitted with generalized seizures and unexplained coma. Biochemical analysis demonstrated moderate chronic hypocalcemia (1.8 mmol/l) and severe metabolic acidosis (pH=7.12, bicarbonate 4 mmol/l) with normal lactacidemia but increased lactaciduria (2,220  $\mu\text{mol/l}$  or 1,522  $\mu\text{mol/mmol}$  of creatinine). He experienced multiple and short absences without any other neurological clinical signs. Computed tomography and magnetic resonance imaging and electroencephalography failed to reveal any abnormalities. Neurological acquisitions and muscle testing were normal for age.

He also experienced three episodes of severe pulmonary edema, needing artificial ventilation. None of the episodes could be related to hypertension, infection, or overweight. Cardiac ultrasound examination was normal at this time but during follow-up we discovered a dilated cardiomyopathy with decreased cardiac fractional shortening (CFR) (25%) at 2.5 years of age. In the following weeks, the myocardial function decreased (12%) with the occurrence of clinical signs of cardiac insufficiency. Myocardial function improved to 30% after 6 weeks of carnitine treatment (1.5 g/day) proposed because of slightly low serum carnitine (23 ng/ml). Ocular examinations did not reveal edema or retinitis pigmentosa. Discrete hepatomegaly was noted without ultrasound abnormalities or biological disorders.

When he was 4 years old, weighing 12.4 kg (–2 SD) with a height of 92 cm (–2 SD), and head circumference 48 cm (–2 SD), he received a cadaveric renal graft. During the first 24 months of the post-transplant follow-up, the renal function was good (serum creatinine=60  $\mu\text{mol/l}$ ) without recurrence of proteinuria or unusual events. Blood arterial pressure was normal without treatment, and cardiac function returned to normal values (CRF>40%).

### Case 2

A boy, the first child of unrelated parents, was born after a 38-week pregnancy and mild intrauterine growth retardation (birth weight 2,670 g, length 45 cm, head circumference 32 cm). He was referred to our institution at the age of 3 days for generalized edema. The placental weight was not available. Significant proteinuria was detected by dipstick. Renal ultrasonography was normal. Cardiac ultrasonography at this time showed a severe dilated cardiomyopathy (CRF <20%, flow 174 ml/kg), although no clinical cardiac failure was detectable. At 6 days of life the patient developed acute cardiac failure and died of cardiogenic shock. Metabolic acidosis was noted (pH=7.23), alanine, proline, and glutamine were elevated in blood samples and lactaturia was detected in urine at 4 days of life.

### Case 3

The second child of these parents was a girl (patient 3). She was born after a normal pregnancy. The mother was immunized for rubella and toxoplasmosis serology was negative. The delivery was normal (birth weight 2,700 g, length 47 cm, head circumference 33 cm). The placental weight was 440 g. At 3 min of life, she had a cardiac arrest and was admitted to the intensive care unit. She developed severe heart failure in the first hours of life and died at 27 h of age. Metabolic acidosis was noted (pH=6.79, total CO<sub>2</sub> 10 mmol/l), serum protein was low (43 g/l), and alanine and proline were elevated in blood samples. Urinary samples were not obtained because of anuria.

### Methods

Plasma lactate, pyruvate, and ketone bodies were determined by the enzymatic method and urinary organic acids were studied by gas chromatography-mass spectrometry. Deltoid muscle, liver, and kidney biopsies were obtained under local anesthesia (patient 1) or after death (patients 2 and 3) and mitochondria were prepared as described previously [22]. Fumarase (EC 4.2.1.2.), citrate synthase (EC 4.1.3.7), lactate dehydrogenase (EC 1.1.1.27), cytochrome c oxidase (EC 1.9.3.1), and succinate cytochrome reductase activities were measured spectrophotometrically according to standard procedures. Polarographic studies on mitochondria-enriched preparations were performed in a 250- $\mu\text{l}$  cell [22].

The kidney biopsy of patient 1 was fixed in 2.5% glutaraldehyde, post fixed in 2% osmium tetroxide, and embedded in epoxy resin. Nephrectomy and autopsy kidney specimens were fixed in 10% buffered formalin and embedded in paraplast. Sections (4  $\mu\text{m}$ ) were stained with trichrome-light green, trichrome-safran, or periodic acid-Schiff.

Screening for mtDNA deletions and mutations (MELAS A3243G, MERFF A8344G, NARP P8993G) was carried out as described previously [22]. *NPHS1* sequencing was performed as described previously [4].

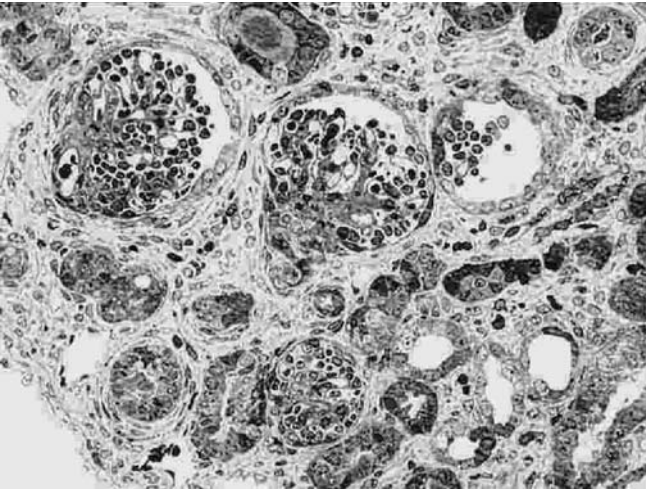
## Results

### Morphological findings

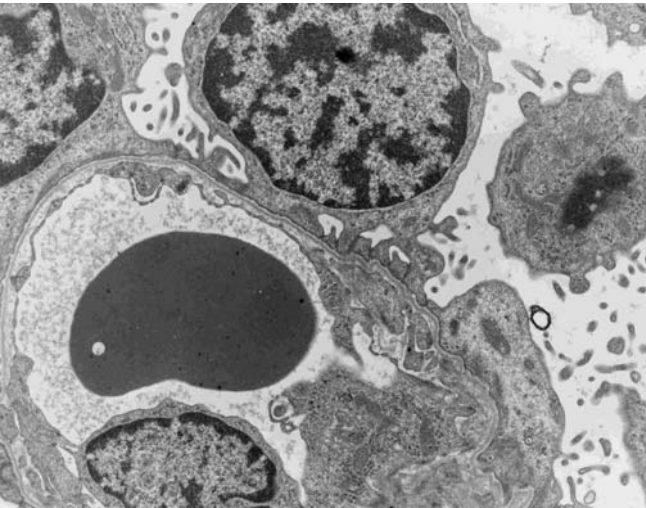
Light microscopy of the renal biopsy of patient 1 performed at 1 month of age showed diffuse mesangial hypercellularity and focal tubular dilatation with some obstructions by protein casts (Fig. 1). Electron microscopy (Fig. 2) showed extensive effacement of foot processes and no split diaphragm was visible on higher magnification (not shown).

At the time of nephrectomy (Fig. 3), lesions were severe and diffuse, resulting in marked cortical atrophy. Most glomeruli were sclerotic, while in the deep cortex, some were enlarged and contained foam cells and fibrin thrombi. Tubules were atrophic or completely dedifferentiated. Striking alterations affected the vascular system from large to small arteries. They consisted of marked thickening of the muscular layer associated with intimal proliferation, leading to marked narrowing or complete obliteration of the capillary lumen.

No specific lesion was observed in the renal specimen of patient 2 (light microscopy). Glomeruli were nearly normal except for the presence of moderate hypercellularity. Focal dilatations involving proximal tubules, and albumin casts were observed. In patient 3, the renal pa-



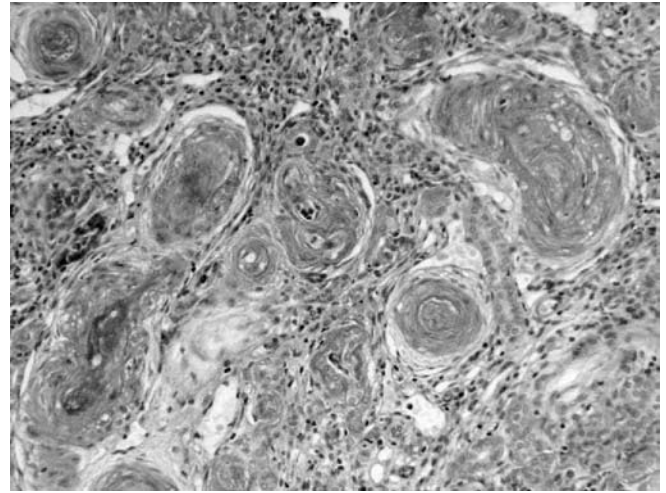
**Fig. 1** Kidney biopsy of patient 1 (1 month old) ( $\times 200$ , toluidine blue staining) showing moderate mesangial hypercellularity, interstitial edema, and cellular hypertrophy in the distal tubule



**Fig. 2** Kidney biopsy of patient 1 (1 month old) ( $\times 8,000$ ) showing extensive effacement of foot processes with microvilli formation. At higher amplification, no slit diaphragm was visible

renchyma was nearly normal except for the presence of moderate tubular dilatations.

Histopathology of the skeletal muscle of patient 1 at 4 years of age showed an irregular size of fibers, an excess of type I fibers, and a mild lipidosis consistent with metabolic disease without specificity (it is interesting to note that at the age of 2 years muscle histology was considered normal). The liver was normal in the three patients. The heart was normal in patients 1 and 3. Histological signs of dilated cardiomyopathy without specificity were observed in patient 2.



**Fig. 3** Nephrectomy in patient 1 (22 months old) ( $\times 100$ , trichrome-safran staining). Note the important arterial lesions, with thickening of the media and endarterial proliferation with spumous cells leading to arterial obstruction

#### Metabolic and enzymological studies

Plasma lactate, lactate/pyruvate ratios and amino acid chromatography of patient 1 were in the normal range (Table 1). Urinary organic acid chromatography was also in the normal range, except during acute episodes of metabolic acidosis when lactaturia was observed. High urinary lactate and metabolic acidosis were also detected in patients 2 and 3.

RC enzymological studies (enzymatic activity and ratios) of liver biopsies revealed a deficiency of complex V of the RC in all three children. In patient 2, liver biopsy revealed a combined deficiency of complex II and complex V.

Spectrophotometry of the renal biopsy has been possible in patient 1 only and showed complex II and V deficiency. An isolated complex II deficiency was found in the endomyocardial biopsy of patient 1. Polarographic (patient 1) and spectrophotometric studies (patients 1, 2, and 3) of isolated mitochondria of skeletal muscle and cultured skin fibroblasts (patients 1 and 2) were in the normal range.

#### Molecular studies

Sequencing the coding region of the *NPHS1* gene failed to detect any deleterious mutation in the three patients. No mtDNA deletion or 3243 mtDNA MELAS, 8344 and 8993 mutation was found in heart, muscle, and kidney (patient 1) or muscle and liver (patients 1, 2, and 3) and sequencing the mitochondrial complex V subunits (ATPase 6 and ATPase 8) failed to detect mutations in kidney, muscle, liver, and fibroblasts (patient 1) and liver (patients 2 and 3).

**Table 1** Spectrophotometric analysis of mitochondrial respiratory chain activities in the kidney [*CII* (complex II) succinate ubiquinone reductase, *CIII* (complex III) ubiquinol cytochrome C reductase, *CII+III* (complex II+III) succinate cytochrome C reductase, *CIV* (complex IV) cytochrome c oxidase]

Activities (nmol/min per mg protein)	Patient 1	Patient 2	Patient 3	Control
Liver				
CV	<b>62</b>	<b>54</b>	<b>42</b>	60–105
CII	184	<b>86</b>	123	110–167
CIII	453	253	131	89–335
CII+III	67	<b>27</b>	<b>20</b>	37–144
CIV	227	308	182	125–230
CIV/V	<b>3.6</b>	<b>5.7</b>	<b>4.3</b>	2.2±0.4
CIV/II	1.2	<b>3.6</b>	1.5	1.5±0.2
Kidney				
CV	<b>10</b>	-	-	114–156
CII	<b>20</b>	-	-	88–145
CIV	41	-	-	178–266
CIV/V	<b>4.1</b>	-	-	1.9±0.2
CIV/II	2.1	-	-	1.8±0.2
Heart				
CII	<b>29</b>	-	-	66–126
CV	74	-	-	83–241
CIV	194	-	-	368–776
CIV/II	<b>6.8</b>	-	-	5.1±0.3
CIV/V	2.6	-	-	3.0±0.5

Abnormal values are indicated in *bold*. The *bold characters* are the absolute low values and the high ratios. High absolute values are considered as adapted activity of other respiratory chain complexes. Since control absolute activities do not follow a Gaussian distribution, only a range is given for these values. However, since enzyme activity ratios follow such a Gaussian distribution, mean±1 SD is indicated

## Discussion

Owing to the ubiquitous nature of the mitochondrial RC, genetic defects of oxidative phosphorylation are known to account for a variety of symptoms in childhood, including renal disease (proximal tubulopathy, tubulointerstitial nephritis, renal insufficiency, delayed-onset NS) [23]. Proximal tubulopathy has only been described in the neonatal period [24, 25, 26, 27, 28, 29, 30, 31, 32]. Delayed-onset steroid-unresponsive NS with focal segmental glomerulosclerosis, mostly ascribed to the 3243 MELAS mutation, has been reported in children and adults, in association with muscle weakness, neurological disturbance, deafness, pigmentary retinopathy, and/or diabetes mellitus [9, 10, 11, 12, 13, 14, 15]. Proteinuria was the first symptom of the disease in 12 patients aged 10–32 years [16, 17, 18, 19, 20, 21]. There have been rare reports of NS linked to RC disorders in the absence of the MELAS mutation; one was associated with quinone deficiency [9, 14, 15]. To our knowledge, neonatal nephrotic syndrome has never been reported in RC disorders.

Here we report RC enzyme deficiency in one patient presenting with well-documented congenital NS, and two siblings with renal and cardiac involvement in the early neonatal period. In these three patients clinical, biological, and histological data allowed us to exclude classical etiologies of neonatal NS. Transient urinary lactate accumulation (patients 1 and 2), transient acidosis with coma (patient 1), and associated cardiomyopathy prompted us to consider and eventually confirm an RC deficiency in these patients.

By light microscopy, renal lesions characterized by the association of mild mesangial hypercellularity and focal proximal tubular dilatation were not specific. In patient 1, with isolated NS at birth, they were initially regarded as

consistent with the diagnosis of Finnish type NS, but search for the *NPHS1* mutation was negative. A very unusual finding in this patient was the presence of severe arteriolar changes on the renal biopsy specimen obtained at 1 month of age, and involving all the arterial system at the time of nephrectomy. Whether related to the mitochondrial deficiency or not, they could explain the severe hypertension observed in the child during the course of the disease.

In these patients, the precocity and severity of cardiomyopathy (patient 2 and 3), the fact that complex V deficiency was observed early in life (patient 2 and 3), in different tissues (patient 1), and in a moderate NS without massive proteinuria (patient 1) prompted us to consider those as primitive genetic RC disorders, rather than a secondary dysfunction of the RC. In the same way, the observation of a complex II deficiency prompted us to consider a primitive RC deficiency and not a secondary downregulation of mitochondria-encoded RC component, since this complex is encoded by nuclear genes. Interestingly, complex V or complex II+V deficiency was consistently observed in all three patients, suggesting either a mutation in an assembly protein gene or a gene encoding a complex II (or V) subunit with a secondary complex V (or II) deficiency. Interestingly, patient 1 had an apparently isolated glomerular involvement with no other symptom until 19 months of age. This suggests that RC deficiency should be considered in apparent cases of NS of the Finnish type without *NPHS1* mutations.

It should be borne in mind that mitochondria anomalies have been previously observed in renal biopsies of NS, irrespective of the cause. In particular, mitochondrial dysfunction and downregulation of mitochondria-encoded RC components have been observed in Finnish NS [31, 32]. Apart from a possible causative role of mitochondria in the disease, this suggests a critical role of mitochon-

dria, the first source of energy in the kidney, in maintaining the glomerular permeability barrier [31].

In conclusion, it appears that genetic defects of the mitochondrial RC should be regarded as a possible cause of congenital NS, especially when no *NPHS1* mutation is found in the patient.

## References

- Habib R (1993) Nephrotic syndrome in the first year of life. *Pediatr Nephrol* 7:347–353
- Salomon R, Gubler MC, Niaudet P (2000) Genetics of the nephrotic syndrome. *Curr Opin Pediatr* 12:129–134
- Khoshnoodi J, Tryggvason K (2001) Congenital nephrotic syndromes. *Curr Opin Genet Dev* 11:322–327
- Kestila M, Lenkkeri U, Mannikko M, Lamerdin J, McCready P, Putaala H, Ruotsalainen V, Morita T, Nissinen M, Herva R, Kashtan CE, Peltonen L, Holmberg C, Olsen A, Tryggvason K (1998) Positionally cloned gene for a novel glomerular protein—nephrin—is mutated in congenital nephrotic syndrome. *Mol Cell* 1:575–582
- Habib R, Loirat C, Gubler MC, Niaudet P, Bensman A, Levy M, Broyer M (1985) The nephropathy associated with male pseudohermaphroditism and Wilm's tumor (Drash syndrome): a distinctive glomerular lesion—report of 10 cases. *Clin Nephrol* 24:269–278
- Boute N, Gribouval O, Roselli S, Benessy S, Lee H, Fuchshuber A, Dahan K, Gubler MC, Niaudet P, Antignac C (2000) *NPHS2* encoding the glomerular protein podocin, is mutated in autosomal recessive steroid-resistant nephrotic syndrome. *Nat Genet* 24:349–354
- Kaplan JM, Kim SH, North KN, Rennke H, Correia LA, Tong HQ, Mathis BJ, Rodriguez-Perez JC, Allen PG, Beggs AH, Pollak MR (2000) Mutations in *ACTN4*, encoding actinin-4 cause familial focal segmental glomerulosclerosis. *Nat Genet* 24:251–256
- Winn MP, Conlon PJ, Lynn KL, Howell DN, Slotterbeck BD, Smith AH, Graham FL, Bembe M, Quarles LD, Pericak-Vance MA, Vance JM (1999) Linkage of a gene causing familial focal segmental glomerulosclerosis to chromosome 11 and further evidence of genetic heterogeneity. *Genomics* 58:113–120
- Brun P, Ogier de Baulny H, Peuchmaur M, Lombes A, Simon D, Loirat C (1994) Les atteintes rénales des cytopathies mitochondriales. In: Arthuis M, Beaufrils F, Caille B, Dommergues JP, Fontaine JL, Griscelli C, Job JC, Lasfargues G, Lenoir G, Mathieu H, Paillerets F de, Saudubray JM (eds) Journées Parisiennes de Pédiatrie Flammarion Médecine Sciences, Paris, pp 227–234
- Nakamura S, Yoshinari M, Doi Y, Yoshizumi H, Katafuchi R, Yokomizo Y, Nishiyama K, Wakisaka M, Fujishima M (1999) Renal complication in patients with diabetes mellitus associated with an A to G mutation of mitochondrial DNA at the 3243 position of leucine tRNA. *Diabetes Res Clin Pract* 44:183–189
- Tanaka K, Ueno M, Atsumi T, Fukagawa M, Koike Y (1986) A case of mitochondrial encephalomyopathy with nephrotic syndrome. *Rinsho Shinkeigaku* 26:1190–1196
- Hirano M, Konishi K, Arata N, Iyori M, Saruta T, Kuramochi S, Akizuki M (2002) Renal complications in a patient with A to G mutation of mitochondrial DNA at the 3243 position of leucine tRNA. *Intern Med* 41:113–118
- Hameed R, Raafat F, Ramani P, Gray G, Roper HP, Milford DV (2001) Mitochondrial cytopathy presenting with focal segmental glomerulosclerosis, hypoparathyroidism, sensorineural deafness, and progressive neurological disease. *Postgrad Med* 77:523–526
- Niaudet P, Rötig A (1996) Renal involvement in mitochondrial cytopathies. *Pediatr Nephrol* 10:368–373
- Rotig A, Appelkvist EL, Geromel V, Chretien D, Kadhon N, Edery P, Lebeideau M, Dallner G, Munnich A, Ernster L, Rustin P (2000) Quinone-responsive multiple respiratory-chain dysfunction due to widespread coenzyme Q10 deficiency. *Lancet* 356:391–395
- Mochizuki H, Joh K, Kawame H, Imadachi A, Nozaki H, Ohashi T, Usui N, Eto Y, Kanetsuna Y, Aizawa S (1996) Mitochondrial encephalomyopathy preceded by de Toni-Debré-Fanconi syndrome or focal segmental glomerulosclerosis. *Clin Nephrol* 46:347–352
- Shigemoto M, Yoshimasa Y, Yamamoto Y, Hayashi T, Suga J, Inoue G, Okamoto M, Jingami H, Tsuda K, Yamamoto T, Yagura T, Oishi M, Tsujii S, Kiyosawa K (1998) Clinical manifestations due to point mutation of the mitochondrial tRNA<sup>Leu</sup>(UUR) gene in five families with diabetes mellitus. *Intern Med* 37:265–272
- Kurogouchi F, Oguchi T, Mawatari E, Yamaura S, Hora K, Takei M, Sekijima Y, Ikeda S, Kiyosawa K (1998) A case of mitochondrial cytopathy with a typical point mutation for MELAS, presenting with severe focal-segmental glomerulosclerosis as main clinical manifestation. *Am J Nephrol* 18:551–556
- Cheong HI, Chae JH, Kim JS, Park HW, Ha IS, Hwang YS, Lee HS, Choi Y (1999) Hereditary glomerulopathy associated with a mitochondrial tRNA(Leu) gene mutation. *Pediatr Nephrol* 13:477–480
- Doleris LM, Hill GS, Chedin P, Nochy D, Bellanne-Chantelot C, Hanslik T, Bedrossian J, Caillat-Zucman S, Cahen-Varsaux J, Bariety J (2000) Focal segmental glomerulosclerosis associated with mitochondrial cytopathy. *Kidney Int* 58:1851–1858
- Hotta O, Inoue CN, Miyabayashi S, Furuta T, Takeuchi A, Taguma Y (2001) Clinical and pathologic features of focal segmental glomerulosclerosis with mitochondrial tRNA(Leu)(UUR) gene mutation. *Kidney Int* 59:1236–1243
- Rustin P, Chretien D, Bourgeron T, Rötig A, Saudubray JM, Munnich A (1994) Biochemical and molecular investigations in respiratory chain deficiencies. *Clin Chim Acta* 228:35–51
- Munnich A, Rustin P (2001) Clinical spectrum and diagnosis of mitochondrial disorders. *Am J Med Genet* 106:4–17
- Eviatar L, Shanske S, Gauthier B, Abrams C, Maytal J, Slavin M, Valderrama E, DiMauro S (1990) Kearns-Sayre syndrome presenting as renal tubular acidosis. *Neurology* 40:1761–1763
- Szabolcs AMJ, Seije R, Shanske S, Bonilla E, Di Mauro S, D'Agati V (1994) Deletion of mitochondrial DNA: a cause of chronic tubulointerstitial nephropathy. *Kidney Int* 45:1388–1396
- Rotig A, Goutieres F, Niaudet P, Rustin P, Chretien D, Guest G, Mikol J, Gubler MC, Munnich A (1995) Deletion of mitochondrial DNA in patient with chronic tubulointerstitial nephritis. *J Pediatr* 126:597–601
- Niaudet P, Heidet L, Munnich A, Schmitz J, Bouissou F, Gubler MC, Rotig A (1994) Deletion of the mitochondrial DNA in a case of the De Toni-debré-fanconi syndrome and Pearson syndrome. *Pediatr Nephrol* 8:164–168
- Niaudet P, Rötig A (1997) The kidney in mitochondrial cytopathies. *Kidney Int* 51:1000–1007
- Lonlay P de, Valnot I, Barrientos A, Gorbatyuk M, Tzagoloff A, Taanman JW, Benayoun E, Chretien D, Kadhon N, Lombes A, Baulny HO de, Niaudet P, Munnich A, Rustin P, Rotig A (2001) A mutant mitochondrial respiratory chain assembly protein causes complex III deficiency in patients with tubulopathy, encephalopathy and liver failure. *Nat Genet* 29:57–61
- Goto Y, Itami N, Kajii N, Tochimaru H, Endo M, Horai S (1990) Renal tubular involvement mimicking Barter syndrome in a patient with Kearns-Sayre syndrome. *J Pediatr* 116:904–910
- Solin ML, Pitkanen S, Taanman JW, Holthofer H (2000) Mitochondrial dysfunction in congenital nephrotic syndrome. *Lab Invest* 80:1227–1232
- Holthofer H, Kretzler M, Haltia A, Solin ML, Taanman JW, Schagger H, Kriz W, Kerjaschki D, Schlondorff D (1999) Altered gene expression and functions of mitochondria in human nephrotic syndrome. *FASEB J* 13:523–532