Familial mitochondrial tubulointerstitial nephropathy

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Mutations in the mitochondrial genome have been found to be responsible for several neuromuscular and cardiac diseases. Mitochondrial genome alterations can, however, present as renal tubular dysfunction [1,2]. Recently, aberrant mitochondria and mitochondrial DNA (mtDNA) deletion were diagnosed ultrastructurally in a renal biopsy specimen from a patient with chronic tubulointerstitial nephropathy (TIN) [3]. We demonstrate the renal biopsy findings in a family with three affected individuals presenting with chronic progressive TIN, distorted mitochondria, and mtDNA point mutation. The disease, and the mutation appeared to have been maternally inherited.

Renal biopsies were performed on a 12-year-old boy, his 11-year-old sister, and a 17-year-old maternal male cousin (biopsied 15 years earlier). They all had progressively impaired renal function. Two other maternal relatives are known to have died earlier because of chronic renal failure, but renal biopsy was not carried out on these patients. Detailed renal functional data were available from the siblings: decreased GFR (creatinine clearance: boy: 38 ml/min/1.73 m², girl: 30 ml/min/1.73 m²); increased renal sodium loss (fractionated Na excretion: 1.38%, 1.25% [normal: <1], UNa/UK: 8.19, 4.79, normal: 1.5 ± 1); serum Na 117 mM/l, 122 mM/l; decreased urinary concentrating capacity (DDAVP-test: 690 mosm/l, 620 mosm/l [normal: >1000]); elevated PTH level: 89 pg/ml, (588 ± 1996–06 to B.I. and 673 ± 1996–06 to S.T.); serum Na 117 mM/l, 122 mM/l; decreased urinary concentrating capacity (DDAVP-test: 690 mosm/l, 620 mosm/l [normal: 1000]); elevated PTH level: 89 pg/ml, (588 ± 1996–06 to B.I. and 673 ± 1996–06 to S.T.).

Extrarenal features in both siblings included thoracolumbar scoliosis, weakness of the intercostal muscles, progressive breathing difficulties, low vital capacity, mitral prolapse, and cardiac conduction defects. Pigment retinopathy was observed in the girl, and a psychiatric disorder in the boy. The 35-year-old cousin at biopsy had thoracic kyphoscoliosis. He has been on chronic hemodialysis since the age of 20, and has severe hyperparathyroidism with progressive bone deformities.

Renal biopsy specimens showed tubular atrophy, moderate interstitial mononuclear infiltrates, interstitial fibrosis, sclerosis of some glomeruli and arteriolar sclerosis. Immunofluorescence was negative. In all three cases, electron microscopy showed various mitochondrial lesions in many of the distal tubular epithelial cells (Figure 1): an increased thickness of the internal membranes; a distended empty core (Figures 2 and 4), also seen by light microscopy (Figure 6); or dense inclusions (Figures 2 and 3) enveloped occasionally by irregular or concentric cristae (Figure 3). Additionally, some epithelial cells were filled so densely with aberrant mitochondria that they resembled oncocytes (Figure 5).

mtDNA from the blood of these patients was analysed, and an A to G mutation was detected in position 3686 [4]. We interprete the mutation as a probable causative factor of the aberrant mitochondria and renal disease. The formation of oncocyte-like cells may be connected with the mtDNA mutation as renal tumours composed of oncocytes are characterised by an altered restriction pattern of the mtDNA [5]. The arteriolar lesions in our patients in childhood may be explained by the suggestion that premature arterio(sclerosis) can result from a mtDNA mutation [6].

These illustrations provide a detailed ultrastructural documentation of mitochondrial TIN and emphasise the need to pay careful attention to mitochondrial changes in tubules in patients with idiopathic chronic TIN.

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References
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