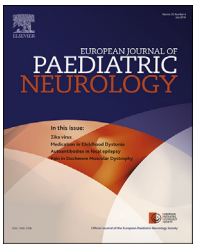
EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY XXX (2016) 1–6

Official Journal of the European Paediatric Neurology Society



Review article

Stroke-like episodes, peri-episodic seizures, and MELAS mutations

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ARTICLE INFO

Article history:
Received 11 March 2016
Received in revised form
26 July 2016
Accepted 1 August 2016

Keywords:
Encephalopathy
Mitochondrial DNA
Cerebrum
Brain
Stroke
Electroencephalography

ABSTRACT

Purpose: Stroke-like episodes (SLEs) are a hallmark of various mitochondrial disorders, in particular MELAS syndrome. SLEs manifest with vasogenic oedema (DWI and ADC hyperintensity) or partial cytotoxic oedema (DWI hyperintensity, ADC hypointensity) in the acute and subacute stage, and with gyriform T1-hyperintensity (cortical necrosis) in the chronic stage.

Principal results: SLEs must be clearly distinguished from ischaemic stroke, since management of these two entities is different. SLEs may go along with or without seizures or epileptiform discharges on EEG. However, in MELAS syndrome seizures may also occur in the absence of SLEs. Focal and generalised seizures have been reported but it is currently unknown if the one or the other prevail. SLEs with and without seizures may respond to NO-precursors l-arginine, succinate, or citrulline. As a supportive measure a ketogenic diet should be initiated. Seizures prior to or during a SLE or paroxysmal EEG-activity during a SLE should be initially treated with antiepileptic drugs (AEDs) with low mitochondrion-toxicity. Only in case these AEDs are ineffective, AEDs with higher mitochondrion-toxicity should be added.

Major conclusions: All patients with SLEs need to have an EEG recorded irrespective if they have manifesting seizures or not. There are no mtDNA or nDNA mutations which predispose for SLEs with seizures.

Contents

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http://dx.doi.org/10.1016/j.ejpn.2016.08.002

Please cite this article in press as: Finsterer J, Wakil SM, Stroke-like episodes, peri-episodic seizures, and MELAS mutations, European Journal of Paediatric Neurology (2016), http://dx.doi.org/10.1016/j.ejpn.2016.08.002

1. Introduction

Stroke-like episodes (SLEs) are a dominant phenotypic feature of various mitochondrial disorders (MIDs) (Table 1).[1] The most well-known is mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome. SLEs are the hallmark of MELAS and manifest clinically as hemianopsia, hemiparesis, confusion, migraine-like headache, vomiting, or seizures.[2] Seizures, in particular status epilepticus, is strongly associated with SLEs but the underlying mechanism behind this relation is currently not fully understood.[3] This review focuses on the presentation and discussion of recent and previous findings concerning the relation between SLEs and epilepsy and on mutations associated with epilepsy in SLEs.

2. Methods

Data for this review were identified by searches of MEDLINE, Current Contents, EMBASE, Web of Science, Web of Knowledge, LILACS, SCOPUS, and Google Scholar for references of relevant articles using the search terms “stroke-like episode”, “stroke-like lesion”, “stroke”, “MELAS”, “MERRF”, “LHON”, “CPEO”, “mtDNA”, “respiratory chain”, and “Leigh syndrome”, in combination with “epilepsy”, “seizures” and “EEG”. Randomized (blinded or open label) clinical trials, longitudinal studies, case series, and case reports were considered. In case a paper was not accessible, the abstract was cited if it contained relevant information. Only articles published in English, French, Spanish, or German between 1966 and 2016 were included. Appropriate papers were studied and discussed for their usefulness to be incorporated in this review.

3. Results

3.1. MIDs with SLEs

Though MELAS is the syndromic MID most frequently associated with SLEs, they may occur also in other MIDs, such as in myoclonic epilepsy with ragged-red fibers (MERRF),[4,5] Kearns–Sayre syndrome (KSS),[6] Leigh-syndrome,[7] Leber's hereditary optic neuropathy (LHON),[8] chronic progressive external ophthalmoplegia (CPEO),[9] propionyl-CoA carboxylase deficiency,[10] in patients carrying *POLG1* mutations,[11] in triple-H syndrome, in mitochondrial spinocerebellar ataxia due to twinkle mutations,[12] and particularly in non-syndromic MIDs.[7,13–17] Surprisingly, SLEs have been also reported in patients with non-mitochondrial disorders, such as X-chromosomal Charcot–Marie–Tooth disease (CMTX1),[18] Emery–Dreifuss muscular dystrophy,[19] congenital disorder of glycosylation 1a,[20,21] Sneddon syndrome,[22] and in cystinosis.[23] Whether non-mitochondrial SLEs have the same pathogenetic background as mitochondrial SLEs remains speculative. Possibly, SLEs in non-mitochondrial disorders originate from a double trouble in which a subclinical MID may be the second abnormality or in which the condition has been misdiagnosed.

3.2. Imaging of SLEs

The imaging correlate of a SLE is the stroke-like-lesion (SLL), which can be best visualised on magnetic resonance imaging

Table 1 – MIDs with SLEs, underlying mutations, and seizures before, during or shortly after a SLE.

MID	Mutation	Additional manifestations	Seizures	EEG	Reference	PT
MELAS	m.3243A>G	MLH, HAO	No	ED	[28]	AB
MELAS	m.3243A>G	Impaired cognition	Yes	nr	[47]	FP
MELAS	m.12706T>C	Impaired cognition	Yes	nr	[47]	FP
Nr	m.8993T>G	nr	Yes	nr	[29]	FP
MELAS	m.12147A>G	nr	Yes	ED	[29]	FP
MELAS	m.13513G>A	Renal failure	Yes	nr	[48]	AB
MELAS	m.6597C>A	Myopathy, amenorrhoea	Yes	nr	[49]	FP
MELAS	m.3243A>G	MLH	Yes	nr	[50]	FP
KSS	mtDNA del	CPEO, ataxia	Yes	nr	[6]	AB
MELAS	m.3243A>G	Myocloni, ataxia	Yes	nr	[51]	AB

PT: paper type, MLH: migraine-like headache, HAO: hemianopsia, ED: epileptiform discharges, nr: not reported.

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