Mitochondrial diseases and status epilepticus

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Abstract

This narrative review focuses on the pathophysiology, diagnosis and management of status epilepticus in the context of primary mitochondrial disease. Epilepsy is common in mitochondrial disease, reported in greater than 20% of adult cases and 40-60% of paediatric cohorts. Status epilepticus is less frequently reported and appears to associate with particular subgroups of mitochondrial disorders, namely defects of the mitochondrial DNA and its maintenance, and disorders of mitochondrial translation and dynamics. Mechanisms underlying mitochondrial status epilepticus are incompletely understood, and may include bioenergetic failure, oxidative stress, immune dysfunction and impaired mitochondrial dynamics. Treatments tried in mitochondrial status epilepticus include antiepileptic drugs, anaesthetic agents, magnesium, high dose steroids, immune globulins, vagal nerve stimulation and surgical procedures, all with variable success. The outcome of mitochondrial status epilepticus is extremely poor, and effective therapeutic options have not been reported. Improved understanding of the mechanisms underpinning mitochondrial status epilepticus is needed in order to develop more effective treatments.

Key Words:

Mitochondrial epilepsy pathophysiology, *POLG*, mitochondrial translation, mitochondrial dynamics, treatment

Key Bullet Points:

- Mitochondrial status epilepticus is genetically heterogeneous
- Known genetic causes include defects of mitochondrial DNA and its maintenance and disorders of mitochondrial translation and dynamics
- The outcome of mitochondrial status epilepticus is extremely poor, with a high mortality rate
- Effective therapies have not been reported for mitochondrial status epilepticus
- Improved understanding of mechanisms underlying mitochondrial status epilepticus will facilitate development of effective therapies

Mitochondrial function, genetics and disease

Mitochondria are virtually ubiquitous, highly dynamic cellular organelles with essential roles in cell metabolism, including aerobic energy generation, defence against oxidative stress and calcium homeostasis. In addition, mitochondria in specific cell types have specialised roles including biosynthesis of neurotransmitters, cholesterol and steroid hormones, and disposal of waste nitrogen via the urea cycle.

A unique feature of mitochondria is that they possess their own genetic material, the small circular mitochondrial genome. This genome has particular properties, including high copy number, a genetic code differing from that of nuclear DNA, and exclusive maternal inheritance.

Primary mitochondrial diseases are defined as inherited disorders that cause disease by directly or indirectly affecting the mitochondrial oxidative phosphorylation system. These are pleiotropic disorders with widely differing phenotypes and genotypes that collectively affect at least 1 in 5000 live births. Currently, all 37 mitochondrial genes and >250 nuclear genes have been reported to cause mitochondrial disease, and epilepsy may be a feature of more than half of these gene defects (Table 1).

Epilepsy in mitochondrial disease

Mitochondrial disorders are characterised by extreme clinical heterogeneity, and it is said that affected patients may present with any symptom or combination of symptoms, affecting any organ (or indeed multiple organs simultaneously) at any age [1]. The types of epilepsy reported in mitochondrial disease are also heterogeneous, but the most frequently reported seizure types are myoclonic seizures, focal motor seizures with secondary generalisation, epilepsia partialis continua and generalised tonic clonic seizures [2 3 4].

Status epilepticus in mitochondrial disease

Status epilepticus has recently been redefined as “a condition resulting either from a failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures (after time point t1). It is a condition, which can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures” [5]. Epilepsia partialis continua (EPC), a focal motor status epilepticus, is an unusual manifestation of epilepsy but is observed relatively frequently in primary mitochondrial diseases [6].

In the general population status epilepticus affects ~10-60 people per hundred thousand per year [7] [8] [9]. The prevalence of mitochondrial status epilepticus is unknown. Status epilepticus was reported in only 4 of a series of 60 patients with clinical seizures related to mitochondrial disease, including one patient with EPC and one with convulsive and two with non-convulsive status epilepticus [4]. Although status epilepticus is less frequently reported than other types of seizures in patients with mitochondrial disease, mitochondrial disorders are thought to be a relatively common cause of status epilepticus [10] [11]. It is not clear whether status occurs less frequently in some forms of mitochondrial disease, or if it is under-reported. The most frequent causes of mitochondrial status epilepticus are mitochondrial DNA (mtDNA) mutations (especially those associated with the mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) and myoclonus epilepsy with ragged-red fibres (MERRF) syndromes) and defects of mtDNA maintenance, particularly biallelic mutations in *POLG* (Figure 1).

Mitochondrial DNA disorders

MELAS

MELAS is a maternally inherited disorder. The condition usually presents towards the end of the first decade with a stroke-like episode, frequently associated with a focal seizure. Other clinical features include ataxia, cognitive decline, sensorineural hearing loss, optic atrophy, diabetes mellitus, renal impairment, short stature and cardiomyopathy. MELAS is usually caused by a point

mutation of mtDNA, specifically m.3243A>G in the *MT-TL1* gene encoding a transfer RNA (tRNA) for leucine in ~80% of cases. The m.3243A>G mutation is regarded as 'common', being present in 1 in 400 people, but only rarely causes the MELAS syndrome [12]. It is thought that patients with MELAS have very high mutational loads in brain. Rarely, mutations of *POLG* can mimic MELAS syndrome [13].

Status epilepticus was reported in 5/63 cases (7.9%) with MELAS in one series, always in the context of a stroke-like episode [14]. Although stroke-like episodes usually occur by the end of the first decade in MELAS, initial presentation with status epilepticus as the first manifestation has been reported in the sixth decade [15] [16]. Status epilepticus in MELAS may present in unusual ways, for example as an aggressive confusional state [17]. Nonconvulsive status epilepticus has also been reported in MELAS [18]. Status epilepticus may be a terminal event in MELAS and was associated with sudden death in one case [19].

MERRF

MERRF is another maternally inherited mitochondrial encephalomyopathy, usually caused by the m.8344A>G mutation in *MT-TK* encoding the mitochondrial tRNA for lysine. Clinical features include myoclonus, epilepsy, ataxia, cognitive decline, myopathy, sensorineural hearing loss, pigmentary retinopathy and multiple symmetric lipomatosis. Seizures are a frequent problem and have been reported in 46 to 92% of patients in different series [20] [14]. Status epilepticus occurred in 2/24 (8%) of cases in an Italian patient registry [20]. As for MELAS syndrome, status epilepticus may be associated with stroke-like episodes in MERRF (author's unpublished observation).

Other mitochondrial DNA mutations

Status epilepticus has also been reported in association with a number of other mtDNA point mutations, mostly involving tRNA genes (*MT-TF*, *MT-TK*, *MT-TL1*, *MT-TV*, *MT-TW* and *MT-TH*), but also in genes encoding subunits of complexes I, III and IV (*MT-ND1*, *MT-ND4*, *MT-ND6*, *MT-CYB* and *MT-CO1*). Mutations of these mitochondrial genes are comprehensively catalogued in the Mitomap online database (www.mitomap.org).

Nuclear gene disorders

POLG disease

The most frequent cause of mitochondrial status epilepticus is Alpers syndrome (progressive neuronal degeneration of childhood), initially described as a triad of neurodevelopmental regression, intractable seizures and hepatic dysfunction [21]. However it is now recognised that many affected individuals do not have liver disease [22]. The disorder is caused by biallelic mutations in *POLG*, encoding the catalytic subunit of DNA polymerase gamma (the enzyme responsible for replicating mtDNA), which lead to progressive depletion of the mtDNA [23]. A recent multinational retrospective cohort study of early onset *POLG* disease revealed that 68% of children developed status epilepticus during their life course and 58% had EPC [22]. Eighty-nine percent of cases had therapy resistant epilepsy. Similar findings were obtained in a systematic review of 229 patients with *POLG*-related epilepsy in whom seizure semiology had been reported; 49% had generalised status epilepticus whilst 34% had focal motor status [24].

Other disorders of mtDNA maintenance

Several defects of mtDNA maintenance may manifest as dominant or recessive disease. The dominant disorders are generally associated with progressive external ophthalmoplegia related to the accumulation of multiple mtDNA deletions, whilst the recessive disorders are characterised by progressive depletion of mtDNA. The mtDNA depletion disorders may be classified broadly into myopathic, hepatocerebral and encephalomyopathic variants. The latter two groups are frequently complicated by epilepsy including status epilepticus. For example, biallelic mutations of *TWNK*, encoding a mitochondrial DNA helicase, may cause infantile onset spinocerebellar ataxia (IOSCA) associated with EPC and status epilepticus [25]. Biallelic mutations of *RRM2B*, encoding ribonucleotide reductase TP53 inducible subunit M2B, may present as an infantile onset encephalomyopathy characterised by severe muscle weakness, respiratory failure, ophthalmoplegia, sensorineural hearing loss, renal tubulopathy and intractable seizures [26]. Status epilepticus has also been reported in two brothers with *TK2* mutations, a disorder of mitochondrial nucleoside salvage that more typically is associated with a purely myopathic phenotype [27].

Disorders of mitochondrial translation

A rapidly expanding group of disorders are nuclear-encoded disorders affecting the mitochondrial protein synthesis apparatus. This group of disorders includes defects of mitochondrial RNA processing (e.g. *TRNT1* mutations) [28], tRNA aminoacylation, ribosomal structural proteins, and elongation of the polypeptide chain. Together, these disorders number >50 different gene defects and status epilepticus has been reported in several of these (Figure 1). For example, mutations in *CARS2*, *FARS2*, *NARS2* and *PARS2*, encoding the tRNA aminoacyl synthetases for cysteine, phenylalanine, asparagine and proline respectively, may all cause disorders resembling Alpers syndrome, with drug-resistant intractable seizures and episodes of status epilepticus [29 30 31]. Mutations of genes encoding three other tRNA aminoacyl synthetases (*RARS2*, *VARS2* and *QARS*) have also been reported to cause status epilepticus [32 33 34].

Disorders of mitochondrial dynamics

The dynamic nature of mitochondria is essential to support the energetic and calcium buffering needs of neurons for neurotransmission. It is therefore unsurprising that several defects of mitochondrial dynamics have been linked to status epilepticus, including *DNM1L* mutations encoding the mitochondrial fission protein DRP1 [35]. Mutations of the JAK-STAT cytokine STAT2 also caused intractable epilepsy associated with defective mitochondrial fission [36]. Most recently, mutations of *TRAK1*, encoding a kinesin required for mitochondrial trafficking in neurons, have also been reported to cause a fatal early-onset encephalopathy with status epilepticus [37].

Other gene defects

Other defects of mitochondrial function associated with status epilepticus include impaired assembly of OXPHOS enzyme complexes, especially complex IV (e.g. mutations in the COX assembly genes *COX10*, *PET100* and *FASTKD2*) [38 39 40], and defects of substrate supply due to mutations of transporters (e.g. two mitochondrial glutamate carriers SLC25A12 and , and SLC25A22, and the thiamine transporter SLC19A3) [41 42 43]. Recurrent episodes of status epilepticus have been reported in patients with disorders of mitochondrial cofactor biosynthesis,

including *COQ8A* (*ADCK3*) mutations leading to coenzyme Q_{10} deficiency [44] and *BOLA3* mutations leading to defective synthesis of lipoic acid (an essential cofactor of several mitochondrial enzymes) [45].

Pathophysiological mechanisms

Status epilepticus can be viewed as a failure of processes that terminate seizures, or reinforcement of processes that propagate seizure activity [46]. Seizure termination may be related to depletion of neurotransmitters and/or ATP, ionic and/or acid/base changes, and release of adenosine or seizure-terminating peptides.

The reasons why defects of mtDNA and its maintenance and of mitochondrial protein synthesis particularly associate with status epilepticus remain obscure. The most obvious explanations, such as bioenergetic failure and/or oxidative stress (overproduction of reactive oxygen species), cannot be the sole cause since these are common to other mitochondrial disorders that are not associated with epilepsy or status epilepticus [47]. It has been suggested that status epilepticus may be a 'system or network phenomenon' [11]. Mitochondrial abnormalities that follow bioenergetic failure and oxidative stress include inability to maintain calcium and other ionic gradients, eventually leading to opening of the mitochondrial permeability transition pore and apoptotic cell death [46 47]. An additional possibility is that an immune-mediated component of mitochondrial epilepsy drives continuing seizure activity. There is most evidence to support this hypothesis in the case of POLG deficiency. Folate receptor blocking autoantibodies and oligoclonal bands have been observed in the cerebrospinal fluid of patients with *POLG* mutations, and one case had neuropathological evidence of an autoimmune disease process resembling acute disseminated encephalomyelitis [48 49]. The observation of intractable seizures in patients with STAT2 deficiency leading to impaired innate immunity lends further weight to the possibility that mitochondrial status epilepticus may be propagated by a failure of normal immune mechanisms [36].

Mitochondrial dynamics has an emerging role in the pathophysiology of status epilepticus. As discussed above, mutations of the mitochondrial fission protein DRP1 have been reported in infants with status epilepticus [35]. Recent studies in animal models also support a role for disordered mitochondrial dynamics in the pathophysiology of status epilepticus. Drp1 mRNA levels were downregulated in a rat model of status epilepticus, leading to an imbalance of mitochondrial fission and fusion [50]. Another study suggested that alterations of mitochondrial dynamics in status epilepticus may be specific to particular brain regions; astrocytes in the CA1 region showed mitochondrial elongation induced by status epilepticus whereas status-induced astroglial apoptosis in the molecular layer of the dentate gyrus was associated with decreased mitochondrial length [51]. Further studies are needed to fully understand the role of mitochondrial fission and fusion in the pathophysiology of status epilepticus.

Management

Status epilepticus is a life-threatening neurological emergency with high mortality and morbidity. Treatment of status epilepticus in mitochondrial disease has not been systematically reviewed, so it is not possible to comment on the relative efficacy of different antiepileptic drugs and anaesthetic agents for this group of disorders. Reported therapies include benzodiazepines (most commonly midazolam or lorazepam), barbiturates and propofol. Sodium valproate should be avoided in *POLG* disease since its administration may precipitate liver failure in this disorder [52]. One report described response to ketamine in a 22 year old woman with *POLG* mutations whose seizures had been resistant to benzodiazepines, phenytoin, thiopental and propofol [53]. However the long term outcome for this patient was not reported. Magnesium infusion has been suggested as a therapy for super-refractory status epilepticus [54]. One study reported apparent cessation of seizures after increasing serum magnesium levels from ~0.8 to ~3.5mmol/L in two teenagers with *POLG* mutations [55]. Again, the long term outcome was not described, and there has only been one further report of magnesium therapy for mitochondrial epilepsy; the combination of levetiracetam and magnesium citrate apparently led to temporary seizure cessation in a 22 year old woman with MELAS [56]. Of note, one case report described magnesium toxicity in a woman with pre-eclampsia

and the m.3243A>G MELAS mutation [57]. Thus, the efficacy and safety of this treatment remain uncertain.

Other measures that have been reported in mitochondrial status epilepticus, again with questionable efficacy, include high dose steroids and intravenous immunoglobulin [58]. Seizures stopped after vagal nerve stimulation (VNS) in a 16 year old girl with MERRF, and there were no further episodes of status epilepticus during 1.5 years of follow-up [59]. However, VNS was not associated with significant seizure reduction in five children with biochemically but not genetically confirmed mitochondrial disease [60]. Palliative functional hemispherectomy was reported to allow a child with Alpers syndrome and refractory status epilepticus to be extubated and discharged home [61]. However, she died of liver failure only a few months later, so it is debatable whether such an invasive procedure was justified given the ultimately fatal outcome [62] [63].

In patients with status epilepticus, treatment of the underlying disease is clearly important. However for most forms of mitochondrial disease there are no curative options at present. Treatment of mitochondrial disease currently consists of symptomatic measures, which should include correction of electrolyte disturbances (which may be secondary to renal tubulopathy), management of acidosis and/or hypoglycaemia, and treatment of underlying/precipitating infections. The role of vitamin supplements is unproven in mitochondrial disease, but given that there is likely little to lose in the ICU setting, most physicians would probably prescribe a trial of vitamins/cofactors including riboflavin and coenzyme Q_{10} [58]. Status epilepticus is a known harbinger of stroke-like episodes in MELAS syndrome, and there is some evidence that these may be prevented/ameliorated by the administration of L-arginine or citrulline [64].

The role of dietary therapies remains uncertain. Reports of the efficacy of ketogenic diet or other forms of a high-fat, low-carbohydrate diet in mitochondrial status epilepticus are limited to single case studies [65] [56]. Formal clinical trials have not been performed. Recent preclinical data have suggested a possible role for decanoic acid in seizure control [66]. Decanoic acid is a fatty acid that is elevated in the blood of individuals on a ketogenic diet. It appears to have pleomorphic roles,

including stimulating mitochondrial biogenesis and inhibiting AMPA receptors [67] [68]. Preliminary data have suggested positive effects of decanoic acid on mitochondrial function in fibroblasts from patients with a mitochondrial encephalomyopathy (Leigh syndrome) caused by complex I subunit mutations [69], but this has not yet been investigated as a treatment for mitochondrial epilepsy in clinical trials.

The outcome of mitochondrial status epilepticus is extremely poor. Four of 11 patients with mitochondrial disease admitted to the ICU with seizures died in one series [70]. Provision of psychological support for the family and palliative care for the patient, in a hospice or home setting as appropriate to the needs of the family, is vitally important.

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Ethical Publishing Statement

I confirm that I have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Figure 1 Legend

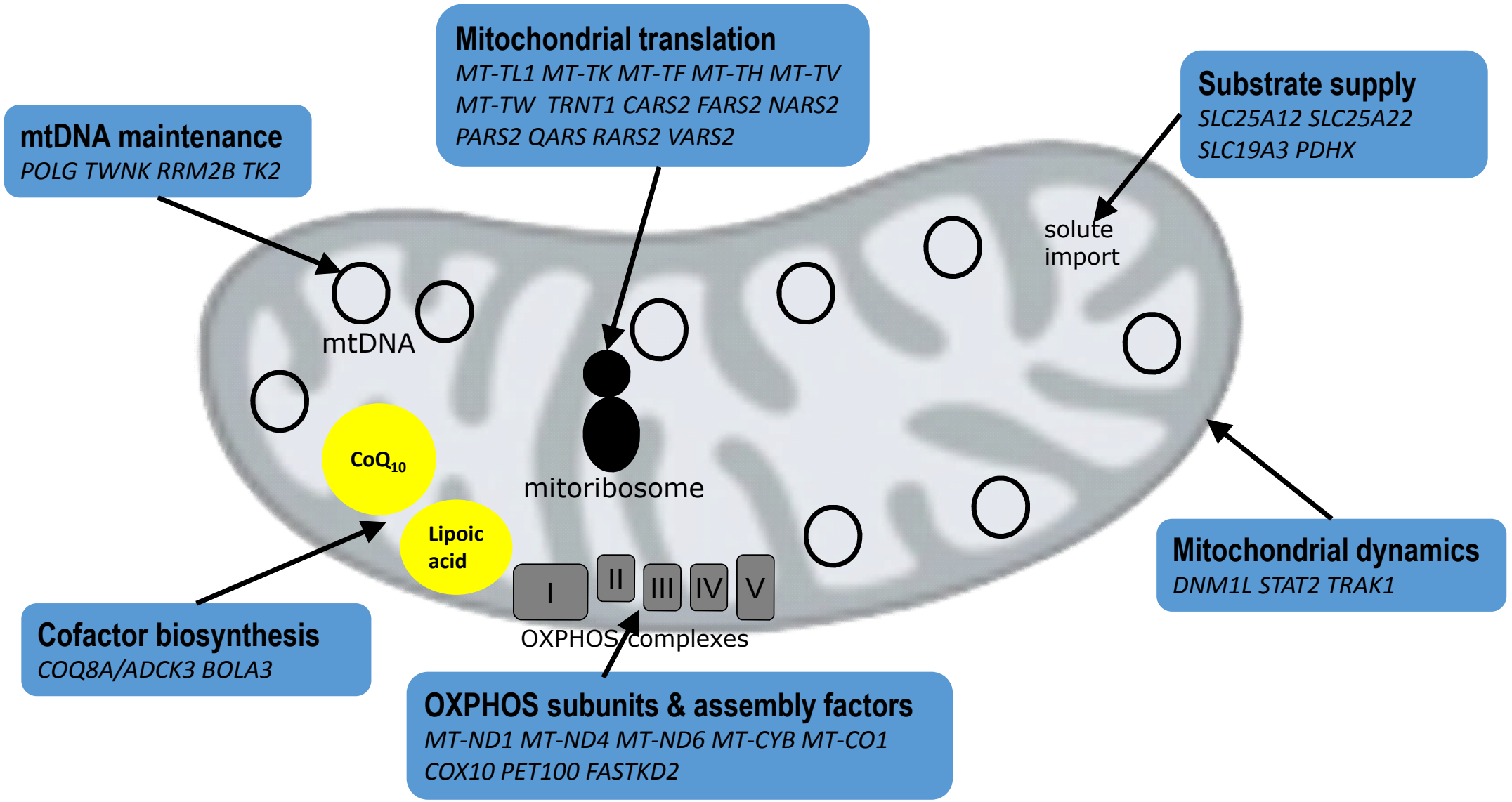
Molecular mechanisms associated with mitochondrial status epilepticus.

Key: CoQ_{10}, coenzyme Q_{10}; mtDNA, mitochondrial DNA; OXPHOS, oxidative phosphorylation.

Table 1 – Gene defects underlying mitochondrial epilepsy and status epilepticus

Disease mechanism	Biochemical defect	Gene defects and modes of inheritance
OXPHOS subunit defects	Complex I	*Mat:* ***MT-ND1 MT-ND4 MT-ND6*** *MT-ND3 MT-ND5* *AR: NDUFV1 NDUFS2 NDUFS3 NDUFS4 NDUFS6 NDUFS7 NDUFS8 NDUFA2 NDUFA10 NDUFA11 NDUFA13* *XL: NDUFA1 NDUFB11*
	Complex II	*AR: SDHA SDHD*
	Complex III	*Mat:* ***MT-CYB*** *AR: UQCRC2*
	Complex IV	*Mat:* ***MT-CO1*** *MT-CO2* *AR: COX6B1 COX8A NDUFA4*
	Complex V	*Mat: MT-ATP6* *AR: ATP5A1*
OXPHOS assembly factor defects	Complex I	*AR: NDUFAF1 NDUFAF2 NDUFAF3 NDUFAF4 NDUFAF5 NDUFAF6 FOXRED1 ACAD9 NUBPL C17orf89*
	Complex II	*AR: SDHAF1*
	Complex III	*AR: BCS1L HCCS UQCC2 TTC19*
	Complex IV	*AR:* ***COX10 PET100 FASTKD2*** *SURF1 SCO1 SCO2 COX15*
	Complex V	*AR: ATPAF2 TMEM70*
mtDNA maintenance defects	Multiple RC enzymes (but can be isolated deficiency or normal enzyme activities)	*AR:* ***POLG TWNK RRM2B TK2*** *DGUOK SUCLA2 SUCLG1 TYMP MPV17 FBXL4 ABAT*
Mitochondrial translation defects	Multiple RC enzymes (but can be isolated deficiency or normal enzyme activities)	*Mat:* ***MT-TL1 MT-TK MT-TF MT-TH MT-TV MT-TW*** *MT-TC MT-TD MT-TI MT-TN MT-TP MT-TQ MT-TS1 MT-TS2 MT-TT* *AR:* ***CARS2 FARS2 NARS2 PARS2 RARS2 VARS2 QARS TRNT1*** *KARS EARS2 MRPS22 MTFMT MTO1 GTPBP3 PNPT1 TRIT1 LRPPRC TFSM GFM1 RMND1* *XL: HSD17B10*
Pyruvate dehydrogenase deficiency	Pyruvate dehydrogenase	*AR:* ***PDHX*** *PDHB DLD* *XL: PDHA1*
Defects of cofactor biosynthesis and transport	Coenzyme Q_{10}	*AR:* ***COQ8A/ADCK3*** *COQ8B/ADCK4PDSS2 COQ2 COQ4 COQ6 COQ9*
	Iron sulphur clusters and lipoic acid	*AR:* ***BOLA3*** *NFU1 NFS1 LIAS*
	Thiamine	*AR:* ***SLC19A3*** *SLC25A19 TPK1*
	NADP	*AR: NADK*
	Manganese	*AR: SLC39A8*
Mitochondrial import	Multiple RC enzymes or normal enzyme activities	*AR: SLC25A1 SLC25A12 SLC25A22 DNAJC19 TIMM50 AIFM1*
Defects of mitochondrial dynamics and lipid membranes	Multiple RC enzymes or normal enzyme activities	*AR:* ***DNM1L STAT2 TRAK1*** *MFF SLC25A46 SERAC1 AGK*
Defects of mitochondrial quality control	Multiple RC enzymes or normal enzyme activities	*AR: CLPB AFG3L2 HSPD1 HTRA2 MIPEP SACS*
Respiratory chain toxicity	Multiple RC enzymes, isolated complex IV deficiency or normal enzyme activities	*AR: ETHE1 HIBCH ECHS1 NAXE*
Other mechanisms	Multiple RC enzymes, isolated complex IV deficiency or normal enzyme activities	*AR: APOPT1 TXN2 PPA2*

Key: AR autosomal recessive; Mat maternal inheritance; NADP nicotinamide adenine dinucleotide phosphate; XL X-linked; **Genes indicated in bold font have been associated with status epilepticus**


Mitochondrial translation
MT-TL1 MT-TK MT-TF MT-TH MT-TV
MT-TW TRNT1 CARS2 FARS2 NARS2
PARS2 QARS RARS2 VARS2
mtDNA maintenance
POLG TWNK RRM2B TK2
Substrate supply
SLC25A12 SLC25A22
SLC19A3 PDHX
solute
import
mtDNA
CoQ10
Lipoic
acid
mitoribosome
I
II
III
IV
V
OXPHOS complexes
Cofactor biosynthesis
COQ8A/ADCK3 BOLA3
OXPHOS subunits & assembly factors
MT-ND1 MT-ND4 MT-ND6 MT-CYB MT-CO1
COX10 PET100 FASTKD2
Mitochondrial dynamics
DNM1L STAT2 TRAK1