Pediatr Nephrol (2013) 28:357–361
DOI 10.1007/s00467-012-2362-y

EDITORIAL COMMENTARY

Mitochondrial disease—an important cause of end-stage renal failure

Shamima Rahman · Andrew M. Hall

Received: 26 October 2012 / Accepted: 29 October 2012 / Published online: 12 December 2012
© IPNA 2012

Abstract Kidneys are highly aerobic organs. They receive roughly a quarter of the cardiac output and contain a high density of mitochondria, particularly in the cortical tubules, which are required to produce adenosine triphosphate (ATP) in sufficient quantity to power the re-uptake of over 98 % of the filtered load. Given the dependence of renal function on aerobic metabolism, it is not surprising that impairment of normal mitochondrial function—due to insults such as ischaemia, drug toxicity and genetic mitochondrial disease—can lead to kidney failure. In this edition of *Pediatric Nephrology*, D'Aco and colleagues (doi:10.1007/s00467-012-2354-y) describe a patient who developed end-stage renal failure caused by a pathogenic mutation (m.586G>A) in the gene encoding the mitochondrial tRNA for phenylalanine, which adversely affects the translation of mitochondrial DNA. The pathogenicity of this mutation was confirmed in cybrid studies using fibroblasts obtained from the patient. In light of this report, m.586G>A should now be added to the rapidly expanding list of mitochondrial and nuclear gene mutations causing mitochondrial disease with renal involvement. Furthermore, mitochondrial disease should be considered as an underlying aetiology in cases of unexplained renal failure, particularly in the context of a multisystem disorder. Renal replacement therapy is an option for patients with mitochondrial disease, but life expectancy even with this therapy may be limited by co-morbidities.

Keywords Mitochondrial disease · Metabolism · Renal involvement · Kidney failure · Mutation

S. Rahman (✉)
Mitochondrial Research Group, Clinical and Molecular Genetics Unit, UCL Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK
e-mail: shamima.rahman@ucl.ac.uk

S. Rahman
Metabolic Unit, Great Ormond Street Hospital, London, UK

S. Rahman
MRC Centre for Neuromuscular Diseases, National Hospital for Neurology, London, UK

A. M. Hall
UCL Centre for Nephrology, Royal Free Hospital, London, UK

Background

Mitochondria are dynamic subcellular organelles with critical roles in energy generation. The kidney has a high energy requirement, and inherited mitochondrial dysfunction is an under-recognised cause of renal disease in childhood. Disorders of mitochondrial oxidative phosphorylation (OXPHOS) represent one of the most common groups of inborn errors of metabolism, with a combined minimum birth prevalence of 1 in 5,000. Mitochondria are unique organelles in that they contain their own genetic material: the 16.5-kb multicopy maternally inherited mitochondrial genome encodes 13 protein components of the respiratory chain and OXPHOS system and 24 RNA molecules needed for intramitochondrial synthesis of these 13 proteins. Neuromuscular presentations with characteristic combinations of clinical problems caused by specific mitochondrial DNA (mtDNA) mutations are relatively well-recognised: the so-called 'classical mitochondrial syndromes', such as mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), myoclonus epilepsy with ragged red fibres (MERRF), Pearson marrow pancreas and Kearns–Sayre syndromes [1]. MELAS and MERRF are most frequently associated with specific mtDNA point mutations (m.3243A>G and m.8344A>G, respectively) while most cases of the Pearson and Kearns–Sayre syndromes are caused by large-scale rearrangements of the mtDNA. Renal complications may occur in all four of these syndromes, typically manifesting as focal segmental glomerulosclerosis (FSGS) in patients with the m.3243A>G

mutation and renal tubulopathy (Fanconi syndrome) in children with Pearson and Kearns–Sayre syndromes [2–4]. These problems usually occur in the context of neuromuscular disease, and diagnosis is relatively straightforward, although m.3243A>G-related renal disease has occasionally been confused with Alport syndrome because of the association with sensorineural hearing loss in both of these conditions [5]. Importantly, renal impairment can be the presenting feature in patients with previously undiagnosed mitochondrial disease.

End-stage renal disease caused by a mtDNA mutation affecting translation

The ubiquitous nature of mitochondria, being present in all cells except mature red blood cells, means that any combination of organs may be affected, giving rise to myriad clinical presentations [6]. Indeed, it is increasingly the case that patients with 'classical' mitochondrial disease represent the minority, while the majority of cases do not fit neatly into a recognised syndrome. In this edition of *Pediatric Nephrology*, D'Aco et al. present a case of end-stage renal disease (ESRD) caused by a mtDNA point mutation, m.586G>A, in the *MT-TF* gene encoding the mitochondrial tRNA for phenylalanine [7]. This 16-month-old patient did not have a classical mitochondrial syndrome, but did have multisystem disease features, including developmental regression, persistent lactic acidosis, hypotonia, faltering growth, gastro-intestinal dysmotility, pancreatitis, adrenal insufficiency, anaemia and neutropaenia, which alerted the physicians to the suspicion of an underlying mitochondrial disorder.

MtDNA is notoriously polymorphic and proving mutation pathogenicity can be challenging. Evidence in favour of mutation pathogenicity for m.586G>A was that it was heteroplasmic (i.e. mutant and wild-type mtDNA co-existed) in the patient's tissues and was absent in the blood of her asymptomatic mother. Further evidence of a mtDNA mutation is provided if the mutation is associated with the same phenotype in two unrelated pedigrees. However, the m.586G>A mutation has previously been reported in an adult patient with a completely different phenotype, specifically movement disorder and psychiatric disturbance with no evidence of renal impairment [8]. The variant phenotypes observed in these two patients raised the possibility that the mutation was a coincidental finding and not pathogenic. In order to address this, D'Aco et al. employed the gold standard method of transmitochondrial cybrid generation in which enucleated patient cells are fused with a donor cell line lacking mtDNA (so-called rho zero cells) to determine whether the biochemical phenotype tracks with the patient's mtDNA [9]. Their findings showed that cybrids with 100 % m.586G>A mutation had significantly reduced oxygen consumption and reduced tRNA phenylalanine levels and that the amount of mutation influenced the degree of respiratory impairment in a dose-dependent manner, thereby providing overwhelming evidence that this mutation is pathogenic [7].

Renal phenotypes in mitochondrial disease—a brief overview

How does the case presented by D'Aco et al. [7] fit with the literature to date on renal involvement in mitochondrial disease? This is a rapidly evolving field, and much remains to be learned about the complex relationship between genotype and phenotype. One helpful way to navigate this subject is to categorise pathogenic mutations according to genome (nuclear vs. mitochondrial) and/or according to the function of the affected gene product (OXPHOS complex subunit or assembly, mtDNA maintenance, mtDNA translation etc.). In the following sections we will apply this approach to briefly summarise the expanding volume of literature describing renal involvement in mitochondrial disease. Overall, it can be concluded that tubulo-interstitial disease is the most common renal phenotype in children presenting at a young age with severe multisystem disease (as in the case described by D'Aco et al. [7]), usually due to widely expressed nuclear DNA mutations or large-scale mtDNA deletions. However, as discussed below, there are some notable exceptions to this generalisation. The proximal tubule is especially vulnerable to mitochondrial dysfunction since it has very high energy requirements but lacks the capability to synthesise adenosine triphosphate (ATP) anaerobically from glycolysis [10].

At the other end of the spectrum of disease severity lie individuals with point mutations of mtDNA (most commonly m.3243A>G), who survive well into adulthood and may present with renal disease alone, or in combination with mild/subclinical abnormalities in other organs. Glomerular pathology (FSGS) is typically reported in these individuals, with or without associated tubulo-interstitial abnormalities [11]. This raises the prospect that patients with unexplained chronic kidney disease, who unfortunately often present late to a nephrologist due to the silent nature of kidney disease, may in some cases have an underlying mitochondrial disorder.

Nuclear-encoded mitochondrial disease

Most of the approximately 1,500 proteins localised inside mitochondria are actually encoded by nuclear genes, and it is likely that mutations in many of these genes will cause mitochondrial disease [12]. More than 100 Mendelian-

inherited mitochondrial diseases have been reported in the past 17 years since a homozygous mutation of the SDHA subunit of respiratory chain complex II was first linked to Leigh syndrome, a neurodegenerative disorder [13]. Many of these nuclear-encoded defects are associated with renal phenotypes, either as part of a multisystem disease or as the main and sometimes only organ affected (Table 1). It is important for the nephrologist to be aware of this new class of disease, particularly those conditions for which specific treatment is available, namely the disorders of coenzyme Q_{10} biosynthesis. Seven genetic defects of coenzyme Q_{10} biosynthesis have been reported to date, and three of these (defects of COQ2, PDSS2 and COQ6) have been associated with a prominent renal phenotype [14]. These patients presented with steroid-resistant nephrotic syndrome, variably associated with multisystem features that included sensorineural hearing loss, epilepsy, ataxia and stroke-like episodes. Several patients progressed to end-stage renal disease (ESRD) requiring transplantation. However, and importantly, Montini et al. reported that pre-symptomatic treatment with high doses of coenzyme Q_{10} was associated with an excellent clinical outcome in a patient with *COQ2* mutations, with no progression of renal disease and no evidence of neurological dysfunction [15]. Renal tubulopathy was noted in the only patient reported with *COQ9* mutation to date [16].

Abnormalities in the mitochondrial proteome

The mitochondrial proteome includes proteins required for (1) maintenance and (2) translation of the mitochondrial genome, (3) assembly of the five OXPHOS complexes, (4) import of solutes and (5) proteins into the various mitochondrial compartments (outer membrane, intermembrane space, inner membrane and matrix), (6) biosynthesis of membrane phospholipids (including cardiolipin and coenzyme Q_{10}) and (7) mitochondrial dynamics (fission, fusion and motility). Defects have been reported in all seven of these categories of proteins. Proximal tubulopathy has been reported in several defects of mitochondrial salvage of nucleosides (mutations of *RRM2B*, *DGUOK*, *TK2* and *SUCLA2*), leading to impaired mtDNA replication and consequently a quantitative reduction of mtDNA, known as the mtDNA depletion syndrome (Table 1). Mutations of MPV17, a protein of unknown function that appears to be necessary for mtDNA replication, are also associated with proximal tubulopathy. Patients with defects in the assembly of complexes I, III, IV and V may also present with tubulopathy (Table 1). Patients with mutations in *BCS1L* affecting complex III assembly typically present in infancy with tubulopathy associated with liver failure and encephalopathy [17]. *SURF1* mutations cause Leigh syndrome with defective complex IV assembly and appear to be particularly associated with distal renal tubular acidosis, although proximal tubulopathy may also occur [18]. Proximal tubulopathy with generalised aminoaciduria and a hyperechogenic appearance of the renal parenchyma on ultrasound have been reported in several patients with *TMEM70* mutations affecting complex V assembly [19].

Disorders of mitochondrial translation

Defects of mitochondrial translation are a rapidly expanding subgroup of mitochondrial disease, and renal dysfunction has been reported in several of these. The first diseases noted to affect mitochondrial translation involved the mitochondrial tRNA genes, either point mutations (as in MELAS

Table 1 Molecular mechanisms leading to nuclear-encoded mitochondrial kidney disease

Molecular defect	Gene(s)	Renal involvement	Other clinical features
Mitochondrial DNA maintenance	*RRM2B*, *DGUOK*, *TK2*, *SUCLA2*, *MPV17*	Proximal tubulopathy	Mitochondrial DNA depletion syndrome (3 main phenotypes: hepatocerebral, myopathic and encephalomyopathic)
Mitochondrial translation (aminoacylation)	*SARS2*	Tubulo-interstitial disease with salt wasting and hypomagnesaemia	Pulmonary hypertension
Mitochondrial ribosome	*MRPS22*	Tubulopathy	Hypertrophic cardiomyopathy and encephalomyopathy
Mitochondrial translation (elongation)	*TFSM*	Tubulopathy	Intrauterine growth retardation, hepatic insufficiency and hypotonia
Complex I assembly	*NDUFAF2*	Renal tubular acidosis	Leigh syndrome
Complex III assembly	*BCS1L*	Proximal tubulopathy	Encephalopathy and liver failure
Complex IV assembly	*COX10*, *SURF1*	Tubulopathy, distal renal tubular acidosis (SURF1)	Leigh syndrome
Complex V assembly	*TMEM70*	Proximal tubulopathy	Hypertrophic cardiomyopathy
Coenzyme Q_{10} biosynthesis	*PDSS2*, *COQ2*, *COQ6*, *COQ9*	Steroid resistant nephrotic syndrome, tubulopathy	Seizures, ataxia, hearing loss, multisystem disease

syndrome) or large-scale rearrangements (as in Pearson and Kearns–Sayre syndromes). Thus, mitochondrially encoded disorders of mitochondrial translation have long been recognised to cause renal disease. More recently, nuclear-encoded defects of mitochondrial translation have been described that may affect proteins involved in the modification of tRNAs, aminoacylation, the structure, function or assembly of ribosomes, and the initiation, elongation and termination of mitochondrial translation [20]. The tRNA aminoacyl synthetases are responsible for charging tRNA molecules with their cognate amino acid. Mutations of *FARS2* were recently identified in an exome sequencing study [21]. These mutations would be expected to impair the insertion of phenylalanine onto the tRNA phenylalanine molecule, and so it would be interesting to determine whether affected patients shared any of the clinical features previously associated with *MT-TF* mutations, specifically end-stage renal failure as reported by D'Aco et al. in this issue of the *Pediatric Nephrology* [7]. However, affected patients with *FARS2* mutations actually present with a severe seizure disorder in the Alpers syndrome spectrum—and not with renal disease [21]. Other nuclear-encoded mitochondrial translation defects have been linked to renal dysfunction. For example, mutations of *SARS2*, which affect the aminoacylation of tRNA serine, were recently reported in HUPRA syndrome (hyperuricaemia, pulmonary hypertension and renal failure in infancy with alkalosis) [22]. This is a fatal multisystem disorder in which affected infants have tubulointerstitial disease leading to salt wasting, hypomagnesaemia and end-stage renal failure by 1 year of age. Renal biopsy revealed various tubulo-interstitial changes, including dedifferentiated, atrophic tubules with thick basement membrane, some completely denuded tubules and hyperplastic arteriolitis in the interstitium [22]. Tubulopathy has also been reported in two other defects of mitochondrial translation: two sisters with *MRPS22* mutations affecting the integrity of the mitochondrial small ribosome had tubulopathy with hypertrophic cardiomyopathy, hypotonia, lactic acidosis and hyperammonaemia, while a girl with mutations in *TFSM* encoding the translation elongation factor EFTs presented with intrauterine growth retardation, tubulopathy, hepatic insufficiency and hypotonia [23].

Summary—investigation and diagnosis of mitochondrial disease in patients with renal impairment

The kidneys are commonly affected in mitochondrial disease, and patients with a confirmed diagnosis should therefore be screened appropriately, ideally with a detailed assessment of tubular function. Mitochondrial disease should be considered in the differential diagnosis for patients presenting with unexplained renal failure. Certain clinical clues may point to the diagnosis, including involvement of other aerobic organs, a maternal family history (for mtDNA mutations) and the presence of dysmorphic mitochondria on electron microscopy of a kidney biopsy. However, these features may not always be present and, therefore, reaching a definitive diagnosis can be challenging. Serum lactate and pyruvate levels may be raised, but not always, and these may be wasted in the urine of patients with a proximal tubulopathy. A skeletal muscle biopsy is frequently performed for histological examination and OXPHOS function tests, but these may be normal (as in the patient described by D'Aco et al. [7]). More recently, urinary epithelial cells have been shown to provide a non-invasive alternative source of tissue for mtDNA mutation screening [24], which may be particularly appropriate in patients with renal involvement. As discussed above, if mutations of mtDNA are detected, expression in cell cybrid systems may be required to prove pathogenicity, especially in the case of novel mutations.

Sadly, treatment options in mitochondrial disease remain limited, with the possible exception of coenzyme Q_{10} deficiency, where supplementation early in the course of the disease may improve the outcome. Renal replacement therapy, in the form of either dialysis or transplantation, is an option in patients with mitochondrial disease. However, as in all patients with end-stage renal failure, prognosis is ultimately determined by the number and severity of co-morbidities.

Acknowledgements SR is supported by Great Ormond Street Hospital Children's Charity and receives research grant funding from Ataxia UK, the Child Health Research Appeal Trust, Climb, the Medical Research Council, Sparks and The Wellcome Trust. AMH is supported by The Academy of Medical Sciences, The Wellcome Trust and St Peter's Trust for Kidney, Bladder and Prostate Research.

References

1. Rahman S, Hanna MG (2009) Diagnosis and therapy in neuromuscular disorders: diagnosis and new treatments in mitochondrial diseases. J Neurol Neurosurg Psychiatry 80:943–953
2. Niaudet P, Rotig A (1997) The kidney in mitochondrial cytopathies. Kidney Int 51:1000–1007
3. Martin-Hernandez E, Garcia-Silva MT, Vara J, Campos Y, Cabello A, Muley R, Del Hoyo P, Martin MA, Arenas J (2005) Renal pathology in children with mitochondrial diseases. Pediatr Nephrol 20:1299–1305
4. Emma F, Bertini E, Salviati L, Montini G (2012) Renal involvement in mitochondrial cytopathies. Pediatr Nephrol 27:539–550
5. 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
6. Munnich A, Rustin P, Rotig A, Chretien D, Bonnefont JP, Nuttin C, Cormier V, Vassault A, Parvy P, Bardet J, Charpentier C, Rabier D, Saudubray JM (1992) Clinical aspects of mitochondrial disorders. J Inherit Metab Dis 15:448–455
7. D'Aco KE, Manno M, Clarke C, Ganesh J, Meyers KEC, Sondheimer N (2012) Mitochondrial tRNAPhe mutation as a

cause of end-stage renal disease in childhood. Pediatr Nephrol. doi:10.1007/s00467-012-2354-y
8. Young TM, Blakely EL, Swalwell H, Carter JE, Kartsounis LD, O'Donovan DG, Turnbull DM, Taylor RW, de Silva RN (2010) Mitochondrial transfer RNA(Phe) mutation associated with a progressive neurodegenerative disorder characterized by psychiatric disturbance, dementia, and akinesia-rigidity. Arch Neurol 67:1399–1402
9. King MP, Attardi G (1989) Human cells lacking mtDNA: repopulation with exogenous mitochondria by complementation. Science 246:500–503
10. Bagnasco S, Good D, Balaban R, Burg M (1985) Lactate production in isolated segments of the rat nephron. Am J Physiol 248: F522–F526
11. Guery B, Choukroun G, Noel LH, Clavel P, Rotig A, Lebon S, Rustin P, Bellane-Chantelot C, Mougenot B, Grunfeld 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
12. Pagliarini DJ, Calvo SE, Chang B, Sheth SA, Vafai SB, Ong SE, Walford GA, Sugiana C, Boneh A, Chen WK, Hill DE, Vidal M, Evans JG, Thorburn DR, Carr SA, Mootha VK (2008) A mitochondrial protein compendium elucidates complex I disease biology. Cell 134:112–123
13. Bourgeron T, Rustin P, Chretien D, Birch-Machin M, Bourgeois M, Viegas-Pequignot E, Munnich A, Rotig A (1995) Mutation of a nuclear succinate dehydrogenase gene results in mitochondrial respiratory chain deficiency. Nat Genet 11:144–149
14. Rahman S, Clarke CF, Hirano M (2012) 176th ENMC international workshop: diagnosis and treatment of coenzyme Q(10) deficiency. Neuromuscul Disord 22:76–86
15. Montini G, Malaventura C, Salviati L (2008) Early coenzyme Q10 supplementation in primary coenzyme Q10 deficiency. N Engl J Med 358:2849–2850
16. Duncan AJ, Bitner-Glindzicz M, Meunier B, Costello H, Hargreaves IP, Lopez 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
17. De Lonlay P, Valnot I, Barrientos A, Gorbatyuk M, Tzagoloff A, Taanman JW, Benayoun E, Chretien D, Kadhom N, Lombes A, de Baulny HO, Niaudet P, Munnich A, Rustin P, Rotig A (2001) A mutant mitochondrial respiratory chain assembly protein causes complex III deficiency in patients with tubulopathy, encephalopathy and liver failure. Nat Genet 29:57–60
18. Tay SK, Sacconi S, Akman HO, Morales JF, Morales A, De Vivo DC, Shanske S, Bonilla E, Dimauro S (2005) Unusual clinical presentations in four cases of Leigh disease, cytochrome C oxidase deficiency, and SURF1 gene mutations. J Child Neurol 20:670–674
19. Honzik T, Tesarova M, Mayr JA, Hansikova H, Jesina P, Bodamer O, Koch J, Magner M, Freisinger P, Huemer M, Kostkova O, Van CR, Kmoch S, Houstek J, Sperl W, Zeman J (2010) Mitochondrial encephalocardio-myopathy with early neonatal onset due to TMEM70 mutation. Arch Dis Child 95:296–301
20. Chrzanowska-Lightowlers ZM, Horvath R, Lightowlers RN (2011) 175th ENMC international workshop: mitochondrial protein synthesis in health and disease, 25–27th June 2010, Naarden, The Netherlands. Neuromuscul Disord 21:142–147
21. Elo JM, Yadavalli SS, Euro L, Isohanni P, Gotz A, Carroll CJ, Valanne L, Alkuraya FS, Uusimaa J, Paetau A, Caruso EM, Pihko H, Ibba M, Tyynismaa H, Suomalainen A (2012) Mitochondrial phenylalanyl-tRNA synthetase mutations underlie fatal infantile Alpers encephalopathy. Hum Mol Genet 21:4521–4529
22. Belostotsky R, Ben-Shalom E, Rinat C, Becker-Cohen R, Feinstein S, Zeligson S, Segel R, Elpeleg O, Nassar S, Frishberg Y (2011) Mutations in the mitochondrial Seryl-tRNA synthetase cause hyperuricemia, pulmonary hypertension, renal failure in infancy and alkalosis, HUPRA syndrome. Am J Hum Genet 88:193–200
23. Vedrenne V, Galmiche L, Chretien D, De Lonlay P, Munnich A, Rotig A (2012) Mutation in the mitochondrial translation elongation factor EFTs results in severe infantile liver failure. J Hepatol 56:294–297
24. Blackwood JK, Whittaker RG, Blakely EL, Alston CL, Turnbull DM, Taylor RW (2010) The investigation and diagnosis of pathogenic mitochondrial DNA mutations in human urothelial cells. Biochem Biophys Res Commun 393:740–745