

MITO 101 - Renal

**Agnès Rötig
Patrick Niaudet**

INSERM U781 and Service de Néphrologie Pédiatrique, Necker Hospital,
Université Paris V- René Descartes,
Paris, France

Renal involvement is not a common feature of mitochondrial disease. Moreover, renal disease is always associated with involvement of other tissues, as indicated by the frequent coexistence of diabetes, deafness, myopathy, encephalopathy, or liver failure.

Clinical evaluation

Routine laboratory tests include plasma sodium, potassium, bicarbonates, phosphorus, uric acid, plasma and urinary lactate and organic acids, proteinuria, hematuria, creatininemia and clearance of creatinine.

Clinical features of mitochondrial renal dysfunction

Renal disease has been reported more frequently in children than in adults.

Pediatric presentation.

Tubulopathy. In children, the most frequent renal manifestation is proximal tubulopathy resulting in a more or less complete and severe form of DeToni–Debré–Fanconi syndrome^{1,2}. Extra-renal symptoms are always present and include myopathy, neurological symptoms, diabetes mellitus, or cardiac problems³⁻⁵.

Tubular acidosis. Patients may also present with isolated proximal tubular acidosis and hypercalciuria or with signs of salt depletion and hypokalemic metabolic alkalosis as observed in Bartter's syndrome⁶⁻⁸.

Nephrotic syndrome. Children may present with steroid-resistant nephrotic syndrome and focal segmental glomerular sclerosis (FSGS)⁹.

Tubulointerstitial nephropathy. Tubulointerstitial nephropathy has been described in a few patients⁹⁻¹². Children present with polyuria secondary to impaired urinary-concentrating ability and progress to end-stage renal failure. Patients do not show proximal tubular defects.

Distal renal tubular acidosis (RTA) is quite unusual in mitochondrial cytopathy. Most often, patients have proximal RTA with a defect of bicarbonate reabsorption in the proximal tubule. Distal RTA is related to impaired acid excretion in the distal tubule. Patients present with plasma acidosis but without other signs of proximal tubular defect such as glucosuria, aminoaciduria, proteinuria, hypophosphatemia. A screening simple test is to measure urinary pH. If it is higher than 6.5 while there is plasma acidosis, then distal RTA is suspected.

Adult presentations

Renal lesions consist of FSGS, tubulointerstitial nephropathy, or bilateral enlarged cystic kidneys^{13,14}. Proteinuria accompanied by nephrotic syndrome is seldom observed. Patients do not show proximal tubular dysfunction. Most patients progress to end-stage renal failure at a median age of 33 years. Diabetes mellitus develops in the majority of patients, but usually several years after the nephropathy had been discovered¹⁴⁻¹⁵. Hearing loss is also a common finding, which often precedes the onset of renal disease and diabetes mellitus¹⁶⁻¹⁸.

Metabolic investigation of the renal dysfunction

Metabolic abnormalities such as hyperlactatemia and high L/P ratio may not be present in patients with proximal tubulopathy because the impaired proximal tubular functions may lower blood lactate and increase urinary lactate. For this reason, normal plasma lactate does not rule out a mitochondrial disorder with proximal tubulopathy. Nevertheless, abnormal urinary lactate and Krebs cycle intermediates point toward respiratory chain deficiency.

Enzymological investigation of mitochondrial renal dysfunction

Accessible peripheral tissues should be tested (including skeletal muscle, cultured skin fibroblasts, and circulating lymphocytes) and are often informative, thus making a kidney biopsy often unnecessary for enzymological studies of the RC. It is mandatory to take skin biopsies from patients for subsequent biochemical and genetic investigations in cultured fibroblasts, which is feasible even post-mortem.

Genetic features and genetic counselling in mitochondrial renal dysfunction

Any mode of inheritance can be observed in mitochondrial diseases, whatever the clinical symptoms, including renal involvement¹⁹. Accordingly, mutations in both mitochondrial and nuclear genes have been identified in patients with mitochondrial disorder and renal involvement. Nevertheless, most of the adult patients with renal disease and diabetes, deafness and/or hearing loss present the MELAS mutation (A3243G change in the tRNA^{Leu} gene)¹³⁻¹⁸. This mutation is maternally inherited and heteroplasmic. Maternal relatives of patients are generally healthy as long as they have no more than 85% mutant mtDNA. Therefore, after diagnosis of the MELAS mutation in a patient, maternal relatives have to be informed and/or tested.

Management and treatment

So far, neither preventive therapy nor a cure is available for improving clinical involvement in mitochondrial disease. More specifically, corticosteroid therapy is ineffective on the course of proteinuria in patients who received this treatment. Renal transplantation has been successfully performed in some patients and no recurrence of the disease was observed on kidney graft¹³. Renal transplantation may be therefore offered to these patients, although steroid therapy increases the risk of developing diabetes mellitus. The treatment of distal RTA is bicarbonate supplementation.

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