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Review Article

Mitochondrial metabolic stroke: Phenotype and genetics of stroke-like episodes

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ABSTRACT

Stroke-like episodes (SLEs) are the hallmark of mitochondrial encephalopathy with lactic acidosis and stroke-like episode (MELAS) syndrome but rarely occur also in other specific or nonspecific mitochondrial disorders. Pathophysiologically, SLLs are most likely due to a regional disruption of the blood-brain barrier triggered by the underlying metabolic defect, epileptic activity, drugs, or other factors. SLEs manifest clinically with a plethora of cerebral manifestations, which not only include features typically seen in ischemic stroke, but also headache, epilepsy, ataxia, visual impairment, vomiting, and psychiatric abnormalities. The morphological correlate of a SLE is the stroke-like lesion (SLL), best visualised on multimodal MRI. In the acute stages, a SLL presents as vasogenic edema but may be mixed up with cytotoxic components. Additionally, SLLs are characterized by hyperperfusion on perfusion studies. In the chronic stage, SLLs present with a colorful picture before they completely disappear, or end up as white matter lesion, cyst, laminar cortical necrosis, focal atrophy, or as toenail sign. Treatment of SLLs is symptomatic and relies on recommendations by experts. Beneficial effects have been reported with nitric-oxide precursors, antiepileptic drugs, antioxidants, the ketogenic diet, and steroids. Lot of research is still needed to uncover the enigma SLE/SLL.

1. Introduction

Stroke-like episodes (SLEs) are episodic, cerebral events in mitochondrial disorders (MIDs), which characteristically spread, regress, vanish, or recur, and may mimic ischemic stroke clinically but not on imaging studies [1]. SLEs are commonly regarded as pathognomonic for mitochondrial encephalopathy, lactic acidosis, and stroke-like episode (MELAS) syndrome [1]. MELAS is diagnosed in the presence of encephalopathy (including epilepsy and dementia), SLEs, and of ragged-red fiber (RRF) myopathy [2,3]. Though SLEs most frequently occur in MELAS, they have been reported in other MIDs and even non-MIDs as well (Table 1). The morphological equivalent of a SLE is the stroke-like lesion (SLL), best detectable on cerebral MRI [4] but also visible on cerebral CT scans [5]. In a recent Chinese study on 138 patients with MELAS, SLEs were an independent risk factor for death [6]. Purpose of this review is to discuss the phenotypic heterogeneity and the peculiarities of SLLs on imaging, to discuss the genetic heterogeneity of disorders associated with SLEs, to provide the reader with a diagnostic algorithm to detect SLEs with a high accuracy, and to provide a proposal for the therapeutic management of SLEs in the acute and chronic setting (see Fig. 1).

2. Methods

Data for this review were identified by searches of MEDLINE for references of relevant articles. Search terms used were “stroke-like episode”, “stroke-like lesion”, “mitochondrial”, “mtDNA mutation”, “L-arginine”, “citrulline”, and “NO-precursors” combined with “MELAS”, “MERRF”, “Leigh syndrome”, “LHON”; “Kearns Sayre syndrome (KSS)”, “progressive external ophthalmoplegia (PEO)”, and “mitochondrial disorder”. Results of the search were screened for potentially relevant studies by application of inclusion and exclusion criteria for the full texts of the relevant studies. Randomized controlled trials (RCTs), observational, controlled studies case series, and case reports were included. Only original, peer-reviewed articles about humans, and published in English between 1966 and 2018 were included. A prerequisite was that the diagnosis MID was genetically confirmed. Reviews, editorials, and letters were only exceptionally considered. Reference lists of retrieved studies were checked for reports of additional studies. Websites checked for additional, particularly genetic information and for assessing the pathogenicity of mutations were the following:

Neuromuscular homepage: https://neuromuscular.wustl.edu/

Genetics Home Reference:

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Table 1
Mitochondrial and non-mitochondrial disorders, in which SLEs have been reported.

Disorder	Frequency	Reference
Mitochondrial		
MELAS	Pathognomonic	[61]
MERRF	Rare	[62]
CPEO	Rare	[63]
KSS	Rare	[64]
LHON	Rare	[65]
Leigh syndrome	Rare	[64,66]
SLSJCOX deficiency	Rare	[5]
POLG1-related (e.g. MIRAS)	Rare	[67]
Triple-H syndrome	Rare	[68]
CoQ-deficiency	Rare	[69]
Phospho-mannomutase deficiency	Rare	[70]
MELAS/LS	Rare	[71]
MIMODS	Rare	[72–74]
Non-mitochondrial		
Canavan disease	Rare	[75]
EDMD	Rare	[76]
Congenital glycosylation disorder 1A	Rare	[77]
X-linked HMSN1A	Rare	[78]
CMTX1	Rare	[79]
CJD	Rare	[80]
Proprionyl-CoA carboxylase def.	Rare	[81]
Sneddon syndrome	Rare	[82]
Cerebral amyloid angiopathy	Rare	[83]
Cystinosis	Rare	[84,85]

EDMD: Emery-Dreyfuss muscular dystrophy, congenital glycosilation disorder 1a [43], X-linked HMSN1A, hereditary motor and sensory neuropathy type 1A, CMTX1: Charcot-Marie-Tooth disease type 1×, CJD: Jacob-Creutzfeld disease, SLSJCOX deficiency: Saguenay-Lac St. Jean cytochrome oxidase deficiency.

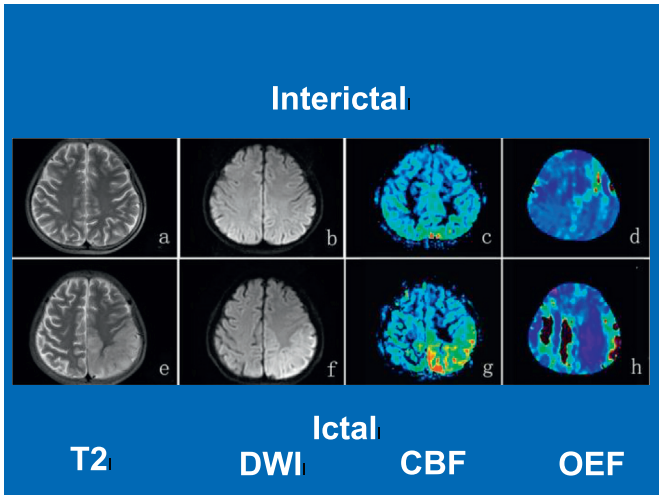

Fig. 1. Ictal and interictal MRI of a 14yo male with MELAS due to the variant m.3243A > G. In the acute phase (lower panel) the SLL in the left occipito-temporal region presents as hyperintensity on T2 and -DWI, as reduced oxygen-extraction on OEF. [permission applied from Yu et al., PlosOne 2013].

https://ghr.nlm.nih.gov/condition/mitochondrial-encephalomyopathy-lactic-acidosis-and-stroke-like-episodes

OMIM Entry: mitochondrial myopathy:
https://www.omim.org/entry/540000

3. Results

3.1. Phenotype of SLEs

3.1.1. Clinical presentation

SLEs manifest clinically with numerous phenotypic features of which some are more frequent than others (Table 2). Frequent clinical manifestations of a SLE are migraine or migraine-like headache, drowsiness, visual field defects, seizures, or vomiting (Table 2). Seizures during SLEs are usually generalized tonic-clonic or a generalized status epilepticus but also focal seizures, complex partial seizures, epilepsia partialis continua, and focal status epilepticus have been reported. Infrequent manifestations of a SLE include prolonged headache, hemiparesis, aphasia, loggorhea, ataxia, impaired face recognition, cortical blindness, visual aura, cognitive impairment, psychosis, depression, disorientation, delusions, hallucinations, desinhibition, agitation, or euphoria (Table 2). However, there are no systematic studies about the frequency of clinical manifestations of SLEs available from the literature. A SLE may manifest with either neurological or psychiatric abnormalities, or with both.

Table 2
Clinical manifestations of a SLE.

Manifestation	Frequency	Reference
Neurologic		
Migraine	Frequent	[35]
Migraine-like headache	Frequent	[51]
Drowsiness	Frequent	[35]
Seizures, epilepsy	Frequent	[35,85]
Vomiting	Frequent	[51]
Visual field defects	Frequent	[85]
Visual aura	Rare	[86]
Prolonged headache	Rare	[35]
Hemiparesis	Rare	[35]
Aphasia	Rare	[24,83]
Logorrhea	Rare	[87]
Ataxic gait	Rare	[24]
Impaired face recognition	Rare	[87]
Cortical blindness	Rare	[85]
Psychiatric		
Psychosis	Rare	[25,33]
Visual hallucinations	Rare	[66]
Cognitive impairment	Rare	[85]
Depression (precedes SLE)	Rare	[87]
Disorientation	Rare	[87]
Delusion, hallucination	Rare	[35]
Desinhibition, agitation	Rare	[87]
Euphoria	Rare	[87]

SLE: stroke-like episode.

3.1.2. MRI findings

3.1.2.1. Acute stage. Concerning the location and distribution of SLLs, they most frequently are located in an occipito-temporal distribution [7]. However, SLLs may also occur in the frontal or parietal lobes, infratentorially, or even in the spinal cord [8]. Supratentorial SLLs may occasionally extend to the cortico-ponto-cerebellar tract [9]. SLLs even occur in the optic nerve [10]. In the acute stage, a SLL may present as hyperintensity on T2/FLAIR, DWI, and ADC, suggesting a vasogenic edema but in other patients cytotoxic edema (DWI hyperintens, ADC hypointens) may be found. Additionally, PWI most frequently discloses hyper-perfusion in the area of the SLL. Hyperperfusion during the acute stage has been also found in 7 of 9 SLEs investigated with SPECT (Fig. 1) [11]. Atypical presentations of a SLL on MRI, include a vasogenic edema mixed with ischemic lesions [11], or cytotoxic edema in a non-vascular distribution [12]. The mixture of vasogenic and cytotoxic edema can be explained by affection of arteries within the region of the vasogenic edema by the metabolic defect. This may lead to stenosis or occlusion of arteries and thus to territorial ischemia within a SLL. SLLs may present as a single lesion (classical type) or as disseminated lesions (non-classical type), as has been previously reported in Japanese patients. SLLs progressively expand over days or weeks to regress spontaneously thereafter again [11]. In some cases, intracortical hemorrhage has been described [11]. The oxygen extraction fraction on MR OEF sequences is markedly reduced within

SLLs but also on the non-affected brain [13]. SLLs may be accompanied by, most frequently, ipsilateral lesions of the thalamus, hypertrophy of the inferior olivary nucleus in *POLG1* carriers, cerebellar atrophy, or basal ganglia calcification on SWI, particularly in m.3243A > G carriers.

3.1.2.2. Chronic stage. The chronic stage starts with recovery of hyperperfusion, with clinical improvement, or with regression of the SLL. Onset of the chronic stage is further characterized by normalisation of the oxygen extraction fraction, which is markedly decreased during the acute stage [14]. In the chronic stage findings on MRI are quite heterogeneous [1]. Together with clinical remission, ADC maps lastly become normal again [15]. Normalisation of T2-weighted images and DWI sequences usually takes longer. The endstage of a SLL can be quite variable and may present as normal brain, as white matter lesion, as cortical laminar necrosis, as cystic lesions, as focal atrophy [11,16], as cortical hemorrhage with iron and calcium deposition [16], or as toenail sign [17]. Factors which influence the type of outcome of a SLL remain speculative.

3.1.3. Presentation on MR-spectroscopy

H-MR-spectroscopy (H-MRS) studies of SLLs reveal elevated lactate and glucose, but severely reduced NAA, NAA/creatine ratio, glutamate, and total creatine conentrations [18–20]. These findings indicate a high degree of nonoxidative glycolysis, reflecting either impaired oxidative energy metabolism or the use of anerobic metabolism by infiltrating macrophages as well as damage or loss of viable neuroaxonal tissue [18]. In the chronic stage of a SLL the NAA/Cr ratio gradually increases in association with normalisation of the ADC maps [19,21]. In some patients with a SLL, elevation of cerebral lactate and the decrease of NAA, glutamate, or creatine may not be restricted to the extent of the SLL but may occur ubiquitously within the brain [18].

3.1.4. Electroencephalography (EEG)

EEG findings during a SLE have been only rarely reported. The EEG may demonstrate focal or generalized periodic sharp waves, focal or generalized status epilepticus, focal periodic epileptiform discharges, or myoclonus-contingent 4–5 Hz theta bursts.

3.1.5. SLEs and ischemic stroke

SLEs may not only be a differential diagnosis of ischemic stroke, but patients with a MID associated with SLEs may also carry classical risk factors for ischemic stroke. These include atrial fibrillation, atherosclerosis, systolic dysfunction, ventricular arrhythmias, arterial hypertension, smoking, hyperlipidemia, or low output failure. Additionally, there is primary arteriopathy in mitochondrial disorders, affecting large arteries (macroangiopathy) or small arteries (microangiopathy) manifesting as atherosclerosis, spontaneous aortic rupture, spontaneous carotid artery dissection, ectasia of arteries, aneurysm formation, leukoencephalopathy, migraine-like headache, stroke, or peripheral retinopathy [22]. Whether mitochondrial vasculopathy also results in spontaneous vasoconstriction or vasospasm is currently unknown but there are indications that MELAS may be occasionally associated with vasoconstriction syndrome [23].

3.2. Pathophysiology

The pathophysiological background of SLEs/SLLs is unclear, but three hypotheses are most frequently promoted to explain the phenomenon.

3.2.1. Metabolic hypothesis

According to the metabolic hypothesis SLLs are due to a regional breakdown of the mitochondrial energy metabolism either in neurons, glial cells, or in cells constituting the blood brain barrier (BBB) (e.g. astrocytes, pericytes). Arguments for this hypothesis are that MIDs are generally characterized by a metabolic defect, that the extension of a SLL is not confined to a vascular territory, and that anti-oxidative therapy occasionally has a beneficial effect [24]. A further argument in favor of the metabolic hypothesis and disruption of the BBB is that steroids have been reported beneficial in single patients with a SLE. Why SLLs have a regional, non-vascular extension and show a dynamic progression or regression over time, remains speculative.

3.2.2. Vascular hypothesis

According to the vascular hypothesis SLLs result from hypoperfusion due to a vascular compromise from macro- or microangiopathy [22].

3.2.2.1. Arguments in favor. Arguments in favor of the vascular hypothesis are that muscle biopsy with ragged-red fibers and COX-negative fibers frequently contain vessels with SDH-hyper-reactive fibers, which is also conceivable for the cerebrum, and that there are MELAS patients with reversible vasoconstriction syndrome causing cerebral ischemia via this mechanism [23]. A further argument in favor of the vascular hypothesis is that energy deficiency in MIDs can stimulate proliferation of mitochondria in the smooth muscle and endothelial cells of small blood vessels leading to angiopathy, narrowing of the vessel diameter, and thus impaired perfusion of the microvasculature in several organs [25].

3.2.2.2. Arguments against. An argument against the vascular hypothesis, however, is that the acute stage of a SLL is characterized by reversible hyperperfusion with increased cerebral blood flow within the area of a SLL [26]. In a study of 20 MELAS patients, an increased cerebral blood flow (CBF) was observed in all SLLs [26]. Six patients additionally showed dilation of intra-cerebral arteries [26]. Other studies applying perfusion weighted imaging (PWI) and SPECT also showed hyperperfusion in the acute stage of a SLE [27]. It was concluded that reversible dilation of cerebral arteries within a SLL is a typical feature recognised during the acute stage of a SLE [26]. Hyperperfusion during the acute stage of a SLE may be a mechanism to compensate for the impaired metabolism. Further arguments against the vascular hypothesis are that a SLL is not confined to the vascular territory of a large cerebral artery and that cerebral arteries can be completely normal in patients experiencing SLEs.

3.2.3. Epileptogenic hypothesis

The third commonly proposed hypothesis to explain the pathogenesis of a SLL is that seizures or epileptic activity trigger a metabolic breakdown [11,28]. During epileptic activity neurons utilize glycogen as a source of ATP [29]. Glycolytic by-products simultaneously damage mitochondrial functions [29]. This leads to a breakdown of the BBB and consecutively to a vasogenic edema [29]. It is also speculated that the metabolic defect leads to hyperexcitability of neurons and consecutively to seizure activity. As a consequence, patients with a SLE require EEG recordings irrespective if there are clinical seizures or not. If there is paroxysmal activity on EEG without seizures, these patients require antiepileptic treatment in the acute stage of a SLL [28]. Epilepsy is generally a frequent feature of MIDs. In a study of 165 patients with a MID, 61% had an abnormal EEG and among these 85% had epileptiform discharges [30]. In a study of 182 adult MIDs, the prevalence of epilepsy was 23% with a mean age at onset of 29y [31]. Epilepsy in MELAS may not only manifest with convulsions but also with visual hallucinations [32] or psychosis [33]. In a study of 14 SLEs in 16 MELAS patients, epileptiform discharges were recorded on EEG in 9 of 11 SLEs [11].

3.2.4. Others

In addition to the three main hypotheses about the pathogenesis of SLLs, other explanations for the development of a SLL have been generated. A rare trigger of a SLE is radiation therapy [34,35]. Whether

Table 3
Genetic background of mitochondrial disorders associated with SLEs.

Gene	Mutations	Phenotype	Reference
MT-TL1 (tRNA(Leu))	m.3243A > G	MELAS	[37]
	m.3271 T > C	MELAS	[37,88]
	m.3252A > G	MELAS	[2]
	m.3256C > T	MELAS	[2]
	m.3260A > G	MELAS	[89]
	m.3291 T > C	MELAS	[2]
	m.3302A > G	MELAS	[2]
ND	m.12770A > G	MELAS	[2]
	m.13513G > A	MELAS	[49,65]
	m.13042A > T	MELAS	[2]
	m.13045A > C	MELAS	[2]
	m.13046 T > C	MELAS	[2]
	m.13084A > T	MELAS	[2]
	m.13514G > A	MELAS	[2]
	m.13528A > G	MELAS	[2]
	m.13513G > A	MIMODS	[49]
	m.13094 T > C	MELAS	[90]
	m.10158 T > C	MELAS	[85,91]
	m.10191 T > C	MELAS/LS	[71]
MT-CO1	m.6597C > A	MELAS-like	[92]
tRNA(Lys)	m.8344A > G	MERRF/MELAS	[93]
tRNA(Ser)	m.7512 T > C	MELAS	[94]
tRNA(Val)	m.1644G > A	MELAS plus	[95]
FASTKD2	pR205X, p.L255P	MELAS-like	[96]
POLG1	c.3556G > C	MELAS	[97]
BCS1L	c,217C > T, c.1102 T > A	MELAS	[98]
TWINKLE	Y508C, A318T	MIMODS	[99]
CABC1	R213W, G272 V, G272D E551K, c.1812_1813insG	Encephalopathy	[100]

MIMODS: mitochondrial multiorgan disorder syndrome, np: not provided, LS: Leigh hyperperfusion on CBF, and as reduced.

drugs, infections, insolation, allergy, stress, pain, fear, or malnutrition can trigger the development of a SLE remains speculative. In a single patient with MELAS infection with chickenpox triggered the development of a SLE [36].

3.3. SLEs and genetics

Since SLEs most frequently occur in MELAS, and since MELAS is due to the *MT-TL1* variant m.3243A > G in 80% of the cases, patients with a SLE most frequently carry this mutation and need to be initially tested for it. About 10% of the MELAS cases are due to mutations in the m.3271 T > C variant [37]. More rarely, other *MT-TL1* mutations are made responsible for MELAS (Table 3) [2]. The gene second most frequently mutated in association with MELAS is the *ND5* gene (Table 3). Several mutations in this gene and other mtDNA-related genes encoding subunits of complex-I have been reported in association with SLEs (Table 3) [2]. Single cases were reported in whom SLEs were associated with mutations in the tRNA(Lys) and MT-COI genes respectively (Table 3). Nuclear genes associated with SLEs include the *POLG1, FASTKD2,* and *BCS1L* genes respectively (Table 3) [37]. How many of the patients carrying any of these mutations develop a SLE and if some mutations are more frequently associated with SLEs than others, remains unknown. Whether the severity of SLEs and extent of a SLL is correlated with the amount of heteroplasmy or the mtDNA copy number, is controversially discussed.

3.4. Frequency of SLEs

No reliable studies about the frequency of SLEs are available but in several cohort studies the number of patients with a SLE has been assessed [6]. In a Chinese study of 138 MELAS patients, SLEs were the most frequent initial manifestation occurring in 70% of the cases [6].

3.5. Diagnosing SLEs

Diagnosing SLEs relies on the clinical presentation and the typical MRI findings. The clinical presentation of a SLE can be quite heterogeneous (Table 2). Clinical features suggesting the presence of a SLE include migraine, seizures, confusion, vomiting, and visual field defects (Table 2). However, also other clinical manifestations may indicate a SLE (Table 2). Diagnosing a SLE is impeded by the fact that MIDs may occasionally manifest with macro-angiopathy of the extra-cranial or intra-cranial cerebral arteries [22]. MRI studies may be also misinterpreted if arteries within a SLL are affected by the defect, leading to micro-infarcts. Whether SLLs occur without clinical manifestations is a matter of discussion. Supportive for diagnosing SLLs can be the MRS but a lactate peak and a decreased NAA/Cr ratio may also occur in MID patients without a SLL [38]. Perfusion studies may show hyperperfusion in the acute stage of a SLL. Generally, a SLE should be diagnosed if at least one of the clinical manifestations listed in Table 2 is present and if multimodal cerebral MRI shows a SLL. A SLE can be suspected if classical clinical manifestations of an ischemic stroke are accompanied by atypical clinical features.

3.6. Treatment

3.6.1. NO-precursors

L-arginine (0.5 g/kg body weight) is widely used for the treatment of acute SLEs although there is little evidence for the effectiveness of this treatment [29,39]. Accordingly, the beneficial effect is generally controversially discussed [40–47]. A recent study about the effect of L-arginine in SLEs of 23 MELAS patients had a poor design, did not consider heteroplasmy rates of mtDNA variants, and did not consider epileptic activity as a possible driver of a SLE [39]. In a retrospective study of 71 pediatric patients with MIDs and SLEs, L-arginine or citrulline proved beneficial, particularly in SLEs with hemiplegia in 46% of the patients with a SLE [48]. L-arginine may particularly prevent the progression of a SLE [49]. L-arginine may be beneficial even in recurrent SLEs [50]. However, there are also studies which did not find a beneficial effect of L-arginine [48]. In the same retrospective study of 71 MID patients 53% of the SLEs did not respond to L-arginine [48].

3.6.2. Antiepileptic therapy

An alternative treatment of SLEs is midazolam [51]. Midazolam is assumed to play a role in suppressing neuronal hyperexcitability and trigemino-vascular activation [51]. Concerning the treatment of seizures occurring before, during, or between SLEs, no guidelines are available. According to expert opinions, however, it is crucial to avoid mitochondrion-toxic AEDs, in particular valproic acid, phenytoin, phenobarbital, and carbamazepine as first line treatment [52]. Disregarding the recommendations of the ILAE, non-mitochondrion-toxic AEDs should be applied in patients experiencing a SLE, even in the absence of clinical seizures but already in case paroxysmal activity can be recorded [52].

3.6.3. Antioxidants

In single cases, antioxidants have been administered orally in the acute stage of a SLE with success [24]. In a 21yo Chinese male, 900 mg/d coenzyme-Q were given daily in the acute stage of a SLE with a beneficial effect [24]. In a 16yo female with MELAS edaravone, a radical scavenger, was given together with glycerol and L-arginine resulting in significant improvement of the SLE [53]. In a 32yo female with MELAS ubiquinone was given together with tocopherol [54]. Progression of a SLL in a MELAS patient could be prevented by administration of edaravone (60 mg/d) during 14d [54].

3.6.4. Steroids

Though not well appreciated in the literature, steroid responsiveness is consistently observed in MELAS patients and withdrawal of

steroids results in deterioration of the condition. Steroids have been proposed for the acute stage of a SLE to repair the BBB [29]. In another patient with MELAS due to the variant m.3243A > G intravenous corticosteroids resulted in marked and sustained improvement of a SLE [55]. (60 mg/d) during 14d [54]. There is also a study about mitochondrial encephalopathies demonstrating partial or complete steroid-responsiveness of these patients [56].

3.6.5. Others

Butylphthalide (0.2 g), an ingredient of celery responsible for the aroma of the plant, was given for acute SLEs in combination with coenzyme-Q and levetirazetam in a 21yo male with recurrent SLEs [24]. Seizures associated with SLEs have been reported to beneficially respond to a ketogenic diet [57]. In a 16yo female with MELAS, glycerol was given together with L-arginine and edaravone resulting in clinical improvement of the SLE and resolution of the MRI abnormalities [45]. In a 17yo female with MELAS, dichloroacetic acid, given for lactic acidosis, also improved the clinical manifestations of the SLE [58]. Psychiatric abnormalities in MIDs usually respond to drugs also given in non-MID patients in this indication. Whether agents such as elamipretide (cardiolipin protector) [59], bezafibrate, epicatechin, and RTA 408 (enhancer of mitochondrial biogenesis) [59], or creatine (energy buffer) [59] may have a beneficial effect for SLLs is currently unsolved. Since SLLs may be cytotoxic / ischemic in nature without occlusion of any arteries [60] secondary prophylaxis with anti-thrombotic medication can be considered.

3.7. Outcome

Only few studies assessed the outcome of SLEs. In a Chinese study of 138 MELAS patients SLEs were the most frequent cause of death in 43% of the cases [6].

4. Conclusions

This review shows that SLEs may not only occur in MELAS but, though more rarely, also in other MIDs. SLEs most frequently present with migraine or migraine-like headache, seizures, drowsiness, vomiting, and visual field defects. A SLE should be generally suspected if features of an ischemic stroke are accompanied by atypical CNS features. As soon as a SLE is suspected, a multimodal cerebral MRI should be carried out. If the typical features of a SLL are detected, treatment with L-arginine, coenzyme-Q, AEDs, or steroids should be initiated, although the evidence for such interventions is poor. Why SLLs also occur in non-mitochondrial disease remains elusive, but it can be speculated that the SLE is the initial manifestation of a so far subclinical MID and that the initial diagnosis is either wrong or a second trouble. It is also conceivable that non-mitochondrial cerebral disorders, such as ischemia, infections or prion disorders, cause metabolic stress by impairing mitochondrial functions and thus trigger the development of a SLL. Accordingly, SLLs should be regarded as a reaction to a secondary mitochondrial defect. Overall, we have to learn more about the pathogenesis of SLLs about triggering factors, and agents that may beneficially influence this phenomenon. Since patients with a SLE are still frequently misdiagnosed, we also need to educate more extensively those who manage and treat these patients. Assuming that mitochondrion-toxic agents may trigger or sustain the presence of a SLL, we should identify mitochondrion-toxic agents prior to their application. We should take care not to be harmful with a wrong diagnosis and thus inappropriate treatment to these patients.

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Author contribution

JF: design, literature search, discussion, first draft, critical comments.

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