Abstract Mitochondrial cytopathies constitute a group of rare diseases that are characterized by their frequent multisystemic involvement, extreme variability of phenotype and complex genetics. In children, renal involvement is frequent and probably underestimated. The most frequent renal symptom is a tubular defect that, in most severe forms, corresponds to a complete De Toni-Debré-Fanconi syndrome. Incomplete proximal tubular defects and other tubular diseases have also been reported. In rare cases, patients present with chronic tubulo-interstitial nephritis or cystic renal diseases. Finally, a group of patients develop primarily a glomerular disease. These patients correspond to sporadic case reports or can be classified into two major defects, namely 3243 A>G tRNA^{LEU} mutations and coenzyme Q10 biosynthesis defects. The latter group is particularly important because it represents the only treatable renal mitochondrial defect. In this Educational Review, the principal characteristics of these diseases and the main diagnostic approaches are summarized.

Keywords Mitochondria · Oxidative phosphorylations · Coenzyme Q10

Components of the mitochondrial respiratory chain

Mitochondria are intracellular organelles that play a cardinal role in generating adenosine triphosphate (ATP) through oxidative phosphorylation (OXPHOS) and in modulating other cell functions, such as apoptosis, response to oxidative stresses, heat production, and various anaplerotic reactions [1, 2]. In this review, we restrict the term mitochondrial cytopathy to genetic defects that directly or indirectly impair OXPHOS. Briefly, the respiratory chain is composed of five protein complexes that have two major functions, namely, to transfer protons and electrons [from reduced nicotinamide adenine dinucleotide phosphate (NADPH) and reduced flavin adenine dinucleotide (FADH₂) to oxygen molecules] across the inner mitochondrial membrane and to generate ATP (Table 1). The first task is performed by complexes I–IV and generates the electrochemical gradient that allows complex V, or ATP synthase, to form ATP from adenosine diphosphate (ADP) and inorganic phosphate (reviewed in [1–4]).

Within the mitochondrial respiratory chain, ubiquinone, or coenzyme Q10 (CoQ₁₀), plays a crucial role in shuttling electrons from complexes I and II to complex III (Fig. 1) [5]. CoQ₁₀ is a ubiquitous lipophilic vitamin-like substance first isolated in 1957 from beef mitochondria, which has the
highest concentration in tissues, with elevated energy turnover (heart, brain, liver, kidney). It is comprised of a quinone group and of a polyisoprenoid tail of different length in different species: 6 subunits in yeast (CoQ₆), 9 subunits in mice (CoQ₉), and 10 subunits in humans (CoQ₁₀) (Fig. 1). It is endogenously synthesized through a multi-enzyme complex located at the inner mitochondrial membrane [6], which is encoded by at least 16 genes. The functions of CoQ₁₀, however, are not restricted to bioenergetics; CoQ₁₀ is also an important cofactor of several mitochondrial dehydrogenases, a modulator of the mitochondrial permeability transition pore that acts as a gating channel for apoptosis, and an important antioxidant [7]. Approximately 0.2% of oxygen molecules are not reduced into water during OXPHOS and form reactive oxygen species (ROS) that can be converted into highly reactive hydroxyl radicals (OH•) that cause oxidative damage to DNA, lipids, and proteins [1, 2]. Accumulation of free radicals probably plays a crucial role in the physiopathology of many mitochondrial diseases [8]. In normal conditions, ROS are scavenged by superoxide dismutase, catalase, and glutathione peroxidase, but CoQ₁₀ and other molecules, such as vitamin C and vitamin E (α-tocopherol), also play a crucial role as lipid-soluble antioxidants [1, 5].

Genetics

Each mitochondria has several copies of its own double-stranded mitochondrial DNA (mtDNA) that forms a circular string of 16,569 bp. mtDNA encodes 37 genes, including all 22 transfer RNAs (tRNAs) necessary for protein synthesis, two ribosomal RNA (rRNA) subunits, and 13 structural proteins of the mitochondrial respiratory chain (Table 1). The majority of structural proteins that compose mitochondria (>1,000) and the totality of functional proteins that are necessary for mitochondria assembly and degradation are encoded by nuclear genes [3, 9]. Spermatozoa do not contribute to the zygote with mitochondria; mutations in mtDNA are therefore inherited from the mother (i.e., maternal inheritance). mtDNA abnormalities were first linked to human disease in 1988. In that year, Leber’s

| Complex | Name                                      | Subunits encoded by mtDNA | Subunits encoded by nuclear genes | Total subunits |
|---------|-------------------------------------------|----------------------------|----------------------------------|---------------|
| Complex I | NADH-ubiquinone oxidoreductase | ND1, ND2, ND3, ND4, ND5, ND6, ND4L | ~39 | ~46 |
| Complex II | Succinate-ubiquinone oxidoreductase | None | 4 | 4 |
| Complex III | Ubiquinol-cytochrome c oxidoreductase | Cytochrome-b | 10 | 11 |
| Complex IV | Cytochrome c oxidase | COX I, COX II, COX III | 10 | 13 |
| Complex V | ATP synthase | ATPase 6, ATPase 8 | 12 | 14 |
| Total | | | ~75 | ~88 |

mtDNA mitochondrial DNA, NADH nicotinamide adenine dinucleotide, reduced, ATP adenosine triphosphate, COX cytochrome c oxidase.
hereditary optic neuropathy and other progressive muscle disorders were found to be caused by mutations in mtDNA [10, 11]. Since the first descriptions, a large number of disease-causing mutations in mtDNA have been reported and are collected in the MITOMAP human mitochondrial genome database (http://www.mitomap.org). Their prevalence in the general population is probably underestimated and may be as high as 1–2:10,000 live births [12].

Mutations primarily include base substitutions or insertions–deletions. Diseases resulting from missense mutations are generally maternally transmitted. They can directly alter mitochondrial proteins or impair protein synthesis if they involve structural RNAs [tRNAs or rRNA]. Insertion–deletion mutations can be spontaneous, maternally inherited, or Mendeliany inherited due to predisposing nuclear mutations. Spontaneous rearrangements of mtDNA can also be responsible for various clinical syndromes and reflect the gradual loss of autonomy throughout evolution of the mitochondrial genome, which has become increasingly dependent upon factors encoded by nuclear genes for transcription, translation, and replication. These disorders are due to mutations in nuclear genes that directly or indirectly control mtDNA number, function, or integrity [13]. Progressive mtDNA depletion diseases represent other examples of the interplay between mitochondrial and nuclear genomes and are secondary to defects in nuclear genes that regulate mtDNA replication. Finally, somatic mtDNA mutations are very frequent and may occur preferentially in specific tissues, particularly in skeletal muscles [13].

As opposed to nuclear genes, the genetic information for proteins encoded by mtDNA is present in hundreds of copies per cell. Mutations can affect all mtDNA copies of an affected individual—a condition referred to as homoplasmymay affect only a portion of the entire mtDNA endowment of cells—termed heteroplasmy. In case of heteroplasmy, the impact of a given mutation depends on the relative proportion of mutated and wild-type mtDNA copies [8]. Cell dysfunction occurs when the proportion of mutated mtDNA exceeds a given threshold level, which is dependent on cell OXPHOS rates [3]. Tissues with high metabolic rates, such as brain, skeletal muscles, heart, and renal tubules, are particularly exposed [3]. Symptoms may be delayed until late childhood or adulthood, when the number of cells with a high copy number of mutated mtDNA exceeds the compensatory ability of neighboring cells. Examples of this phenomenon include Leber’s optic atrophy, myoclonic epilepsy with ragged red fibers (MERRF) syndrome or focal segmental glomerulosclerosis (FSGS) related to tRNA\textsuperscript{LEU} mutations. Conversely, a positive selection, favoring replication of healthier cells, can occur in tissues with high cell turnover. Mutations may also be distributed unevenly during early stages of embryogenesis, which causes differences in penetrance of a given mutation in tissues originating from different embryonic lineages. Finally, the proportion of mutated mitochondria varies significantly from one oocyte to the other, causing significant differences in disease expression among siblings [13]. For all the above reasons, diseases caused by mtDNA mutations are characterized by the extreme heterogeneity of their clinical symptoms.

A few years after the first reports of diseases caused by mtDNA mutations, mitochondrial cytopathies caused by defects in nuclear genes were reported [14]; these conditions are inherited with a Mendelian trait in an autosomal recessive or dominant mode. Surprisingly, a similar variability in the clinical picture as in mtDNA defects also characterizes nuclear gene mutations. Such phenotypic variability is related, at least in part, to the stochastic nature of mitochondrial physiology, where a dynamic balance exists between high rates of endogenous mtDNA mutations and mtDNA repair mechanisms, including control of mtDNA copy number [15], and between constitutive mitochondrial damage and mitochondria turnover processes (assembly and degradation). These mechanisms are also thought to play a significant role during aging. From a taxonomic perspective, several classifications of mitochondrial cytopathies have been proposed based on mutation type, and/or biochemical defects, and/or clinical symptoms [1, 3].

### Clinical symptoms of mitochondrial cytopathies

Nearly all organs may be affected by mitochondrial cytopathies. The clinical presentation is heterogeneous; it may reflect involvement of single organs but commonly symptoms are multisystemic. The most frequent symptoms and features [16] are summarized in Table 2.

Skeletal muscles are frequently affected, in part because somatic mutations occur more frequently in myoblasts or myoblast precursors. Exercise intolerance is a common complaint, which is often dismissed as psychogenic or mislabeled as chronic fatigue syndrome or rheumatic fibromyalgia, unless patients have objective muscle weakness, increased serum creatine kinase levels, or abnormal electromyography findings [13]. Many patients with mtDNA mutations fall into this group; the frequent lack of a clear maternal inheritance further deflects the physician from considering a mitochondrial cytopathy [13]. If not initially present, central nervous system (CNS) symptoms develop at some stage of the disease in most patients. Some symptoms, such as sensorineural deafness or myocardopathy, may remain subclinical for many years and require systematic screening. Endocrine (diabetes mellitus) and
Table 2 Symptoms related to mitochondrial cytopathies

| Affected system    | Manifestations                                                                                      |
|--------------------|---------------------------------------------------------------------------------------------------|
| Neurological       | Apnea, hypotonia, lethargy, developmental delay, psychomotor regression, ataxia, stroke-like episodes, hemiparesis, spasticity, seizures, dementia, leukodystrophy, myoclonus, cortical blindness, migraine, polyneuropathy (sensory and/or motor), neurogenic bladder |
| Muscular           | Myopathy, hypotonia, exercise intolerance                                                          |
| Hearing            | Hearing loss                                                                                      |
| Cardiac            | Cardiomyopathy, arrhythmias, heart block                                                           |
| Renal              | Proximal tubulopathy, De Toni-Debré-Fanconi syndrome, proximal tubular acidosis, Barter-like tubulopathy, hypermagnesuria, proteinuria, nephrotic syndrome, tubulointerstitial nephritis, myoglobinuria, renal failure |
| Endocrine          | Diabetes mellitus, hypoparathyroidism, hypothyroidism, hyporeninemic hypoadosteronism, growth hormone deficiency |
| Gastrointestinal   | Liver dysfunction, hepatomegaly, liver failure, vomiting, diarrhea, malabsorption, pseudoobstruction, intestinal dysmotility, exogenous pancreatic insufficiency |
| Hematological      | Sideroblastic anemia, neutropenia, thrombocytopenia                                                  |
| Ocular             | Progressive external ophthalmoplegia, ophtalmoparesis, pigmentary retinal degeneration, ptosis, cataract, optic atrophy, blindness |
| Antenatal symptoms | Dysmorphic features, malformations, intrauterine growth retardation, polyhydramnios                |
| Cutaneous          | Mottled pigmentation, discoloration, acrocyanosis, vitiligo, cutis marmorata, anhidrosis and jaundice, hyperhidrosis, trichothiodystrophy, hirsutism alopecia, alopecia with brittle hair, symmetric cervical lipomas |

Diagnosis of mitochondrial cytopathies

When suspecting a mitochondrial disorder, the first step is generally to measure serum lactate levels, which are frequently elevated, although often fluctuating. In oligosymptomatic diseases, such as in certain renal mitochondrial cytopathies, serum lactate may be normal. In addition to blood, however, lactate can also be measured in other body fluids, such as cerebrospinal fluid (CSF) and urine. Brain lactate levels can be estimated by magnetic resonance (MR) spectroscopy. If lactate levels are normal in all sampled tissues, further genetic studies are not usually recommended, unless other evidences of a mitochondrial defect subsist. The diagnostic workup of renal mitochondrial cytopathies requires a combination of different approaches, including enzymology and biochemistry analyses, molecular genetics, pathology (histology, histochemistry, electron microscopy), and neuroradiology studies, possibly coupled with MR spectroscopy. Measurement of urine organic acids by gas chromatography/mass spectrometry (GC-MS) is often useful. Impaired respiratory chain activity causes accumulation of reduced NADH, promoting conversion of acetoacetic acid into 3OH-butyrate in the mitochondrion and the conversion of pyruvate into lactate in the cytosol [18]. These compounds are easily detected in urines and, when present in high amounts, are highly evocative of a mitochondrial dysfunction. Excess of other intermediate metabolites of the Krebs cycle and other metabolic pathways are also frequently observed. When the muscle biopsy is available, the presence of ragged red fibers is a specific finding in patients with mitochondrial diseases.

In tissues, the general rule is to perform tests on samples collected from the most affected organs. However, in many cases, this approach may be unreasonably aggressive, and biochemical studies performed on cultured fibroblasts from a skin biopsy are sufficient. Measuring respiratory-chain complexes in the kidney, for example, requires a surgical biopsy to obtain at least 3–4 mm³ of renal cortex. Similarly, CoQ₁₀ determination has been traditionally performed on skeletal muscle [19], which is an invasive procedure in infants, in whom obtaining sufficient amounts of tissue can be problematic. Moreover, muscle biopsies need to be performed before initiating CoQ₁₀ supplementation. Fortunately, CoQ₁₀ can be reliably measured in cultured skin fibroblasts [20], which also allow measuring the rate of ubiquinone biosynthesis [21]. Fibroblasts can be easily

ophthalmologic (ophthalmoplegia, ptosis, pigmentary retinal degeneration) symptoms also frequently develop in the course of the disease. Various skin and hair lesions have also been described [17].

Overall, a major characteristic of mitochondrial cytopathies is the progressive nature of the multisystemic involvement, with increasing symptoms developing during the course of the disease, as more tissues become affected. To date, >40 clinical syndromes, based on the association of different symptoms, have been reported [1, 3]. They are often designated by acronyms, such as CPEO (chronic progressive external ophthalmoplegia), MELAS (myopathy, encephalomyopathy, lactic acidosis, and stroke-like episodes), MERRF, KSS (Kearns-Sayre syndrome), LHON (Leber’s hereditary optic neuropathy), or NARP (neuropathy, ataxia, and retinitis pigmentosa), for example. However, patients frequently have distinctive characteristics, and many of these syndromes overlap, which ultimately requires genetic testing for accurate diagnosis [1].

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expanded and shipped, even unfrozen, to specialized laboratories for diagnosis. Treatment can be started before obtaining a skin biopsy, because oral CoQ10 supplementation does not influence test results in vitro. CoQ10 determinations can also be performed in blood mononuclear cells [22]. However, no data on normal CoQ10 levels in mononuclear cells of patients with primary CoQ10 deficiencies are available; in addition, samples need to be processed rapidly and cannot be shipped easily to laboratories that can measure CoQ10 concentrations.

Respiratory-chain activity can be assessed by various methods (reviewed in [23]). Polarographic studies enable integrated function of the mitochondrial respiratory chain to be determined by measuring oxygen consumption in the presence of oxidative substrates, such as pyruvate, glutamate, malate, or succinate. Spectrophotometric studies allow activities of the individual mitochondrial respiratory chain complexes to be assayed. Complex II–III activity is highly dependent upon endogenous CoQ10 [24]. Therefore, decreased complex II–III activity in the presence of both normal complex II and III activities may suggest a defect in CoQ10 biosynthesis [25]. Results are influenced by the number of tested mitochondria; typically, data are normalized to the activity of citrate synthase. Both relative and absolute values need to be analyzed to distinguish between selective defects (low normalized values/normal citrate synthetase activity) and severe mitochondria damage or depletion (low or normal normalized values/low citrate synthetase activity).

In tissue sections, the activity of mitochondrial enzymes, such as cytochrome c oxidase (COX) and succinate dehydrogenase (SDH), can be easily assessed with histochemistry techniques [3, 26–28]. These assays are routinely performed on muscle biopsy specimens but can also be applied to other tissues, such as the renal cortex. Contrary to biochemical measurements, these studies only require frozen sections; they should be performed preferably in parallel with sections obtained from a normal kidney specimen mounted on the same microscopy slide. Because COX is encoded in part by mtDNA, and SDH is entirely encoded by nuclear genes, these studies can demonstrate heteroplasmia by showing cells with high SDH activity secondary to compensatory mitochondrial proliferation and low COX activity [29]; in other cases, they may show a more diffuse decrease in the activity of both enzymes (Fig. 2). Electron microscopy, when available, generally demonstrates abnormal mitochondria and mitochondrial proliferation or depletion. Mitochondrial depletion is particularly apparent in proximal tubular cells, which are rich in these organelles; mitochondrial proliferation in podocytes of patients with steroid-resistant nephrotic syndrome (SRNS) is evocative of a CoQ10 defect.

Renal mitochondrial diseases

Kidney involvement is more frequently reported in children than in adults [18]. Several renal diseases have been reported over the past 2 decades, including tubular disorders, chronic tubulointerstitial nephritis, cystic renal disease, and glomerulopathies [18]. Glomerular diseases comprise a small collection of sporadic cases and two major clinical entities that, when kidneys are affected, primarily present with glomerular involvement, namely, mtDNA mutations in the gene encoding for the tRNA<sub>LEU</sub> and CoQ10 biosynthesis defects. In addition, myoglobinuria, especially when recurrent, is commonly associated with mitochondrial metabolic disorders that impair the use of glycogen or fatty acids as sources of energy for muscle contraction [30] and may cause tubular damage.

Tubular defects and other tubulointerstitial disorders

Proximal tubular cells have high metabolic rates and are rich in mitochondria. Not surprisingly, the most frequent renal tubular finding is a proximal tubular defect, which has been reported in at least 60 patients; of these, 39 were summarized by Niaudet and Rötig in 1997 [18]; 21 additional patients could be identified in the literature [31–34], including a large Spanish cohort reported by Martín-Hernández in 2005 [35]. In approximately one third of patients, tubulopathy corresponded to overt De Toni-Debré-Fanconi syndrome, usually associated with low-molecular-weight proteinuria. In the remaining patients, urinary losses were moderate and often restricted to some substrates that are normally reabsorbed by proximal tubular cells. In nearly all patients, extrarenal signs were present, but cases in which tubulopathy was the only sign of a mitochondrial disease have been reported [32, 33], suggesting that lactaciduria should be checked in all patients presenting with idiopathic De Toni-Debré-Fanconi syndrome [35]. This tubulopathy is frequently associated with Pearson and Kearns–Sayre syndromes [18, 35]. The most frequent biochemical findings were complex III and/or complex IV defects (nearly half of patients), followed by complex I defects. From a genetic standpoint, all mutation types have been reported, but the most frequent finding is the presence of large mtDNA deletions. In the neonatal period or in the first months of life, Fanconi syndrome is often observed in patients with BCSL1 gene mutations associated with hepatopathy and complex III deficiency [36]. Several patients had a pattern of symptoms consistent with known mitochondrial associations, including MERRF, Pearson’s, Kearns–Sayre, and Leigh syndromes. Symptoms were present in the neonatal period in one third of patients and in 80% of cases by 2 years of age [18]. Renal biopsies, when available, showed chronic tubulointerstitial changes, with damaged proximal tubular epithelia; electron microscopy
often showed proliferation of abnormal mitochondria [18, 31].

Other tubular defects include a few cases reported as renal tubular acidosis with hypercalciuria [37, 38] and patients with a Bartter-like phenotype, which seems more frequently associated with Kearns–Sayre syndrome [29, 39]. Finally, severe hypomagnesemia is often mentioned in the descriptions of patients with mitochondrial tubulopathies and has also been reported as an isolated finding caused by excessive urinary magnesium losses [40]. Nine

Fig. 2 Detection of cytochrome c oxidase (COX) and succinate dehydrogenase (SDH) activities in kidney cortex sections. Examples of abnormal histochemical staining in the renal cortex of three patients

\[\text{COX} \quad \text{SDH}\]

\(a\) Uneven staining for COX and SDH in different tubular sections; \(b\) very low COX activity with normal SDH activity; \(c\) undetectable activity of both enzymes in tubular cells
patients presenting with chronic renal failure secondary to tubulointerstitial nephritis, without evidence of a primary tubular defect, have been reported [41–43]. Cystic renal changes have also been rarely described in association with mitochondrial cytopathies [44–46]. When approaching patients with a mitochondrial tubulopathy, clinicians should keep in mind that mitochondrial damage can also be secondary to other causes, including metabolic diseases (tyrosinemia type I, for example [47]), drugs (ifosfamide, for example [48]), or toxic agents, in particular heavy metals (cadmium, for example [49]). Recently, a De Toni-Debré-Fanconi syndrome secondary to antimitochondrial antibodies in two patients with primary biliary cirrhosis was described [50]. Finally, renal symptoms of mitochondrial tubulopathies are frequently sub-clinical or can be overshadowed by extra-renal symptoms. Among the 42 children with established mitochondrial disorders studied by Martin-Hernández et al for example, 50% had a renal tubular dysfunction, but only eight had overt disease, indicating that both tubular and glomerular functions should always be monitored in patients with mitochondrial disorders [35].

Sporadic cases of glomerular involvement

Sclerotic glomerular lesions are often described in renal mitochondrial diseases and are thought to be secondary to tubular and tubulointerstitial lesions. Few sporadic cases presenting with primary glomerular lesions have been reported. Güçer et al. described two patients with different mtDNA deletions [51]. The first patient was a 9-year-old girl with a common 4.9-kb mtDNA deletion, who presented with hematuria and proteinuria associated with ptosis and ophthalmoplegia, failure to thrive, high serum lactate and pyruvate levels, and ragged red fibers on muscle biopsy. Her renal function remained stable on angiotensin-converting enzyme (ACE) inhibitors after 5 years. The second patient presented with nephrotic syndrome (NS) at 4 months of age associated with poor feeding, vomiting, seizures, and nystagmus. Her laboratory investigations demonstrated high serum and CSF lactate levels and massive cerebral atrophy with white matter degeneration. On renal biopsy, podocytes showed proliferation of pleomorphic mitochondria. She rapidly died and was found to have a heteroplasmic mtDNA deletion [52]. Goldenberg et al. reported three patients presenting with congenital NS [53]: Two siblings presented with NS and heart failure and died within the first week of life; they both had low complex [II + III] activity, raising the hypothesis of a CoQ10 biosynthesis defect. The third patient had intrauterine growth retardation and presented with NS at birth without lactic acidemia but with increased lactaciduria. In his second year of life, the patient developed end-stage renal disease (ESRD), seizures, and carnitine-responsive cardiac failure. Hameed et al. described a 6-year-old boy who presented with SRNS associated with hypoparathyroidism and sensorineural deafness [44]. The child progressed to ESRF and was successfully transplanted. He later developed an encephalomyopathy. MR studies were consistent with a previous encephalopathy or with leukodystrophy; muscle biopsy showed ragged red fibers. Three other cases were summarized by Niaudet et al. [18].

Renal disease in tRNA_{LEU} gene mutations

To date, the most prevalent mtDNA defect is the 3243 A > G point mutation in the leucine tRNA gene, which was initially described in children with MELAS syndrome [2, 3]. The clinical manifestations of the 3243 A > G mutation, however, are not restricted to full-blown MELAS syndrome but can also express as diabetes, deafness, gastrointestinal and/or neuromuscular symptoms [2, 54]. This mutation is observed in nearly 1% of the diabetic population [55]. In 1997 Jansen et al. reported on their screening for the 3243 A > G mutation in diabetic patients with a history of maternally inherited diabetes and/or sensorineural hearing loss and described four women who had undergone renal transplantation for a proteinuric renal disease. Since then, at least 27 cases (+ several of their relatives) have been described, which were identified by screening patients with renal diseases and a personal or familial (maternal) history of diabetes or deafness [54–62]. When sensorineural deafness is present, patients can also be misleadingly diagnosed with Alport syndrome; a total of 90 Alport patients have been systematically screened in two studies for a MELAS mutation, allowing identification of two misdiagnosed cases [55, 59]. The majority of patients in these reports were females (20/27). When studied, diabetes and/or deafness was very frequently present in the proband’s mother and other family members [55, 57–59]. Age at mtDNA mutation diagnosis ranged from 14 to 30 years. The prevalent renal histology findings (22/27) were consistent with FSGS. Four cases of chronic tubulointerstitial nephritis and one case presenting with cystic kidney disease have also been described [54, 62]. A peculiar vasculopathy with hyalinosis of small arteries and myocyte necrosis was noted in two reports [56, 57]. By electron microscopy, pleomorphic mitochondrial accumulation has been occasionally documented in podocytes [58] or in tubular cells [62] but is usually absent. All patients had high urinary protein excretion; NS developed in approximately one third of cases. Proteinuria generally began in the second or third decade of life, with the youngest patient diagnosed at age 5 [54]. Most patients were hypertensive; two female patients developed preeclampsia [56]. Chronic or end-stage renal failure developed within 10 years in
approximately 50% of cases. A majority of patients had extrarenal symptoms at diagnosis; some—in particular, younger patients—developed these symptoms during follow-up [54–62]. Deafness was present in 22/27 cases; nearly half required hearing aids after the age of 30. Diabetes mellitus was reported in 15/27 patients. Other reported findings include neuromuscular symptoms (five patients), retinal dystrophy (two patients), and cardiomyopathy (two patients). Serum lactate and pyruvate were generally normal.

CoQ₁₀ biosynthesis defects

Primary CoQ₁₀ deficiency deserves a special mention among mitochondrial renal defects because it is the only treatable mitochondrial disorder. It was first reported in 1989 in association with myopathy and encephalopathy [19] and later with the cerebellar ataxia [63]. The link between CoQ₁₀ and renal disease was established in 2000 when three siblings were diagnosed with a complex clinical syndrome characterized by progressive encephalopathy and SRNS [64]. Two siblings developed ESRF and required transplantation at age 8 and 9, respectively; the third sibling had a more severe phenotype characterized by progressive encephalopathy and SRNS [64]. Two other siblings with similar clinical features were reported in 2005 [65]. Both developed SRNS at 12 months of age. The first child developed ESRF and required transplantation at age 8 and 9, respectively; the third sibling had a more severe clinical course and died at 8 years of age after rapid neurological deterioration. The two surviving children were treated with oral CoQ₁₀ (5 mg/kg daily), which resulted in a substantial improvement of their neurologic condition over 3 years, demonstrating that primary CoQ₁₀ deficiencies may respond to oral CoQ₁₀ supplementation. Two other siblings with similar clinical features were reported in 2005 [65]. Both developed SRNS at 12 months of age. The first child developed progressive encephalomyopathy and stroke-like episodes at 18 months. Oral CoQ₁₀ therapy was initiated at 22 months of age and was able to stop encephalomyopathy progression. The younger sister was treated immediately after she developed proteinuria and had an excellent clinical response without developing neurologic symptoms [66]. Mutations in the COQ2 gene were identified in these two siblings as the first report of a genetic defect associated with primary CoQ₁₀ deficiency [67]. COQ2 encodes for parahydroxybenzoate polyphenol transferase, the enzyme that joins the polyphenoid tail to the quinone group of CoQ₁₀ [68] (Fig. 1). COQ2 mutations have been found in four additional patients, all presenting with congenital or early-onset SRNS [25, 69]. Mutations in two other genes involved in CoQ₁₀ biosynthesis have been identified in patients with similar clinical features, namely, in the COQ1-PDSS2 gene (one patient) [70] and in the COQ6 gene (11 patients from five different kindreds) [71]. Although disease characteristics and progression are variable, all patients developed a glomerulopathy. Symptoms always began within the first years of life; SRNS was the presenting symptom in most cases and remained the only clinical manifestation in milder forms. Unless treated, renal disease rapidly progressed to ESRF. Associated clinical features include deafness and encephalomyopathy in COQ6 patients; severe forms with neonatal onset may also present with liver failure and severe lactic acidosis [25, 69]. Defects in genes required for CoQ₁₀ biosynthesis can also present with other phenotypes. The only reported patient with COQ9 mutations, for example, had severe multisystem disorder with a renal tubulopathy but no apparent glomerular involvement [72]; patients with mutations in the COQ8-ADCK3, or COQ1-PDSS1 genes, on the other hand, do not develop renal disease (Table 3) [69, 73, 74]. The reasons underlying these discrepancies remain unclear; the number of reported patients is too small to draw final conclusions and to analyze genotype–phenotype correlations.

The histological picture in CoQ₁₀-related diseases with glomerular involvement varies, from FSGS to collapsing glomerulopathy [25, 75]; electron microscopy generally shows numerous dysmorphic mitochondria in the cytoplasm of podocytes [25, 75]. One of the most important aspects of CoQ₁₀ biosynthesis defects is the clinical response to oral supplementations. Despite improvement in neurological symptoms after high oral doses of CoQ₁₀, the initial reports did not show the same benefits on renal lesions, because patients already had advanced kidney disease [64, 65]. Conversely, when treatment was initiated in one girl immediately after onset of renal symptoms, prompt reduction of proteinuria was observed; the patient had normal renal function nearly 5 years after starting treatment [66].

| Table 3 Characteristics of known coenzyme Q₁₀ (CoQ₁₀) biosynthesis gene defects |
|-----------------|-----------------|-----------------|-----------------|
| Gene            | Number of patients | Renal phenotype | Other features          | Response to therapy |
| COQ1-PDSS1      | 2                | No              | Multisystem disorder   | ±                |
| COQ1-PDSS2      | 1                | SRNS            | Progressive encephalomyopathy | +++             |
| COQ2            | 6                | SRNS            | Progressive encephalomyopathy with liver failure | +++             |
| COQ6            | 10               | SRNS            | Deafness seizures       | +++             |
| COQ7            | -                | ?               | (Mouse knock-out is lethal) | ?                |
| COQ8-ADCK3      | >10              | No              | Tubulopathy             | ±                |
| COQ9            | 1                | Tubulopathy     | Lactic acidosis, encephalomyopathy | ±                |
similar response has also been documented in two patients with COQ6 mutations [71].

However, several issues remain open. The bioavailability of CoQ10, for example, is poor; moreover, transfer of exogenous CoQ10 to mitochondria is a slow process that requires almost 1 week in cultured cells [76]. The relationship between CoQ10 plasma and tissue levels is poor [77]. Empirically, CoQ10 doses of 30–50 mg/kg per day have been given to patients [66, 71], but there is no practical method to monitor the efficacy of therapy other than observing the clinical response. In theory, higher dosages could be advantageous, especially in the first phase of treatment, in order to restore normal body CoQ10 content. Currently, a multicenter trial testing the efficacy of 10 mg/kg per day of CoQ10 in children with biochemically proven deficiencies of complex I, III, or IV or with mutations in respiratory-chain genes is underway (NCT00432744). Different pharmaceutical formulations of CoQ10 are commercially available; although it is probably preferable to prescribe oral suspensions rather than tablet preparations that contain crystalline forms of CoQ10 [78], no systematic pharmacokinetic studies have been performed in CoQ10-deficient patients. Hopefully, studies on animal models, such as the kd mouse that harbors a homozygous mutation in the PDSS2 gene [79], will also help optimize treatment. Regardless of the results of these studies, evidence indicates the absolute necessity of initiating treatment early to prevent the development of irreversible lesions, especially in the brain and kidneys [66]. Therefore, a suspicion of a mitochondrial dysfunction secondary to CoQ10 deficiency should always arise in patients with early-onset SRNS, especially when podocyte mitochondrial abnormalities are observed by electron microscopy, in the presence of lactaciduria or when neurologic or muscular symptoms are present. The diagnosis of CoQ10 deficiency is only available in specialized centers and can be performed on cultured skin fibroblasts. Meanwhile, treatment can be started in highly evocative patients. No data are available on prenatal diagnosis, which would allow treatment immediately after birth and, potentially, maternal supplementation during pregnancy.

Questions:

1. Which of these statements is correct in respect to mtDNA:
   A. As opposed to nuclear DNA, mtDNA is single stranded
   B. Contains the nuclear information of all mitochondrial proteins
   C. Mutations are always evenly distributed in cells
   D. It forms a circular string that varies in length among individuals
   E. None of the above is correct

2. Which of the following organic acids is highly evocative of a renal mitochondrial cytopathy when found in excess in urine:
   A. 3 OH-butyrate
   B. Succinate
   C. Fumarate
   D. Phenyl acetone
   E. None of the above

3. The most frequent renal disease in mitochondrial cytopathies is:
   A. Renal vascular disease
   B. Chronic interstitial nephritis
   C. Proximal tubulopathy
   D. Glomerulopathy
   E. None of the above

4. Which of the following statements is correct:
   A. Clinical or subclinical renal involvement is always present in mitochondrial cytopathies
   B. All patients with mitochondrial cytopathies have neuromuscular symptoms
   C. Patients generally become symptomatic after the age of 5 years
   D. FSGS lesions in patients with a maternal history of diabetes and deafness is evocative of a mutation of the tyrosine tRNA gene
   E. None of the above

5. Which of the following statements is correct:
   A. Mitochondrial coenzyme Q10 derives primarily from de novo synthesis
   B. Coenzyme Q10 is present in the normal diet
   C. Mutations in genes involved in the biosynthesis of coenzyme Q10 may cause NS
   D. Symptoms related to coenzyme Q10 defects may be prevented by oral ubiquinone supplements
   E. All of the above

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Answers:

1. E
2. A
3. C
4. E
5. E