

Epileptic Syndromes in Mitochondrial Disease

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The Causal Disease

Mitochondria are subcellular organelles whose major function is the production of adenosine triphosphate (ATP) by the process called oxidative phosphorylation. The energy released by the metabolism of nutrients, i.e., glucose and fatty acids, is conserved by the mitochondrial respiratory chain (MRC), an enzyme pathway located in the inner mitochondrial membrane. This enzyme pathway is biologically unique, both because it is the major site of ATP production, but also because it contains subunits encoded by two different genomes. The MRC comprises five large multi-subunit complexes containing >80 proteins (Figure 48.1). The majority of these proteins are encoded by genes found on chromosomes in the cell nucleus, but 13 are encoded by a genome found inside the mitochondrion (Figure 48.1). This mitochondrial DNA (mtDNA) also encodes 22 transfer RNA (tRNA) and 2 ribosomal RNA (rRNA) involved in intra-mitochondrial protein synthesis (Figure 48.2). Mitochondria, and thus the DNA they contain, are inherited solely from the mother meaning that disease due to mutations in this genome can show strict maternal inheritance. Defects involving the other respiratory chain proteins with genes encoded in the nucleus (nuclear DNA or nDNA defects) show classical patterns of inheritance.

All cells depend on ATP to perform their required functions. Certain cells, such as neurons, skeletal muscle, and retinal ganglion cells appear to have a greater need for readily available energy than others, e.g., skin fibroblasts. This is often cited as one of the reasons why such tissues are more often affected by diseases due to MRC dysfunction. Since all cells contain mitochondria, however, any and indeed all tissues may be involved. The original mitochondrial disease descriptions were of patients with myopathy or encephalopathy and this led to descriptive terms such as mitochondrial encephalomyopathy together with a number of eponymous syndromes. Subsequently, MRC dysfunction has been shown to cause disease including diabetes mellitus, anemia, deafness, and gastric obstruction, as well as epilepsy and other neurological disorders [1, 2]. This has led to problems with nomenclature. For the purposes of this chapter, we will focus only on disorders due to MRC dysfunction and use the collective term *mitochondrial cytopathy*. Disorders arising from disruption of other mitochondrial metabolic pathways such as fatty acid oxidation, urea or citric acid cycle, etc., will not be discussed.

Central nervous system neurons are terminally differentiated cells lacking significant capacity to regenerate, and thereby to select against defective cells; they are also cells with a high energy demand. These factors are thought to

explain, in large part, their vulnerability to mitochondrial dysfunction and offer a potential explanation for why epileptic seizures occur frequently. Decreased intracellular ATP levels can, moreover, increase neuronal excitability by impairing sodium-potassium ATPase activity and decreasing the membrane potential. Since mitochondria also store intracellular calcium, mitochondrial dysfunction can increase excitability, and thus expose the neuron to damage by impairing calcium sequestration [3]. Other potential factors include lactic acid in high local concentration, which may provoke vasoconstriction sufficient to induce hypoxia. Dysfunction in MRC may also lead to increased free-radical production. It is known that free-radicals are signaling molecules, but they may also initiate damage, for example through apoptosis [4]. Disruption of glutamate transport and NAD⁺ depletion have also been cited as potential mechanisms, as has immune activation [5]. Whatever the initial mechanism, cortical damage can induce further seizures that, in turn, cause more damage. The resulting vicious circle may constitute an additional factor in the further destruction of surviving neurons, and clinical prognosis [6].

Mitochondrial diseases are common. Early studies from the UK showed that 9.2 per 100 000 people of working age (>16 and <60/65 years for female/male) had a clinically manifest mtDNA disease with 16.5 per 100 000 children and adults younger than retirement age at risk of developing mtDNA disease [7]. More recent population studies, also from the North East of England, showed that 1 per 4300 had either a mitochondrial or nuclear gene mutation responsible for their mitochondrial disorder [8]. These figures are based on patients with *known* mutations and there is currently no way of estimating how many more mutations or genes are still to be discovered. A study looking at the frequency of just 10 mtDNA mutations in 3168 neonatal-cord-blood samples (from sequential live births) also showed that at least 1 in 200 healthy humans harbors a pathogenic mtDNA mutation that could potentially cause disease in the offspring of female carriers [9].

Since nuclear genes supply all mitochondrial proteins except for the 13 encoded by mtDNA (Figure 48.1), defects in nuclear genes can affect the MRC in many ways: by damaging individual components of this pathway or proteins involved in its assembly, by disrupting the transport of proteins/co-factors that must be transferred from the cytosol to the mitochondrion (carriers and chaperone proteins) and by disrupting mtDNA maintenance. Examples of all are now recognized and while

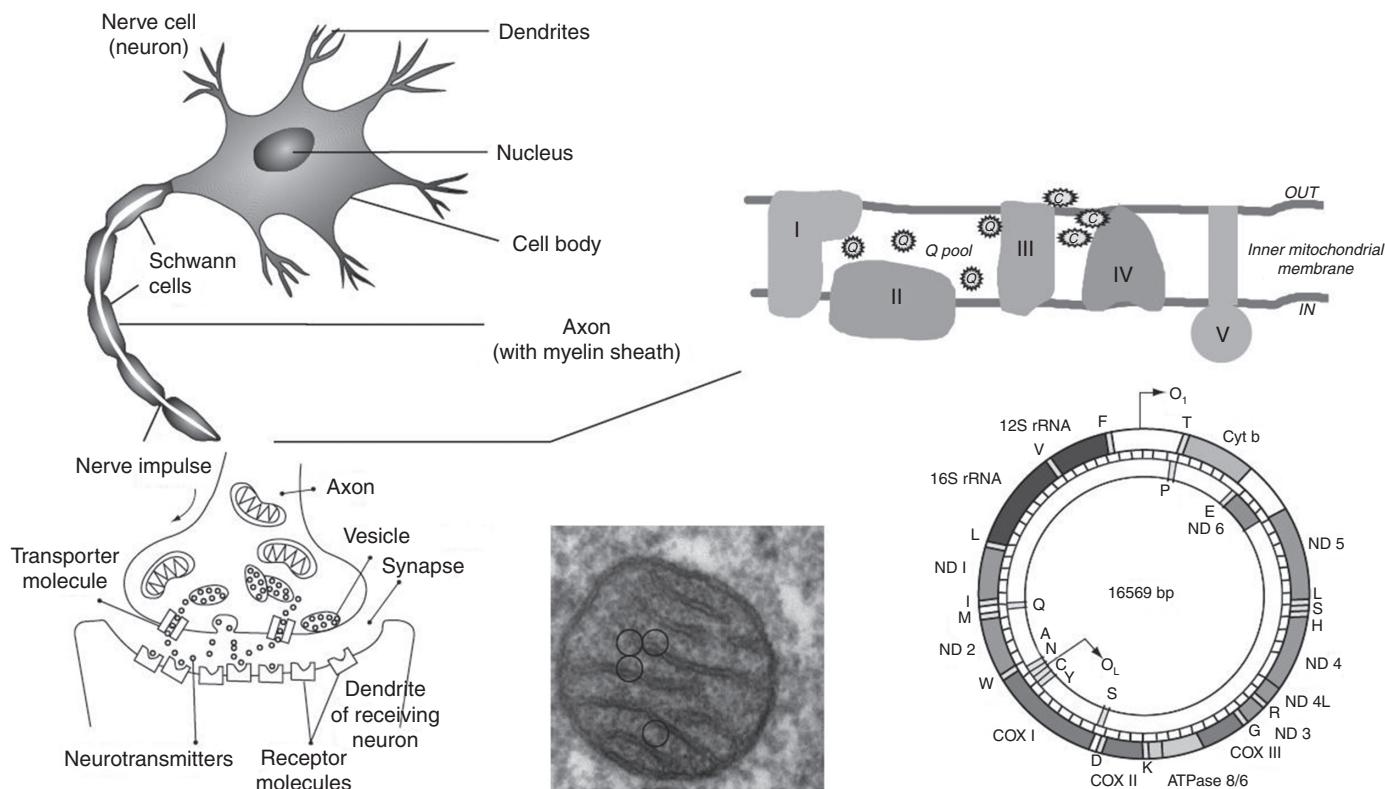


Figure 48.1 The mitochondrial respiratory chain. Neurons, as all cells, require energy and the vast majority is provided by the respiratory chain that sits in the inner mitochondrial membrane. Reduced co-factors (NADH and flavoproteins) generated by the breakdown of metabolic fuels (e.g., glucose and fatty acids), are reoxidized by respiratory chain complexes and the energy released during this process is conserved and used to drive the phosphorylation of ADP to ATP. This process is called oxidative phosphorylation. The mitochondrial respiratory chain comprises five multi-subunit complexes (depicted by Roman numerals) and four of these contain proteins encoded by the genome found inside mitochondria (mtDNA). MtDNA encodes seven (of a total of 45) proteins in complex I, one (of 11) in complex III, three (of 13) in complex IV, and two (of 14) in complex V. Complex II (succinate dehydrogenase) contains no mtDNA-encoded subunits.

many are associated with epilepsy, some are not [1]. Interestingly, children appear more frequently affected by disease caused by nuclear gene defects while mtDNA mutations are more common in adults [11].

Epilepsy in the Disease

Epilepsy can be a presenting symptom or occur during the course of most forms of MRC disease, whether caused by mutations in mtDNA or nuclear genes. It is not, however, seen in all [12]. In this chapter we have chosen to highlight the types of epilepsy associated with MRC disease by focusing on selected, recognizable syndromes including two mtDNA disorders: (1) myoclonus epilepsy with ragged red fibers (MERRF) and mitochondrial myopathy encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), and (2) syndromes associated with mutations in the nuclear gene, *POLG*, which is now recognized as one of the commonest causes of mitochondrial disease.

The syndromes of MERRF and MELAS are typical, sufficiently common to permit characterization, and associated with an epileptic semiology representative of mtDNA disease. Both can also be caused by different mtDNA mutations, thus confirming the pleiomorphic nature of mtDNA disease. The reader wishing for detailed descriptions of these, and other less common mtDNA diseases, should use the available

databases [12] and reviews [1, 2, 13] and references contained therein. Nuclear DNA gene defects are increasingly recognized, but one group appears more common, namely syndromes associated with mutations in the *POLG* gene [14].

In a retrospectively recruited cohort of 182 consecutive adult patients attending a specialized mitochondrial disease clinic, the overall prevalence of epilepsy was 23.1%, with mean age of epilepsy onset at 29.4 years [15]. No specific type of epilepsy characterizes mitochondrial disease, but interestingly, both mtDNA and nDNA defects are often associated with an occipital lobe predilection, at least initially. Myoclonus occurs in all types of mitochondrial disease, but whether this is purely cortical or brainstem (or both) is unclear and both may occur. Most commonly the epilepsy in mitochondrial cytopathy is multifocal, and, thus, secondary generalized epilepsy combining focal and generalized features. The presence of epilepsy did not appear to increase mortality in a mixed group of patients with mitochondrial disease [15], but this is not true in the case of patients with *POLG* mutation.

Myoclonus Epilepsy with Ragged Red Fibers

Epileptic seizures are one of the defining features of the MERRF syndrome [16], the other being ragged red fibers, mitochondria accumulation in muscle fibers detected by Gomori-trichrome staining that has become the

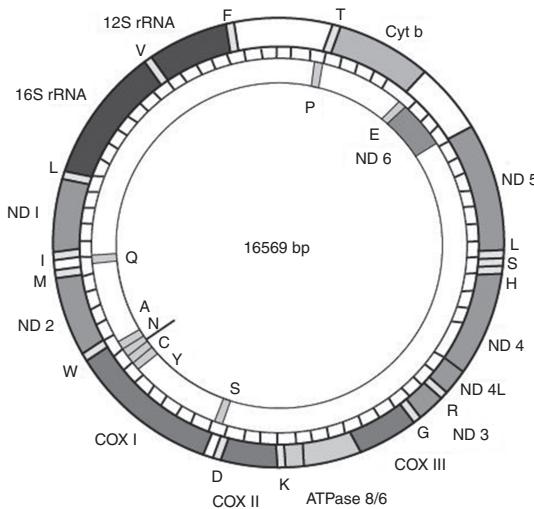


Figure 48.2 Mitochondrial DNA is a compact circular genome 16.5 kilobases in size with little non-coding sequence. In addition to the 13 proteins, it also encodes 22 transfer RNA (tRNA) and two ribosomal RNA (rRNA) that are involved in intramitochondrial protein synthesis. MtDNA is found in multiple copies inside each mitochondrion. Mutations affecting this genome can therefore affect some or all of the copies. A cellular phenotype arises only when sufficient copies are affected and the level (i.e., the percentage of mutated compared with normal copies) at which this occurs is termed the threshold. The existence of two populations of mtDNA is called heteroplasmy and most mtDNA mutations only produce a phenotype at high levels of heteroplasmy and are thus considered as 'functionally' recessive. The common mutations of mtDNA are shown.

morphological hallmark of mitochondrial disease (see Figure 48.5 below). Several different mutations cause this syndrome. The first described was the 8344A>G [17] in the mitochondrial tRNA gene for lysine (Figure 48.2). Subsequently, two more mutations in this gene were identified and both appeared to cause the same clinical syndrome (*m.8356T>C* and *m.8361G>A*) [18, 19]. Several other mutations [12, 20] have now been described giving clinical syndromes in which myoclonic epilepsy occurs, but which involve other features such as cardiomyopathy or diabetes mellitus. Indeed, overlap syndromes with features of both MERRF and MELAS are described, highlighting the marked phenotypic variability of mitochondrial disorders and the lack of consistent phenotype–genotype correlation. Nevertheless, the mutations in tRNA lysine cause a syndrome that is now well recognized and, for an mtDNA disorder, relatively frequent.

Patients usually present with progressive myoclonus and most have GTCSs (9 of 13 cases in Berkovic's series [21]; 12 of 13 in Whittaker's series [15]). The myoclonus may be indistinguishable from that seen with other progressive myoclonus epilepsies, e.g., Unverricht–Lundborg or Lafora body disease. Myoclonic jerks may correlate with EEG spike or polyspike activity, and we have seen suppression of epileptic activity following eye opening. The myoclonus can be virtually constant, but may also be intermittent, photosensitive, and intensified by action, such as writing, eating, etc. Focal clonic and tonic seizures have been reported [21, 22]. Visual or somatosensory symptoms may precede motor symptoms. The GTCS seizures are generally easy to control with traditional AEDs whereas the myoclonus may be relatively refractory and

develop into continuous generalized myoclonus [21]. In addition to seizures, patients commonly develop ataxia, deafness, dementia, and a clinical myopathy. Interestingly, there is also an association with multiple symmetrical lipomatosis.

Mitochondrial Myopathy Encephalopathy, Lactic Acidosis, and Stroke-Like Episodes

The defining features of MELAS syndrome are the finding of lactic acidosis and the occurrence of stroke-like episodes [23, 24]. Neither, however, is constant and diabetes, deafness, progressive external ophthalmoplegia, gastroenteropathy and cyclical vomiting, failure to thrive, myopathy, and peripheral neuropathy also occur with variable frequency [1]. The syndrome can be caused by several different mtDNA mutations (Figure 48.2), but one, the *m.3243A>G* in the tRNA for leucine (UUR) [25], is by far the commonest. This mutation can give MELAS, with stroke-like episodes and epilepsy, or more benign phenotypes such as maternally inherited diabetes, deafness, encephalopathy, or progressive external ophthalmoplegia with a proximal myopathy.

Epilepsy occurs primarily in the group of patients that develop stroke-like lesions (Figure 48.3A), and seizures are often preceded by or associated with migraine-like headache. These lesions evolve gradually [26], showing predilection for the occipital and temporal lobes, and seizure semiology often reflects disturbance in these locations. MRI shows evolving lesions that appear to reflect initial cellular damage followed by vasogenic edema [27]. Why certain areas of the brain are targeted remains an unanswered question, however, the pathological process underlying the stroke-like lesions appears primarily cellular and not vascular. Whatever the underlying defect, however, seizures increase the metabolic demand placed on neurons, exposing patients to risk of further damage and therefore further seizures.

In a review of 110 reported cases of MELAS in which stroke-like episode was a defining feature, 96% had seizures, with 38% having myoclonic seizures [28]. In 28% of cases, seizures were the initial clinical manifestation. Both generalized and focal seizures are seen (26/42) and in 10 of 42 patients, generalized epilepsy was defined, including one patient with absence seizures [22]. The commonest type of focal seizures they found were motor, followed by visual seizures and seizures originating in the temporal lobe. Status epilepticus (SE) occurred in 6/42 in this series [22], but clinical experience shows that SE is frequent in patients with MELAS and similar mitochondrial disorders and can be the initial presentation.

When present, myoclonic seizures appear less severe and less common than in patients with MERRF. Noticeably, there may be overlap syndromes between MELAS and MERRF [21]. Interictal EEG changes in MELAS patients were reported to be localized to the parieto-occipital regions or as diffuse sharp wave paroxysms, whereas EEG discharges associated with focal motor seizures had a congruous fronto-central location [29]. Most likely the age of seizure onset influences the seizure semiology in MELAS, absence seizures reflecting young age, whereas non-convulsive status epilepticus with regional

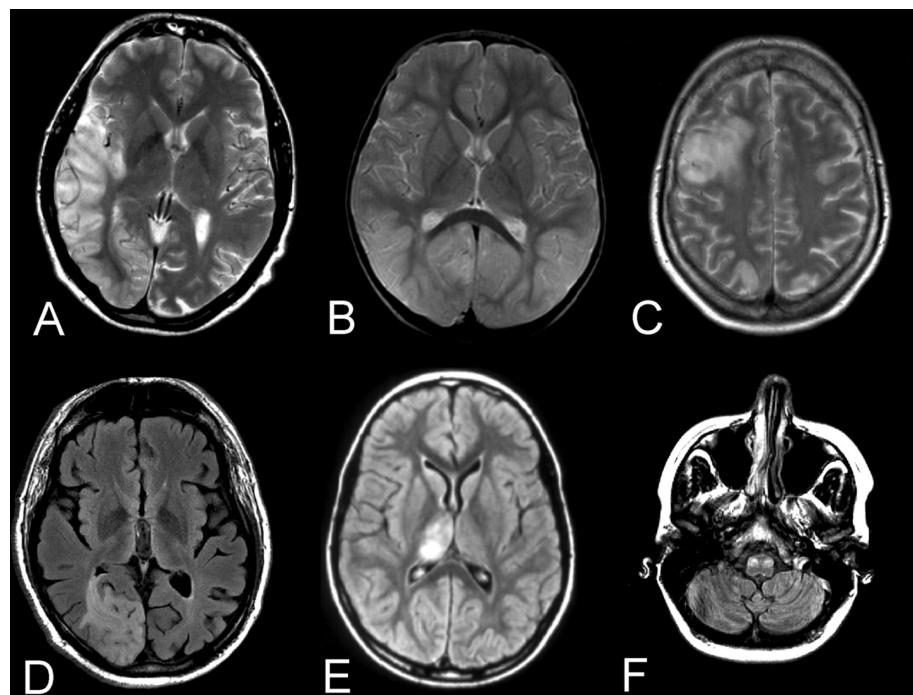


Figure 48.3 MRI images. (A) T2-weighted image showing a right temporo-occipital high signal lesion (fresh, edematous cortex) in MELAS. This is a typical finding in this disorder and is what can be called a stroke-like lesion. Patient with *m.3243A > G* mtDNA mutation. (B) T2-weighted image showing bilateral temporo-occipital, cortical, high signal lesions in a child with Alpers' syndrome and mutation in *POLG*. (C) T2-weighted image showing right frontal and parieto-occipital and left frontal high signal lesions from a patient with mitochondrial spinocerebellar ataxia and epilepsy (MSCAE) during an episode of status epilepticus and encephalopathy. (D) T2-FLAIR image showing a right occipital high signal lesion developing in a patient with MSCAE and status epilepticus. (E) T2-FLAIR image showing a right thalamic high signal lesion. These are typical for MSCAE and persist in contrast to the lesions depicted in (B), (C), and (D) which are evanescent. (F) T2-FLAIR image showing bilateral inferior olfactory high signal lesions. These too are typical for MSCAE, but only one patient had the clinical correlate of palatal myoclonus.

epileptic activity in the right posterior quadrant occurred in late onset MELAS [30].

Syndromes Related to Polymerase Gamma (*POLG*) Mutations

The *POLG* gene encodes the catalytic subunit of the mitochondrial DNA polymerase, the enzyme that replicates and repairs mtDNA. By directly affecting mtDNA, mutations in this nuclear gene can either induce qualitative mtDNA defects (multiple mtDNA deletions or point mutations) or quantitative loss of mtDNA known as depletion. Moreover, mutations in this gene appear to be common and give rise to a variety of disorders ranging from infantile hepatocerebral disease such as Alpers' syndrome, ataxia and epilepsy, to Parkinsonism, and progressive external ophthalmoplegia [31–34].

Alpers–Huttenlocher Syndrome

This syndrome comprises refractory seizures, psychomotor retardation, and liver involvement and is caused by a variety of different mutations in the *POLG* gene [35, 36]. Initial presentation is most often with status epilepticus that can be focal or generalized and from which the child might never recover. Mental retardation can be present before the onset of seizures, or begin thereafter. Liver failure, perhaps the least consistent feature, may be present at onset or only develop during the terminal illness. The majority of children with this disease die within a few months of onset, but some survive several years. Elevated lactate in blood or CSF is an inconsistent feature. A predilection for involvement of the occipital lobes is seen in MRI (Figure 48.3B, C); lesions affecting the cortex have features similar to those seen in acute hypoxia. The seizure

semiology in this syndrome is very similar if not identical to that we have described for patients with MSCAE and *POLG* mutation (see below).

Mitochondrial Spinocerebellar Ataxia and Epilepsy

Mitochondrial spinocerebellar ataxia and epilepsy (MSCAE) is a teenage-onset disorder comprising spinocerebellar ataxia, peripheral neuropathy, and epilepsy. Liver failure (cf. Alpers' syndrome) occurs spontaneously, but is most often seen after exposure to sodium valproate. There is a high prevalence in Scandinavia and Finland, but, similar to Alpers' syndrome, MSCAE is also found throughout the world [36–38]. Onset of MSCAE can be with ataxia or epilepsy, but all patients will eventually develop ataxia if they survive, while only ~80% appear to develop epilepsy [39]. This must be interpreted with caution, however, since patients with MSCAE can develop an explosive and fatal epilepsy >30 years after presenting with ataxia. While several *POLG* mutations are described giving this later-onset (than Alpers' syndrome) disease, two are by far the most common; the *c.1399G>A* that gives *p.A467T* and the *c.2243G>C* giving the *p.W748S* [34].

In MSCAE, epilepsy is the presenting symptom in ~65% of patients [39]. Occipital lobe epileptic features appear to be the initial symptoms in the majority and seizure phenomena include flickering colored light that may persist for weeks, months, or even years, ictal visual loss, nystagmus or oculoclonus, dysmorphopsia, micro-/macropsia, and palinopsia, often combined with headache, emesis, or both. Refractory simple focal seizures with visual symptoms in one visual hemifield occurring daily for weeks, months, or even years was seen in over 50% of cases and the epileptic origin of these symptoms could be substantiated by ictal EEG (Figure 48.4A).

All of the patients with epilepsy develop focal clonic or myoclonic seizures, most often involving an arm, shoulder, neck and head. They manifest as focal motor seizures without impairment of consciousness and often continue to focal motor status. Occasionally, persisting focal or generalized myoclonic jerks can be observed. Palatal myoclonus was seen in one patient who also had involvement of the inferior olivary nuclei. Focal motor seizures are sometimes accompanied by a clear epileptic EEG correlate, sometimes with rhythmic focal slowing of the contralateral, posterior hemispheric quadrant, or occipital electrodes (Figure 48.4B). No clear correlation between frequency of focal clonic movements of arm–shoulder–head and frequency of occipital slow waves is seen, but EEG changes can be considered epileptiform in nature [39]. Focal seizures with impairment of awareness with motor symptoms occur in >50% of patients and may be underreported, and generalized tonic–clonic seizures, all considered secondarily generalized, occur in >90% of cases.

All patients who develop epilepsy experience status epilepticus and this can begin explosively several decades after disease onset. Status epilepticus can also be the presenting seizure phenomenon, although the median time from onset of epilepsy to the first status is 2 months.

An EEG showing occipital slow wave and epileptic activity occurs as an early feature in the majority of patients [39] and ictal registrations revealed either severe general slowing, with or without epileptic activity, or, as in the majority of patients, consistent focal occipital, or temporo-occipital, epileptic discharges occurring in T5, T6, O1, and O2 electrodes (Figure 48.4A–D).

Other Mitochondrial Cytopathies

There are a large number of reports describing single patients or families with different forms of mitochondrial cytopathy, many of whom have epilepsy. Early work was descriptive and defined mitochondrial disease only in terms of biochemical or morphological abnormalities making it difficult to compare these cases with what we know from genetically defined cytopathies. In our experience, and based on those reviews available, the type of epilepsy seen in these cases does not differ from that seen in the examples we have discussed above. It seems safe to say, therefore, that any and all types of epileptic seizures can occur in mitochondrial cytopathy.

Diagnostic Tests for the Disease

Diagnosis of mitochondrial cytopathy is based on the usual algorithm of clinical suspicion and supplementary laboratory investigation [40]. When faced by a complex systemic disorder, considering the possibility that MRC dysfunction might be the cause is, perhaps, the crucial step. In addition to the clinical findings, the finding of elevated lactate in body fluids is a common, but inconsistent finding in mitochondrial cytopathies. Imaging techniques such as MRI can demonstrate patterns of involvement that suggest mitochondrial etiology, particularly involvement of the occipital lobes (Figure 48.3) and in MSCEA, involvement of the thalamus and inferior

olivary nuclei (Figure 48.3E, F), but these are not diagnostic. Dystrophic calcification particularly affecting the basal ganglia is seen in MELAS, which has significant epileptic component, but also in Kearns–Sayre syndrome, which does not. MRS can demonstrate elevated lactate in regions of the brain, while PET scanning can provide metabolic information suggesting lowered ATP production. Neither of these techniques provides unequivocal evidence of respiratory chain dysfunction, however, and it is usually necessary, therefore, to take a tissue biopsy.

The usual site for tissue sampling is skeletal muscle, which will often show abnormalities even in the absence of clinical myopathy. Proper handling of the muscle sampling is crucial because all investigations are performed on frozen, not fixed, material. Standard histological and histochemical analysis may demonstrate mitochondrial accumulation (ragged red fibers) or fibers lacking complex IV activity (cytochrome oxidase [COX] negative fibers) (Figure 48.5). Muscle can also be used for biochemical measurements of respiratory chain complexes and studies of mtDNA. These are techniques that demand a high technical proficiency and it is advisable when faced with the possibility of MRC to contact a specialized laboratory in order to ascertain what is required.

Investigations such as COX/SDH staining provide information concerning where further studies should be directed: for instance, a mosaic of COX positive and deficient fibers is a strong indication that the patient has a defect involving mtDNA, but cannot distinguish between primary (i.e., mutation in mtDNA) or secondary (mutation in nuclear gene involved in mtDNA maintenance) defects. A more detailed description of the investigation of mitochondrial cytopathies can be found in the available literature, e.g., [40].

Since the MRC is controlled by two genomes, establishing the final, genetic diagnosis can be demanding. Unlike the majority of nuclear genes, where we have two copies, mitochondrial DNA is present in multiple copies in every cell. Mutations affecting this genome can affect all or only a proportion of copies [13]. In classical genetics we use the concepts of heterozygosity (each gene copy has a different sequence) and homozygosity (both gene copies have identical sequences). Thus, dominant disorders arise when a mutation in one gene copy is sufficient to cause disease, and recessive disorders require mutations affecting both copies. In mitochondrial genetics, the situation is complicated by the presence of multiple genomes and an uneven tissue distribution [41]. Mutations can affect a percentage of mtDNA copies from <1% to >99%. Where all copies in an individual have the same sequence we call this homoplasmy (cf. homozygosity); where there are mtDNAs with two different sequences, e.g., one with a mutation and one normal, this is called heteroplasmy (cf. heterozygosity). In addition, based on factors such as whether the cell retains the capacity to divide and therefore select against cells with impaired energy metabolism, the level of mutation in one tissue can differ dramatically from another. In many mtDNA disorders, particularly those in which the defect is unknown, this will



Figure 48.4 Representative EEGs. (A) Ictal EEG during SFS status epilepticus. Patient complained of continuous colored blinking light in the left visual hemifield. Patient with *POLG* mutation. (B) Ictal EEG during continuous focal clonic jerking of the left arm, shoulder, and head. Patient with *POLG* mutation. (C) Diffuse cerebral slowing with epileptiform discharges in the temporal and occipital electrodes, left more than right, during non-convulsive status epilepticus with disorientation, headache, vomiting, and aimless wandering. Patient with *POLG* mutation. (D) Interictal epileptic discharges in a patient showing transient suppression of epileptic discharges during eye opening. Patient with *POLG* mutation.

mean that it is not possible to use blood as a source of genetic material since the level will be too low.

Principles of Management

Treatment Guidelines

No cures for mitochondrial cytopathies currently exist. Precise diagnosis is vital since this will provide information concerning the possibility to treat [42] and the known potential complications, e.g., development of cardiac involvement or diabetes mellitus. It is important to avoid potential mitochondrial toxins (antibiotics such as tetracyclines, gentamycin, ciprofloxacin), antiviral agents (AZT), and sodium valproate. The latter is absolutely contraindicated in patients with *POLG* disease. Fasting increases the demand on the MRC, as does fever. This means that care must be taken even when the patient develops a simple viral infection. The use of vitamins, including ubiquinone, has not been shown to have any measurable effect on MRC function, but many still use these, often in combination.

Epilepsy Treatment

We advise treating GTCSs with traditional AEDs such as sodium-channel blockers, although we have experienced worsening of myoclonic seizures by lamotrigine and gabapentin in *POLG*-related disease [39]. Carbamazepine, oxcarbazepine, and phenytoin have proven effective, but in combination with a benzodiazepine, e.g., clobazam or clonazepam, although in some patients it has also been necessary to add a third drug. Levetiracetam or topiramate can also be used against myoclonic seizures. Again, we would stress that patients with known *POLG* mutations must absolutely avoid sodium valproate and this applies even to patients where the diagnosis is in doubt, so it is best to avoid this drug. The ketogenic diet [43] has been used in the treatment of mitochondrial epilepsy, but we have no experience with this or the modified Atkins diet in our patients. One of our patients tried a modified Atkins diet on her own volition, but with no effect on the epilepsy.

Patients with mitochondrial cytopathies such as MELAS and *POLG*-associated disorders have a high risk of status epilepticus. Even patients with an apparently benign course can suddenly

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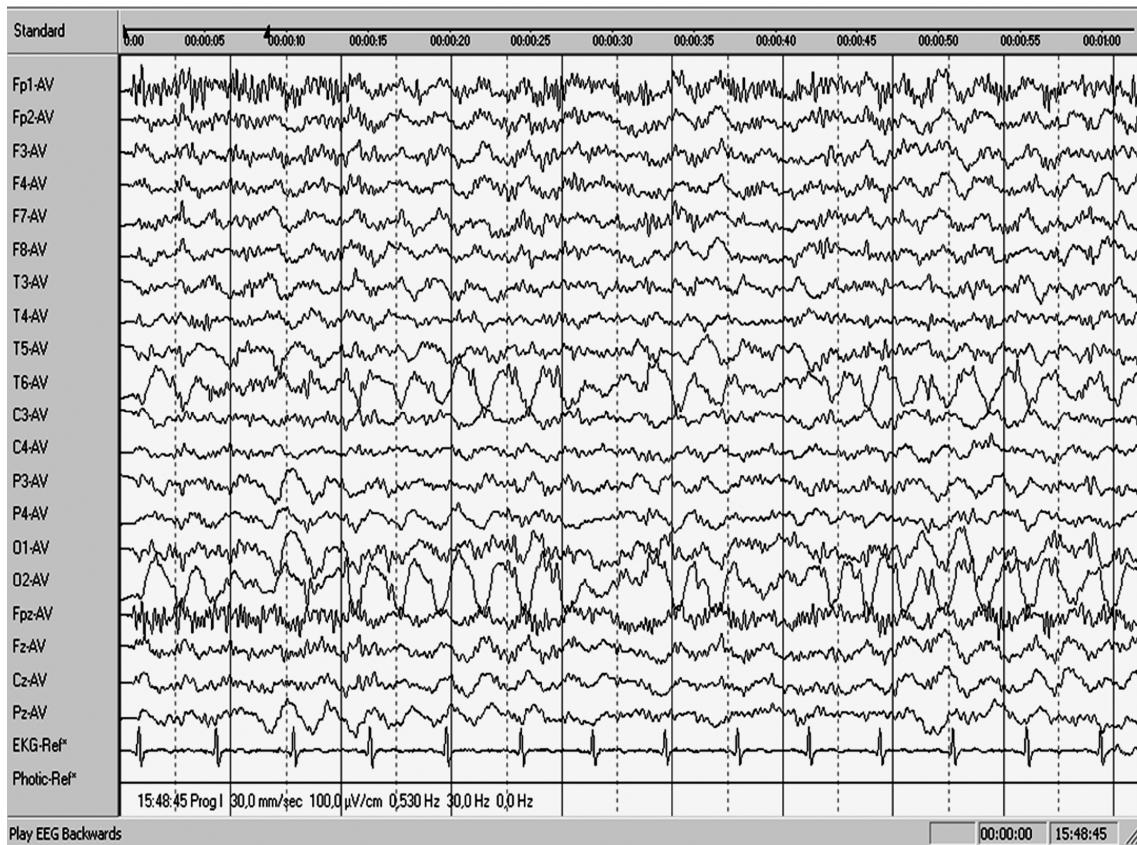


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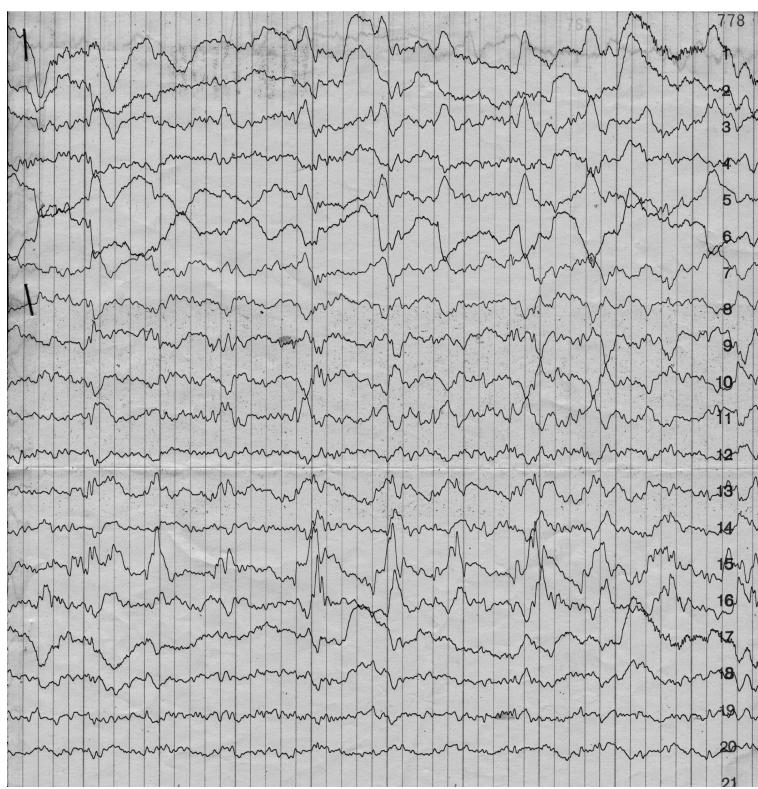


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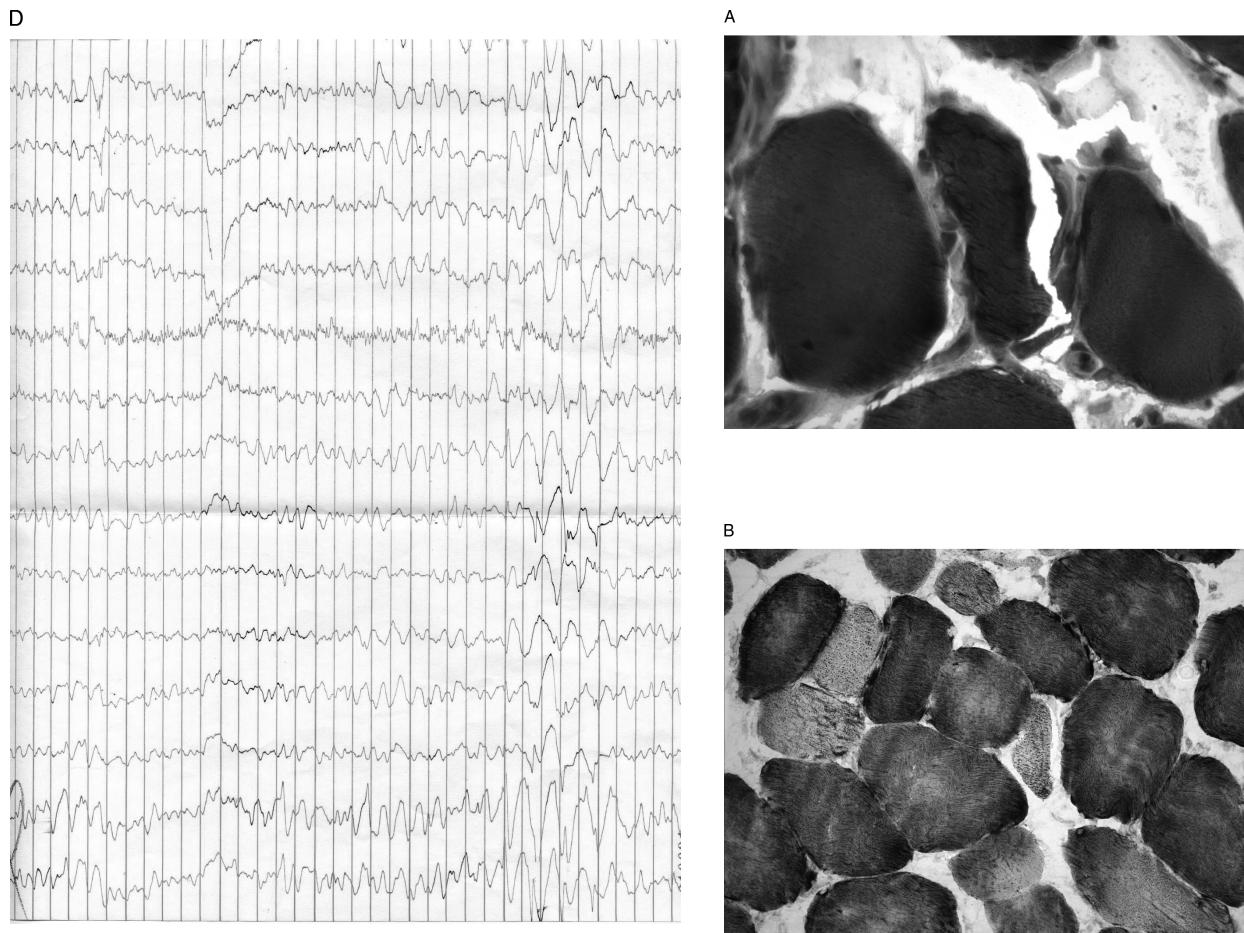


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decompensate and develop focal or generalized status. While we do not suggest starting AED treatment before the start of any seizure disorders, we do advocate a high index of suspicion and this includes routine and regular EEG monitoring. Due to the potential for generating secondary damage, we strongly advise aggressive treatment once seizures have started. In mtDNA disorders such as MELAS and MERRF, treatment appears to be effective, at least initially. *POLG*-related disorders, such as Alpers' syndrome and MSCAE, can be extremely difficult to treat and we have experience of patients in whom it has been impossible to control focal motor status for long time periods, i.e., weeks, and months even with combinations of AEDs in maximal doses.

Convulsive status epilepticus [44] is treated aggressively using traditional protocols. Benzodiazepine infusion is evaluated as a first-line treatment together with fosphenytoin and occasionally phenobarbital (supervision in intensive care unit). Subsequently, we use thiopental narcosis where necessary together with cerebral functioning monitoring with the aim of achieving burst suppression for at least 24–48 h. Daily EEGs are performed including when monitoring protracted recovery periods that may extend to several days. In recent years, we have had some success using propofol as a first-line agent, since the level of narcosis is more easily monitored and can

be terminated more rapidly when successful treatment is achieved [45]. Some patients still required thiopental narcosis, however, despite the initial use of propofol. Repeated treatment with thiopental has been successful, but several of our patients, particularly with *POLG* mutations, have died after prolonged periods of recurrent CSE and non-convulsive SE with multiple organ failure following the use of every known and available AED.

Conclusions

Mitochondrial cytopathy due to genetic defects in mtDNA or nDNA may cause epileptic seizures and may even be important in propagating the epileptic process in disorders caused

by mechanisms other than MRC defects. Differences in the seizure semiology seen in the different syndromes may reflect age of seizure initiation, e.g., infancy or adulthood, the intracerebral distribution of mtDNA defects, including level of heteroplasmy, or simply phenotypic variation that in itself reflects the different genetic make-up each individual carries. Most seizure types have been reported in mitochondrial cytopathy including generalized ones such as atypical absences, myoclonic seizures, atonic and tonic seizures, GTCSs, and focal seizure types with or without secondary generalization.

The epilepsies in mitochondrial cytopathies often reveal both focal and generalized features. In some cases clearly syndromic epilepsies can be delineated, as for example in *POLG*-related epilepsy [39], myoclonus epilepsy of MERRF [21], and MELAS [10]. An exceptional feature in mitochondrial cytopathies is the apparent occipital predilection. This can be seen radiologically and in the localization of the epilepsy in *POLG*-related disorders [39] and MELAS [10] but not in MERRF [21].

Molecular and biochemical diagnosis of mitochondrial cytopathies are technically demanding areas and best left to

centers that specialize in this area. The major challenge for the general physician is to recognize that mitochondrial dysfunction might be the cause. Thereafter, the decision to investigate or refer to another center will depend on the availability of local genetic and pathological expertise.

Treatment of mitochondrial cytopathies comprises awareness of the potential complications and early and aggressive control of seizures. In the absence of current disease-modifying treatments, it is essential to focus on what is achievable. Standard AED treatment appears effective in most of the mtDNA disorders, but *POLG*-related epilepsy remains a major therapeutic challenge.

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