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24.19.5 Mitochondrial disease 6343 is failure of substrate utilization or supply when energy demands increase during exercise or starvation. In other disorders, there is disruption of the plasma membrane. Apparently idiopathic cases are probably due to an unidentified metabolic defect or infection. FURTHER READING Anderson L, et al. (2014). Effectiveness of enzyme replacement therapy in adults with late-onset Pompe disease: results from the NCS-LSD cohort study. Journal of Inherited Metabolic Disease, 37, 945–52. Brini M (2004). Ryanodine receptor defects in muscle genetic diseases. Biochem Biophys Res Commun, 322, 1245–55. Christopher-Stine L (2006). Statin-myopathy: an update. Curr Opin Rheumatol, 18, 647–53. Engel AG, Franzini-Armstrong C, eds (2004). Myology, 3rd edition. McGraw-Hill, New York, NY. Hanna M (2006). Genetic neurological channelopathies. Nature Clin Pract Neurol, 2, 252–63. Karpati G, Hilton-Jones D, Griggs R (eds) (2001). Disorders of volun- tary muscle, 7th edition. Cambridge University Press, Cambridge. Mastaglia F (2006). Drug induced myopathies. Pract Neurol, 6, 4–13. Mastaglia F, Hilton-Jones D (2007). Handbook of neurology—myopathies. Elsevier, Amsterdam. Padala S, Thompson PD (2012). Statins as a possible cause of inflam- matory and necrotizing myopathies. Atherosclerosis, 222, 15–21. Wagenmakers AJM, Coakley JH, Edwards RHT (1988). The metabolic consequences of reduced habitual activities in patients with muscle pain and disease. Ergonomics, 31, 1519–27. World Health Organization (1980). International classification of impairments, disabilities, and handicaps. WHO, Geneva. http://apps. who.int/iris/bitstream/10665/41003/1/9241541261_eng.pdf World Health Organization (2000). International classification of functioning and disability ICIDH-2. WHO, Geneva. http://www3. who.int/icf/icftemplate 24.19.5 Mitochondrial disease Patrick F. Chinnery and D.M. Turnbull ESSENTIALS Mitochondrial encephalomyopathies are caused by primary de- fects of the respiratory chain that lead to disturbed generation of adenosine triphosphate by aerobic metabolism. This characteristic- ally impairs the function of high-demand tissues such as the brain, eye, cardiac, and

skeletal muscle, as well as endocrine organs. The numerous proteins involved are encoded by genes in mitochon- drial or nuclear DNA. Mutations in these genes can lead to clinical disorders. Clinical features The clinical presentation of mitochondrial disease is highly vari- able: the same clinical syndrome can be caused by different gen- etic defects, and the same genetic defect may present in a variety of different ways. Several characteristic syndromes are described, including those produced by the following: Large-scale single deletions of mitochondrial genome—typically cause progressive ophthalmoplegia and ptosis, and limb muscles may be affected; can also cause an extended phenotype of cere- bellar ataxia, pigmentary retinopathy, sensorineural deafness, dia- betes mellitus, and heart block (Kearns–Sayre syndrome). These are typically not inherited. Point mutations in the mitochondrial genome are a major cause of inherited visual loss, particularly in young adult males (Leber's her- editary optic neuropathy). Other syndromes include mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes and Leigh's syndrome of subacute necrotizing encephalomyopathy, with characteristic lesions in basal ganglia, cerebellum, and brain- stem. These may be maternally inherited. Autosomal recessive nuclear genetic mutations cause a range of overlapping phenotypes from severe infantile encephalomyopathy through to ophthalmoplegia, ataxia, and encephalopathy presenting in middle age. Autosomal dominant ophthalmoplegia is also seen. Many patients do not fit precisely into one of these defined clin- ical syndromes and often have systemic involvement, which may be more prominent than the neurological features. Investigation and treatment Investigation—aside from general investigations to characterize the pattern and nature of organ involvement, the diagnostic strategy depends on the clinical context: (1) Defined clinical syndrome—in some patients it is possible to identify a specific clinical syndrome with a clear maternal family history suggestive of a mitochondrially inherited disorder. Under these circumstances it is appropriate (after counselling) to proceed directly to molecular genetic testing. (2) Cases not fitting a defined clinical syndrome —the key investiga- tion is a biopsy of affected tissue (usually muscle) for biochemical studies of oxidative phosphorylation, leading on to molecular ana- lysis of mitochondrial and nuclear DNA before whole exome and whole genome sequencing. However, in consanguineous popula- tions whole-exome sequencing before biopsy should be considered, especially in children. Treatment—there is no definitive treatment for most patients with mitochondrial disease. Some very rare enzyme defects have specific treatments (e.g. Q10 biosynthesis disorders). Management is aimed at minimizing disability, preventing complications, and genetic coun- selling. Multidisciplinary expertise is needed to provide adequate nu- trition and physiotherapy, and to address endocrinological, cardiac and ophthalmic complications. Introduction Mitochondria are ubiquitous intracellular organelles that are involved in many different metabolic pathways. Disorders of intermediary metabolism (such as fatty acid β-oxidation or tri- carboxylic acid cycle defects) involve mitochondrial enzymes, but the term 'mitochondrial disease' usually means a disease which is due to an abnormality of the final common pathway of energy metabolism—the mitochondrial respiratory chain, which is linked to the production of adenosine triphosphate (ATP) by oxidative

 phosphorylation. The respiratory chain is essential for aerobic metabolism, and respiratory chain defects characteristically af- fect tissues and organs that are heavily dependent upon oxidative metabolism (such as the central nervous system, the eye, skeletal muscle, myocardium, and endocrine organs). Although mitochondrial dysfunction has been demonstrated in many sporadic and inherited disorders, these are not primarily disorders of the mitochondrial respiratory chain and are not con- sidered further here. Biochemistry and genetics of the respiratory chain The intermediary metabolism of carbohydrates, amino acids, and fatty

acids generates the reduced cofactors NADH, NADPH, and FADH2. These cofactors transfer electrons to the mitochondrial re- spiratory chain. As the electrons are passed through complexes I to IV of the respiratory chain along the inner mitochondrial mem- brane, protons are pumped out of the mitochondrial matrix into the intermembrane space. This creates an electrochemical gradient that is harnessed by complex V (ATP synthase) to generate ATP from adenosine diphosphate (ADP). Each respiratory chain complex con- tains many polypeptide subunits, some of which are coded by genes within the nucleus and some of which are encoded by the mitochon- drial genome (mtDNA). The mitochondrial genome encodes seven complex I sub- units (NADH-ubiquinone oxidoreductase), one of the complex III subunits (ubiquinol-cytochrome c oxidoreductase), three of the complex IV (cytochrome c oxidase) subunits, and the ATPase 6 and ATPase 8 subunits of complex V. Interspaced between the protein-encoding genes are two ribosomal RNA genes (12S and 16S rRNA), and 22 transfer RNA genes that provide the necessary RNA components for the mitochondrial translation machinery. The re- maining polypeptides, including all of the complex II subunits, are synthesized from nuclear gene transcripts within the cytosol. These are subsequently imported into the mitochondria through the inner and outer membrane translocation complexes. There are many additional proteins that are essential for the normal as- sembly and function of the mitochondrial respiratory chain. There are currently estimated to be more than 1000 nuclear encoded mitochondrial proteins. As a result, mitochondrial respiratory chain disorders can be due to mutations affecting both nuclear and mitochondrial genes. The classification and investigation of mitochondrial respiratory chain disorders has been revolutionized by the recent advances in our understanding of the underlying genetic defects affecting both mtDNA and nuclear DNA (Table 24.19.5.1). Basic mitochondrial genetics There are two main differences between nuclear DNA and mtDNA that are important for the expression and transmission of mitochon- drial genetic disease, as follows. Heteroplasmy and the threshold effect Each mammalian cell contains over 1000 copies of the small (16.5 kb) mitochondrial genome. Individuals with mtDNA disease often harbour a mixture of mutated and wild-type (normal) mtDNA—a situation known as heteroplasmy. Single cells only express a respira- tory chain defect when the proportion of mutated mtDNA exceeds a critical threshold with low levels of wild-type mtDNA. Different organs, and even adjacent cells within the same organ, may con- tain different amounts of mutated mtDNA. This variability, coupled with tissue-specific differences in the threshold and the varied de- pendence of different organs on oxidative metabolism, explains in part why certain tissues are preferentially affected in patients with mtDNA disease. In general, postmitotic (nondividing) tissues such as neurons, skeletal and cardiac muscle, and endocrine organs har- bour much higher levels of mutated mtDNA and are often clinic- ally involved. In contrast, rapidly dividing tissues such as the bone marrow are only rarely clinically affected (one example is Pearson’s syndrome—see next). Maternal inheritance and the transmission of heteroplasmy After fertilization of the oocyte, sperm mtDNA is actively degraded. Consequently, mtDNA is transmitted exclusively down the maternal line. This means that affected males with mtDNA disease cannot transmit the genetic defect. Deleted molecules are rarely transmitted from clinically affected females to their offspring (risk c.1 in 24). By contrast, a female harbouring a heteroplasmic mtDNA point mu- tation, or mtDNA duplications, may transmit a variable amount of mutated mtDNA to her children. Early during development of the female germ line, the number of mtDNA molecules within each oo- cyte is drastically reduced before being subsequently amplified to reach a final number of more than 100 000 in each mature oocyte. This restriction and amplification (also called the mitochondrial ‘genetic bottleneck’) contributes to the variability between indi- vidual oocytes, and the different levels of mutant mtDNA seen in the

offspring of a single heteroplasmic female. Clinical presentation of respiratory chain disorders Mitochondrial disease is highly variable both clinically and at the genetic level. The same clinical syndrome can be caused by dif- ferent genetic defects (which may be within nuclear or mitochon- drial genes), but the same genetic defect may present in a variety of different ways. It is often possible to identify well-defined clinical syndromes (Table 24.19.5.1), but many patients present with a col- lection of clinical features that are highly suggestive of respiratory chain disease but do not fit into a discrete clinical category. Defined clinical syndromes (See Table 24.19.5.1.) Large-scale deletions can cause chronic progressive external oph- thalmoplegia and bilateral ptosis (PEO). Some of these patients have limited limb muscle involvement. In contrast, similar deletions may also cause chronic progressive external ophthalmoplegia with bilateral sensorineural deafness, cerebellar ataxia, pigmentary ret- inopathy, diabetes mellitus, and cardiac conduction defects leading to complete heart block. When this begins in teenage years and is associated with a raised cerebrospinal fluid protein, it is called the Kearns–Sayre syndrome (KSS), which is a progressive neurological

24.19.5 Mitochondrial disease 6345 Table 24.19.5.1 Mitochondrial disease clinical syndromes due to mutations of mtDNA and nuclear DNA Clinical syndrome Clinical symptoms/signs Age of onset Inheritance Genes Alpers–Huttenlocher syndrome Seizures, developmental delay, hypotonia, hepatic failure Infancy/childhood AR POLG Ataxia neuropathy syndromes (ANS): Including MIRAS, SCAE, SANDO) SANDO: PEO, dysarthria, sensory neuropathy, cerebellar ataxia. Other ANS: Sensory axonal neuropathy with variable degrees of sensory and cerebellar ataxia. Epilepsy, dysarthria, or myopathy are present in some Teenage or adult AR POLG, C10orf2, OPA1, SPG7 Autosomal dominant optic atrophy (DOA) Slowly progressive visual failure. 20% have deafness, PEO, ptosis, neuropathy, myopathy Childhood AD OPA1 Deafness sensorineural hearing loss Sensorineural hearing loss Childhood M mtDNA point mutations (eg. m.1095T>C, m.1555A>G, m.7445A>G) Kearns–Sayre syndrome (KSS) PEO, ptosis, pigmentary retinopathy, cardiac conduction abnormality, ataxia, CSF elevated protein, diabetes mellitus, sensorineural hearing loss, myopathy <20 years S mtDNA single deletions Leber hereditary optic neuropathy (LHON) Subacutre sequential monocular visual loss. males:females 4:1 Adulthood M mtDNA point mutations (m.11778G>A, m.3460G>A, or m.14484T>C in 90%) Leigh syndrome Encephalopathy precipitated by illness, brainstem, and cerebellar dysfunction, neuropathy, cardiomyopathy Infancy AR, M, XLR mtDNA point mutations (usually MTATP6) Mutations in nDNA-encoded respiratory chain components and assembly factors. PDH deficiency Maternally inherited diabetes and deafness (MIDD) Noninsulin-treated diabetes Sensorineural hearing loss Adulthood M mtDNA point mutations (m.3243A>G is the most common) Mohr-Tranebjaerg Syndrome Deafness, dystonia Adulthood XLR TIMM8A Mitochondrial DNA depletion syndrome Diffuse myopathy, encephalomyopathy, or hepatocerebral syndrome Congenital or infantile presentation, with hypotonia, respiratory weakness, and death within few years of life AR DGUOK, TK2, C10orf2, POLG, RRM2B, SUCLA2, SUCLG1, MPV17 Mitochondrial cardiomyopathy Cardiomyopathy (hypertrophic or dilated). May be neutropenia (Barth Syndrome) Infancy, childhood, or adulthood M, AR, XLR mtDNA point mutations COX15, SLC25A3, TAZ Mitochondrial myopathy (isolated) Axial/proximal myopathy. May have other features of mitochondrial disease (ataxia, polyneuropathy) Any age of onset S, M mtDNA point mutations mtDNA single large-scale deletions Myoclonus, epilepsy, and ragged-red fibres (MERRF) Stimulus sensitive myoclonus, generalized seizures, ataxia, cardiomyopathy. A minority of patients have PEO Childhood M mtDNA point mutations (m.8344A>G most common) POLG Myopathy, encephalopathy, lactic acidosis, stroke-like episodes (MELAS) Stroke-like episodes with

encephalopathy, migraine, seizures. Variable presence of myopathy, cardiomyopathy, deafness, diabetes, ataxia. A minority of patients have PEO Typically <40 years of age but childhood more common M mtDNA point mutations
(m.3243A>G in 80%) Myopathy, neurogastrointestinal encephalopathy (MNGIE) PEO, ptosis, gut dysmotility, proximal myopathy, axonal polyneuropathy, leukodystrophy Childhood to early adulthood AR TYMP Neurogenic weakness with ataxia and retinitis pigmentosa (NARP) Ataxia, pigmentary retinopathy, weakness Childhood M MTATP6 (usually at m.8993T>G/C) Pearson syndrome Sideroblastic anaemia, pancreatic failure Infancy S, M Single large-scale mtDNA deletions Progressive external ophthalmoplegia (PEO) Ptosis, ophthalmoparesis. Proximal myopathy and dysphagia Any age of onset. Typically more severe phenotype with younger onset S, M, AR, AD mtDNA deletions mtDNA point mutations POLG, POLG2, SLC25A4, C10orf2, RRM2B, TK2, OPA1, SPG7 Sengers syndrome Cataract, cardiomyopathy, myopathy, lactic acidosis AR AGK AGK
Inheritance pattern: AD, autosomal dominant; AR, autosomal recessive; M, maternal/mitochondrial; S, sporadic; XLR, X-linked recessive. Other abbreviations: MIRAS, mitochondrial recessive ataxia syndrome; PEO, progressive external ophthalmoplegia; PDH, pyrivate dehydrogenase; SANDO, sensory ataxia neuropathy dysphagia and ophthalmoplega; SCAE, spinocerebellar ataxia with epilepsy.

section 24 Neurological disorders 6346 disorder associated with severe disability. Hypoparathyroidism and hypothyroidism are well-recognized features of KSS. These two syn- dromes (PEO and KSS) are the extremes of a spectrum of disease and many individuals lie somewhere between the pure extraocular muscle and severe central neurological phenotypes. Pearson’s syndrome of exocrine pancreatic failure, sideroblastic anaemia, and marrow panhypoplasia is usually due to a mtDNA deletion. Pearson’s syndrome also presents in infancy and many individuals who have survived into later childhood subsequently developed the Kearns–Sayre phenotype. Although many patients with PEO and KSS are sporadic cases, PEO can also be inherited as either an autosomal dominant (adPEO) or recessive (arPEO) trait. These patients have multiple deletions of mtDNA in skeletal muscle, which arise due to a primary nuclear genetic defect. A high incidence of psychiatric disease, a parkin- sonian syndrome and primary gonadal failure have been docu- mented in some families with adPEO. Some arPEO cases have a profound peripheral neuropathy and ataxia (referred to as SANDO, sensory ataxic neuropathy with dysarthria and ophthalmoparesis), and some family members present with adult-onset ataxia without ophthalmoplegia (also called mitochondrial recessive ataxia syn- drome, MIRAS) which is common in Scandinavia. Mutations in the gene encoding the mitochondrial polymerase (polγ, encoded by the nuclear gene POLG) are a major cause of adPEO and arPEO. adPEO can also be caused by mutations in PEO1 (which codes for the mtDNA helicase Twinkle), SLC25A4 (which codes for the adenine nucleotide translocase ANT1), POLG2 (which codes for the acces- sory subunit of polγ), and RRM2B. AdPEO and optic atrophy are caused by mutations in OPA1, and arPEO with a spastic paraparesis and ataxia is caused by mutations in SPG7. Pathogenic point mutations of mtDNA are more common than rearrangements. This is partly because mtDNA deletions cause sporadic disease, whereas many mtDNA point mutations are trans- mitted down the maternal line. The m.3243A>G mutation in the leucine tRNA gene was first described in a patient with mitochon- drial encephalomyopathy with lactic acidosis and stroke-like epi- sodes. Different families harbouring the same genetic defect may have different phenotypes. For example, some families harbouring m.3243A>G have predominantly diabetes and deafness, some have chronic progressive external ophthalmoplegia, and some present with hypertrophic cardiomyopathy. It is currently not known

why this is the case, but it is likely that additional nuclear genetic factors play an important role in modifying the expression of the primary mtDNA defect. This single mutation is important since it has been estimated that between 0.5 and 1.5% of cases of diabetes mellitus in the general population are associated with the m.3243A>G mutation and accounts for about a third of all adult mitochondrial disease. Patients may present with myoclonic epilepsy, ataxia, optic at- rophy, and have ragged-red fibres in skeletal muscle (MERRF); this is usually due to a point mutation of mtDNA (e.g. m.8344A>G). mtDNA mutations are the major cause of visual loss in young adult males. About one-half of all males who harbour one of three point mutations of mtDNA (m.11778G>A, m.14484T>C, m.3460G>A) develop bilateral sequential visual loss in the second or third decade—a disorder known as Leber hereditary optic neur- opathy. Most individuals with these mutations are homoplasmic, harbouring only mutated mtDNA. It is not clear why the disease only affects approximately one-half of the males and only 10% of females who inherit the primary mtDNA defect. Clinical penetrance is in- creased by cigarette smoking and a high alcohol intake. Additional, as yet unknown, nuclear genetic factors may also be important in modulating the phenotype. Leigh's syndrome (subacute necrotizing encephalomyopathy) is a relapsing encephalopathy with prominent cerebellar and brain- stem signs that usually presents in childhood and is associated with characteristic neuroimaging abnormalities involving the basal ganglia. Leigh's syndrome can be due to an X-linked pyruvate de- hydrogenase deficiency or a defect of the mitochondrial respiratory chain. Complex I deficiency or cytochrome c oxidase deficiency are common findings in Leigh's syndrome. In these patients it may be possible to identify recessive mutations in nuclear complex I genes, or genes involved in the assembly of the respiratory chain complexes (e.g. SURF1). Point mutations at position m.8993 in the ATPase 6 gene of mtDNA may cause neurogenic weakness with ataxia and retinitis pigmentosa. These particular mutations are also associated with some forms of childhood Leigh's syndrome. Alpers–Huttenlocher syndrome is a severe autosomal recessive hepatoencephalopathy with intractable seizures and visual failure which presents in early childhood and is associated with depletion (loss) of mtDNA in affected tissues. Mutations in POLG are a major cause of Alpers–Huttenlocher syndrome. Sodium valproate precipi- tates fulminant liver failure in these patients and should not be used. Other causes of mtDNA depletion include mutations in MPV also cause liver disease, TK2 (encoding thymine kinase) which pre- sents with a progressive childhood myopathy or spinal muscular at- rophy, DGUOK (encoding dexyguanosine kinase) which presents in childhood with a myopathy and liver failure, and SUCLA2 (coding for ADP-forming succinyl-CoA synthase) which presents in early childhood with an encephalomyopathy. Cytochrome c oxidase deficiency may also present in childhood with an infantile myopathy and a severe lactic acidosis, which may also be associated with a cardiomyopathy and the Toni–Fanconi– Debre syndrome. Despite maximal supportive intervention, this is usually a fatal disorder and a severe depletion of mtDNA occurs in a proportion of these cases. It is important to recognize that isolated myopathy and lactic acidosis may be self-limiting, often with a sig- nificant improvement by 1 year of age and complete resolution by the age of 3 years. This is associated with the homoplasmic m.14674T>C mtDNA mutation. Other homoplasmic mtDNA mutations known to cause disease include m.1555A>G which causes nonsyndromic deafness that may be precipitated by aminoglycosides; and m.1624T>C which can cause Leigh's syndrome. Coenzyme Q10 deficiency can present in childhood with recurrent myoglobinuria, myopathy, and seizures. In some families it presents with an infantile encephalomyopathy with renal tubular defects. Finally, it may also present with ataxia and variable involvement of other regions of the central nervous system, peripheral nerve, and muscle. Mutations in genes coding for enzymes involved in the bio- synthesis of coenzyme Q10 have been found in some families (e.g.

COQ2, ADCK3). Nonspecific clinical presentations Many patients do not present with a characteristic phenotype. Children may present in the neonatal period with a metabolic encephalopathy and systemic lactic acidosis, often associated with

24.19.5 Mitochondrial disease 6347 hepatic and cardiac failure. This may be associated with depletion in the total amount of mtDNA within affected tissues (see earlier). This syndrome may be fatal. Childhood presentations may be even less specific, with neonatal hypotonia, feeding and respiratory difficulties, and failure to thrive. A respiratory chain defect should be considered in any patient who has a disease with multiple organ involvement, particularly if there are central neurological features (such as seiz- ures and dementia), a myopathy, cardiomyopathy, and endocrine abnormalities such as diabetes mellitus (Fig. 24.19.5.1). Bilateral sen- sorineural deafness and ocular features (retinopathy, optic atrophy, ptosis, and ophthalmoparesis) are common. Renal tubular defects, gastrointestinal hypomotility, cervical lipomatosis, and psychiatric features are also well described in patients with respiratory chain dis- ease. Patients with biochemical defects affecting multiple respiratory chain enzymes are common. These disorders can present from floppy infants with poor feeding at birth to myopathy and ophthalmoplegia in old age. Many are caused by mutations of mtDNA, but a vast array of autosomal recessive nuclear gene defects are also implicated, causing defective intramitochondrial protein synthesis. Investigation of respiratory chain disease The investigation of patients with a suspected mitochondrial encephalomyopathy involves the careful assimilation of clinical and laboratory data. In a significant proportion of cases (such as Leber’s hereditary optic neuropathy), it is possible to identify a specific clin- ical syndrome with a clear maternal family history. Under these cir- cumstances it is appropriate to carry out a molecular genetic test on a blood sample. In many situations, particularly in sporadic cases, this is not appropriate because the clinical features overlap with those of many other disorders. Even if the patient has a mitochondrial dis- order, numerous different genetic defects may be responsible, some of which will not be detectable by analysis of blood samples. Investigations fall into two main groups: clinical investigations used to characterize the pattern and nature of the different organs involved, and specific investigations to identify the biochemical or genetic abnormality. General clinical investigations It is essential to search for the more common features of respira- tory chain disease, especially those which are potentially treatable. This includes cardiac assessment (ECG, echocardiography, and MRI) and endocrine assessment (oral glucose tolerance test, HbA1c, thyroid function tests, alkaline phosphatase, fasting cal- cium, and parathyroid hormone levels). The organic and amino acids in urine may be abnormal even in the absence of overt tubular disease. Measuring blood and cerebrospinal fluid lactate levels is more helpful in the investigation of children than adults. These measurements must be interpreted with caution because there are many causes of blood and cerebrospinal fluid lactic acidosis, including fever, sepsis, dehydration, seizures, and stroke. The cere- brospinal fluid protein may be elevated. The serum creatine kinase level may be raised but is often normal. Neurophysiological studies may identify a myopathy or neuropathy. Electroencephalography may reveal diffuse slow-wave activity consistent with a subacute encephalopathy, or evidence of seizure activity. Cerebral imaging may be abnormal, showing lesions of the basal ganglia, high signal in the white matter on MRI or generalized cerebral atrophy. Specific investigations A skeletal muscle biopsy is invaluable in the investigation of respira- tory chain disease. Histochemical and biochemical investigations, in conjunction with the clinical assessment, often indicate where the underlying genetic abnormality must lie. Other clinically affected tissues may also be biopsied, and cultured skin fibroblasts may be investigated particularly in children. Histochemistry and

biochemistry Histochemical analysis may reveal subsarcolemmal accumulation of mitochondria (so-called ‘ragged-red’ fibres), or cytochrome c oxidase deficiency. A mosaic of cytochrome c oxidase-positive and Central nervous system Encephalopathy Stroke-like episodes Seizures and dementia Psychosis and depression Ataxia Migraine Cardiac Hypertrophic cardiomyopathy Dilated cardiomyopathy Heart block Pre-excitation syndrome Renal Renal tubular defects Toni-Fancomi Debre syndrome Gastrointestinal Dysphagia Pseudo-obstruction Constipation Hepatic failure Eye External ophthalmoplegia Ptosis Cateract Pigmentary retinopathy Optic atrophy Hearing Bilateral sensorineural deafness Endocrine and diabetes Diabetes mellitus Hypoparathyroidism Hypothyroidism Gonadal failure Peripheral nervous system Myopathy Axonal sensorimotor neuropathy CELL Nuclear subunits mtDNA subunits I II III IV V D-LOOP CYT b ND5 L (CUN) S (AGY) H ND4 ND4L ND3 COX III OL W ND2 M I ND1 16SrRNA 12SrRNA F T Q L (UUR) V P E ND6 OH Y C N A Nucleus The mitochondrial genome G R Mitochondrion ATPase8 ATPase6 S (UCN) COX II COX I D K Fig. 24.19.5.1 The clinical features and biochemical and molecular genetic basis of mitochondrial disease.

section 24 Neurological disorders 6348 cytochrome c oxidase-negative muscle fibres suggests an underlying primary mtDNA defect or a secondary defect of mtDNA as seen in patients with POLG mutations. Patients who have cytochrome c oxi- dase deficiency due to a nuclear genetic defect usually have a global deficiency of this enzyme affecting all muscle fibres. Electron micros- copy may identify paracrystalline inclusions in the intermembrane space, but these are nonspecific and may be seen in other non- mitochondrial disorders. Respiratory chain complex assays can be carried out on various tissues. Measurement of the individual re- spiratory chain complexes determines whether an individual has multiple complex defects that would suggest an underlying mtDNA defect, involving either a tRNA gene or a large deletion, or a nuclear genetic defect affecting protein translation within mitochondria. Isolated complex defects may be due to mutations in either mito- chondrial or nuclear genes. Co-enzyme Q10 can be measured dir- ectly in affected tissues. Molecular genetic investigations Under certain circumstances, the clinical and/or biochemical features may point towards a specific genetic defect detected by targeted molecular genetic analysis in a blood sample (e.g. Leber hereditary optic neuropathy, or POLG diseases), or urinary epi- thelium for some mtDNA defects (e.g. m.3243A>G). In other pa- tients, the first step is to exclude a defect of mtDNA, testing for mtDNA deletions, depletion or point mutations by sequencing in an affected tissue (see next). In patients where the clinical and biochemical features implicate a nuclear genetic diagnosis (e.g. paternal transmission, or multiple deletions of mtDNA), or the mtDNA is normal, then nuclear genetic analysis is carried out. If there is one obvious candidate gene known to be a common cause of the clinical and biochemical phenotype (e.g. SURF1 in isolated COX deficiency), then it is appropriate to sequence a specific gene. In other patients, a long list of genes may be implicated. These may form part of a panel tested using next generation sequencing (e.g. in patients with complex I deficiency). If an obvious panel of genes is not indicated, then exome or whole genome sequencing should be performed. For some mtDNA defects (particularly mtDNA deletions and depletion) the abnormality is not detectable in a DNA sample extracted from blood, and the analysis of DNA extracted from muscle is essential to establish the diagnosis. Urinary epithe- lium can also be used in some circumstances. Many patients with mitochondrial disease have a previously unrecognized mtDNA defect and it is necessary to sequence directly the mitochondrial genome. Interpretation of the sequence data can be extremely dif- ficult. mtDNA is highly polymorphic and any two normal indi- viduals may differ by up to 60 base pairs. In the strictest sense, a mutation can only be considered to be pathogenic if

it has arisen independently several times in the population, it is not seen in controls and it is associated with a potential disease mechanism. These stringent criteria depend upon a good knowledge of poly- morphic sites in the background population. If a novel base change is heteroplasmic, this suggests that it is of relatively recent onset. Family, tissue segregation and single cell studies may show that higher levels of the mutation are associated with mitochondrial dysfunction and disease, which strongly suggests that the muta- tion is causing the disease. Management There is currently no definitive treatment for patients with mito- chondrial disease, except for patients with deficiency of coenzyme Q10. Management is aimed at minimizing disability, preventing complications and genetic counselling. Supportive care and surveillance Many patients with mitochondrial disorders require follow-up over many decades. An integrated approach is essential involving the primary physician, other specialist physicians (ophthalmology, diabetes, and cardiology), specialist nurses, physiotherapists, and speech therapists. Vigilant clinical monitoring over many years can prevent the development of complications, such as those secondary to cardiac and endocrine involvement. Specific procedures may be indicated at various stages of disease. These include cardiac pacing, ptosis correction, cataract surgery, percutaneous gastrostomy, and even transplantation for organ limited disease. Genetic counselling The detailed investigation of patients with respiratory chain disease usually leads to a specific molecular genetic diagnosis. This has pro- found implications on the counselling given to patients and their families. Similar clinical phenotypes can have very different gen- etic causes. For example, PEO can be maternally inherited (due to m.3243A>G), autosomal dominant (due to OPA1) or autosomal re- cessive (e.g. due to POLG). If it is possible to identify the causative mutations in both the offspring and parents, then this will allow con- fident genetic counselling for the whole family. If, as in some cases, it is not possible to identify the underlying gene defect, or the genetic defect in the affected child cannot be traced back to the parents, then counselling is less straightforward. If a causative primary mtDNA defect is identified, then the impli- cations for counselling are distinctly different. Males cannot transmit pathogenic mtDNA defects. Patients who carry mtDNA deletions rarely have a family history suggestive of mtDNA disease, and there is low risk that they will transmit the mtDNA defect to any offspring. Women harbouring heteroplasmic pathogenic mtDNA point muta- tions may transmit the genetic defect to their offspring. The mito- chondrial genetic ‘bottleneck’ leads to a variation in the proportion of mutated mtDNA that is transmitted to any offspring (see earlier). It is therefore possible for a female to have mildly affected as well as severely affected children. The risk of having affected offspring varies from mutation to mutation, and although there does appear to be a relationship between the level of mutated mtDNA in the mother and the risk of affected offspring, there are insufficient data from prospective studies to allow accurate risk prediction. Nuclear genetic defects follow well described inheritance patterns, but the clinical penetrance of many recently identified nuclear gene defects has yet to be established, creating uncertainty in the clinic. Prognosis In general, the prognosis depends upon the extent of central neuro- logical involvement. Patients with Leber’s hereditary optic neuropathy

 rarely have significant central neurological features and have a normal lifespan. The prospect for visual recovery varies. After the initial nadir, individuals harbouring the m.11778G >A mutation are the least likely to regain functional vision, while those harbouring the m.14484T >C mutation are the most likely to regain their sight. Children presenting with an encephalopathy have a poor prog- nosis. Although residual neurological deficits are common after re- peated childhood encephalopathic episodes, the disease may enter a more stable ‘chronic’ phase during teenage years and adulthood. A similar course may be seen in adults presenting with a relapsing encephalopathy. In contrast, a large proportion of adults with mtDNA

defects and chronic progressive external ophthalmoplegia have very mild disease that may remain limited to the extraocular muscles for many decades. For specific mtDNA mutations, there also appears to be a relationship between the proportion of mutated mtDNA in skeletal muscle and the severity of the disease. Although the proportion of mutated mtDNA in muscle may give some guide to prognosis, there is insufficient information available to allow ac- curate prognostic counselling based upon these determinations. A significant proportion of patients have distinct phenotypes associ- ated with unique genetic defects and the prognosis must be guarded in these families. Pharmacological treatments and novel approaches under development No medicines are licenced for the treatment of mitochondrial dis- eases, and there is no objective evidence that any treatment is effective. Anecdotal reports describe benefits from ubiquinone (coenzyme Q10) in patients with disorders of coenzyme Q10 biogenesis, and some patients have a riboflavin-responsive disorder. Several clinical trials are currently evaluating the effects of novel treatment approaches in patients with mitochondrial disease (https://ClinicalTrials.gov), and idebenone shows promise as the first treatment for Leber hereditary optic neuropathy. Bone marrow transplantation is effective in pa- tients with very rare autosomal recessive enzyme defects (caused my mutations in TP). Dichloracetate can be used to reduce lactic acid levels but may cause an irreversible toxic neuropathy and is therefore not used in adults. Exercise is important for patients with mtDNA disease, and isometric muscle contraction may lead to an improve- ment in muscle strength. Finally, several centres are investigating methods for correcting the underlying mtDNA defect using targeted antigenomic molecules and gene therapy, and new approaches are being developed to prevent the transmission of mtDNA mutations through mitochondrial donation. FURTHER READING Anderson S, et al. (1981). Sequence and organization of the human mitochondrial genome. Nature, 290, 457–65. Chinnery PF, et al. (2014). The challenges of mitochondrial replace- ment. PLoS Genet, 10, e1004315. Di Mauro S, et al. (2013). The clinical maze of mitochondrial neur- ology. Nat Rev Neurol, 9, 429–44. Gorman GS, et al. (2015). Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial disease. Annals of Neurology, 77, 753–9. Klopstock T, et al. (2011). A randomized placebo-controlled trial of idebenone in Leber’s hereditary optic neuropathy. Brain, 134, 2677–86. Klopstock T, et al. (2013). Persistence of the treatment effect of idebenone in Leber’s hereditary optic neuropathy. Brain, 136, e230. Koopman WJ, Willems PH, Smeitink JA (2012). Monogenic mito- chondrial disorders. N Engl J Med, 366, 1132–41. Pfeffer G, et al. (2012). Treatment for mitochondrial disorders. Cochrane Database Syst Rev, 4, CD004426. Pfeffer G, et al. (2013). New treatments for mitochondrial disease—no time to drop our standards. Nat Rev Neurol, 9, 474–81. Stewart JB, Chinnery PF (2015). The dynamics of mitochondrial DNA heteroplasmy: implications for human health and disease. Nat Rev Genet, 16, 530–42. Taylor RW, et al. (2014). Use of whole-exome sequencing to determine the genetic basis of multiple mitochondrial respiratory chain com- plex deficiencies. JAMA, 312, 68–77. Vafai SB, Mootha VK (2013). Medicine: a common pathway for a rare disease? Science, 342, 1453–4.

Revision #1
Created 2026-01-22 16:43:29 UTC by Omar Ayman
Updated 2026-01-22 16:43:29 UTC by Omar Ayman