Epilepsy in mitochondrial disorders

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Introduction

Overview

Mitochondrial diseases that arise from defects in the respiratory chain, the metabolic pathway that produces ATP, are potent causes of epilepsy and are usually part of a syndrome, eg, myoclonus epilepsy with ragged-red fibers (MERRF) or mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). The seizures can be focal or generalized and show a predilection for the occipital lobes, and there is a high risk of status epilepticus. In this clinical article the author reviews the types of mitochondrial disease commonly associated with epilepsy and the seizures that are known to occur.

Key points

- Mitochondrial dysfunction is a potent cause of epilepsy, and status epilepticus can be the presenting feature.
- Both partial and generalized epilepsy and myoclonus occur in mitochondrial disease.
- Mitochondrial epilepsy shows predilection for the occipital lobes.
- Sodium valproate is absolutely contraindicated in patients with mitochondrial epilepsy caused by POLG mutations.

Historical note and terminology

The historical note and nomenclature for specific mitochondrial disorders is discussed in their respective sections.

Clinical manifestations

Presentation and course

Epilepsy can be the presenting symptom or occur during the course of most forms of mitochondrial respiratory chain disease, whether caused by mutations in mitochondrial DNA (mtDNA) or in genes encoded by nuclear DNA (nDNA) defects. No specific type of epilepsy characterizes mitochondrial disease, but an occipital lobe predilection, at least initially, is seen in several mtDNA- and nDNA-induced epilepsies. Myoclonus occurs in all types of mitochondrial disease, but whether this is purely cortical or brainstem, or both, is unclear, and both probably occur. Most commonly, the epilepsy in mitochondrial respiratory chain disease is symptomatic, multifocal, and, thus, secondary generalized epilepsy, combining focal and generalized features (Chevallier et al 2014).

Because mitochondrial diseases often affect several tissues, it is common for epilepsy to occur together with other tissue manifestations, ie, as part of a syndrome. Specific mitochondrial syndromes in which epilepsy is a major feature include 2 linked to mtDNA mutations, myoclonus epilepsy with ragged-red fibers (MERRF) and mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), and epileptic syndromes caused by mutations in the nuclear encoded POLG gene. These demonstrate the characteristic features of “mitochondrial epilepsy” and will be described in detail.

Myoclonus epilepsy with ragged-red fibers (MERRF). Epileptic seizures are 1 of the defining features of MERRF syndrome (Fukuhara et al 1980); others are myoclonus and the morphological hallmark of mitochondrial myopathy, namely, ragged-red fibers seen on muscle biopsy. Interestingly, there is also an association with multiple symmetrical lipomatosis. In a review of this disorder, it was pointed out that myoclonus was an inconsistent feature of this disease and more associated with the presence of ataxia than of epilepsy (Mancuso et al 2014).
Several different mtDNA mutations cause this syndrome. The first described was the m.8344 A>G in the mitochondrial tRNA gene for lysine. Subsequently, 2 more mutations in this gene were identified, and both appeared to cause the same clinical syndrome (m.8356T>C and m.8361G>A). Several other mutations have now been described, giving clinical syndromes in which myoclonic epilepsy occurs, but which involve other features such as cardiomyopathy or diabetes mellitus (Ruiz-Pesini et al 2007). 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 can present with progressive myoclonus, and most have generalized tonic-clonic seizures (Berkovic et al 1989). The myoclonus may be indistinguishable from that seen in other progressive myoclonus epilepsies, eg, Unverricht-Lundborg or Lafora body disease. Myoclonic jerks may correlate with electroencephalographic (EEG) spike or polyspike activity, and suppression of epileptic activity following eye opening has been seen. The myoclonus can be virtually constant, but may also be intermittent, photosensitive, and intensified by action, such as writing, eating, etc. Focal clonic and atonic seizures have been reported (Berkovic et al 1989). Visual or somatosensory symptoms may precede motor symptoms.

The generalized tonic-clonic seizures are generally amenable to traditional antiepileptic drugs, whereas the myoclonus may be relatively refractory and develop into continuous generalized myoclonus (Berkovic et al 1989). In addition to seizures, patients commonly develop ataxia, deafness, dementia, and a clinical myopathy.

Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). The defining features of this syndrome are the finding of lactic acidosis and the occurrence of stroke-like episodes (Pavlakis et al 1984; Montagna et al 1988). Diabetes, deafness, progressive external ophthalmoplegia (PEO), gastroenteropathy and cyclical vomiting, failure to thrive, myopathy, and peripheral neuropathy also occur with variable frequency (DiMauro and Schon 2008). The syndrome can be caused by several different mtDNA mutations, but 1, the m.3243A>G in the tRNA for leucine (UUR), is by far the commonest (Goto et al 1990). This mutation can cause MELAS, with stroke-like episodes and epilepsy, or more benign phenotypes such as maternally inherited diabetes, deafness and encephalopathy, or PEO with a proximal myopathy.

Epilepsy occurs primarily in the group of patients that develop stroke-like lesions, and seizures are often preceded by, or associated with, migraine-like headache. Stroke-like lesions evolve gradually (Iizuka et al 2003) and show 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 (Tzoulis and Bindoff 2009). Why certain areas of the brain are targeted and what type of pathological process underlies the stroke-like lesions, ie, whether the process is primarily vascular or cellular, remain unanswered questions. Once initiated, however, seizures increase the metabolic demand placed on neurons, exposing patients to a risk of further damage and, therefore, further seizures.

In a review of 110 reported cases of MELAS in which stroke-like episodes was a defining feature, 38% had myoclonus and 96% had seizures (Hirano and Pavlakis 1994). In 28% of the cases, seizures were the initial clinical manifestation. Both generalized and focal seizures were seen (26/42), and in 10 of 42 patients, generalized epilepsy was defined, including 1 patient with absence seizures (Hirano and DiMauro 1997). The commonest type of partial seizures found were motor, followed by visual and temporal lobe seizures. Status epilepticus occurred in 6 of 42 patients in this series, but clinical experience shows that status epilepticus is frequent in patients with MELAS and similar mitochondrial disorders, and can be the initial presentation.

In a study of Italian patients with the m.3243A>G mutation, seizures were the second most common presenting complaint, but present in only 18% (Mancuso et al 2014). Although seizures were again significantly associated with stroke-like episodes, the differences between this study and the 1 from 1994 reflect the extended range of phenotypes now associated with this mutation and the greater impact of more common features such as diabetes and deafness on the presentation of this mitochondrial phenotype. Interestingly, this study of 126 m.3243A>G carriers demonstrated a significantly greater number of males with stroke-like episodes.

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. In a later publication, interictal EEG changes in MELAS patients were localized to the parieto-occipital regions or as diffuse sharp wave paroxysms, whereas EEG discharges
associated with partial motor seizures had a congruous frontocentral location (Canafoglia et al. 2001). The age of epilepsy debut may likely influence the seizure semiology in MELAS, with absence seizures reflecting young age, whereas a complex partial status epilepticus with regional epileptic activity in the right posterior quadrant occurred in late-onset MELAS (Leff et al. 1998).

**Other mtDNA mutations.** Over 150 mutations in mtDNA have been described, and mutations in mitochondrial tRNA genes are particularly common. Many cause syndromes that also include epilepsy. These are rare compared with the syndromes described above, however, and the epilepsy that evolves does not differ significantly from what is described in the MERRF and MELAS sections.

**POLG-related syndromes.** The POLG gene encodes the catalytic subunit of the mitochondrial DNA polymerase, the enzyme that replicates 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; parkinsonism; and PEO (Luoma et al. 2004; Hakonen et al. 2005; Hudson and Chinnery 2006; Tzoulis et al. 2006).

Alpers-Huttenlocher syndrome comprises refractory seizures, psychomotor retardation, and liver involvement and is caused by a variety of different mutations in the POLG gene (Ferrari et al. 2005; Nguyen et al. 2005). 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 it may 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, usually profoundly affected. Elevated lactate in blood or CSF is an inconsistent feature. MRI shows predilection for involvement of the occipital lobes.

**Mitochondrial spinocerebellar ataxia and epilepsy (MSCAE).** This disorder usually starts in the teenage years, either with ataxia or epilepsy; all patients eventually develop ataxia if they survive. Figures suggest that approximately 80% of patients develop epilepsy (Engelsen et al. 2008), but this must be interpreted with caution because patients with MSCAE can develop an explosive and fatal epilepsy more than 30 years after presenting with ataxia. Although several POLG mutations are described as causing this disease that presents later than Alpers, the 2 most common are the c.1399G>A that gives p.A467T and the c.2243G>C that gives p.W748S.

Epilepsy is the presenting symptom of MSCAE in approximately 65% of patients (Engelsen et al. 2008). Occipital lobe epileptic features are 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 ocular clonus; dysmorphopsia; micro-/macropsia; and palinopsia, often combined with headache and/or emesis. Refractory simple partial seizures with visual symptoms in 1 visual hemifield occurring daily for weeks, months, or even years has been seen in over 50% of cases, and the epileptic origin of these symptoms could be substantiated by ictal EEG.

All patients with epilepsy develop focal clonic or myoclonic seizures, most often involving an arm, shoulder, the neck, and/or head and manifesting as simple partial motor seizures that often continue on to focal motor status. Occasionally, persisting focal or generalized myoclonic jerks can be observed. Motor simple partial seizures are sometimes accompanied by a clear epileptic EEG correlate, sometimes with rhythmic focal slowing of the contralateral, posterior hemispheric quadrant or the occipital electrodes. 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. Complex partial seizures with motor symptoms occur in more than 50% of patients and may be underreported. Generalized tonic-clonic seizures, all considered secondary generalized tonic-clonic (sGTC) seizures, occur in more than 90% of cases. All patients who develop epilepsy develop 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 epilepticus is 2 months.

EEG showing occipital slow-wave and epileptic activity occurs as an early feature in the majority of patients. Ictal registrations reveal either severe general slowing, with or without epileptic activity, or, as in the majority of patients, consistent focal occipital or tempo-occipital epileptic discharges.

**Other nuclear gene defects.** Although many mitochondrial nuclear gene defects can cause epilepsy, those due to
POLG mutation are, by far, the best described. Nevertheless, a similar syndrome with epilepsy and encephalopathy is seen with an early-onset disease due to mutations in the mitochondrial helicase Twinkle (Lönnqvist et al 2009), and it is highly likely that other nDNA defects, particularly those having a similar role to POLG and Twinkle (ie, involved in mtDNA homeostasis), will also be associated with similar clinical syndromes. Epilepsy is also common in pediatric disorders, such as Leigh syndrome, which are caused by defects in complex I or IV. Initial presentation with an epileptic seizure is well recognized, but as above, no particular seizure type is indicative of 1 of these disorders. Diseases associated with defects of ubiquinone biosynthesis are also potent causes of epilepsy, particularly those caused by mutations in ADCK3 (Zsurka and Kunz 2015).

Prognosis and complications

A wide spectrum of phenotypes are associated with mtDNA diseases, and the same mutation, eg, the common m.3243A>G, can give rise not only to MELAS, but also to diabetes, deafness, PEO, other endocrine disturbances, myopathy, gastroparesis, and cyclical vomiting. It is essential, therefore, that clinical follow-up recognizes this fact and that screening protocols are instituted. Mitochondrial syndromes such as MELAS, MERRF, and MSCAE are progressive and associated with poor prognosis and shortened lifespan. MELAS, as the name implies, is associated with stroke-like episodes that predispose to seizures and status epilepticus. Cardiomyopathy and diabetes mellitus are complications of MELAS that occur with relatively high frequency, and these must be actively sought and treated (Ng et al 2015). MERRF is less aggressive, but it is also associated with sudden death that might be cardiac in origin.

Acute encephalopathy and status epilepticus have a high mortality in patients with MSCAE. More than 70% of patients who develop status epilepticus die, compared with none of those who do not develop epilepsy. Because POLG mutations lead to defects in mtDNA, POLG-related disease manifests almost the same spectrum of phenotypes as mtDNA disease. Interestingly, however, neither diabetes nor cardiomyopathy is common.

In a review of 182 adult patients with mitochondrial disease attending a specialized clinic, the prevalence of epilepsy was 23.1% and the most common genotypes involved those caused by the m.3243A>G and m.8344A>G mtDNA mutations. The prevalence was 34.9% with m.3243A>G and 92.3% with m.8344A>G (especially myoclonus). Interestingly, however, the standardized mortality ratio, which was high for the whole group (2.86), did not differ between those with epilepsy and those without (Whittaker et al 2015).

Biological basis

Etiology and pathogenesis

Mitochondria are organelles with multiple functions, of which ATP production is arguably the most important. The pathway that generates ATP, the mitochondrial respiratory chain, is controlled by 2 genomes: 1 in the mitochondrion itself, mitochondrial DNA (mtDNA), and the other the nuclear genome DNA (nuclear DNA). Mitochondrial disease can arise from mutations occurring in either genome, and inheritance is, therefore, complex with maternal, recessive, dominant, and X-linked transmission all possible.

In classical genetics, the concepts of heterozygous (each gene copy has a different sequence) and homozygous (both gene copies have an identical sequence) are used. Dominant disorders arise when a mutation in 1 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 (McFarland et al 2004). Mutations can affect a percentage of mtDNA copies, from less than 1% to more than 99%. In homoplasy (cf. homozygous), all copies in an individual have the same sequence; in heteroplasy (cf. heterozygous), there are mtDNA with 2 different sequences, eg, 1 with a mutation and 1 normal. In addition, the level of mutation in 1 tissue can differ dramatically from another based on factors such as whether the cell retains the capacity to divide and, therefore, select against cells with impaired energy metabolism. In many mtDNA disorders, particularly those in which the defect is unknown, this will mean that it is not possible to use white blood cells, which retain the capacity to divide, as a source of genetic material because the level can fall below the level of detection.

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 in large part thought to explain their vulnerability to mitochondrial dysfunction and offer a potential explanation as to why epileptic seizures frequently occur. Evidence that neuronal energy failure is actually occurring in vivo has been
provided by MRI studies of so-called "stroke-like" lesions in both MELAS and POLG-related disease (Tzoulis and Bindoff 2012).

Decreased intracellular ATP levels can, moreover, increase neuronal excitability by impairing sodium-potassium ATPase activity and decreasing the membrane potential. Because mitochondria also store intracellular calcium, mitochondrial dysfunction can increase excitability and, thus, expose the neuron to damage by impairing calcium sequestration (Kunz 2002). Mitochondrial respiratory chain dysfunction may also lead to increased free radical production. It is known that free radicals are signaling molecules, but they may also initiate damage, eg, through apoptosis (Rahman 2015). In addition, studies in status epilepticus suggest that mitochondrial dysfunction does also play a role in seizure-related cell death (Kovac et al 2012). Whatever the initial mechanism, cortical damage can induce further seizures, which, in turn, cause more damage. The resulting vicious cycle may constitute an additional factor in the further destruction of surviving neurons.

**Epidemiology**

Mitochondrial diseases are common. Studies in the United Kingdom showed that 9.2 in 100,000 people of working age (over 16 and under 60/65 years of age, female/male) had a clinically manifest mtDNA disease, and a further 16.5 in 100,000 children and adults younger than retirement age were at risk of developing 1 (Schaefer et al 2008). Studies from Sweden showed that the incidence of mitochondrial encephalomyopathies in preschool children (under 6 years of age) was 1 in 11,000 (Darin et al 2001), and in Australia, an estimated minimum birth prevalence of 6.2 in 100,000 was found (Składal et al 2003). These figures are based only on patients with known mtDNA mutations; there is currently no way of estimating how many more mutations are still to be discovered, but several new mtDNA mutations are published each year. In a major study published in 2008, Elliott and colleagues determined the frequency of 10 mtDNA mutations in 3168 neonatal-cord blood samples from sequential live births and found that at least 1 in 200 healthy humans harbors a pathogenic mtDNA mutation that potentially causes disease in the offspring of female carriers (Elliott et al 2008).

**Prevention**

There are currently no studies dealing with this issue. In practice, however, because of the clear danger for status epilepticus, the author has a very low threshold for initiating anticonvulsant treatment in patients with the m.3243A>G and POLG mutations.

**Differential diagnosis**

Epilepsy as the only manifestation of syndromic mitochondrial disorders is highly unusual. Differential diagnosis depends on the other features present, eg, stroke-like episodes, myopathy, progressive myoclonic epilepsy, and lactic acidosis.

Stroke-like episodes are highly suggestive of mitochondrial etiology (occur in MELAS and POLG-related disease, but also other mtDNA disorders and even other metabolic conditions), but stroke occurring in isolation is more likely to be an ischemic stroke, which can also be associated with secondary epilepsy.

Myopathy and epilepsy is another combination that should prompt the clinician to consider mitochondrial disease as the primary diagnosis. The combination of myopathy and mental retardation gives a wider differential diagnosis that includes congenital muscular and myotonic dystrophies; refer to general muscle tracts for more information.

Progressive myoclonic epilepsy can occur with Unverricht-Lundborg disease, Lafora body disease, neuronal ceroid lipofuscinosis, and sialidosis.

Lactic acidosis is a hallmark of mitochondrial disease, but can also occur in other metabolic diseases such as very long-chain acyl-CoA dehydrogenase deficiency and early-onset trifunctional enzyme deficiency.

**Diagnostic workup**

Diagnosis of mitochondrial diseases is based on the usual algorithm of clinical suspicion and supplementary laboratory investigation (Taylor et al 2004). Elevated lactate in blood or CSF is a common, but inconsistent, finding and can be absent even in MELAS. The finding of raised lactate is, however, associated with the presence of stroke-like episodes,
and thus the risk of epilepsy in patients with the m.3243A>G mutation (Mancuso et al 2014). CSF lactate can be raised by seizure activity and some infections, so even the finding of elevated levels should be interpreted cautiously. Imaging techniques such as MRI can demonstrate patterns of involvement that suggest a mitochondrial etiology, particularly involvement of the occipital lobes and, in MSCAE, involvement of the thalamus and inferior olivary nuclei, but these are not diagnostic. Dystrophic calcification particularly affecting the basal ganglia is seen in MELAS, which has a significant epileptic component, but also in Kearns-Sayre syndrome, which does not. MR spectroscopy can demonstrate elevated lactate in regions of the brain, whereas PET scanning can provide metabolic information suggesting lowered ATP production. Neither of these techniques provides unequivocal evidence of mitochondrial respiratory chain dysfunction, however, and it is usually necessary to take a biopsy. The usual tissues that are investigated are skeletal muscle and skin fibroblasts, depending on whether mtDNA or nDNA disease is being questioned.

Skeletal muscle biopsy often shows 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. The presence of mitochondrial accumulation (ragged-red fibers) or fibers lacking complex IV activity [cytochrome oxidase (COX) negative fibers] are common features that suggest mitochondrial respiratory chain disease. Muscle or fibroblasts can be used for biochemical measurements of respiratory complexes and studies of mtDNA. These are techniques that demand a high technical proficiency, and it is advisable to contact a specialized laboratory in order to ascertain what is required. MELAS and MERRF are caused by mutations in mtDNA, thus, the most direct method of making the diagnosis is to demonstrate the mtDNA mutation. Because mutations affecting this genome are most often heteroplasmic, demonstrating their presence requires an understanding of which tissues and which techniques are appropriate (Taylor and Turnbull 2005). If 1 of these diseases is suspected, it is advisable to contact a specialized center that can advise on which sample to take and how to proceed if it is negative. MSCAE is caused by mutations in the nuclear gene POLG, and MSCAE is inherited as an autosomal recessive disease. Mutations screening can be performed on DNA extracted from a blood sample, but because there are many different mutations, this should be performed by a laboratory with experience in finding and evaluating DNA changes.

**Management**

**General guidelines.** There are no cures for mitochondrial disease. Precise diagnosis will provide information concerning known potential complications, eg, development of cardiac involvement or diabetes mellitus, and it is important to avoid potential mitochondrial toxins (antibiotics such as tetracyclines, gentamicin, and ciprofloxacin), antiviral agents, and sodium valproate. The latter is absolutely contraindicated in patients with POLG disease and probably should be avoided generally in patients suspected of having mitochondrial disease before the diagnosis is finally clarified. Fasting increases the demand on the mitochondrial respiratory chain, as will fever. This means that care must be taken even when the patient develops a simple viral infection. Ubiquinone is still widely used and has been shown to have effect in certain mitochondrial diseases, such as Leber hereditary optic neuropathy (Klopstock et al 2011).

**Epilepsy treatment.** No 1 antiepileptic drug is specifically indicated in mitochondrial disease. Because the seizure type is most often secondary generalized, carbamazepine, oxcarbazepine, and phenytoin are often effective; however, they generally require combination with a benzodiazepine, eg, clobazam or clonazepam. It is also often necessary to add a third antiepileptic drug. Drugs such as sodium channel blockers, lamotrigine, and gabapentin can worsen myoclonic seizures, and levetiracetam or topiramate can also be used if myoclonic seizures are a major feature. Again, it must be stressed that patients with known POLG1 mutations must absolutely avoid sodium valproate, and this applies even in patients where the diagnosis is suspected.

Patients with MELAS and POLG1 have a high risk of status epilepticus. Even patients with an apparently benign course can suddenly decompensate and develop focal or generalized status epilepticus. Although we do not suggest starting antiepileptic drug treatment before the start of any seizure disorders, a high index of suspicion is advocated, and this includes routine and regular EEG monitoring. Due to the potential for generating secondary damage, aggressive treatment is strongly advised once seizures have started. In mtDNA disorders such as MELAS and MERRF, treatment appears to be effective, at least initially. POLG1-related disorders, such as Alpers and MSCAE, can be extremely difficult to treat, and patients in whom it has been impossible to control focal motor status for long periods of time, ie, weeks, even with combinations of antiepileptic drugs in maximal doses, have been encountered.

Convulsive status epilepticus must be treated aggressively. Benzodiazepine infusion is often used as first-line
treatment, together with phenytoin and, occasionally, phenobarbital (supervision in intensive care unit). If unsuccessful, thiopental narcosis, together with cerebral monitoring to achieve burst suppression for at least 24 to 48 hours, can be used. Propofol narcosis can also be used as a first-line agent because the level of narcosis is more easily monitored and can be terminated more rapidly when successful treatment is achieved. Repeated treatment with thiopental has been successful, but several patients, particularly with POLG1 mutations, have died after prolonged periods of recurrent convulsive status epilepticus and nonconvulsive status epilepticus, with multiple organ failure following the use of every known and available antiepileptic drug.

In keeping with the treatment of several other intractable epilepsies, the use of ketogenic diet for mitochondrial disease has been suggested by several authors (Gano et al 2014). Although there are theoretical reasons why this form of treatment may be effective in mitochondrial disease, there are currently no trials on which to base clinical judgement.

Special considerations

Pregnancy

There is little information concerning pregnancy and most types of mtDNA disease, including MELAS and MERRF. In the author's experience, several women with MSCI have presented with status epilepticus during pregnancy, but whether pregnancy has triggered it or whether it is simply coincidental is unclear.

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**References especially recommended by the author or editor for general reading.

ICD and OMIM codes

ICD codes

ICD-10:
Mitochondrial myopathy, not elsewhere classified: G71.3

OMIM numbers

Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; MELAS: #540000
Myoclonic epilepsy associated with ragged-red fibers; MERFF: #545000
Mitochondrial spinocerebellar ataxia with epilepsy; MSCAE: #607459

Profile

Age range of presentation

0-23 months
02-05 years
06-12 years
13-18 years
19-44 years

Sex preponderance

male=female

Family history

family history typical

Heredity

heredity typical
autosomal recessive
autosomal dominant
maternal
X-linked

**Population groups selectively affected**

none selectively affected

**Occupation groups selectively affected**

none selectively affected

**Differential diagnosis list**

congenital muscular dystrophy
early-onset trifunctional enzyme deficiency
ischemic stroke
Lafora body disease
myotonic dystrophy
neuronal ceroid lipofuscinosis
sialidosis
Unverricht-Lundborg disease
very long-chain acyl-CoA dehydrogenase deficiency

**Other topics to consider**

Epilepsy
MELAS
Mitochondrial disorders
Myoclonus epilepsy with ragged-red fibers
POLG-related disorders

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