Stroke and Stroke-like Episodes in Muscle Disease

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Abstract: *Background:* Though not obvious at a first glance, myopathies may be associated with ischemic stroke. Stroke-like episodes resemble ischemic stroke only to some extent but are a unique feature of certain mitochondrial disorders with a pathogenesis at variance from that of ischemic stroke. Only limited data are available about ischemic stroke in primary myopathies and the management of stroke-like episodes in mitochondrial disorders. This review aims to summarize and discuss current knowledge about stroke in myopathies and to delineate stroke-like episodes from ischemic stroke.

Methods: Literature review *via* PubMED using the search terms "stroke", "cerebrovascular", "ischemic event", "stroke-like episode", "stroke-mimic", "mitochondrial disorder".

Results: Stroke in myopathies is most frequently cardioembolic due to atrial fibrillation or atrial flutter, dilated cardiomyopathy, or left-ventricular hypertrabeculation (noncompaction). The second most frequent cause of stroke in myopathies is angiopathy from atherosclerosis or vasculitis, which may be a feature of inflammatory myopathies. Atherosclerosis may either result from classical risk factors, such as diabetes, arterial hypertension, hyperlpidemia, or smoking, associated with muscle disease, or may be an inherent feature of a mitochondrial disorder. In case of severe heart failure from cardiomyopathy as a manifestation of muscle disease low flow infarcts may occur. Thrombophilic stroke has been described in polymyositis and dermatomyositis in association with anti-phospholipid syndrome. Stroke-like episodes occur particularly in mitochondrial encephalopathy, lactacidosis and stroke-likeepisode syndrome but rarely also in Leigh-syndrome and other mitochondrial disorders. Stroke-like episodes are at variance from ischemic stroke, pathogenically, clinically and on imaging. They may be the manifestation of a vascular, metabolic or epileptic process and present with predominantly vasogenic but also cytotoxic edema on MRI. Differentiation between ischemic stroke and stroke-like episodes is essential in terms of management and prognosis. Management of ischemic stroke in patients with myopathy is not at variance from the treatment of ischemic stroke in non-myopathic patients. There is no standardized treatment of stroke-like episodes but there is increasing evidence that these patients profit from the administration of L-arginine and consequent antiepileptic treatment if associated with seizure activity.

Conclusions: Ischemic stroke may be a complication of myopathy and needs to be delineated from stroke-like episodes, which are unique to mitochondrial disorders, particularly mitochondrial encephalopathy, lactacidosis and stroke-likeepisode syndrome. Ischemic stroke in myopathies is most frequently cardioembolic and treatment is not at variance from non-myopathic ischemic stroke. Treatment of stroke-like episodes is not standardized but seems to respond to L-arginine and adequate antiepileptic treatment.

Keywords: Cerebral infarction, ischemic stroke, genetics, cardiomyopathy, noncompaction, atrial fibrillation, neuromuscular disorder, MELAS-syndrome, stroke-like episode.

INTRODUCTION

Myopathies are a heterogeneous group of neurological disorders primarily affecting the striated skeletal muscle due to mutations in genes encoding for components of the myocyte (primary myopathies) or due to secondary affection of the muscle within the scope of a general disorder primarily affecting organs other than the muscle (secondary myopathies). Ischemic stroke is one of the most prevalent neurological disorders and the third most frequent cause of death [1]. Stroke-like episodes (SLEs) are phenotypic features predominantly of mitochondrial disorders (MIDs), most frequently mitochondrial encephalopathy, lactacidosis, SLE (MELAS)-syndrome, and mimic the clinical manifestations of ischemic stroke to some extent [2]. Their prevalence is much lower than that of ischemic stroke. Though myopathies do not seem to be obviously associated with stroke at a first glance, there is a strong causal relation if there is cardiac involvement in myopathies, if the underlying cause of myopathy is a MID, or if the muscle disease is part of a multisystem disease, which also manifests with classical risk factors for ischemic stroke, such as diabetes, hyperlipidemia, or arterial hypertension. This review aims to give an overview about the current knowledge concerning the relation between muscle disease and ischemic stroke and SLEs with regard to pathogenesis, diagnosis, treatment and outcome.

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CLASSIFICATION OF ISCHEMIC STROKE

Ischemic stroke is generally graded according to the TOAST-classification, which denotes five subtypes of is chemic stroke following its pathogenesis: 1) atherosclerosis of large arteries 2) cardioembolism, 3) small-vessel occlusion, 4) stroke due to other etiology (vasculitis, dissection, coagulation disorder etc.), and 5) stroke of undetermined etiology [3]. Narrowing or occlusion of large extra- or intra-cerebral arteries by arteriopathy or embolism leads to ischemia of the downstream vascular territory. Narrowing or occlusion of small intra-cerebral arteries by arteriopathy or embolism leads to ischemia only of a small vascular territory, morphologically manifesting as white matter lesions or lacunas. In addition to cardioembolic or angiopathic causes, ischemic stroke may result from hemodynamic, thrombophilic, or metabolic abnormalities [4].

RISK FACTORS FOR STROKE IN MYOPATHIES

Risk factors for the development of ischemic stroke in myopathies are cardiac disease, frequently associated with myopathies, or atherosclerosis either due to classical risk factors from a multisystem disease or due to a manifestation of a MID [5]. Other risk factors may be low output failure, arterial hypotension or thrombophilic conditions. Predisposing for stroke may be also MELAS-syndrome, which is pathogenically characterised by arteriopathy [6] and frequently also presents with metabolic muscle disease or compromised cardiac function. Cardiac involvement predisposing for ischemic stroke includes sarrhythmias, such as atrial fibrillation, heart failure from hypertrophic cardiomoypathy, dilative cardiomyopathy, restrictive cardiomoypathy, or noncompaction without heart failure. Another risk factor for ischemic stroke may be cryptogenic intraventricular thrombus formation in the absence of atrial fibrillation or heart failure, as has been described in Duchenne muscular dystrophy (DMD) [7].

ETIOLOGY OF ISCHEMIC STROKE IN MYOPATHIES

A) Cardioembolism

Cardiac disease is a frequent feature of many of the primary muscle disorders. Cardiac involvement in myopathies may manifest as cardiac conduction disorder or cardiomyopathy. Conduction disorders may manifest as impulse generation or impulse conduction abnormality.

1. Atrial Fibrillation/Flutter

The arrhythmia most frequently associated with stroke in myopathies is atrial fibrillation. Impaired contractility of the left atrial wall favors thrombus formation within the left

Table 1.   **Myopathies in which Atrial Fibrillation or Atrial Flutter has been Found**

Myopathy	Reference	Stroke
Primary myopathies		
Muscular dystrophies		
Dystrophinopathies	[9,10,12]	[9,10]
Emery-Dreifuss muscular dystrophy 1 (emerin)	[8]	[8]
Emery-Dreifuss muscular dystrophy 2 (laminA/C)	[8]	[8]
Limb girdle muscular dystrophies		
LGMD1B	[76-81]	NR
Myotonic dystrophies		
Myotonic dystrophy 1	[12,82-84]	[11,12]
Myotonic dystrophy 2	[13]	[13]
Facio-scapulo-humeral muscular dystrophy	[85]	NR
Myofibrillar myopathies	[86]	NR
Desmin myopathy	[87,88]	NR
Rigid spine syndrome	[89]	NR
Danon's disease	[90]	[90]
Barth syndrome	[4]	NR
McLeod syndrome	[91,92]	NR
Congenital myopathies	[93]	NR
Metabolic myopathies		
Glycogenosis	[94]	NR
Mitochondrial myopathy	[95]	NR
Congenital fiber type dysproportion	[96]	NR
Epidermiolysis bullosa simplex	[97]	NR
Secondary myopathies		
Polymyositis	[98]	NR
Dermatomyositis	[14]	[14]
Colchicine-induced myopathy	[99]	NR
Hypothyroid myopathy	[100]	NR
Hyperthyroid myopathy	[101]	NR

atrium or the left atrial appendage, which are consecutively flushed out to the arterial bed, including the cerebral arteries. Myopathies in which atrial fibrillation has been described are listed in Table **1**. That stroke has not been reported in each of the myopathies listed in this table may be due to the poor follow-up of most myopathy patients. In a series of 11 patients with Emery-Dreyfuss muscular dystrophy ischemic stroke has been reported in four of them who presented with atrial fibrillation or flutter. The outcome was not reported but three of these patients had autosomal dominant (Lamin A/C) and one X-linked (emerin) Emery-Dreyfuss muscular dystrophy [8]. Stroke was also reported during an episode of atrial fibrillation in a patient with Becker muscular dystrophy [9]. Among five patients with DMD, one experienced ischemic stroke [10]. He had a history of atrial fibrillation but also of dilative cardiomyopathy. Transient ischemic attack and stroke have been also described in a patient with myotonic dystrophy 1 in whom paroxysmal atrial fibrillation was recorded [11]. Screening of 52 patients with DMD, 61 with myotonic dystrophy 1 and 14 with Becker muscular dystrophy revealed atrial flutter in 3 with MD1, and 1 with DMD. Atrial fibrillation was detected in none of them. Only one of the included patients developed ischemic stroke during atrial flutter [12]. In a study on 38 patients with myotonic dystrophy 2, five had developed ischemic stroke. Two of

these patients had atrial fibrillation with normal systolic function [13]. Ischemic stroke may be associated also with secondary myopathy. In a patient with dermatomyositis, restrictive cardiomyopathy, and atrial fibrillation, a transient ischemic attack has been reported [14]. Arrhythmias leading to cardioembolism may also result from hyperkaliemia following rhabdomyolysis.

2. Dilative Cardiomyopathy

Dilative cardiomyopathy is prone to heart failure and arrhythmias [15]. Thus patients with myopathy in whom cardiac involvement manifests as dilative cardiomyopathy are also at increased risk to thromboembolism. Though the exact pathogenesis of the intracardiac thrombus formation in dilative cardiomyopathy remains elusive it can be speculated that impaired hemodynamics activates the coagulation cascade. In addition to embolism, dilative cardiomyopathy may be associated with arterial hypotension and thus cerebral hypoperfusion. Studies about myopathies with dilative cardiomyopathy which were associated with stroke are listed in Table **2**. According to these studies ischemic stroke has been reported in two patients with DMD [16]. Both patients experienced ischemic stroke at age 21y in sinusrhythm but with an ejection fraction (EF) below 20% and together with increased thrombin-ATIII complexes and increased D-dimer.

Table 2.   Myopathies Associated with Dilative Cardiomyopathy and Stroke

Myopathy	Reference	Stroke
Muscular dystrophies		
Dystrophinopathies	[16,102]	[10,16,17]
Limb girdle muscular dystrophies	[103,104]	NR
Laminopathies	[81,105-107]	NR
LGMD1B	[108]	NR
LGMD1E	[108]	NR
LGMD2D-F	[108]	NR
LGMD2I	[108,109]	NR
Congential muscular dystrophies		
Fukuyama type CMD	[110]	NR
Merosin-deficient CMD	[111]	NR
Myofibrillar myopathies	[112]	NR
Desminopathy	[113]	NR
Other		
Vacuolar myopathy (LAMP2)	[114,115]	NR
Barth syndrome	[116,117]	[18]
McLeod syndrome	[118]	NR
Reducing body myopathy	[119,120]	NR
Congenital myopathies		
Nemaline myopathy	[121, 122]	NR
Central core disease	[123]	NR
Centronuclear myopathy	[124,125]	NR
Congenital fiber type dysproportion	[96,126,127]	NR
Metabolic myopathies		
Glycogenosis type IV	[128]	NR
Primary carnitin deficiency	[129]	NR
Mitochondrial disorders	[130,131]	NR
Kearns-Sayre syndrome	[132]	NR

CMD: congenital muscular dystrophy

The second patient had experienced a TIA already five months prior to the stroke. Ischemic stroke was also reported in a 13yo DMD patient in sinusrhythm and with an EF of 35-40% [17]. Five months later he experienced a second stroke in the same vascular territory as before [17]. Stroke was also reported in another five patients with DMD and dilative cardiomyopathy aged 16-20y of whom one presented with atrial fibrillation on ECG [10]. Additionally, stroke has been described in a patient with Barth syndrome and dilative cardiomyopathy who was in sinusrhythm at the time of the event [18].

3. Left Ventricular Hypertrabeculation (LVHT, Noncompaction)

LVHT is an increasingly recognized abnormality of the left ventricular myocardium, characterised by a two-layered structure mainly of the apex and the lateral wall. The epicardial layer consists of normal myocardium whereas the endocardial layer has a spongy-like structure of interwoven myocardial strings, which are all covered with endocardium [19,20]. LVHT is most frequently diagnosed on echocardiography if there are more than three single trabeculations at end-diastole, if there is the two-layered structure at end-systole, and if the perfusion of the intertrabecular spaces from the ventricular side can be visualized at end-diastole [21]. Depending on the study, LVHT is associated with myopathy in up to 80% of the cases. Most frequently LVHT is associated with Barth syndrome and MIDs [22]. Myopathies in which LVHT has been described so far are listed in Table **3**. Frequent complications of LVHT are heart failure, ventricular arrhythmias, and stroke or embolism [22]. Though stroke has been reported in a number of LVHT patients who were not neurologically investigated (Table **4**), it was described only in two patients with neuromuscular disorder and LVHT so far [Finsterer *et al*., submitted], suggesting that stroke in LVHT patients with myopathy is underestimated. One reason for the low rate of stroke in LVHT-patients with myopathy is that usually LVHT-patients are not referred to the neurologist, why a possible neuromuscular disorder frequently remains undetected. Whether the stroke risk and prevalence of stroke is truly increased in patients with LVHT is under debate. There are studies, which do not report an increased incidence of stroke among LVHT patients [23-25], whereas others do [26-29]. In a study on 229 patients with LVHT but without atrial fibrillation or flutter four experienced ischemic stroke during a mean follow-up of 7.3y [23]. In a study on 62 LVHT patients the incidence of stroke was 10% compared to 15% in controls matched for age, sex and systolic function [24]. Arguments for an increased stroke risk are that reduced perfusion of intertrabecular spaces, occurrence of ventricular arrhythmias, and increased incidence of heart failure favor thrombus formation. Nevertheless, there is no general need to put LVHT patients on oral anticoagulation (OAC) unless classical indications for OAC are present.

B) Macroangiopathy

1. Atherosclerosis

In a patient with MELAS-syndrome due to the heteroplasmic transition m.617G>A in the tRNA(Phe) gene recurrent ischemic strokes occurred, which were accompanied by transient occlusion of the middle cerebral, anterior cerebral and internal carotid arteries [30]. Strokes were presumably attributed to artery-to-artery embolisms originating from the carotid artery stenosis [30]. The cause of the carotid internal stenosis was not found. Since classical risk factors for atherosclerosis were absent, carotid internal artery stenosis was attributed to the MID. Atherosclerosis in the absence of classical risk factors for macroangiopathy has been also reported in other patients with MID [5]. Macroangiopathic ischemic stroke must be clearly delineated from SLE, which

Table 3.   Myopathies Associated with Noncompaction

Myopathy	Reference	Stroke
Muscular dystrophies		
Myotonic dystrophy I	[133]	NR
Dystrophinopathies	[134]	NR
Barth syndrome	[18]	[18]
Zaspopathy	[135]	NR
Laminopathies	[136]	NR
Dystrobrevinopathies	[137]	NR
Oculopharyngeal muscular dystrophy	[138]	NR
Metabolic myopathies		
Mitochondrial disorder	[139]	[Finsterer, submitted]
Myoadenylate-deaminase deficiency	[140]	NR
Glycogenosis type II (M. Pompe)	[unpublished]	NR
Non-myopathic		
Charcot-Marie-Tooth neuropathy type 1A	[141]	NR
Friedreich ataxia	[unpublished]	NR

Table 4.   Studies Reporting Stroke in LVHT Patients

Study	NOP investigated	NOP stroke	Additional findings
Münkle et al. 2010 [142]	1	1	Severe heart failure
Mello et al. 2010 [143]	1	1	Chagas disease
Stöllberger et al. 2010 [144]	1	1	Heart transplantation
Vatthyam et al. 2009 [145]	1	1	Fatal acute heart failure,
Steffel et al. 2009 [146]	78	Not reported	Risk of embolism associated with ECG
Stanton et al. 2009 [147]	30	2	Death only with decreased systolic function
Sahin & Karsidag 2009 [28]	1	1	None
Fazio et al. 2009 [26]	1	1	Not reported
Fazio et al. 2008 [23]	229	4	Decreased systolic function (50% of pat.)
Finsterer et al. 2008 [24]	104	16 (15%)	At least 1 classical risk factor in 15 pat.
Sir et al. 2008 [29]	1	1	None
Oduncu et al. 2008 [27]	1	1	Bivenricular noncompaction
Baez-Escudero et al. 2008 [148]	1	1	Systolic dysfunction
Finsterer et al. 2008 [149]	1	1	Stroke-like-episodes, endocarditis
Nakajima et al. 2007 [150]	1	1	Decreased systolic function
Celebi et al. 2007 [151]	1	1	Essential thrombocytosis
Fernandez Sanchez et al. 2006 [152]	1	1	Pregnant women shortly before delivery
Walpot et al. 2005 [153]	1	1	Not reported
Stöllberger & Finsterer2005 [25]	62	6	Incidence of stroke lower than in controls
Hascelik et al. 2003 [154]	1	1	18 months-old girl with elevated factor VIII"

NOP: Number of patients

is speculated to be microangiopathy-related or due to non-ischemic neurovascular events [30].

2. Vasculitis

Vasculitis of the large arteries associated with stroke has been particularly reported in inflammatory myopathies, such as polymyositis or dermatomyositis. A patient with polymyositis experienced an ischemic stroke and myocardial infarction shortly after high dose steroids [31]. Whether stroke in this patient was due to vasculitis or due to steroid-induced diabetic angiopathy remains speculative [31]. Ischemic stroke was also reported in a 47yo female with dermatomyositis. Stroke in this patient was attributed to cerebral vasculitis, which was confirmed by conventional angiography and brain biopsy [32]. Dermatomyositis and vasculitis responded favorably to cyclophosphamide [32]. Ischemic stroke was additionally reported in a 47yo female under intravenous immunoglobulines (IVIG) for dermatomyositis [33]. Whether stroke in this patient was truly due to vasculitis or a side effect of IVIG remained speculative [33]. Stroke in addition to livedo reticularis, recurrent abortions, and mitral regurgitation, was also described in a female with polymyositis/dermatomyositis, lupus erythematosus, and antiphospholipid syndrome [34]. In a recent study on patients with dermatomyositis or polymyositis cerebrovascular events were found in 0.51% of the cases. Arterial hypertension and hyperlipidemia were positive predictors of these events, while non-steroid treatment was inversely related with the incidence of cerebrovascular events.

C) Small Vessel Disease

Whether there is truly microangiopathy in patients with MELAS-syndrome remains speculative. Though there are some indications that small vessels are affected in MELAS-patients, no patients with myopathy and stroke exclusively attributable to micrangiopathy have been reported so far. Nevertheless, one pathogenetic concept to explain the occurrence of SLEs relies on the speculation that MELAS-syndrome is an angiopathy which also affects the cerebral arteries and subsequently causes ischemia. Small vessel disease may also occur in HIV-infection, which may not only go along with myositis but also with endothelial dysfunction and hyperlipidemia.

D) Stroke of Other Determined Etiology

In a single patient with DMD but without a history of atrial fibrillation or heart failure ischemic stroke occurred due to embolisation of an intracardiac thrombus [7]. The cause of thrombus formation in this patient, however, remained elusive. In a single patient with Kearns-Sayre syndrome acute stroke occurred due to embolisation from a thrombus within the left atrial appendage [35]. In two patients with spontaneous dissection of the internal carotid artery resulting in ischemic stroke, muscle biopsy revealed ragged-red fibers, severely decreased succinate dehydrogenase and cytochrome-c-oxidase stains, and blood chemical investigations revealed increased resting lactate [36]. Despite

the absence of the m.3243A>G mutation, MELAS-syndrome was suspected [36]. Since patients with myopathy often develop arrhythmias, they may also require implantation of a device, which is associated with the risk of embolic stroke. A rare secondary cause of stroke in myopathies may be hyper-viscosity resulting from immunoglobulin therapy for myositis. If patients with polymyositis receive plasma exchange arterial hypotension resulting in low-flow infarcts may be a possible side effect.

E) Ischemic Stroke of Undetermined Etiology (Cryptogenic Stroke)

Cryptogenic stroke has been reported in a number of patients with myopathy. Recurrent pontine stroke was reported in a 4yo DMD patient. Left ventricular function was normal and there was no indication of atrial fibrillation [37]. In this case the diagnosis of DMD was uncertain since immunehistochemistry and genetic testing for dystrophin were not available at the time of diagnosis. TIA manifesting for two hours as aphasia and right-sided hemi-syndrome occurred in a 41yo male with MD1 [38]. Though the authors attributed the cerebrovascular event to mitral valve prolapse syndrome, the proposed causal relation remains questionable. In a patient with autosomal dominant Emery-Dreyfuss muscular dystrophy a fatal stroke-like episode at age 43y was reported [39].

STROKE-LIKE EPISODES

SLEs are episodic events predominantly in MIDs, which characteristically spread and recur, and mimic ischemic stroke clinically to some extent but not on imaging studies [40]. So far, SLEs have been reported in MELAS-syndrome, MERRF-syndrome, Kearns-Sayre syndrome, Saguenay-Lac St. Jean cytochrome oxidase deficiency [41], and Leigh syndrome [42]. Interestingly, SLEs have been also reported in non-mitochondrial disease, such as Emery-Dreyfuss muscular dystrophy [42], congenital glycosilation disorder 1a

[43], X-linked HMSN1A [44], Jacob-Creutzfeld disease [45], proprionyl-CoA carboxylase deficiency [46], Sneddon syndrome [47], or cystinosis [48]. Most frequently SLEs occur in MELAS-syndrome of which they are an integral part of the phenotype. SLEs fundamentally differ from ischemic stroke also with regard to treatment, and prognosis (Table **5**) [49].

1. Clinical Presentation

In accordance with ischemic stroke, SLEs may manifest as hemiparesis or aphasia. Contrary to ischemic stroke, stroke-like episodes may be associated with visual impairment other than hemianopsia, migraine or migraine-like headache, seizures (non-convulsive epileptic state, repetitive complex partial seizures, tonic clonic seizures), ataxia, blurred vision, phasic alertness, amnesia, cognitive impairment, dementia, confusional state, hallucinations, psychosis, or coma [49,50]. Frequently, presenting manifestations include headache, followed by hemianopsia, psychosis, aphasia, and seizures [51]. Other presenting symptoms may include gaze deviation, mental state changes, tremor, seizures, weakness, aphasia, or sensory, visual or hearing disturbance [2].

2. Imaging

The equivalent of SLEs on imaging are stroke-like lesions (SLLs), which present as hyperintensity on T2, DWI, and apparent diffusion coefficient (ADC) maps, and hypoperfusion on perfusion weighted imaging (PWI) in the acute stage (Table **5**) indicating vasogenic edema [52]. In most cases, however, there is coexistence of cytotoxic (DWI: hyperintense, ADC: hypointense, intracellular edema) and vasogenic edema (DWI: hyperintense, ADC: hyperintense, extracellular edema) within the same SLL [2,43], particularly at onset of a SLE [53]. In single cases the entire lesion may be hypointens on ADC. The cytotoxic edema was speculated to derive from gradually evolving metabolic cell death [2].

Table 5. Ischemic Stroke Compared to Stroke-like Episode [2,155]

	Ischemic stroke	Stroke-like epsiode
Acute stage (<6h)		
T2	Normal	Swelling, subtle hyperintensity
DW	Hyperintensity, vascular territory	Hyperintensity outside vascular territory
ADC	Hypointense	Hypo- and hyperintensity
PWI	Hypoperfusion	Hyperperfusion
Subacute stage (5 days)		
T2	Hyperintens	Hyperintens
DWI	Hyperintens	Hyperintens
ADC	Hypointensity	White matter hypointens
		Cortex: hyperintens
Chronic stage		
FLAIR	Hyperintensity, atrophy	Hyperintensity, atrophy,
ADC	Isointens	Isointens, hyperintensity
PWI	Normo- hypoperfusion	Hypoperfusion
Laminar cortical necrosis		

Hyperperfusion in the acute stage has been also shown by HMPAO-SPECT, xenon-CT, and PET studies [51,52,54,55, 56]. In the subacute stage, T2 and DWI are hyperintense [51]. The ADC may be hyperintense in the cortex but hypointense in the subcortical white matter (Table **5**). During the chronic stage atrophy, cysts, or laminar cortical necrosis may develop, and the SLL may become hyperintense on T2 and ADC but may show hypoperfusion on PWI (Table **5**) [2,54,57]. Conventional angiography or MRA are usually normal in patients with SLEs [58]. SLLs usually persist for weeks or even months but may suddenly disappear even after years [59]. Contrary to ischemic stroke, SLLs are not confined to a vascular territory. Most frequently they are located in the parieto-occipital region and show a characteristic dynamic spread to other homo- or contralateral cortical or subcortical regions [2,40]. Some of the lesions disappear after a couple of weeks, whereas others newly develop or persist [2].

3. MR-spectroscopy

Hydrogen-MR-spectroscopy (H-MRS) of a SLL may show a reduced N-acetyl-aspartate (NAA)/creatine (Cr) ratio and an increased lactate-peak [51,60]. In the later stages of a SLL the NAA/Cr ratio may gradually increase together with the increase of the ADC [2,51]. In single patients the increase in lactate and glucose and the decrease of NAA, glutamate, or creatine is not restricted to the SLL but may occur ubiquitously within the brain [61].

4. Pathogenesis

SLEs are usually non-ischemic events, characterized by increased capillary permeability, hyperperfusion, neuronal hyperexcitability, and neuronal loss [62]. Though the pathogenesis of SLEs is controversial, there is largely consensus that SLLs represent a vasogenic edema [62]. Vasogenic edema may be attributable to mitochondrial microangiopathy, resulting in hypoxia and capillary leakage [63]. Arguments against mitochondrial angiopathy, however, are that the prevalence of ischemic stroke is not increased in MIDs with SLEs, that ischemic lesions within SLLs are rare, that MID patients with SLEs usually lack mitochondrial angiopathy on autopsy, and that there is hyperperfusion during the acute stage of a SLE [2,40,55,56]. Arguments for mitochondrial angiopathy are that SLLs occasionally also include areas of cytotoxic edema and that COX-deficiency and heteroplasmy rates are highest in leptomeningeal or cortical arteries [64]. There is also one report about a MELAS patient who exhibited a segmental narrowing of the crural segment of the right posterior cerebral artery during the SLE [65]. According to a second hypothesis, SLLs are due to focal disturbance of the energy production resulting in anaerobic metabolism, neuronal damage, or death from acidosis [40], and consecutively hyperperfusion and vasogenic edema [51]. A third hypothesis explains SLLs by focal neuronal hyperexcitability, demanding increased provision of energy, and resulting in a mismatch between demand and availability of energy [54,66]. An argument in favor of the "epilepsy" hypothesis is that focal epileptiform discharges are recorded in up to 80% of the patients during a SLE [67].

5. Treatment

Treatment of SLEs can be generally causal or non-causal (symptomatic) [49,67]. Since the pathogenic mechanism underlying SLEs remains elusive, a causative treatment is not yet available [68]. Thus, only symptomatic measures can be offered. Among the various symptomatic measures applied for MIDs (drugs, hemodialysis, invasive measures, surgical therapy, dietary measures, physiotherapy), specific and non-specific drug therapy is generally available for the management of SLEs, with the restriction that evidence for the effectivity of a specific or non-specific drug treatment has not been provided by appropriately designed studies. Symptomatic drug treatment of SLEs include antiepileptic treatment if SLEs are accompanied by seizures, analgetic treatment if SLEs are accompanied by headache [69], or anti-psychotic or sedative therapy if SLEs are dominated by confusion, agitation, anxiety, hyperactivity, or psychosis. Non-specific drug therapy includes drugs, which remove noxious metabolites, such as antioxidants or lactate lowering agents, electron donors/acceptors, alternative energy providers, cofactors, or other agents. The classification is partially insufficient since some agents have both an antioxidative effect and are effective at the same time as electron donors/acceptors or cofactors of respiratory chain functions. Drugs with overlapping effect include riboflavin, vitamin C, vitamin E, or the quinones. Non-specific drug treatment of SLLs includes application of drug cocktails which comprise coenzyme Q, idebenone, L-arginine, tocopherol nicotinate, edaravone, prednisolone, glycerol, ATP, cytochrome-c, flavin mononucleotide, thiamine diphosphate, biotin, carnitine, succinate, or dichloracetate in various combinations [67,70]. In some studies some of these agents were given in monotherapy, such as creatine monohydrate, cysteamine, or succinate [71]. A Cochrane review of 678 abstracts, however, did not provide evidence that coenzyme Q, creatinemonohydrate, dichloracetate, or dimethylglycine are generally effective in MIDs [72]. During recent years some evidence emerged from Japanese studies that L-arginine has a beneficial effect in SLEs [68,73,74]. According to these studies L-arginine is applied in a dosage of 0.5g/kg body weight intravenously during the acute stage, followed by oral application thereafter. L-arginine has been shown to be effective even if SLEs manifest as epileptic activity [73]. Occasionally, L-arginine is given together with steroids, glycerol and edaravone [74]. Even steroids in monotherapy have been shown beneficial in single cases [75].

6. Outcome

In the majority of the cases patients recover, either to the level prior to the SLE or to a lower level. Depending of the manifestations of the SLE, the residual abnormalities may include one or several of the acute stage. If a SLE is associated with severe lactacidosis or intractable seizure activity, its outcome is potentially fatal [59].

CONCLUDING REMARKS

Ischemic stroke should be recognized as a potential manifestation of a myopathy. Stroke occurs most frequently in dystrophinopathies and myotonic dystrophy. The frequency

of stroke in myopathies is most likely underestimated since patients with myopathy are hardly systematically screened for cardiac involvement, since these patients do not undergo regular follow-ups, and since clinical deterioration in these patients is often attributed exclusively to the muscle disease itself. Stroke in myopathy may be also not expected because of absent classical risk factors for stroke (cryptogenic stroke). A strong disadvantage of most descriptions about myopathic patients with risk factors for stroke is the lack of a regular follow-up. Due to these insufficiencies myopathy patients should be systematically referred to the cardiologist. Early cardiac treatment, if indicated, may significantly improve the outcome of these patients, if the measures taken follow the available recommendations. SLEs predominantly occur in patients with MIDs, most frequently in MELAS-syndrome, and are much more frequent than ischemic stroke in patients with myopathy. SLEs should be early recognized and unequivocally delineated from ischemic stroke to initiate appropriate measures. Particularly if SLEs are associated with seizures their outcome can be strongly improved if adequate antiepileptic treatment is effective. Overall, neurologists need to become aware of the potential association between myopathy and cerebrovascular events, which need to be clearly delineated from SLEs indicating a MID. Since no effective therapy is available yet, all effort should be directed towards research on the development of targeting, safe and immediately effective agents.

ABBREVIATIONS

ADC	=	Apparent diffusion coefficient maps
CMP	=	Cardiomyopathy
DMD	=	Duchenne muscular dystrophy
DWI	=	Diffusion weighted imaging
EF	=	Ejection fraction
HMSN	=	Hereditary motor and sensory neuropathy
IVIG	=	Intravenous immunoglobulines
LVHT	=	Left ventricular hypertrabeculation/non-compaction
MELAS	=	Mitochondrial encephalopathy, lactacidosis, and SLE-syndrome
MID	=	Mitochondrial disorder
MRI	=	Magnetic resonance imaging
OAC	=	Oral anticoagulation
PWI	=	Perfusion-weighted imaging
SLE	=	Stroke-like episode
SLL	=	Stroke-like lesion
SPECT	=	Singlephoton emission computed tomography
TOAST	=	Trial of Org 10172 in Acute Stroke Treatment

CONFLICT OF INTEREST

None declared.

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