Acute mitochondrial encephalopathy reflects neuronal energy failure irrespective of which genome the genetic defect affects

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Mitochondrial dysfunction and disease may arise as a result of mutations in either the mitochondrial genome itself or nuclear encoded genes involved in mitochondrial homeostasis and function. Irrespective of which genome is affected, mitochondrial encephalopathies share clinical and biochemical features suggesting common pathophysiological pathways. Two common paradigms of mitochondrial encephalopathy are mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes caused by maternally transmitted mutations of mitochondrial DNA and mitochondrial spinocerebellar ataxia and epilepsy caused by recessively inherited mutations of the nuclear-encoded DNA polymerase gamma, which replicates and repairs the mitochondrial genome. We studied and compared the disease mechanisms involved in these two syndromes. Despite having different genetic origins, their pathophysiological pathways converge on one critical event, damage to the respiratory chain leading to insufficient energy to maintain cellular homeostasis. In the central nervous system, this appears to cause selective neuronal damage leading to the development of lesions that mimic ischaemic damage, but which lack evidence of decreased tissue perfusion. Although these stroke-like lesions may expand or regress dynamically, the critical factor that dictates prognosis is the presence of epilepsy. Epileptic seizures increase the energy requirements of the metabolically already compromised neurons establishing a vicious cycle resulting in worsening energy failure and neuronal death. We believe that it is this cycle of events that determines outcome and which provides us with a mechanistic structure to understand the pathophysiology of acute mitochondrial encephalopathies and plan future treatments.

Keywords: polymerase gamma; POLG; MELAS; MSCAE; stroke

Abbreviations: MELAS = mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes; MERRF = myoclonic epilepsy with ragged red fibres; MSCAE = mitochondrial spinocerebellar ataxia and epilepsy

Introduction

Mitochondrial diseases affect all ages, from infancy to old age, and are among the most common metabolic diseases known. The mitochondrial respiratory chain is the final common pathway for energy production and is under dual genetic control: 13 of the proteins that make up complexes I, III, IV and V are encoded by mitochondrial DNA while the remainder of the >85 proteins
are encoded in the nucleus, translated in the cytoplasm and imported into mitochondria. Numerous other proteins, including those required for mitochondrial DNA homeostasis, intramitochondrial protein synthesis and assembly of the respiratory complexes, are also nuclear encoded and they too are translated in the cytosol and transported across the mitochondrial membranes. The genetic and structural complexities of this system means that a respiratory chain disease may have its origin in one of two genomes, arise due to a defect of a respiratory chain subunit, an assembly factor or defect of protein translation, or because of secondary mitochondrial DNA damage.

Mutations in genes encoding respiratory chain components, or proteins involved in its homeostasis, produce a wide spectrum of clinical disease ranging from myopathy and encephalopathy, to cardiomyopathy, endocrine, renal and gastrointestinal disease. Cellular dysfunction is assumed to arise from disordered energy metabolism, i.e. failure of the respiratory chain to produce ATP, but while this may be confirmed in some instances, e.g. in skeletal muscle from patients with mitochondrial myopathy, demonstrating that energy deficiency occurs in the whole patient is more problematic, particularly for diseases that primarily affect the brain.

Two of the most common mitochondrial encephalopathies are the syndromes of mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) and mitochondrial spinocerebellar ataxia and epilepsy (MSCAE). MELAS is caused by maternally transmitted, mitochondrial DNA point mutations (Goto et al., 1990) while MSCAE is the adult-onset form of encephalopathy caused by autosomal recessive mutations in the gene encoding the catalytic subunit of the mitochondrial DNA polymerase gamma (POLG) (Hakonen et al., 2005; Tzoulis et al., 2006, 2010). Although caused by mutations in different genomes, these two syndromes show clear MRI and post-mortem similarities. Using these common disorders as the paradigm, we postulate that selective neuronal energy failure is the common pathophysiological denominator in acute mitochondrial encephalopathy.

Materials and methods

The MSCAE data were based on our own material (n = 36), which has been previously published (Tzoulis et al., 2006, 2010). Ninety-four MELAS cases were collected from the literature (n = 89) (Goto et al., 1992; DiMauro and Hirano, 1993; Takahashi et al., 1998; Watanabe et al., 1998; Yoneda et al., 1999; Ohshita et al., 2000; Oppenheim et al., 2000; Bataller et al., 2001; Deschaux et al., 2001; Kim et al., 2001, 2011; Iizuka et al., 2002, 2007; Crimi et al., 2003; Jeppesen et al., 2003; Kolb et al., 2003; Wang et al., 2003, 2010; Chung et al., 2005; Betts et al., 2006; Bi et al., 2006; Mizrahi et al., 2006; Tzoulis et al., 2006, 2010; Chan et al., 2007; Conforto et al., 2007; Malfatti et al., 2007; Chou et al., 2008; Ito et al., 2008; Stoquart-Elsankari et al., 2008; Hsu et al., 2009; Karkare et al., 2009; Tzoulis and Bindoff, 2009; Herrero-Martin et al., 2010; Tsuchikawa et al., 2010; Glatz et al., 2011) and our own unpublished material (n = 5). This was a non-systematic review that included all large case series of patients fulfilling the clinical criteria for MELAS (Hirano et al., 1992) caused by a known mitochondrial DNA mutation, in which an adequate description of the clinical and/or radiological features was provided. Statistical comparison of the clinical and radiological features in the two groups was done using Fisher’s exact test and two-tailed P-values were calculated.

MELAS and MSCAE: clinical/pathological comparison

Clinical features

The most common clinical features of MELAS and MSCAE are summarized in Table 1. The first symptoms in both diseases usually appear in childhood or teenage years and presenting features include ataxia, epilepsy, headaches and episodic encephalopathy. Both diseases have an acute-on-chronic course: acute exacerbations associated usually with stroke-like episodes, are superimposed on a progressive neurological deterioration. Stroke-like episodes are characterized by acute or subacute neurological dysfunction, often with prodromal symptoms such as migraine-like headaches and mental changes. Prodromal symptoms may precede the onset of acute neurological dysfunction by up to several days (Tzoulis et al., 2010). Clinical features during episodes include reduced levels of consciousness ranging from lethargy to coma, partial and generalized epileptic activity and focal neurological deficit (Pavlakis et al., 1984; DiMauro and Hirano, 1993; Hirano and Pavlakis, 1994; Tzoulis et al., 2006, 2010). Focal epilepsy is common in both MELAS and MSCAE especially in the form of epilepsy partialis continua. Visual seizures due to an occipital or occipitotemporal EEG focus are common, and status epilepticus is a frequent and often life-threatening occurrence (Schomer, 1993; Engelsen et al., 2008; Karkare et al., 2009; Kaufman et al., 2010).

Table 1 Clinical features of MELAS and MSCAE

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>MELAS</th>
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<th>MSCAE</th>
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<tbody>
<tr>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Stroke-like episodes</td>
<td>76/76</td>
<td>100</td>
<td>26/36</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>62/73</td>
<td>85</td>
<td>26/36</td>
</tr>
<tr>
<td>Headache</td>
<td>48/72</td>
<td>67</td>
<td>29/36</td>
</tr>
<tr>
<td>Myoclonusa</td>
<td>6/40</td>
<td>15</td>
<td>24/36</td>
</tr>
<tr>
<td>Ataxiaa</td>
<td>9/41</td>
<td>22</td>
<td>35/36</td>
</tr>
<tr>
<td>External ophthalmoplegiaa</td>
<td>8/69</td>
<td>12</td>
<td>16/36</td>
</tr>
<tr>
<td>Optic atrophy</td>
<td>3/32</td>
<td>1</td>
<td>0/36</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>3/72</td>
<td>4</td>
<td>0/36</td>
</tr>
<tr>
<td>Deafnessa</td>
<td>36/74</td>
<td>49</td>
<td>1/36</td>
</tr>
<tr>
<td>Heart failurea</td>
<td>13/74</td>
<td>18</td>
<td>0/36</td>
</tr>
<tr>
<td>Diabetes melittusa</td>
<td>14/39</td>
<td>36</td>
<td>0/36</td>
</tr>
<tr>
<td>Liver diseasea</td>
<td>0/76</td>
<td>0</td>
<td>18/36</td>
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</table>

All MELAS patients fulfill the clinical diagnostic criteria for MELAS syndrome (Hirano et al., 1992). Sixty-seven have the common mutation m.3243A>G in the tRNAGlu(UGC)(MT-TL1). Three have other transfer RNA gene mutations. Five have ND5 mutations and one has ND1 mutation. All patients with MSCAE have the POLG1 mutations c.1399G>A, or/and c.2243G>C. *Features showing statistically significant differences between MELAS and MSCAE. Statistical significance was P = 0.0001 for all except progressive external ophthalmoplegia (P = 0.0002) and heart failure (P = 0.0040). We have not calculated significance for stroke-like episodes since this criterion is part of the definition of MELAS. The same is true for ataxia and MSCAE, but this is given.
Extraneural disease occurs in both conditions, but interestingly, apart from skeletal muscle, which is affected in both diseases, this often affects different organs. Sensorineural deafness is common in MELAS, but rare in MSCAE. Optic neuropathy and retinal disease occur in MELAS, but have not been described in MSCAE. Diabetes mellitus, heart disease and nephropathy are seen in MELAS. Acute liver necrosis occurs in POLG-related disorders either spontaneously or precipitated by the antiepileptic drug sodium valproate, but has not been reported in genetically confirmed MELAS (Goto et al., 1992; DiMauro and Hirano, 1993; Takahashi et al., 1998; Yoneda et al., 1999; Bataillard et al., 2001; Deschauer et al., 2001; Iizuka et al., 2002; Crimi et al., 2003; Jeppesen et al., 2003; Kolb et al., 2003; Wang et al., 2003, 2010; Betts et al., 2006; Tzoulis et al., 2006, 2010; Conforto et al., 2007; Malfatti et al., 2007; Hsu et al., 2009; Tsujikawa et al., 2010; Glatz et al., 2011; Kim et al., 2011).

**Neuroimaging**

Imaging of stroke-like cerebral lesions shows major similarities. Lesions consist of oedematous cortical changes often extending into the subcortical white matter and preferentially affecting the posterior brain (Fig. 1) (Iizuka et al., 2003; Tzoulis et al., 2010). In MSCAE, diffusion-weighted imaging performed up to 8 days after clinical onset of a stroke-like episode shows restricted apparent diffusion coefficient in the lesion, which subsequently increases over days to weeks to above normal levels (Tzoulis et al., 2010). In MELAS, decreased apparent diffusion coefficient has been reported in stroke-like lesion up to 14 days from clinical onset (Kim et al., 2001, 2011; Bi et al., 2006; Karkare et al., 2009; Tzoulis and Bindoff, 2009), but increased apparent diffusion coefficient has also been described in the acute phase (Yoneda et al., 1999; Yonemura et al., 2001; Kolb et al., 2003). This apparent contradiction, may, however, have to do with different time intervals from the onset of the stroke-like lesion, which may be difficult to define clinically (Tzoulis and Bindoff, 2009). Irrespective of whether due to MELAS or MSCAE, acute stroke-like lesion show reduced N-acetyl aspartate and increased lactate on magnetic resonance spectroscopy (Feng et al., 2006; Tzoulis et al., 2010). Stroke-like lesions often span arterial territories and may expand or regress during the course of the episode reflecting clinical severity and progression. In the chronic phase,
stroke-like lesions often display gyriform, linear $T_1$ hyperintensity consistent with cortical laminar necrosis (Iizuka et al., 2003; Tzoulis et al., 2010).

Angiography (conventional, computed tomography and magnetic resonance-based) studies have failed to show vascular obstructions associated with stroke-like lesion in either disorder (Hasuo et al., 1987; Ooiwa et al., 1993; Oppenheim et al., 2000; Tzoulis et al., 2010). Most perfusion MRI and single-photon emission computed tomography (SPECT) studies in MELAS show focal lesional hyperperfusion in the acute phase and hypoperfusion in the chronic phase of a stroke-like episode (Iizuka et al., 2007; Ito et al., 2008). Acute lesional hyperperfusion has also been reported, however, in examinations done only a few hours after clinical onset of a stroke-like episode (Koga et al., 2005; Nishioka et al., 2008). Systematic perfusion data from stroke-like episode in MSCAE are currently lacking.

Although stroke-like lesions have similar qualities in both diseases, their anatomical predilection differs (Table 2) most strikingly in the involvement of the temporal lobe; this is the commonest affected area in MELAS, but the rarest in MSCAE. In fact, the few reported cases of temporal stroke-like lesion in MSCAE (Tzoulis et al., 2010) are extensions from occipital lesions, while MELAS stroke-like lesions often start in the temporal lobes (Fig. 1). Interestingly, the inferomedial temporal areas including the hippocampus are consistently spared in both conditions. Differences between MELAS and MSCAE are also evident in the chronic lesions that develop (Table 2). Both conditions show slowly progressive atrophy of the cerebrum and cerebellum that may accelerate after exacerbation (stroke-like episode) episodes. While high $T_2$ signal lesions of the thalami are rare in MELAS, and lesions of the inferior olivary nuclei not reported, both are common features of MSCAE. Calcification of deep grey matter structures such as the caudate, lentiform and dentate nuclei is common in MELAS, but does not occur in MSCAE (Takahashi et al., 1998; Watanabe et al., 1998; Yoneda et al., 1999; Ohshima et al., 2000; Oppenheim et al., 2000; Kim et al., 2001; Wang et al., 2003; Chung et al., 2005; Bi et al., 2006; Mizrachi et al., 2006; Chan et al., 2007; Conforto et al., 2007; lizuka et al., 2007; Chou et al., 2008; Ito et al., 2008; Stoquart-Elsankari et al., 2008; Karkare et al., 2009; Tzoulis and Bindoff, 2009; Herrero-Martin et al., 2010; Tsujikawa et al., 2010; Tzoulis et al., 2010).

### Table 2 Radiological findings of MELAS and MSCAE

<table>
<thead>
<tr>
<th>Finding</th>
<th>MELAS</th>
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<th>MSCAE</th>
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<tr>
<td><strong>Finding</strong></td>
<td>n %</td>
<td>n %</td>
<td>n %</td>
<td></td>
</tr>
<tr>
<td>Chronic lesions</td>
<td></td>
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<td></td>
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<tr>
<td>Thalamic high $T_2$ signal&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2/34 6</td>
<td>18/28 64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal ganglia high $T_2$ signal</td>
<td>3/34 9</td>
<td>0/28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellar white matter high $T_2$ signal&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0/33 5</td>
<td>5/28 18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior olivary high $T_2$ signal&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0/30 8</td>
<td>8/28 29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellar atrophy</td>
<td>10/17 59</td>
<td>21/28 75</td>
<td></td>
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</tr>
<tr>
<td>Cerebral atrophy</td>
<td>5/8 63</td>
<td>11/28 39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcification&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11/25 44</td>
<td>0/28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute lesions</td>
<td></td>
<td></td>
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<tr>
<td>Stroke-like lesional total</td>
<td>38/38 100</td>
<td>19/28 68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke-like lesion occipital</td>
<td>29/38 76</td>
<td>17/19 89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke-like lesiontemporal&lt;sup&gt;a&lt;/sup&gt;</td>
<td>31/38 81</td>
<td>3/19 16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke-like lesionfrontal&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7/38 18</td>
<td>9/19 47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke-like lesionparietal</td>
<td>26/38 68</td>
<td>10/19 53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke-like lesioncerebellum</td>
<td>2/38 5</td>
<td>2/19 11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesional magnetic resonance spectroscopy</td>
<td>↓ NAA, ↑ Lac</td>
<td>↓ NAA, ↑ Lac</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesional cortical apparent diffusion coefficient</td>
<td>Low, high or heterogeneous</td>
<td>low or heterogeneous</td>
<td></td>
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</tr>
</tbody>
</table>

All MELAS patients fulfil the clinical diagnostic criteria for MELAS syndrome (Hirano et al., 1992) and have transfer RNA mutations: 36 have the common m.3243A>G, one has the m.3271T>C and one the m.5521G>A.<sup>a</sup>Features showing statistically significant differences between MELAS and MSCAE. Statistical significance was $P < 0.0001$ except cerebellar white matter lesions ($P = 0.02$), inferior olivary lesions ($P = 0.002$) and frontal stroke-like lesion ($P = 0.031$). We have not calculated significance for stroke-like lesions since this feature is part of the definition of MELAS.

Lac = lactate; NAA = $N$-acetyl aspartate.

### Pathology

Histopathological examination of the affected cerebral areas in both MELAS and MSCAE reveals selective neuronal loss with vacuolation and gliosis of the neuropil and eosinophilic neuronal necrosis. Cortical stroke-like lesions often show a laminar pattern with more severe neuronal loss in the superficial and deep cortical layers, suggestive of pseudolaminar necrosis. The cerebral microvasculature is patent. Cytochrome oxidase and succinate dehydrogenase histochemistry reveals mosaics of cytochrome oxidase negative neurons and skeletal muscle fibres in both conditions. Vessels with cytochrome oxidase-negative/succinate dehydrogenase hyper-reactive walls and signs of mitochondrial proliferation, are typically present in striated muscle and brain of patients with MELAS (Ohama et al., 1987; Betts et al., 2006), but have not been described in MSCAE (Betts et al., 2006; Tzoulis et al., 2010).

### Discussion

We chose MELAS and MSCAE because they are common and among the most extensively studied. The syndrome of MELAS is...
Irrespective of aetiology (Rachinger et al.), MSCAE is caused by recessive POLG mutations; POLG is the only enzyme that replicates mitochondrial DNA and is, therefore, essential for maintenance of the mitochondrial genome. Mutations in this gene lead to tissue-specific mitochondrial DNA defects namely multiple deletions and/or depletion, the quantitative loss of mitochondrial DNA (Winterthun et al., 2005; Hakonen et al., 2008).

While we have focused on these two disorders, stroke-like episodes are known to occur in other acute, mitochondrial encephalopathies both due to different mitochondrial DNA mutations and to mutations in other nuclear genes. In the mitochondrial genome, this includes mutations in complex I subunits (Horvath et al., 2008) and in other mitochondrial transfer RNA genes (de Coo et al., 1998; Hanna et al., 1998; Bataillard et al., 2001; Jakusch et al., 2001) and large-scale mitochondrial DNA deletions (Yamashita et al., 2008). Mutations in other nuclear-encoded genes causing stroke-like episode include Twinkle (now known as C10orf2) (Lonnqvist et al., 2009) and LRPPRC (Debray et al., 2011). It appears therefore, that acute encephalopathy with stroke-like lesions may result from different genetic causes.

Primary (point mutations in mitochondrial DNA) and secondary (e.g. due to POLG mutations) mitochondrial DNA defects will, in theory, disrupt the formation of one or more mitochondrially encoded respiratory chain subunits leading to respiratory chain dysfunction and, presumably, compromised energy generating capacity. Evidence of respiratory chain complex deficiency, based either on histochemical loss of cytochrome oxidase activity or biochemical measurement, is often found in skeletal muscle, but this is not always the case, even in patients with a clinical mitochondrial myopathy. Studies of CNS tissues are more problematic; biopsies of this tissue are rarely taken and studies performed post-mortem are difficult to interpret both due to autolysis, and because this tissue is obtained at the end of a long disease process. Nevertheless, some clues as to the involvement of CNS energy deficiency are found: neurons, which have high energy requirements, are selectively lost in both MELAS and MSCAE; many of the remaining neurons show eosinophilic necrosis (Betts et al., 2006; Tzoulis et al., 2010), a type of neuronal death that, although not condition specific, is consistently associated with cerebral energy deprivation (Uemura et al., 2001; Mena et al., 2004; Riudavets et al., 2005); laminar cortical necrosis in stroke-like lesions seen both histologically and using MRI represents selective and severe neuronal loss in the superficial and deep cortical layers (usually II–II and V–VI) (Betts et al., 2006; Tzoulis et al., 2010), which are known to be most sensitive to energy loss, irrespective of aetiology (Rachinger et al., 2002; Siskas et al., 2003; Yoneda and Yamamoto, 2005; Kondo et al., 2007).

While MELAS and MSCAE have many features in common, loss of cytochrome c oxidase activity in cerebral blood vessels is commonly seen in MELAS, but has not been reported in MSCAE. Moreover, earlier studies have shown that in MELAS, due to the m.3243A>G mutation, not only do blood vessels show cytochrome c oxidase deficiency, but they also accumulate high levels of mutation (DiMauro and Hirano, 1993). These findings have led to the proposal that dysregulation of cerebral blood flow leading to vascular ischaemia contributes to the pathogenesis of the stroke-like lesion in MELAS. Definite evidence to support this is, however, lacking and the observed changes in cerebral perfusion may simply reflect secondary events caused by chemical changes (lactic acidosis, excitotoxins, nitric oxide, etc) in the local milieu in and around a stroke-like lesion.

If we make the reasonable suggestion that neuronal mitochondrial dysfunction is the primary event in the pathogenesis of a stroke-like episode, what controls subsequent development? Factors including the degree of energy deficiency and level of mutation heteroplasmy are certainly important, but the major clinical contributor to the subsequent development and continuation of the pathology is, in our opinion, the presence of epilepsy. Our hypothesis is built on findings generated by neuroimaging techniques such as diffusion-weighted imaging and magnetic resonance spectroscopy, which allow us to study the CNS changes in vivo and follow their evolution over time. Investigations performed early (up to 8–14 days from clinical onset) in the evolution of stroke-like lesions, both in primary and secondary mitochondrial DNA disease, show restricted water diffusion suggesting cytotoxic oedema, the shift of water from the extracellular to the intracellular compartment. Since studies show no change in vascular supply, this is interpreted as local energy loss leading to failure of the membrane sodium–potassium ATPase, which normally maintains the intra and extracellular concentrations of sodium and potassium against their electrochemical gradients. Pump failure leads to intracellular flux of sodium accompanied by water. Such findings are also seen in other causes of neuronal energy failure such as hypoxia and ischaemia (Schaefer et al., 2000), hypoglycaemia (Botcher et al., 2005; Yoneda and Yamamoto, 2005) and carbon monoxide intoxication (Kondo et al., 2007). In addition, spectroscopic findings of reduced N-acetyl aspartate and lactate accumulation in the stroke-like lesion of MELAS and MSCAE are consistent with, but not specific for, energy failure.

Clinically, stroke-like lesions evolve and this process, which can last for days and even weeks, often manifests with visual and cognitive symptoms as well as changes in consciousness and focal motor problems (Tzoulis et al., 2006, 2010). Following lesion evolution by MRI shows that the early cytotoxic oedema gradually changes to extracellular oedema as cells die and leak their contents. The fate of the lesion and, it appears of the patient, depends on whether the lesion regresses or expands. Regression is associated with clinical recovery while progression is associated with clinical decline and often death. The major factor that influences which outcome prevails appears to be the severity of epilepsy (Tzoulis et al., 2010).

Epilepsy is common in both MELAS and MSCAE, as it is in other mitochondrial encephalopathies that involve the cerebral cortex. Epilepsy, and especially status epilepticus, is strongly associated with stroke-like episodes, but the mechanism behind this connection is not fully understood. Neurons are among the most metabolically active cells and most of the ATP generated is used for impulse generation and transmission. It is estimated that ~40–50% of the energy goes to maintain membrane potential by driving the membrane sodium–potassium ATPase pump (Astrup et al., 1981; Ames, 2000), while the remaining energy is consumed for synaptic transmission, calcium homeostasis and other...
cellular processes including axonal transport. ATP deficiency may lead to increased neuronal excitability and epileptogenesis via several mechanisms (Folbergrova and Kunz, 2012): these include disruption of the resting membrane potential due to failure of the membrane sodium–potassium ATPase, decreased activity and/or loss of highly metabolically active inhibitory interneurons (Gulyas et al., 2006) and interruption of calcium homeostasis influencing synaptic transmission (Duchen, 2000).

We believe that the sequence of events underlying the development and progression of the stroke-like lesions is as follows: irrespective of origin, epilepsy increases energy demands. In already metabolically challenged neurons (Farrar et al., 2010; Tzoulis et al., 2010), seizures result in further neuronal damage, possibly due to excitotoxic effects or abnormal calcium handling under repetitive stimulation (Trevelyan et al., 2010). This provokes more severe electrical activity which, if unchecked, can lead to a self-perpetuating cycle and a stroke-like lesion.

Although stroke-like events do occur in most mitochondrial encephalopathies, they appear to be more common in some than others. Severe status epilepticus and stroke-like episodes are significantly more common in MELAS and MSCAE than in the syndrome of myoclonic epilepsy with ragged-red fibres (MERRF) (Canafoglia et al., 2001; Engelsen et al., 2008). Stroke-like episodes with cortical lesions are, however, reported in MERRF (Zeviani et al., 1993; Nakamura et al., 1995; Serra et al., 1996; Canafoglia et al., 2001; Tanji et al., 2003) and appear to be associated with prolonged focal motor seizure activity. Similar to MELAS and MSCAE, these MERRF-related stroke-like lesions show a predilection for the posterior brain, which correlates with the localization of focal epileptic activity on EEG (Serra et al., 1996; Canafoglia et al., 2001). The few reported cases of single-mitochondrial DNA deletion syndromes with stroke-like episodes were also associated with severe epilepsy and status epilepticus (Yamashita et al., 2008). These observations suggest that not only the presence, but also the severity of epilepsy plays a key role in triggering and propagating stroke-like events in mitochondrial encephalopathies.

The difference in epilepsy severity between MELAS or MSCAE and MERRF may reflect the degree or nature of the intrinsic neuronal respiratory chain dysfunction. Studies have shown that complex I deficiency in brain is more pronounced in MELAS (Fornuskova et al., 2008) and MSCAE (Hakonen et al., 2008) than in MERRF, where a complex IV deficiency predominates (Lombes et al., 1989; Tanji et al., 2003). Interestingly, epilepsy appears to be more common with isolated complex I deficiency whether due to mitochondrial DNA or nuclear aetiology (Rahman, 2012). Moreover, both in experimental models and patient studies prolonged seizures are associated with significantly reduced complex I activity in brain tissue from the epileptic focus while complex IV activity was preserved (Kunz et al., 2000; Chuang et al., 2004). Since complex I deficits are typical for MELAS, and reported in MSCAE, it is possible that this is the predisposing factor to the development of epilepsy that subsequently initiates the vicious cycle leading to stroke-like episodes.

MELAS and MSCAE are the most common juvenile/adult mitochondrial encephalopathies and we have used them as paradigms for respiratory chain dysfunction caused by mutations of the mitochondrial and nuclear genomes, respectively. Despite having different genetic origins, their pathophysiological pathways converge on one critical event, damage of the respiratory chain leading to insufficient energy levels to maintain cellular homeostasis. When this occurs in neurons, lesions develop that mimic ischemic damage, but which paradoxically show hyperperfusion. Lesions change with time, both worsening and regressing, but the critical factor that appears to worsen prognosis is the presence and severity of epilepsy. We believe that this cycle of events is what determines outcome and provides a mechanistic structure to understand what is happening in acute mitochondrial encephalopathies.

While the mechanism involved in acute encephalopathy appears to have a common origin in both MELAS and MSCAE, the question of why the disease affects different regions of the brain remains unclear. In primary mitochondrial DNA diseases, heteroplasmy may play a role, but since the involvement of the brain is not random, it is unlikely to be the only explanation. Moreover, this does not explain why nuclear gene defects also manifest this phenomenon. Differential dependency on the respiratory chain or differences in vascular supply are other potential factors, but at present, in the absence of data, these too are just speculative.

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