

Renal manifestations of primary mitochondrial disorders (Review)

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Abstract. The aim of the present review was to summarize and discuss previous findings concerning renal manifestations of primary mitochondrial disorders (MIDs). A literature review was performed using frequently used databases. The study identified that primary MIDs frequently present as mitochondrial multiorgan disorder syndrome (MIMODS) at onset or in the later course of the MID. Occasionally, the kidneys are affected in MIDs. Renal manifestations of MIDs include renal insufficiency, nephrolithiasis, nephrotic syndrome, renal cysts, renal tubular acidosis, Bartter-like syndrome, Fanconi syndrome, focal segmental glomerulosclerosis, tubulointerstitial nephritis, nephrocalcinosis, and benign or malign neoplasms. Among the syndromic MIDs, renal involvement has been most frequently reported in patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes syndrome, Kearns-Sayre syndrome, Leigh syndrome and mitochondrial depletion syndromes. Only in single cases was renal involvement also reported in chronic progressive external ophthalmoplegia, Pearson syndrome, Leber's

hereditary optic neuropathy, coenzyme-Q deficiency, X-linked sideroblastic anemia and ataxia, myopathy, lactic acidosis, and sideroblastic anemia, pyruvate dehydrogenase deficiency, growth retardation, aminoaciduria, cholestasis, iron overload, lactacidosis, and early death, and hyperuricemia, pulmonary hypertension, renal failure in infancy and alkalosis syndrome. The present study proposes that the frequency of renal involvement in MIDs is probably underestimated. Diagnosis of renal involvement follows general guidelines and treatment is symptomatic. Thus, renal manifestations of primary MIDs require recognition and appropriate management, as they determine the outcome of MID patients.

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Abbreviations: CPEO, chronic progressive external ophthalmoplegia; FSGS, focal segmental glomerulosclerosis; GRACILE, growth retardation, aminoaciduria, cholestasis, iron overload, lactacidosis, and early death; GSECs, granular swollen epithelial cells; HUPRA, hyperuricemia, pulmonary hypertension, renal failure in infancy and alkalosis; KSS, Kearns-Sayre syndrome; LHON, Leber's hereditary optic neuropathy; MDS, mitochondrial depletion syndrome; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonus epilepsy with ragged-red fibers; MID, mitochondrial disorder; MIMODS, mitochondrial multi-organ disorder syndrome; MLASA, myopathy, lactic acidosis, and sideroblastic anemia; mtDNA, mitochondrial deoxyribonucleic acid; RTA, renal tubular acidosis; TDFS, Toni-Debré-Fanconi syndrome; TIN, tubulointerstitial nephritis; XLSA, X-linked sideroblastic anemia

Key words: mtDNA mutation, oxidative phosphorylation, renal dysfunction, renal tubular acidosis, respiratory chain

1. Introduction

Depending on the phenotype, mitochondrial disorders (MIDs) are categorised as syndromic or non-syndromic (1). Syndromic MIDs are characterised by recurrent patterns of symptoms and signs, which have the same cause. Many of the syndromic MIDs are known by their acronyms (Table I), although there are a number of syndromic MIDs that have no acronym yet. A characteristic of syndromic MIDs is that they do not affect a single tissue or organ, but involve multiple tissues or organs (2). Multiorgan involvement in MIDs [mitochondrial multiorgan disorder syndrome (MIMODS)] (3) may already be present at onset of the clinical manifestations or may develop during the course of the disease. It appears that MIMODSs evolve as the duration of survival of the patient lengthens. The organs most frequently involved in MIDs are the skeletal muscles, peripheral nerves, central nervous system, eyes, ears, endocrine organs, heart, lungs, gastrointestinal tract, kidneys, bones (including the bone marrow) and the skin. The kidneys are known to be significantly involved in MIDs (4-7), although, to the best of our knowledge, a current, comprehensive and systemic review regarding kidney disease in MIDs is lacking. Transmission of a MID may follow any type of inheritance. The present review aims to summarise and discuss recent

Table I. Renal disease in syndromic MIDs and nsMIDs.

MID	RF	NL	NS	RC	RTA	BLS	TDFS	FSGS	TIN	NC
MELAS	Yes	N	N	N	N	N	N	Yes	N	N
KSS	Yes	N	N	N	Yes	Yes	Yes	N	N	Yes
MDS	N	N	N	N	Yes	N	N	N	N	Yes
LS	N	N	N	Yes	Yes	N	N	N	Yes	N
CPEO	Yes	N	N	N	N	N	N	N	N	N
PS	N	N	N	Yes	Yes	N	N	N	N	N
LHON	N	N	N	N	N	N	N	N	Yes	N
PCQD	N	N	Yes	N	N	N	N	Yes	N	N
XLSA	Yes	N	N	N	N	N	N	N	N	N
GRACILE	N	N	N	N	N	N	Yes	N	N	N
MEGDEL	Yes	N	N	N	N	N	N	N	N	N
HUPRA	Yes	N	N	N	N	N	N	N	N	N
MLASA	N	N	N	N	Yes	N	N	N	N	N
MSL	N	N	N	N	Yes	N	N	N	N	N
PDHD	N	N	N	N	Yes	N	N	N	N	N
nsMIMODS	Yes	Yes	Yes	Yes	Yes	N	N	Yes	Yes	Yes

RF, renal failure; NL, nephrolithiasis; NS, nephrotic syndrome; RC, renal cysts; RTA, renal tubular acidosis; BLS, Bartter-like syndrome; TDFS, Toni-Debré-Fanconi syndrome; FSGS, focal segmental glomerulosclerosis; TIN, tubulo-interstitial nephritis (nephrophthisis); NC, nephrocalcinosis; LS, Leigh syndrome; PCQD, primary coenzyme-Q deficiency; XLSA, X-linked sideroblastic anemia; nsMIMODS, non-specific MIMODS; N, not reported.

findings concerning phenotype, genotype, pathogenesis, diagnosis, treatment and outcome of kidney disease in MIDs.

2. Methods

Data for the present review were identified by searching Medical Literature Analysis and Retrieval System Online (MEDLINE; <https://www.ncbi.nlm.nih.gov/pubmed>), Current Contents (http://wokinfo.com/products_tools/multidisciplinary/CCC/), Excerpta Medica database (EMBASE; <https://www.embase.com/login>), Web of Science (<https://login.webofknowledge.com/error/Error?PathInfo=%2F&Alias=WOK5&Domain=.webofknowledge.com&Src=IP&RouterURL=https%3A%2F%2Fwww.webofknowledge.com%2F&Error=IPEerror>), Web of Knowledge (<https://de.slideshare.net/davehirsty/science-citation-index>), Latin American and Caribbean Health Sciences Literature (LILACS; <http://bases.bireme.br/cgi-bin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&base=LILACS&lang=i&form=F>), bibliographic database for science (SCOPUS; <https://www.scopus.com/>) and Google Scholar (<https://scholar.google.de>) for references to relevant articles using the following search terms: 'Kidney', 'renal', 'renal insufficiency', 'nephrolithiasis', 'nephrocalcinosis', 'renal cysts', 'Bartter-like syndrome', 'Fanconi syndrome', 'Toni-Debré-Fanconi syndrome', 'nephrotic syndrome', 'tubulointerstitial nephritis', and 'renal tubular acidosis' in combination with all acronyms for syndromic MIDs and the terms 'mtDNA', 'respiratory chain', 'electron transport', 'mitochondrion', and 'mitochondrial'. Randomised (blinded or open label) clinical trials and observational studies (longitudinal studies, case series and case reports) were considered. Abstracts and reports from meetings were not included. Only articles in

English, French, Spanish or German, and those published between 1966 and 2016 were considered. Appropriate papers were evaluated and discussed for their usefulness to be incorporated in the review. Reference lists of the appropriate papers were reviewed for further articles matching the search terms. A paper was included if it reported a single patient or a cohort of patients with MIDs who also manifested with any type of primary or secondary kidney disease.

3. Results

Classification. Renal disease in MIDs may be classified as primary or secondary. Secondary kidney disease may result from primary involvement of organs other than the kidneys in the MID. In the case of cardiac involvement in MID, there may be renal infarction from atrial fibrillation or heart failure, or hypertensive kidney disease from mitochondrial arterial hypertension. In the case of mitochondrial diabetes, renal insufficiency may be a consequence of the primary involvement of the pancreas in the MID. Another secondary renal disorder due to a primary mitochondrial defect may be renal insufficiency from rhabdomyolysis due to mitochondrial myopathy or mitochondrial epilepsy (8). Primary renal manifestations of MIDs include acute or chronic renal failure, nephrolithiasis, nephrotic syndrome, renal cysts, renal tubular acidosis (RTA), Bartter-like syndrome, Toni-Debré-Fanconi syndrome (TDFS), focal segmental glomerulosclerosis (FSGS), tubulointerstitial nephritis (TIN), nephrocalcinosis, and benign or malignant neoplasms (9). Renal involvement in MIDs may be classified according to the number of organs that are affected in addition to the kidney. If no other organs are

Table II. Renal dysfunction in Kearns Sayre syndrome.

Renal abnormality	Patients, n	Age, years	Sex	Refs.
Renal insufficiency	1	10	m	78
	4	range, 6-21	f, 1; m, 3	79
	1	NA	NA	80
Renal tubular acidosis	1	7	m	32
	1	18	f	33
	1	14	m	13
Bartter-like syndrome	1	7	f	35
	1	10	m	34
	1	11	f	15
Toni-Debré-Fanconi syndrome	1	10	m	27
	1	10	m	28
	1	5	m	29
	1	18	m	30
	1	8	f	31
	1	43	f	14
	1	13	f	26

f, female; m, male; NA, not accessible.

additionally involved (absence of MIMODS) the mitochondrial nature of renal disease is often difficult to detect (10). However, when more organs are affected, it is more suggestive of a MID. Additionally, renal involvement may be classified according to the priority within the phenotype. In certain cases, renal involvement may dominate the phenotype whereas in other cases, renal disease may be a non-dominant feature. A further differentiation of renal involvement in MIDs relies on whether the underlying genotype manifests clinically or remains subclinical. Subclinical involvement may be detected upon observation of morphological abnormalities of mitochondria and a high quantity of heteroplasmy of mutated mtDNA during kidney biopsy or autopsy (11,12).

Renal disease in syndromic MIDs. Renal involvement has been reported in a number of syndromic MIDs, which predominantly include mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), Kearns Sayre syndrome (KSS; Table II) (13,14) and mitochondrial depletion syndromes (MDSs). On rare occasions, renal disease may be found in other rarer types of syndromic MIDs.

MELAS. MELAS is one of the syndromic MIDs in which renal disease is fairly frequent. In a 14-year-old female with MELAS syndrome, the initial manifestation of the MID was an FSGS, which occurred 3 years prior to diagnosis of the MID (15). In a 35-year-old female with MELAS syndrome resulting from the m.13513G>A mutation, renal failure was the initial manifestation of the MID 9 years before diagnosis of the MID (10). In a 50-year-old male with MELAS syndrome, chronic renal failure requiring hemodialysis was one of the clinical manifestations (16). Chronic renal failure was the indication for renal transplantation in a 58-year-old

male with MELAS syndrome (17). In a 13-year-old Asian female with MELAS syndrome, renal involvement manifested as FSGS (18). In another MELAS patient acute renal failure occurred and was associated with severe hyponatremia due to renal sodium loss (19). Furthermore, in a female MELAS syndrome patient, severe kidney involvement with changes of FSGS was reported (20). Acute or chronic renal failure has been also reported in a number of MELAS patients with or without diabetes, suggesting that renal dysfunction is primary or secondary (21). In a series of 5 MELAS patients, FSGS was a phenotypic feature in all of them; thus, the authors concluded that renal involvement in MELAS may be underestimated (7). Chronic renal failure appears to be a typical manifestation of MELAS (22) and FSGS may be the dominant feature in these patients (23). Kidney cancer was reported in a 41-year-old male who was exhibiting MELAS syndrome (24). A histological work-up additionally revealed arteriolonephrosclerosis (24) and renal cell carcinoma was reported in a 2-year-old male with MELAS syndrome (25).

KSS. Renal abnormalities so far described in KSS include renal failure, RTA, Bartter-like syndrome and TDFS (Table II). In an 11-year-old female with KSS, TDFS was diagnosed 8 years prior to the diagnosis of the MID (15). TDFS was also reported in a 13-year-old female with KSS who additionally manifested with anhidrosis (26), as well as other patients (14,27-31). In a 5-year-old male with KSS, the MID manifested with RTA (Table II) (32), which was also described in an 18-year-old female (Table II) (33). In a 10-year-old male with KSS, the MID manifested in the kidneys as renal tubular dysfunction with isosthenuria, decreased urine-concentrating ability, and excessive excretion of potassium and magnesium (34). In addition, hyperreninemia and hyperaldosteronism were

Table III. Genes in which mutations cause MID with renal involvement.

Mutated gene	Renal disease	Refs.
mtDNA		
tRNA(Leu)	RF, FSGS	(16,81)
tRNA(Phe)	Tubulointerstitial fibrosis, RF, TDFS	(74,82)
tRNA(Tyr)	FSGS, nephrotic syndrome	(75)
tRNA(Ser)	Proteinuria, glomerulosclerosis	(66)
COXIII	RF	(83)
nDNA		
COX10	Tubulopathy	(65)
SURF1	RTA	(48)
BCS1L	Proximal tubulopathy	(68)
UQCC1	Tubulopathy	(72)
TMEM70	RTA, RF, hydronephrosis	(69)
MRPS22	Tubulopathy	(71)
YARS2	Tubulopathy	(53)
SARS2	Tubulopathy	(49)
RRM2B	Proximal tubulopathy, NC	(36,40,41,84)
TWINKLE	Proximal tubulopathy	(38)
MPV17	Tubulopathy	(43)
DGUOK	Tubulopathy	(42)
LARS2	RF	(70)
RMND1	Chronic RF	(73)
ACAD9	Megamitochondria in tubules	(54)
CLPB	Nephrocalcinosis, cysts, aciduria	(85)
ADCK4	Nephrotic syndrome	(77,78)
MRPL44	Renal failure	(86)

RF, renal failure; RTA, renal tubular acidosis; NC, nephrocalcinosis.

present in the absence of arterial hypertension, resulting in a diagnosis of Bartter-like syndrome (34). Furthermore, Bartter-like syndrome has been described in two other patients with KSS, in a 14-year-old male (13) and a 7-year-old female (Table II) (35). In addition, nephrocalcinosis has been identified as a rare feature of KSS (13).

MDS. MDSs are characterised by a reduction in the quantity of mtDNA within a mitochondrion of a cell. MDSs are due to mutations in the ribonucleotide reductase regulatory TP53 inducible subunit M2B (*RRM2B*), MpV17 mitochondrial inner membrane protein (*MPV17*), DNA polymerase γ , catalytic subunit (*POLG1*), DNA polymerase γ 2, accessory subunit (*POLG2*), succinate-CoA ligase ADP-forming β subunit (*SUCLA2*), succinate-CoA ligase GDP-forming β subunit (*SUCLG2*), twinkle mtDNA helicase (*C10orf2*), deoxyguanosine kinase (*DGUOK*), thymidine kinase 2, mitochondrial (*TK2*), F-box and leucine rich repeat protein 4 (*FBXL4*), and transcription factor A, mitochondrial (*TFAM*) genes. In an infant with MDS due to a mutation in the *RRM2B* gene, the MID manifested along with proximal renal tubulopathy and nephrocalcinosis (36). In an infant with MDS, but without detection of the underlying genetic defect, RTA developed 1 year after liver transplantation and was attributed

to tacrolimus toxicity and renal involvement in the MID (37). In three siblings with MDS due to a *C10orf2* (twinkle) mutation, the MDS manifested as hepatocerebral syndrome and as proximal renal tubulopathy (Table III) (38). Renal tubulopathy was also reported in a female newborn with MDS carrying an mtDNA copy number of only 2% (39). In one of two males with MDS due to a mutation in the *RRM2B* gene, proximal renal tubulopathy was described (40). Tubulopathy was also present in a female infant with MDS carrying the *RRM2B* mutation c.368T>C (41). In addition, tubulopathy was detected in three patients during an investigation of 11 patients with MDS due to mutations in the *DGUOK* gene (42). Furthermore, MDS resulting from mutations in the *MPV17* gene may be associated with tubulopathy (Table III) (43).

Other syndromic MIDs with renal involvement. Single cases of renal involvement have been reported in other syndromic MIDs, such as chronic progressive external ophthalmoplegia (CPEO) (44), Pearson syndrome (45), Leber hereditary optic neuropathy (LHON) (46), coenzyme-Q deficiency, X-linked sideroblastic anemia (XLSA) (47), Leigh syndrome (48), or hyperuricemia, metabolic alkalosis, pulmonary hypertension, and progressive renal failure in infancy (HUPRA) syndrome (49). In a 44-year-old female with CPEO, the MID

initially manifested initially with hearing loss at age 22 years, which was followed by renal failure at 30 years of age (44). In an infant with Pearson syndrome due to a single mtDNA deletion, the bone marrow, central nervous system, exocrine pancreas and the kidneys were involved. Renal involvement manifested as severe tubular dysfunction (45). In another patient with Pearson syndrome multiple renal cysts were reported (50). In a 1-year-old female with LHON, renal involvement manifested as nephronophthisis, also referred to as TIN (46). In an infant with primary coenzyme-Q deficiency due to a mutation in the *COQ2* gene, the MID manifested with nephrotic syndrome due to FSGS (51). In an 81-year-old male with XLSA due to mutations in the *ALAS2* gene, renal involvement manifested as severe renal failure requiring haemodialysis (47). In a study of four patients with Leigh syndrome due to a mutation in the *SURF1* gene, three had significant proximal RTA (48). Hyperuricemia, pulmonary hypertension, renal failure in infancy and alkalosis (HUPRA) syndrome due to *SARS2* gene mutations is, by definition, a rare MID that presents along with renal failure (52). In two Palestinian infants with HUPRA syndrome due to a *SARS2* mutation, tubulopathy was a cardinal phenotypic feature of the disease (49). In a Turkish family with myopathy, lactic acidosis, and sideroblastic anaemia (MLASA) syndrome due to a *YARS2* mutation, renal involvement manifested as tubulopathy (53). In a neonate with Leigh syndrome due to a mutation in the *ACAD9* gene, autopsy revealed hyperplasia of mitochondria in renal tubular cells (54). In addition, in a patient with Leigh syndrome due to a mutation in the *ND5* gene renal salt loss was deemed responsible for secondary hyponatremia (55). Diffuse glomerulocystic kidneys were reported in a patient with Leigh syndrome, but without detecting the genetic defect (56). Growth retardation, aminoaciduria, cholestasis, iron overload, lactic acidosis and early death (GRACILE) syndrome is an early-onset, autosomal recessive multisystem MID due to mutations in the *BCSIL* gene. Clinically, GRACILE syndrome is characterised by fetal growth retardation, Fanconi-type aminoaciduria, cholestasis, iron overload, profound lactic acidosis, and early mortality (57). One of the clinical hallmarks of GRACILE syndrome is TDFS-type tubulopathy with aminoaciduria. In a mouse model of GRACILE syndrome, tubulopathy was one of various other phenotypic features (58). Late-onset nephrotic syndrome was described in *Mpv17* knock-out mice (59). In single patients with multiple systemic lipomatosis, which may be due to the m.8344A>G mutation, RTA has been reported (60). In a male infant with pyruvate dehydrogenase deficiency (PDH), RTA was one of the clinical manifestations in addition to lactic acidosis, contributing to the death of this individual (61). Whether renal excretion of urinary phosphatidylethanolamine, cardiolipin, and phosphatidylserine in four patients with myoclonus epilepsy with ragged-red fibres (MERRF) (62) and in one patient with CPEO was truly attributable to renal involvement remains unknown, but they may be derived from sulfatides, which are specific to the kidneys (62).

Renal disease in non-specific syndromic MIDs. In four adult patients with FSGS, kidney disease was attributed to an MID, as renal biopsy revealed the presence of the m.3243A>G mutation in the *tRNA(Leu)* gene (61). Notably, no other organs were affected in these four patients; thus, kidney disease

was the initial manifestation and dominant feature of the MID and, therefore, the phenotype was not consistent with MELAS syndrome at the time of diagnosis (63). In a patient with sensorineural blindness, attributed to a non-genetically proven MID, Bartter-like syndrome was the second phenotypic feature (64). In a consanguineous family with isolated COX-deficiency due to a mutation in the *COX10* gene, which encodes the heme A:farnesyltransferase, increased urinary amino acids suggested proximal renal tubulopathy (65). In a 54-year-old female, the homoplasmic m.7501T>A mutation in the *tRNA(Ser)* gene manifested as proteinuria due to sclerosis of one-quarter of the glomeruli observed during kidney biopsy (66). Almost one-third of the interstitium was fibrotic in this patient. Tubular granular swollen epithelial cells (GSECs), which have been demonstrated to indicate a MID (67), were present in the medulla collecting ducts (66). In a study of six patients with encephalopathy, hepatopathy, and proximal tubulopathy, the causative mutation was detected in the *BCSIL* gene resulting in respiratory chain complex III deficiency (68). In a study of 35 multi-ethnic patients carrying a *TMEM70* mutation, 35% manifested with renal disease in the form of RTA, hydronephrosis and acute or chronic renal failure (69). In a newborn girl with MIMODS due to a mutation in the *LARS2* gene, encoding for a mitochondrial amino-acyl-tRNA synthetase, progressive renal failure was responsible for mortality 5 days after birth (70). In three children from the same consanguineous parents, antenatal skin oedema, hypotonia, cardiomyopathy and tubulopathy were attributed to mutations in the *MRPS22* gene (71). In a consanguineous Lebanese patient with respiratory chain complex III deficiency due to a *UQCC2* gene mutation, renal tubulopathy was one of the phenotypic manifestations, in addition to severe intrauterine growth retardation and neonatal lactic acidosis (72). Chronic renal failure was also reported in an 11-month-old male who presented with truncal ataxia, sensorineural hearing loss, muscle hypotonia, delayed visual maturation, global developmental delay and dilated cardiomyopathy (73). Nuclear genetic studies identified a causative mutation in the *RMND1* gene (73). End-stage renal disease due to TIF was reported in a 16-month-old girl with developmental regression, lactic acidosis, hypotonia, gastrointestinal dysmotility, adrenal insufficiency, arterial hypertension and haematological abnormalities carrying a *tRNA(Phe)* mutation (74). Isolated renal disease as the sole manifestation of a MID was reported in a 9-year-old female with steroid-resistant FSGS (75). The MID was due to a point mutation in the mtDNA located at the *tRNA(Tyr)* gene (75).

Diagnosis. A diagnostic work-up of renal disease in MIDs is not different from a work-up of renal disease in patients without an MID. The diagnosis is based on blood tests, urine analysis, imaging, functional tests and biopsies. Biopsy is important, as it may show abnormalities, which have been reported in MID patients with renal involvement (Table I), as well as morphological abnormalities of mitochondria. A strong indicator for the mitochondrial nature of a kidney disease appears to be the presence of GSECs. MID patients with suspected renal involvement should, therefore, undergo kidney biopsy, to establish whether GSECs are present. In addition, a biopsy may show microvascular degeneration of the renal tubular epithelial cells, such as in Leigh syndrome.

If additional biochemical investigations are performed, dysfunction of one or various respiratory chain complexes may be detected. If genetic studies are conducted, mutations in mtDNA- or nDNA-located genes may be detected (Table III) and, in the case of mtDNA mutations, the heteroplasmy rates may be determined. Notably, a single patient may present with more than one renal abnormality (Table I).

Treatment. Treatment of mitochondrial nephropathy is the same as for non-mitochondrial nephropathy. However, drugs that are mitochondrion-toxic should generally be avoided in MID patients. Though not supported by evidence from appropriate clinical trials, mitochondrial nephropathy may respond to supportive treatment administered to MID patients, such as antioxidants, co-factors or vitamins (76). In patients with steroid resistant nephrotic syndrome due to mutations in the *ADCK4* gene, which is involved in COQ10 biosynthesis, coenzyme-Q may be highly beneficial (77). Renal failure in MIDs may be of such a degree that haemodialysis may be required.

Outcome. To the best of our knowledge, there are no available systematic studies regarding the outcome of renal disease in MIDs. The outcome of renal involvement in MIDs is dependent on the underlying mutation, as well as the type of renal disease. The outcome of renal disease in MIDs is also dependent on whether it is primary or secondary. In the case of mtDNA mutations, the heteroplasmy rate in the kidneys may be significant for the outcome of renal disease. Though not systematically investigated, it is speculated that the severity of renal disease increases and that the outcome of kidney disease becomes worse as the heteroplasmy rate increases.

Conclusion

The present review demonstrates that renal involvement in MIDs is more frequent than originally anticipated, and that primary and secondary renal involvement in MIDs occurs in syndromic and non-syndromic MIDs. Among the syndromic MIDs renal involvement has been most frequently reported in MELAS syndrome, KSS and MDS. Only rarely was renal involvement described in patients with CPEO, Pearson syndrome, LHON, primary coenzyme-Q deficiency, XLSA, Leigh syndrome, PDH deficiency, GRACILE syndrome HUPRA syndrome, or non-specific syndromic MIDs. Primary renal involvement in MIDs includes renal failure, nephrolithiasis, nephrotic syndrome, renal cysts, renal tubular acidosis, Bartter-like syndrome, Fanconi syndrome, FSGS, TIN, nephrocalcinosis and neoplasms. Bartter-like syndrome is characterised by a hyperreninemic hyperaldosteronism, hyponatremia, hypokaliemia, hypo-osmolarity, arterial hypotension despite hyperreninemic hyperaldosteronism and alkalosis.

Diagnosis of renal involvement in MIDs is the same as diagnosing renal disease in non-MID patients. In MID patients with a Bartter-like syndrome, Bartter syndrome must be excluded by showing absence of a mutation in the *SLC12A1* (type 1), *KCNJ1* (type 2), *CICNKB* (type 3), *BSND* (type 4), or the *CSAR* gene (type 5). If mitochondrial nephropathy is the initial manifestation of an MID, diagnosing the MID may

be delayed unless genetic or biochemical investigations are performed with renal biopsies. In particular, patients with one of the frequent renal manifestations of MID should be closely followed up for establishing whether organs other than the kidneys have been affected, and first-degree relatives must be thoroughly investigated for MID. Treatment of renal disease in MIDs follows general guidelines, however, physicians must be wary of prescribing mitochondrion-toxic compounds, which could worsen renal disease and involvement of other organs in MIDs. Antioxidants, vitamins, and other co-factors may be of additional benefit for renal disease in MIDs, but, to the best of our knowledge, no systematic studies have been performed addressing these issues. The focus of future research in MIDs should be directed towards mitochondrial nephropathy, and optimized diagnostic and therapeutic procedures must be established. From a translational perspective, animal models may provide important mechanistic insights into MIDs and may be particularly useful for the development of novel compounds for improving the therapeutic options in MIDs.

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