

Epidemiology and Treatment of Mitochondrial Disorders

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The last ten years have seen a huge increase in the number of different genetic defects found in patients with mitochondrial disorders, but the true impact of mitochondrial disease is only just becoming apparent. Mitochondrial diseases are far more common than was anticipated. Although there have also been major advances in our understanding of mitochondrial pathology, the clinical management of patients with mitochondrial disease is largely supportive. In this article, we focus on primary disorders of the mitochondrial respiratory chain and mtDNA defects. We review the available epidemiological data, outline current strategies for the management of mitochondrial disease, and highlight new therapeutic approaches that may prove useful in the future. © 2001 Wiley-Liss, Inc.

KEY WORDS: mitochondrial disease; mtDNA; genetic epidemiology; gene therapy; MELAS; LHON; MERRF

For mitochondrial diseases, the last decade has been an age of enlightenment. Huge advances in our understanding of the biochemical and molecular basis of mitochondrial pathology have been paralleled by increased numbers of patients and families diagnosed as having mitochondrial disease. Although the literature is littered with reports describing new mutations and new diseases [Servidei, 2000], relatively little is known about the true impact of mitochondrial disorders on the community. Even less is known about how to treat mitochondrial disease. In this article, we will restrict our discussion to primary disorders of the mitochondrial respiratory chain and mtDNA defects. We will review the available epidemiological data and discuss current treat-

ment strategies for patients with mitochondrial disorders, highlighting new avenues for treatment in the future.

THE EPIDEMIOLOGY OF MITOCHONDRIAL DISEASE

Over 70 different polypeptides interact on the inner mitochondrial membrane to form the respiratory chain. The vast majority of subunits are synthesized within the cytosol from nuclear gene transcripts, but 13 essential subunits are encoded by the mitochondrial DNA (mtDNA) and are synthesized within the mitochondrial matrix. As a result, mutations affecting both nuclear and mitochondrial genomes lead to mitochondrial diseases [DiMauro and Schon, 2001; Munnich and Rustin, 2001; Orth and Schapira, 2001; Shoubridge, 2001; Suomalainen and Kaukonen, 2001; Triepels et al., 2001]. Many factors influence the prevalence of these disorders, including the mutation rate, the inheritance pattern, population structure, and the effect of the mutations on reproductive fitness. For example, mtDNA deletions are not transmitted

and are less prevalent than maternally transmitted mtDNA point mutations [Poulton et al., 1998]. The T8993G point mutation of mtDNA often causes a severe infantile encephalopathy, seizures and ataxia (Leigh syndrome), and pedigrees transmitting this mutation are small [White et al., 1999]. By contrast, there are huge multi-generation pedigrees transmitting the G11778A mtDNA mutation that has a reduced penetrance and generally only affects the optic nerve [Howell et al., 1995]. Similarly, there are large autosomal dominant pedigrees transmitting nuclear DNA *Ant 1* mutations leading to the formation of multiple mtDNA deletions and chronic progressive external ophthalmoplegia [Kaukonen et al., 2000; Suomalainen and Kaukonen, 2001]. Autosomal recessive disorders due to primary respiratory chain defects or cytochrome *c* oxidase (COX) assembly defects are probably relatively rare [Morris et al., 1996], and accurate epidemiological research must therefore be based upon a large study population.

Mitochondrial diseases pose particular problems for the genetic epidemiologist. The clinical presentation varies considerably, and while certain clinical syndromes immediately raise the possibility of a mitochondrial disorder (such as progressive external ophthalmoplegia and ptosis), many patients present with non-specific features (such as isolated deafness, cardiomyopathy,

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or diabetes mellitus) [Leonard and Schapira, 2000]. The accurate diagnosis of mitochondrial disease may also be difficult. It is often necessary to carry out a muscle biopsy or fibroblast cultures for highly specialized and labor intensive biochemical and histochemical techniques. It may be necessary to carry out genetic testing on muscle DNA because it is not always possible to identify the underlying mitochondrial genetic defect in blood [Chinnery et al., 1999a]. These problems compound the ethical issues surrounding pre-symptomatic genetic testing in adults and children—particularly when it is not clear what the genetic diagnosis actually means for an individual [Thorburn and Dahl, 2001]. Until recently, it has generally been accepted that mitochondrial disorders are exceedingly rare and, by and large, the investigation of patients with mitochondrial disease has been based in research laboratories. This has led to complex and patchy referral patterns that do not lend themselves to epidemiological investigations. It is because of these

difficulties that most epidemiological studies were designed to determine the frequency of a particular mtDNA mutation in patients with a specific disease phenotype (Table I), but recently there have been a number of studies designed to determine the true prevalence of mitochondrial disorders at a population level (Table II).

The Frequency of Mitochondrial Disease in Patients With a Specific Disease Phenotype

Leber hereditary optic neuropathy (LHON) is the most common mtDNA disorder [Chinnery et al., 2000b] that characteristically presents with subacute bilateral visual failure in young adult males. In the pre-molecular era, LHON was estimated to affect 1 in 50,000 of the general population, based upon large family studies with a characteristic phenotype and a maternal inheritance pattern. It is now well recognized that the vast majority of cases of LHON are due to one of three point mutations of mtDNA affecting complex I, or ND,

genes (G11778A in ND4, G3460A in ND1, T14484C in ND6) [Howell, 1997]. In the Australian population, 2% of individuals who have invalid blind pensions harbor one of these mtDNA mutations [Mackey and Buttery, 1992].

The second most common mtDNA defect is the A3243G point mutation in the leucine (UUR) tRNA gene [Chinnery et al., 2000b]. There has been great interest in the role of mtDNA mutations as a cause of diabetes mellitus. Different values for the frequency of the A3243G point mutation in patients with diabetes mellitus range from 0.5–60%, depending upon the subgroup of diabetics under study and ethnic background (Table I). In the general diabetic population, the A3243G mutation is found in approximately 1% of Caucasian and Japanese populations. A maternal relative with diabetes increases the likelihood that the disorder is due to a mtDNA defect, with values ranging between 1.6% [Majamaa et al., 1998] and 5.5% [Kadowaki et al., 1994], and deafness and diabetes increase the

TABLE I. The Frequency of Mitochondrial Disease in Patients With a Specific Disease Phenotype*

Phenotype	Mutation	Study population		Mutation frequency (%)	
LHON	G11778A, T14484C, G3460A	Invalid blind pensioners	Australia	2	Mackey and Buttery [1992]
Diabetes mellitus	A3243G	Hospital based	Northern England	0.13	Newkirk et al. [1997]
	A3243G	Unselected community-based	Northern Finland	0.5	Majamaa et al. [1998]
	A3243G	Hospital outpatients, all DM	Japan	0.9	Otabe et al. [1994]
	A3243G	Hospital outpatients, NITDM	Japan	1	Odawara et al. [1995]
	A3243G	Maternal family history of diabetes	Northern Finland	1.6	Majamaa et al. [1998]
	A3243G	Diabetes in pregnancy	Japan	5.9	Yanagisawa et al. [1995]
Cerebral infarction	“Mitochondrial disease”	Young stroke (< 30yrs old)	Switzerland	2	Bogousslavsky and Regli [1987]
	A3243G	Occipital infarction in the young (< 45yrs old)	Northern Finland	10	Majamma et al. [1997]
Hypertrophic cardiomyopathy	A3243G	Occipital stroke (all adults)	Northern	6.9	Majamaa et al. [1998]
	A3243G	All adults	Northern Finland	14	Majamaa et al. [1998]
Deafness	A3243G	Unselected adults with hearing aid	Northern Finland	0.07	Majamaa et al. [1998]
	A3243G	Sensorineural deafness and a maternal history	Northern Finland	7	Majamaa et al. [1998]

*NITDM, non-insulin treated diabetes mellitus; DM, diabetes mellitus; LHON, Leber hereditary optic neuropathy.

TABLE II. Population-Based Studies of Mitochondrial Disease*

Study population	Mutation or disease	Disease prevalency/ 100,000 (95% C.I.)	Mutation prevalence/100,000 (95% C.I.)
Northern England	All mtDNA deletions	1.33 ^a (0.76–1.89)	1.33 ^b (0.76–1.89)
Point prevalence August 1997	All mtDNA point mutations	5.24 ^a (4.12–6.37)	7.59 ^b (6.23–8.94)
Male <65yrs	G11778A & G3460A (LHON)	3.29 ^a (2.39–4.18)	6.41 ^b (5.16–7.66)
Female <60yrs	A3243G	0.95 ^a (0.47–1.43)	0.71 ^b (0.29–1.12)
Population size = 2,122,290	A8344G	0.25 ^a (0.01–0.5)	0.09 ^b (0–0.25)
Chinnery et al. [2000b]	All mtDNA mutations	6.57 ^a (5.30–7.83)	12.48 ^b (10.75–14.23)
Northern Finland	A3243G	5.71 (4.53–6.89)	16.3 (11.3–21.4)
Adult point prevalence			
Population size = 245,201			
Majamaa et al. [1998]			
Victoria, Australia	Childhood respiratory chain disease	4.7 ^c (3.2–5.0)	—
Birth incidence from 1,710,000			
Births between 1987–1996			
Skladal et al. [2000]			

^aThe prevalence of mtDNA disease is based upon affected adults (> 16–<65 yrs for males, > 16–< 60 yrs for females) [Chinnery et al., 2000b].

^bThe prevalence of mtDNA mutations is based upon all individuals below retirement age (< 65 yrs for males, < 60 yrs for females) [Chinnery et al., 2000b].

^cBirth prevalence measured between 1987 and 1996.

*CI, confidence interval; LHON; Leber hereditary optic neuropathy.

frequency of the A3243G mutation still further [Kadowaki et al., 1994]. Overall, the prevalence of diabetes in Western Europe is between 3% and 6% of the general population, and based upon data similar to that shown in Table I, the prevalence of mitochondrial diabetes due to the A3243G mutation is estimated at 0.06%, or 60/100,000 of the general population [Gerbitz et al., 1995].

Population-Based Studies of Mitochondrial Disease

Majamaa and colleagues took advantage of the rigorous healthcare registering system in Finland to determine the prevalence of the A3243G point mutation [Majamaa et al., 1998]. By studying 245,201 adults in the province of Northern Ostrobothnia they identified individuals with clinical features and family history suggestive of mitochondrial disease, and determined the frequency of

the A3243G mutation. Of the 615 patients identified, 480 were screened for the A3243G mutation in blood using a radioactive PCR-RFLP technique. MtDNA haplogroup analysis confirmed the presence of 11 independent maternal pedigrees transmitting the A3243G mutation, giving an overall point prevalence of 16.3/100,000 of the adult population (95% C.I. 11.3–21.4/100,000). Subgroup analysis revealed a high prevalence of the A3243G mutation in certain subgroups of the Finnish population (Table I). Deafness is a common feature of mitochondrial disease [Chinnery et al., 2000a], and 7.4% of adults in Northern Ostrobothnia with deafness and a family history of deafness harbored the A3243G mutation. Patients with the A3243G mutation often present with recurrent occipital infarction [Hirano et al., 1992] and, in Northern Finland, 6.9% of individuals with occipital stroke tested positive for A3243G [Majamma et al., 1997]. Even

more remarkably, 14% of adults with hypertrophic cardiomyopathy tested positive for the mutation.

We recently determined the point prevalence for adult mtDNA disease for the mid-year period of 1997 in the Northeast of England [Chinnery et al., 2000b]. Patients were ascertained through the hospital referral system over a ten-year period. Each individual underwent a series of investigations including clinical studies, a muscle biopsy, muscle histochemistry, mitochondrial respiratory chain studies, and mtDNA analysis on muscle DNA. We identified 104 cases (> 16 yrs of age to <65 years of age for males, and to <60 years of age for females) with mtDNA disease in an adult population of 1,582,584. After exploring the family history in each affected individual, we identified 161 maternal relatives at risk of inheriting the mtDNA defect, giving an estimated minimum prevalence of mtDNA defects of 12.48/100,000 for

the population below retirement age. This approach allowed the relative frequency of each mutation to be determined (Table II). Overall, it appears that mtDNA disease is at least as common as many other neurological disorders, including sporadic diseases such as amyotrophic lateral sclerosis [Traynor et al., 1999], inherited disorders such as Huntington's disease [Morrison et al., 1995], and common forms of muscular dystrophy [Emery, 1991].

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How can we explain the discrepancy between the various studies of prevalence? Differences in the genetic background and population structure may influence the prevalence of specific mutations. For example, the T14484C mutation is a rare cause of LHON in the UK and Finland [Mackey et al., 1996], but common in Canada [Macmillan et al., 1998]. This may reflect a founder effect [Macmillan et al., 2000], or possibly regional variations in mtDNA haplogroup frequency, which may influence the penetrance or expression of mtDNA mutations [Howell, 1999]. The A3243G mutation appears to be very common in Finland [Majamaa et al., 1997], but rare in the Black American population [S. DiMauro, personal communication]. We also cannot ignore the effects of study design. In our study, index cases were passively ascertained through the National Health Service, and it is possible that many cases and families remain undetected in the community because of misdiagnosis. Finally, over the last few years we have seen an increasing number of novel phenotypes associated with mtDNA disease. As the spectrum of mtDNA disease continues to expand, further cases will be identified and we will need to revise the epidemiological data accordingly.

Recent evidence from the Finnish population confirms the generally accepted view that mtDNA defects are a rare cause of respiratory chain disorders in children [Uusimaa et al., 2000]. Over

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a seven-year period, Uusimaa and colleagues identified defects of oxidative phosphorylation in 26 children from a pediatric population of 146,482. Despite the high prevalence of the A3243G mutation within the study region [Majamaa et al., 1998], only one child presented with a mtDNA defect (A3243G). Based upon their published data [Uusimaa et al., 2000] it is not possible to calculate an accurate value for the prevalence and incidence of childhood respiratory chain defects, but the data suggest that the prevalence of respiratory chain disease in children is in the same order of magnitude as mtDNA disease in the adult population. Similar data from Victoria, Australia supports this conclusion [Skladal et al., 2000]. Between 1987 and 1996, the minimum birth prevalence of childhood respiratory chain disease was 4.7/100,000 births (95% C.I. = 3.2–5.0) from a largely Caucasian study group. It is possible to combine these data with the adult prevalence figures shown in Table II to calculate an approximate prevalence for all mitochondrial disease, because the point prevalence in adults of all ages corresponds to the birth incidence of individuals who will go on to develop mtDNA disease in later life. Thus, based upon the available evidence, a conservative estimate of the total number of individuals with mitochondrial disease is 11.5/100,000, or 1 in 8500 of the general population. This figure corresponds to the point prevalence at any one time, or the birth incidence of individuals who will subsequently develop mitochondrial disease.

THE MANAGEMENT OF MITOCHONDRIAL DISEASE

Current Management

The management of patients with mitochondrial disease has advanced considerably over the last decade. The importance of making an accurate diagnosis at the biochemical and genetic level cannot be underestimated. A definitive diagnosis forms the basis for future prognostic and genetic counseling [Thorburn and Dahl, 2001], allowing a change in emphasis to supportive care, and removing the need for further unnecessary and invasive clinical tests.

A definitive diagnosis forms the basis for future prognostic and genetic counseling.

Large cohorts of patients with specific mitochondrial disorders have been studied over the last ten years. A thorough knowledge of the likely complications of various mitochondrial disorders helps the clinician to manage patients carefully. For example, patients with the A3243G mutation often develop an asymptomatic cardiomyopathy that responds well to conventional treatments; and aminoglycoside antibiotics must be avoided in patients with mtDNA mutations, particularly the A1555G rRNA mutation, because of the risk of aminoglycoside-induced ototoxicity [Estivill et al., 1998]. Cardiac pacing may prevent sudden death in patients with the Kearns-Sayre syndrome, and the early diagnosis of mitochondrial diabetes may reduce the risk of microvascular complications.

Various pharmacological agents have been used to treat mitochondrial myopathies (Table III). Although subjective and objective improvements have been reported in isolated cases, a lack of response has also been reported for each agent (Table III), and there is a lack of hard evidence supporting their use. In the only double-blind trial, no significant effect was seen with the quinine

TABLE III. Current Drug Treatments Used in Patients With Mitochondrial Disease*

Class	Agent (route of delivery)	Indication	Proposed mechanism	Dose	Effects
Quinone derivatives	Ubiquinone (coenzyme Q ₁₀) (oral)	Isolated ubiquinone deficiency	Redox bypass corrects the deficiency	60–250 mg/day	Significant clinical improvement [Ogasahara et al., 1989; Rotig et al., 2000; Sobreira et al., 1997]
		All mitochondrial disorders	Redox bypass; free radical scavenger	30–260 mg/day	Subjective improvement, particularly reduced fatigue and reduced muscle cramps. Isolated reports of clinical and metabolic improvement [Abe et al., 1991; Bendehan et al., 1992; Gold et al., 1996; Ihara et al., 1989; Nishikawa et al., 1989; Ogasahara et al., 1986; Papadimitiou et al., 1996]; no objective improvement in a multi-center double-blind trial [Bresolin et al., 1990]
	Idebenone (oral)	All mitochondrial disorders, especially LHON	Free radical scavenger, redox bypass of complex I	90–270 mg/day	Improved brain and skeletal muscle metabolism in isolated cases [Ihara et al., 1989; Cortelli et al., 1997]; may enhance the rate and degree of visual recovery in LHON [Mashima et al., 1992; Mashima et al., 2000]
Vitamin supplements	Thiamin (B ₁) (oral)	KSS and other mitochondrial disorders	Co-enzyme for PDHC	Up to 900 mg/day	Isolated reports of improvement [Lou, 1981]; no significant effect in a larger study [Matthews et al., 1993]
	Riboflavin (B ₂) (oral)	Complex I and complex II deficiency	Acts as flavin precursor for complex I and II	100 mg/day	Clinical and biochemical improvements in small groups of patients [Bernsen et al., 1993; Penn et al., 1992]; a large study of 16 different patients failed to show a benefit [Matthews et al., 1993]
	Ascorbate (C) and Menadione (K ₃) (oral)	Complex III deficiency; other mitochondrial disorders	Antioxidant; by-pass of complex III (with Vit. C)	10 mg qds	Symptomatic and bioenergetic improvements in isolated cases [Eleff et al., 1984; Mowat et al., 1999]; no objective improvement in a multi-center double-blind trial [Bresolin et al., 1990]
Metabolic supplements	Succinate (oral)	Complex I deficiency KSS and MELAS	Donates electrons directly to complex II	6 g/day	Improvements reported in isolated cases [Shoffner et al., 1989]
	Creatine	Mitochondrial myopathy	Enhances muscle phosphocreatine	Up to 10 g/day	Reduced fatigue and enhanced muscle strength and aerobic exercise capacity [Tarnopolsky and Martin, 1999; Tarnopolsky et al., 1997]
Dichloracetate	Carnitine	Secondary carnitine deficiency Mitochondrial disorders especially with lactic acidosis	Replacement Reduces lactic acidosis by enhancing PDHC activity	Up to 3 g/day 25 mg/kg/day	Improvements in isolated cases [Hsu et al., 1995] Short-term improvements in muscle and brain oxidative metabolism [DeStefano et al., 1995]; potential complications include a painful peripheral neuropathy [Kurlemann et al., 1995]
Corticosteroids		No clear indication	Unclear, if any	Up to 100 mg/day Prednisone	Improvements have been reported in isolated cases [Gubbay et al., 1989]; but steroids may exacerbate the metabolic encephalopathy [Curless et al., 1986]

*KSS, Kearns-Sayre syndrome; LHON, Leber hereditary optic neuropathy; MELAS, mitochondrial encephalomyopathy with stroke-like episodes; PDHC, pyruvate dehydrogenase complex; qds, four times a day.

derivative ubiquinone (ubiquinone, co-enzyme Q₁₀ [Bresolin et al., 1990]). Many physicians routinely give patients ubiquinone to patients with mitochondrial disorders, and riboflavin to patients with complex I deficiency. Although there is no hard evidence of a convincing clinical benefit (Table III), there are good theoretical reasons why these agents might be useful, and they rarely cause significant side effects.

Strategies Under Development

A deeper understanding of the pathological mechanisms involved in mitochondrial disease will be crucial for the development of new treatments. For example, there is increasing evidence to support the role of reactive oxygen species in the events preceding cell death [Raha and Robinson, 2001], and antioxidants appear to delay clinical progression in various mouse models of mitochondrial disease [Wallace, 1999]. Similarly, given the pivotal role of the mitochondrion in apoptosis [Raha and Robinson, 2001], drugs which inhibit the opening of the mitochondrial permeability transition pore (such as cyclosporin A analogues) may also prove useful. These and other agents must be critically evaluated on animal models of mitochondrial disease before we embark upon clinical trials.

Over the last decade, there has been little progress in the development of novel treatments for nuclear-encoded disorders of the respiratory chain, but a number of strategies are currently being explored for the treatment of mtDNA disorders. One approach has been to express the defective mtDNA protein-encoding gene within the nucleus, and deliver the transcribed gene from the cytosol into the mitochondrial compartment. This approach was successful in yeast [Nagley et al., 1988], but attempts to replicate the experiment in mammalian cells have been fraught with difficulty [Sutherland et al., 1994]. An alternative strategy is to deliver wild-type genes into the mitochondria themselves. While it has been possible to deliver a self-replicating plasmid into isolated mitochondria [Seibel et al.,

1995], delivery of this agent into cells is likely to be difficult, and it is unclear how the expression of the plasmid will be regulated. Recent evidence suggests that tRNA genes may be imported from the cytosol into mitochondria in yeast [Kolesnikova et al., 2000], providing hope that the same mechanism may be harnessed for mitochondrial tRNA gene mutation disorders.

Patients with mtDNA disease often harbor a mixture of mutant and wild-type mtDNA (heteroplasmy). In general, a cell must contain a high percentage level of mutant mtDNA before it develops a respiratory chain defect [Schon et al., 1997]. We have explored the possibility of altering the level of heteroplasmy by selectively inhibiting the replication of mutant mtDNA using sequence-specific peptide nucleic acids (PNAs). Unlike nuclear DNA, mtDNA is continuously turning over, even in post-mitotic tissue such as muscle and neurons [Birky, 1994]. If it is possible to selectively inhibit the replication of mutant mtDNA within a heteroplasmic organelle, then, in theory, the wild-type molecule will eventually re-populate the cell. This approach may reduce the level of mutant mtDNA below the critical threshold and thereby correct the biochemical defect. PNAs inhibit the replication of mtDNA templates *in vitro* without affecting wild-type replication [Taylor et al., 1997; Taylor et al., 2000]. PNAs are readily taken up by cultured human cells, and can be targeted into the mitochondrial compartment by the addition of a nuclear-encoded mitochondrial targeting presequence [Chinnery et al., 1999b]. It remains to be seen whether this approach will alter the level of heteroplasmy in cell lines containing mtDNA point mutations and deletions. There may be alternative methods of manipulating the level of mutant mtDNA. Oligomycin inhibits mitochondrial

ATP synthesis, and leads to an increase in the amount of wild-type mtDNA in cell lines harboring the T8993G mtDNA point mutation [Manfredi et al., 1999].

Satellite cells are dormant muscle precursor cells. In at least some patients with mtDNA disease, satellite cells contain little or no mutant mtDNA [Fu et al., 1996; Weber et al., 1997]. Satellite cells proliferate in response to acute muscle damage, and fuse with mature skeletal muscle fibers. In patients with heteroplasmic mtDNA defects, bupivacaine and concentric exercise (shortening contractions) induce satellite cell proliferation and the subsequent "shifting" of normal mitochondrial genomes into disease muscle fibers, correcting the biochemical defect [Clark et al., 1997; Taivassalo et al., 1999]. It has yet to be established whether this strategy will lead to significant clinical improvements.

CONCLUSIONS

Mitochondrial disorders affect at least 1 in 8500 individuals. These disorders cause chronic morbidity and are often fatal. The current management of patients with mitochondrial disease is largely supportive. Accurate diagnosis is invaluable for the clinician and the patient, allowing prognostic and genetic counseling, and alerting the physician to potential complications in the future. At present we have no way of modifying the disease process for most patients with mitochondrial disease, but novel strategies are under development which provide some hope for the future.

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