Pediatr Nephrol (2012) 27:539–550
DOI 10.1007/s00467-011-1926-6

EDUCATIONAL REVIEW

Renal involvement in mitochondrial cytopathies

Francesco Emma · Enrico Bertini · Leonardo Salviati · Giovanni Montini

Received: 14 March 2011 / Revised: 7 May 2011 / Accepted: 9 May 2011 / Published online: 9 June 2011

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

F. Emma (✉)
Division of Nephrology and Dialysis,
Department of Nephrology and Urology,
Bambino Gesù Children's Hospital and Research Institute,
piazza Sant'Onofrio 4,
00165 Rome, Italy
e-mail: francesco.emma@opbg.net

E. Bertini
Division of Molecular Medicine for Neuromuscular and Neurodegenerative Disorders, Department of Neurosciences,
Bambino Gesù Children's Hospital and Research Institute,
Rome, Italy

L. Salviati
Clinical Genetics Unit, Department of Pediatrics,
University of Padova,
Padova, Italy

G. Montini
Nephrology and Dialysis Unit, Pediatric Department,
Azienda Ospedaliera di Bologna,
Bologna, Italy

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 ($FADH_2$) 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 (CoQ_{10}), plays a crucial role in shuttling electrons from complexes I and II to complex III (Fig. 1) [5]. CoQ_{10} is a ubiquitous lipophilic vitamin-like substance first isolated in 1957 from beef mitochondria, which has the

Table 1 Respiratory chain complexes

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		13	~75	~88

mtDNA mitochondrial DNA, *NADH* nicotinamide adenine dinucleotide, reduced, *ATP* adenosine triphosphate, *COX* cytochrome *c* oxidase

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 (CoQ_6), 9 subunits in mice (CoQ_9), and 10 subunits in humans (CoQ_{10}) (Fig. 1). It is endogenously synthesized through a multienzyme complex located at the inner mitochondrial membrane [6], which is encoded by at least 16 genes. The functions of CoQ_{10}, however, are not restricted to bioenergetics; CoQ_{10} 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 ($OH^{\bullet}$) 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 CoQ_{10} 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

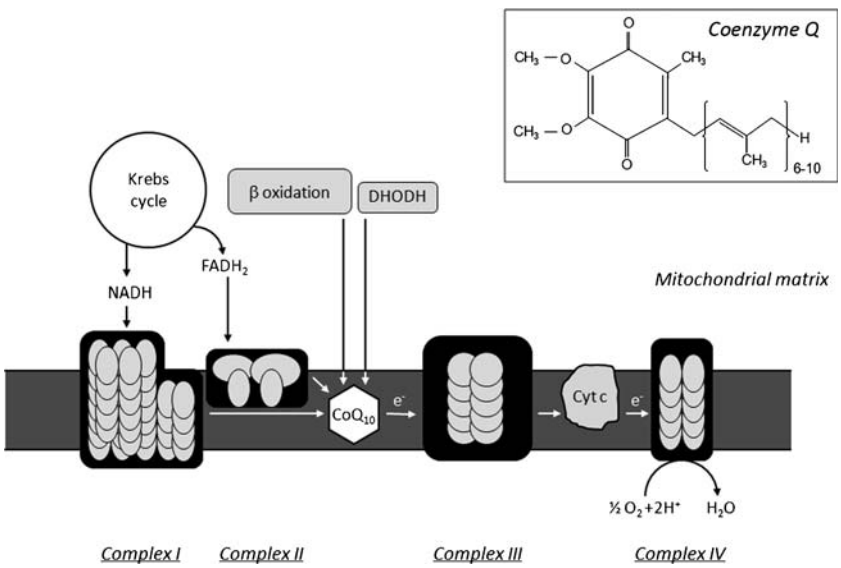

Fig. 1 Coenzyme Q_{10} and the electron flow in the respiratory chain. The figure depicts the central role of coenzyme Q_{10} (CoQ_{10}) in shuttling electrons from complexs I and II to complex III. It is also an important cofactor for several mitochondrial dehydrogenases, such as dihydroorotate dehydrogenase (DHODH). The *insert* shows the structure of CoQ_{10}, which is comprised of a quinone group and a polyisoprenoid tail of different length, ranging from six isoprenyl subunits in yeast to ten subunits in humans. Respiratory chain complexes are detailed in Table 1

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 Mendelianly 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 homoplasmy—or may 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 $tRNA^{LEU}$ 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 myocardiopathy, 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, Bartter-like tubulopathy, hypermagnesuria, proteinuria, nephrotic syndrome, tubulointerstitial nephritis, myoglobinuria, renal failure
Endocrine	Diabetes mellitus, hypoparathyroidism, hypothyroidism, hyporeninemic hypoaldosteronism, 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 ophtalmoplegia, 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, anhydrosis and jaundice, hyperhidrosis, trichothiodystrophy, hirsutism alopecia, alopecia with brittle hair, symmetric cervical lipomas

ophthalmologic (ophtalmoplegia, 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].

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 mm^3 of renal cortex. Similarly, CoQ_{10} 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 CoQ_{10} supplementation. Fortunately, CoQ_{10} can be reliably measured in cultured skin fibroblasts [20], which also allow measuring the rate of ubiquinone biosynthesis [21]. Fibroblasts can be easily

expanded and shipped, even unfrozen, to specialized laboratories for diagnosis. Treatment can be started before obtaining a skin biopsy, because oral CoQ_{10} supplementation does not influence test results in vitro. CoQ_{10} determinations can also be performed in blood mononuclear cells [22]. However, no data on normal CoQ_{10} levels in mononuclear cells of patients with primary CoQ_{10} deficiencies are available; in addition, samples need to be processed rapidly and cannot be shipped easily to laboratories that can measure CoQ_{10} 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 CoQ_{10} [24]. Therefore, decreased complex II–III activity in the presence of both normal complex II and III activities may suggest a defect in CoQ_{10} 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 heteroplasmy 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 CoQ_{10} 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 $tRNA^{LEU}$ and CoQ_{10} 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 MERFF, 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

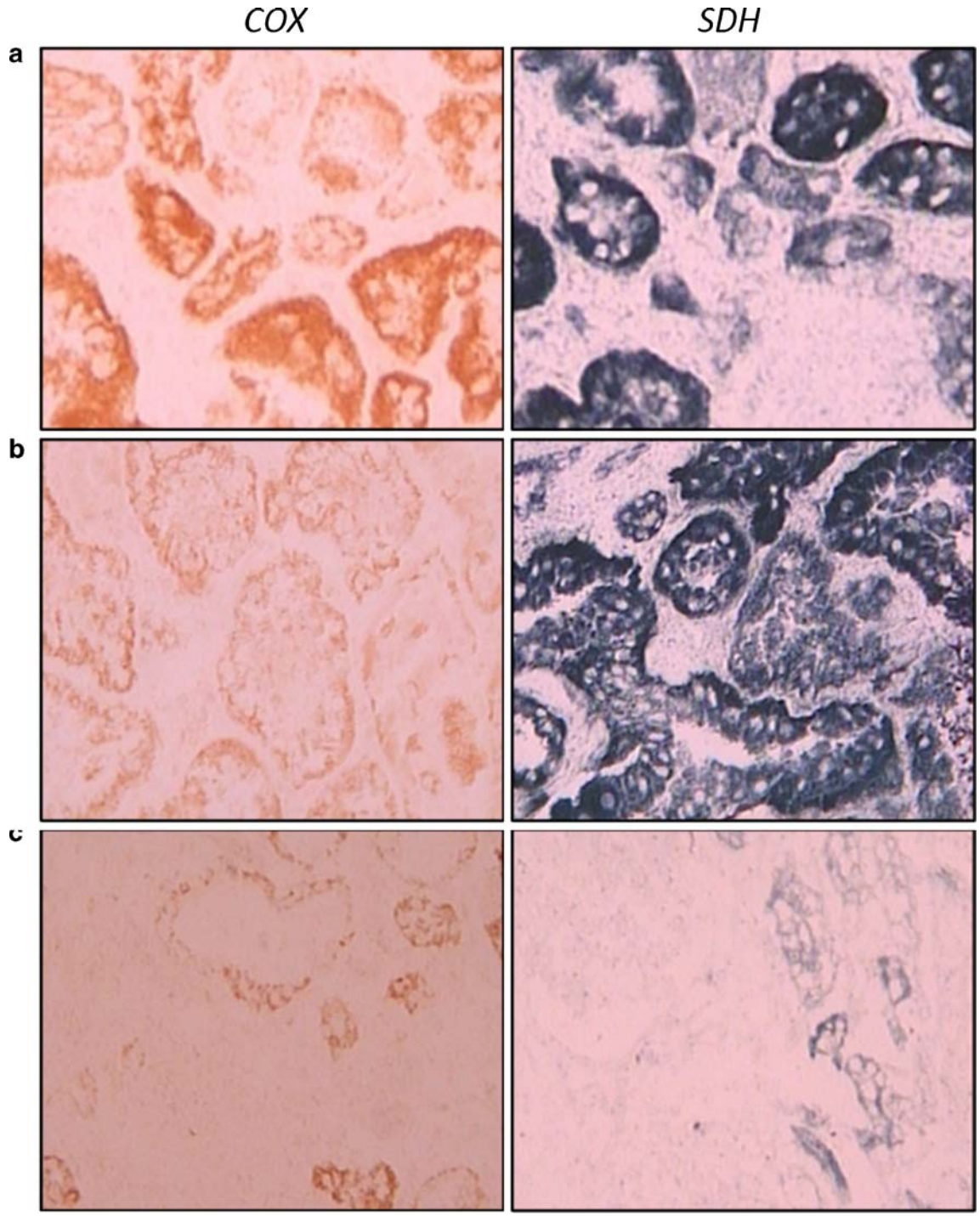

Fig. 2 Detection of cytochrome *c* oxidase (COX) and succinate dehydrogenase (SDH) activities in kidney cortex sections. Examples of abnormal histochemical staining in the renal cortex of three patients with a mitochondrial defect. **a** Uneven staining for COX and SDH in different tubular sections; **b** very low COX activity with normal SDH activity; **c** undetectable activity of both enzymes in tubular cells

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

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 Martín-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 CoQ_{10} biosynthesis defect. The third patient had intrauterine growth retardation and presented with NS at birth without lactacidemia 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 50 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.

CoQ_{10} biosynthesis defects

Primary CoQ_{10} 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 cerebellar ataxia [63]. The link between CoQ_{10} 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 course and died at 8 years of age after rapid neurological deterioration. The two surviving children were treated with oral CoQ_{10} (5 mg/kg daily), which resulted in a substantial improvement of their neurologic condition over 3 years, demonstrating that primary CoQ_{10} deficiencies may respond to oral CoQ_{10} 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 CoQ_{10} 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 CoQ_{10} deficiency [67]. *COQ2* encodes for para-hydroxybenzoate polyprenyl transferase, the enzyme that joins the polyprenoid tail to the quinone group of CoQ_{10} [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 CoQ_{10} 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 CoQ_{10} 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 CoQ_{10}-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 CoQ_{10} biosynthesis defects is the clinical response to oral supplementations. Despite improvement in neurological symptoms after high oral doses of CoQ_{10}, 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]. A

Table 3 Characteristics of known coenzyme Q_{10} (CoQ_{10}) 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	Cerebellar ataxia	±
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 CoQ_{10}, for example, is poor; moreover, transfer of exogenous CoQ_{10} to mitochondria is a slow process that requires almost 1 week in cultured cells [76]. The relationship between CoQ_{10} plasma and tissue levels is poor [77]. Empirically, CoQ_{10} 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 CoQ_{10} content. Currently, a multicenter trial testing the efficacy of 10 mg/kg per day of CoQ_{10} 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 CoQ_{10} are commercially available; although it is probably preferable to prescribe oral suspensions rather than tablet preparations that contain crystalline forms of CoQ_{10} [78], no systematic pharmacokinetic studies have been performed in CoQ_{10}-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 CoQ_{10} 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 CoQ_{10} 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 Q_{10} derives primarily from *de novo* synthesis
   - B. Coenzyme Q_{10} is present in the normal diet
   - C. Mutations in genes involved in the biosynthesis of coenzyme Q_{10} may cause NS
   - D. Symptoms related to coenzyme Q_{10} defects may be prevented by oral ubiquinone supplements
   - E. All of the above

References

1. Finsterer J (2004) Mitochondriopathies. Eur J Neurol 11:163–186
2. Di Donato S (2009) Multisystem manifestations of mitochondrial disorders. J Neurol 256:693–710
3. DiMauro S, Schon EA (2003) Mitochondrial respiratory-chain diseases. N Engl J Med 348:2656–2668

4. Fosslien E (2001) Mitochondrial medicine - Molecular pathology of defective oxidative phosphorylation. Ann Clin Lab Sci 31:25–67
5. Quinzii CM, Hirano M (2010) Coenzyme Q and mitochondrial disease. Dev Disabil Res Rev 16:183–188
6. Casarin A, Jimenez-Ortega JC, Trevisson E, Pertegato V, Doimo M, Ferrero-Gomez ML, Abbadi S, Artuch R, Quinzii C, Hirano M, Basso G, Ocaña CS, Navas P, Salviati L (2008) Functional characterization of human COQ4, a gene required for Coenzyme Q10 biosynthesis. Biochem Biophys Res Commun 372:35–39
7. Artuch R, Salviati L, Jackson S, Hirano M, Navas P (2009) Coenzyme Q10 deficiencies in neuromuscular diseases. Adv Exp Med Biol 652:117–128
8. Zeviani M, Carelli V (2007) Mitochondrial disorders. Curr Opin Neurol 20:564–571
9. DiMauro S, Schon EA (2008) Mitochondrial disorders in the nervous system. Annu Rev Neurosci 31:91–123
10. Wallace DC, Singh G, Lott MT, Hodge JA, Schurr TG, Lezza AM, Elsas LJ, Nikoskelainen EK (1988) Mitochondrial DNA mutation associated with Leber's hereditary optic neuropathy. Science 242:1427–1430
11. Holt IJ, Harding AE, Morgan Hughes JA (1988) Deletions of muscle mitochondrial DNA in patients with mitochondrial myopathies. Nature 331:717–719
12. McFarland R, Taylor RW, Turnbull DM (2007) Mitochondrial disease - its impact, etiology, and pathology. Curr Top Dev Biol 77:113–155
13. Bertini E (2009) Mitochondrial encephalomyopathies and related syndromes: brief review. In: Cappa M, Maghnie M, Loche S and Bottazzo GF (eds) Endocrine involvement in developmental syndromes. Endocr Dev Basel, Karger 14:38–52
14. Moraes CT, Shanske S, Tritschler HJ, Aprille JR, Andreetta F, Bonilla E, Schon EA, DiMauro S (1991) mtDNA depletion with variable tissue expression: a novel genetic abnormality in mitochondrial diseases. Am J Hum Genet 48:492–501
15. Kopsidas G, Kovalenko SA, Heffernan DR, Yarovaya N, Kramarova L, Stojanovski D, Borg J, Islam MM, Caragounis A, Linnane AW (2000) Tissue mitochondrial DNA changes. A stochastic system. Ann NY Acad Sci 908:226–243
16. von Kleist-Retzow JC, Cormier-Daire V, Viot G, Goldenberg A, Mardach B, Amiel J, Saada P, Dumez Y, Brunelle F, Saudubray JM, Chrétien D, Rötig A, Rustin P, Munnich A, De Lonlay P (2003) Antenatal manifestations of mitochondrial respiratory chain deficiency. J Pediatr 143:208–212
17. Bodemer C, Rötig A, Rustin P, Cormier V, Niaudet P, Saudubray JM, Rabier D, Munnich A, de Prost Y (1999) Hair and skin disorders as signs of mitochondrial disease. Pediatrics 103:428–433
18. Niaudet P, Rotig A (1997) The kidney in mitochondrial cytopathies. Kidney Int 51:1000–1007
19. Ogasahara S, Engel AG, Frens D, Mack D (1989) Muscle coenzyme Q deficiency in familial mitochondrial encephalomyopathy. Proc Natl Acad Sci USA 86:2379–2382
20. Montero R, Sánchez-Alcázar JA, Briones P, Hernández AR, Cordero MD, Trevisson E, Salviati L, Pineda M, García-Cazorla A, Navas P, Artuch R (2008) Analysis of coenzyme Q10 in muscle and fibroblasts for the diagnosis of CoQ10 deficiency syndromes. Clin Biochem 41:697–700
21. López-Martín JM, Salviati L, Trevisson E, Montini G, DiMauro S, Quinzii C, Hirano M, Rodriguez-Hernandez A, Cordero MD, Sánchez-Alcázar JA, Santos-Ocaña C, Navas P (2007) Missense mutation of the COQ2 gene causes defects of bioenergetics and de novo pyrimidine synthesis. Hum Mol Genet 16:1091–1097
22. Cordero MD, Moreno-Fernández AM, deMiguel M, Bonal P, Campa F, Jiménez-Jiménez LM, Ruiz-Losada A, Sánchez-Domínguez B, Sánchez Alcázar JA, Salviati L, Navas P (2009) Coenzyme Q10 distribution in blood is altered in patients with fibromyalgia. Clin Biochem 42:732–735
23. Kirby DM, Thorburn DR, Turnbull DM, Taylor RW (2007) Biochemical assays of respiratory chain complex activity. Meth Cell Biol 80:93–119
24. Chretien D, Rustin P, Bourgeron T, Rötig A, Saudubray JM, Munnich A (1994) Reference charts for respiratory chain activities in human tissues. Clin Chim Acta 228:53–70
25. Diomedi-Camassei F, Di Giandomenico S, Santorelli FM, Caridi G, Piemonte F, Montini G, Ghiggeri GM, Murer L, Barisoni L, Pastore A, Muda AO, Valente ML, Bertini E, Emma F (2007) COQ2 nephropathy: a newly described inherited mitochondriopathy with primary renal involvement. J Am Soc Nephrol 18:2773–2780
26. Mita S, Schmidt B, Schon EA, DiMauro S, Bonilla E (1989) Detection of "deleted" mitochondrial genomes in cytochromeoxidase-deficient muscle fibers of a patient with Kearns–Sayre syndrome. Proc Natl Acad Sci USA 86:9509–9513
27. Santorelli FM, Sciacco M, Tanji K, Shanske S, Vu TH, Golzi V, Griggs RC, Mendell JR, Hays AP, Bertorini TE, Pestronk A, Bonilla E, DiMauro S (1996) Multiple mitochondrial DNA deletions in sporadic inclusion body myositis: a study of 56 patients. Ann Neurol 39:789–795
28. Szabolcs MJ, Seigle R, Shanske S, Bonilla E, DiMauro S, D'Agati V (1994) Mitochondrial DNA deletion: a cause of chronic tubulointerstitial nephropathy. Kidney Int 45:1388–1396
29. Emma F, Pizzini C, Tessa A, Di Giandomenico S, Onetti-Muda A, Santorelli FM, Bertini E, Rizzoni G (2006) "Bartter-like" phenotype in Kearns–Sayre syndrome. Pediatr Nephrol 21:355–360
30. DiMauro S, Haller RG (1999) Metabolic myopathies: substrate use defects; in Schapira AHV, Griggs RC (eds): Muscle Diseases. Boston, Butterworth-Heinernann, pp 225–249
31. Au KM, Lau SC, Mak YF, Lai WM, Chow TC, Chen ML, Chiu MC, Chan AY (2007) Mitochondrial DNA deletion in a girl with Fanconi's syndrome. Pediatr Nephrol 22:136–140
32. Kuwertz-Bröking E, Koch HG, Marquardt T, Rossi R, Helmchen U, Müller-Höcker J, Harms E, Bulla M (2000) Renal Fanconi syndrome: first sign of partial respiratory chain complex IV deficiency. Pediatr Nephrol 14:495–498
33. Mochizuki H, Joh K, Kawame H, Imadachi A, Nozaki H, Ohashi T, Usui N, Eto Y, Kanetsuna Y, Aizawa S (1996) Mitochondrial encephalomyopathies preceded by de-Toni-Debré-Fanconi syndrome or focal segmental glomerulosclerosis. Clin Nephrol 46:347–352
34. Gilbert RD, Emms M (1996) Pearson's syndrome presenting with Fanconi syndrome. Ultrastruct Pathol 20:473–475
35. Martin-Hernandez E, Garcia-Silva MT, Vara J, Campos Y, Cabello A, Muley R, del Hoyo P, Angel Martin M, Arenas J (2005) Renal pathology in children with mitochondrial diseases. Pediatr Nephrol 20:1299–1305
36. De Meirleir L, Seneca S, Damis E, Sepulchre B, Hoorens A, Gerlo E, García Silva MT, Hernandez EM, Lissens W, Van Coster R (2003) Clinical and diagnostic characteristics of complex III deficiency due to mutations in the BCS1L gene. Am J Med Genet A 121A:126–131
37. Matsutani H, Mizusawa Y, Shimoda M, Niimura F, Takeda A, Shimohira M, Iwakawa Y (1992) Partial deficiency of cytochrome c oxidase with isolated proximal renal tubular acidosis and hypercalciuria. Child Nephrol Urol 12:221–224
38. Eviatar l, Shanskee S, Gauthier B, Abrams C, Mayral J, Slavin M, Valderrama E, DiMauro S (1990) Kearns-Sayre syndrome presenting as renal tubular acidosis. Neurology 40:1761–1763
39. Goto Y, Itami N, Kajii N, Tochimaru H, Endo M, Horai S (1990) Renal tubular involvement mimicking Bartter syndrome in a patient with Kearns–Sayre syndrome. J Pediatr 116:904–910

40. Katsanos KH, Elisaf M, Bairaktari E, Tsianos EV (2001) Severe hypomagnesemia and hypoparathyroidism in Kearns-Sayre syndrome. Am J Nephrol 21:150–153
41. Ueda Y, Ando A, Nagata T, Yanagida H, Yagi K, Sugimoto K, Okada M, Takemura T (2004) A boy with mitochondrial disease: asymptomatic proteinuria without neuromyopathy. Pediatr Nephrol 19:107–110
42. Tzen CY, Tsai JD, Wu TY, Chen BF, Chen ML, Lin SP, Chen SC (2001) Tubulointerstitial nephritis associated with a novel mitochondrial point mutation. Kidney Int 59:846–854
43. Rötig A, Goutières 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
44. 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 J 77:523–526
45. Gürgey A, Ozalp I, Rötig A, Coşkun T, Tekinalp G, Erdem G, Akeören Z, Caglar M, Bakkaloglu A (1996) A case of Pearson syndrome associated with multiple renal cysts. Pediatr Nephrol 10:637–638
46. Müller-Höcker J, Walther JU, Bise K, Pongratz D, Hübner G (1984) Mitochondrial myopathy with loosely coupled oxidative phosphorylation in a case of Zellweger syndrome. A cytochemical-ultrastructural study. Virchows Arch B Cell Pathol Incl Mol Pathol 45:125–138
47. Endo F, Sun MS (2002) Tyrosinaemia type I and apoptosis of hepatocytes and renal tubular cells. J Inherit Metab Dis 25:227–234
48. Nissim I, Horyn O, Daikhin Y, Nissim I, Luhovyy B, Phillips PC, Yudkoff M (2006) Ifosfamide-induced nephrotoxicity: mechanism and prevention. Cancer Res 66:7824–7831
49. Thévenod F (2003) Nephrotoxicity and the proximal tubule. Insights from cadmium. Nephron Physiol 93:87–93
50. Lino M, Binaut R, Noël LH, Patey N, Rustin P, Daniel L, Serpaggi J, Varaut A, Vanhille P, Knebelmann B, Grünfeld JP, Fakhouri F (2005) Tubulointerstitial nephritis and Fanconi syndrome in primary biliary cirrhosis. Am J Kidney Dis 46:41–46
51. Güçer S, Talim B, Aşan E, Korkusuz P, Ozen S, Unal S, Kalkanoğlu SH, Kale G, Cağlar M (2005) Focal segmental glomerulosclerosis associated with mitochondrial cytopathy: report of two cases with special emphasis on podocytes. Pediatr Dev Pathol 8:710–717
52. Unal S, Kalkanoğlu HS, Kocaefe C, Gucer S, Ozen S, Turanli G, Coskun T (2005) Four-month-old infant with focal segmental glomerulosclerosis and mitochondrial DNA deletion. J Child Neurol 20:83–84
53. Goldenberg A, Ngoc LH, Thouret MC, Cormier-Daire V, Gagnadoux MF, Chrétien D, Lefrançois C, Geromel V, Rötig A, Rustin P, Munnich A, Paquis V, Antignac C, Gubler MC, Niaudet P, de Lonlay P (2005) Bérard E (2005) Respiratory chain deficiency presenting as congenital nephrotic syndrome. Pediatr Nephrol 20:465–469
54. Guéry B, Choukroun G, Noël LH, Clavel P, Rötig A, Lebon S, Rustin P, Bellané-Chantelot C, Mougenot B, Grünfeld JP, Chauveau D (2003) The spectrum of systemic involvement in adults presenting with renal lesion and mitochondrial tRNA(Leu) gene mutation. J Am Soc Nephrol 14:2099–2108
55. Jansen JJ, Maassen JA, van der Woude FJ, Lemmink HA, van den Ouweland JM, t' Hart LM, Smeets HJ, Bruijn JA, Lemkes HH (1997) Mutation in mitochondrial tRNA (Leu(UUR)) gene associated with progressive kidney disease. J Am Soc Nephrol 8:1118–1124
56. Moulonguet Doleris L, 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
57. Löwik MM, Hol FA, Steenbergen EJ, Wetzels JF, van den Heuvel LP (2005) Mitochondrial tRNALeu(UUR) mutation in a patient with steroid-resistant nephrotic syndrome and focal segmental glomerulosclerosis. Nephrol Dial Transplant 20:336–341
58. Hotta O, Inoue CN, Miyabayashi S, Furuta T, Takeuchi A, Taguma Y (2001) Clinical and pathologic features of focal segmental glomerulosclerosis with mitochondrial tRNALeu(UUR) gene mutation. Kidney Int 59:1236–1243
59. 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
60. 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
61. Nakamura S, Yoshinari M, Doi Y, Yoshizumi H, Katafuchi R, Yokomizo Y, Nishiyama K, Wakisaka M, Fujishima M (1999) Renal complications in patients with diabetes mellitus associated with an A to G mutation of mitochondrial DNA at the 3243 position of leucine tRNA. Diab Res Clin Pract 44:183–189
62. 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
63. Musumeci O, Naini A, Slonim AE, Skavin N, Hadjigeorgiou GL, Krawiecki N, Weissman BM, Tsao CY, Mendell JR, Shanske S, De Vivo DC, Hirano M, DiMauro S (2001) Familial cerebellar ataxia with muscle coenzyme Q10 deficiency. Neurology 56:849–855
64. Rötig A, Appelkvist EL, Geromel V, Chretien D, Kadhom N, Edery P, Lebideau 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
65. Salviati L, Sacconi S, Murer L, Zacchello G, Franceschini L, Laverda AM, Basso G, Quinzii C, Angelini C, Hirano M, Naini AB, Navas P, DiMauro S, Montini G (2005) Infantile encephalomyopathy and nephropathy with CoQ10 deficiency: a CoQ10-responsive condition. Neurology 65:606–608
66. Montini G, Malaventura C, Salviati L (2008) Early coenzyme Q10 supplementation in primary coenzyme Q10 deficiency. N Engl J Med 358:2849–2850
67. Quinzii C, Naini A, Salviati L, Trevisson E, Navas P, Dimauro S, Hirano M (2006) A mutation in para-hydroxybenzoate-polyprenyl transferase (COQ2) causes primary coenzyme Q10 deficiency. Am J Hum Genet 78:345–349
68. Forsgren M, Attersand A, Lake S, Grünler J, Swiezewska E, Dallner G, Climent I (2004) Isolation and functional expression of human COQ2, a gene encoding a polyprenyl transferase involved in the synthesis of CoQ. Biochem J 382:519–526
69. Mollet J, Giurgea I, Schlemmer D, Dallner G, Chretien D, Delahodde A, Bacq D, de Lonlay P, Munnich A, Rötig A (2007) Prenyldiphosphate synthase, subunit 1 (PDSS1) and OH-benzoate polyprenyltransferase (COQ2) mutations in ubiquinone deficiency and oxidative phosphorylation disorders. J Clin Invest 117:765–772
70. López LC, Schuelke M, Quinzii CM, Kanki T, Rodenburg RJ, Naini A, Dimauro S, Hirano M (2006) Leigh syndrome with nephropathy and CoQ10 deficiency due to decaprenyl diphosphate synthase subunit 2 (PDSS2) mutations. Am J Hum Genet 79:1125–1129
71. Heeringa SF, Chernin g, Chaki M, Zhou W, Sloan AJ, Ji Z, Xie LX, Salviati L, Hurd TW, Vega-Warner V, Killen PD, Raphael Y, Ashraf S, Ovunc B, Schoeb DS, mcLaughlin HM, Airik R, Vlangos CL, Gbadegesin R, Hinkes B, Saisawat P, Trevisson E, Doimo M, Casarin A, Pertegato V, Giorgi G, Prokisch H, Rötig A,

Antignac C, Nurnberg G, Beker C, Wang S, Ozaltin F, Topaloglu R, Bakkaloglu A, Bakkaloglu SA, Müller D, Beissert A, Mir S, Berdeli A, Özen S, Zenker M, Matejas V, Ocana CS, Navas P, Kusakabe T, Kispert A, Akman S, Soliman NA, Krick S, Mundel P, Reiser J, Nurnberg P, Clarke Cf, Wiggins RC, Faul C, Hildebrandt F (2011) COQ6 mutations cause nephrotic syndrome with sensorineural deafness in humans, concurrent with increased apoptosis. J Clin Invest 121:2013–2024

72. Duncan AJ, Bitner-Glindzicz M, Meunier B, Costello H, Hargreaves IP, López LC, Hirano M, Quinzii CM, Sadowski MI, Hardy J, Singleton A, Clayton PT, Rahman S (2009) A nonsense mutation in COQ9 causes autosomal-recessive neonatal-onset primary coenzyme Q10 deficiency: a potentially treatable form of mitochondrial disease. Am J Hum Genet 84:558–566
73. Lagier-Tourenne C, Tazir M, López LC, Quinzii CM, Assoum M, Drouot N, Busso C, Makri S, Ali-Pacha L, Benhassine T, Anheim M, Lynch DR, Thibault C, Plewniak F, Bianchetti L, Tranchant C, Poch O, DiMauro S, Mandel JL, Barros MH, Hirano M, Koenig M (2008) ADCK3, an ancestral kinase, is mutated in a form of recessive ataxia associated with coenzyme Q10 deficiency. Am J Hum Genet 82:661–672
74. Mollet J, Delahodde A, Serre V, Chretien D, Schlemmer D, Lombes A, Boddaert N, Desguerre I, de Lonlay P, de Baulny HO, Munnich A, Rötig A (2008) CABC1 gene mutations cause ubiquinone deficiency with cerebellar ataxia and seizures. Am J Hum Genet 82:623–630
75. Barisoni L, Madaio MP, Eraso M, Gasser DL, Nelson PJ (2005) The kd/kd mouse is a model of collapsing glomerulopathy. J Am Soc Nephrol 16:2847–2851
76. López LC, Quinzii CM, Area E, Naini A, Rahman S, Schuelke M, Salviati L, Dimauro S, Hirano M (2010) Treatment of CoQ(10) deficient fibroblasts with ubiquinone, CoQ analogs, and vitamin C: time- and compound-dependent effects. PLoS ONE 5:e11897
77. Land JM, Heales SJ, Duncan AJ, Hargreaves IP (2007) Some observations upon biochemical causes of ataxia and a new disease entity ubiquinone, CoQ10 deficiency. Neurochem Res 32:837–843
78. Hatanaka J, Kimura Y, Lai-Fu Z, Onoue S, Yamada S (2008) Physicochemical and pharmacokinetic characterization of water-soluble Coenzyme Q(10) formulations. Int J Pharm 363:112–117
79. Peng M, Falk MJ, Haase VH, King R, Polyak E, Selak M, Yudkoff M, Hancock WW, Meade R, Saiki R, Lunceford AL, Clarke CF, Gasser DL (2008) Primary coenzyme Q deficiency in Pdss2 mutant mice causes isolated renal disease. PLoS Genet 4:e1000061

Answers:

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