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Headache in mitochondrial disorders

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ABSTRACT

Headache is a prominent feature in mitochondrial disorders (MIDs) but no comprehensive overview is currently available. This review aims at summarising and discussing findings concerning type, frequency, pathogenesis, and treatment of headache in MIDs.

The most frequent headache types in MIDs are migraine and migraine-like headache (MLH). MLH is classified as secondary headache. More rarely, tension-type headache, trigemino-autonomic headache, or different secondary headaches can be found. Migraine or MLH may manifest with or without aura. MLH is frequently associated with an ongoing or previous stroke-like episode (SLE) or a seizure but may also occur independently of other neurological features. MLH may be associated with prolonged aura or visual phenomena after headache. Except for MLH, treatment of headache in MIDs is not at variance from other causes of headache. Beyond the broadly accepted subtype-related headache treatment, diet, cofactors, vitamins, and antioxidants may provide a supplementary benefit. Midazolam, L-arginine, or L-citrulline may be beneficial for MLH. The pathogenesis of headache in MIDs largely remains unsolved. However, since migraine and MLH respond both to triptanes, a shared pathomechanism is likely.

In conclusion, migraine and MLH are the prominent headache types in MIDs. MLH may or may not be associated with current or previous SLEs. MLH is pathophysiologically different from migraine and requires treatment at variance from that of migraine with aura.

1. Introduction

Mitochondrial disorders (MIDs) are frequently multisystem disorders or develop from a mono-organ disease to mitochondrial multiorgan disorder syndrome (MIMODS) during the disease course [1]. Potentially affected organs are brain, nerves, muscles, eyes, ears, endocrine organs, heart, lungs, intestines, kidneys, bones, and skin [2]. Among the cerebral abnormalities in MIDs, headache is a well appreciated manifestation [3]. A shortcoming of most reports about headache in MIDs, however, is that a classification and a detailed description of the intensity, localisation, regional radiation, quality, quantity, duration, recurrence frequency, or triggering factors of headache are missing [4]. This review aims at summarising and discussing previous and recent findings concerning frequency, diagnosis, and treatment of headache in MIDs.

2. Methods

Data for this review were identified by searches of MEDLINE for references of relevant articles. Search terms used for this database were “headache”, “cephalalgia”, “migraine”, “migraine-like”, “cluster”, “tension-type”, and “thunderclap”, in combination with “MELAS”, “MERRF”, “CPEO”, “Kearns-Sayre syndrome”; “Pearson syndrome”, “NARP”, “LHON”, “MIDD”, “MNGIE”, “IOSCA”, “LBSL”, “GRACILE”, “SANDO”, MIRAS“, “MEMSA”, “AHS”, “MCHS”, Leigh syndrome, “PCH”, “MLASA”, “Barth syndrome”, “cardio-facio-cutaneous syndrome”, “Mohr-Tranebjaerg syndrome”, “XLASA”, “ADOA”, “ADOAD”, “DISMOAD”, “SCAE”, “HUPRA”, “RARS”, “DARS2”, “mtDNA”, “mitochondrial”, “depletion”, and “stroke-like episode”. 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. Included were original articles (randomized controlled trials (RCTs) and observational studies with controls) and reviews about humans, published between 1966 and 2017. Editorials and letters were not included. For the paucity of epidemiological data also case reports and small case series, and studies whose reports were published only as an abstract were included. Reference lists of retrieved studies were checked for reports of additional appropriate studies.

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Table 1
Types of headache according to ICHD3-beta so far reported in mitochondrial disorders.

Headache type			Mitochondriopathy	Reference
Primary				
	Migraine		MELAS, CPEO, MERRF. LS	[13,15,42]
	Tension-type headache		MERRF	[22]
	Trigeminal autonomic headhace			
		Cluster headache	nsMIMODS	[17]
		Paroxysmal hemicranias	nr	nr
		SUNCT	nr	nr
		Hemicrania continua	nr	nr
	Others			
		Primary cough headache	nr	nr
		Primary exercise headache	nr	nr
		Headache during sexual activity	nr	nr
		Thunderclap headache	nr	nr
		Cold-stimulus headache	nr	nr
		External pressure headache	nr	nr
		Stabbing headache	nr	nr
		Nummular headache	nr	nr
		Hypnic headache	nr	nr
		New daily persistent headache	nr	nr
Secondary				
		Trauma to head or neck	nr	nr
		Cranial/cervical vascular disorder	nr	nr
		Non-vascular intracranial disorder	nr	nr
		Substance abuse or withdrawal	MELAS (steroids)	[30]
		Infection	MELAS	[25]
		Homeostasis	nr	nr
		Disorders of cranium, neck eyes,	MELAS (sinusitis, otitis)	[25]
		Ears, nose, sinuses, teeth, mouth	nr	nr
		Psychiatric disorders	nr	nr
Painful cranial neuropathies			nr	nr
Other facial pains			nr	nr

MELAS: mitochondrial encephalopathy, lactic acidosis and stroke-like episodes, CPEO: chronic progressive external ophthalmoplegia, MERRF: myoclonic epilepsy with ragged-red fibers, LS: Leigh syndrome. MIMODS: mitochondrial multiorgan disorder syndrome, SUNCT: short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing, MLH: migraine-like headache, ns: non-specific, nr: not reported.

3. Results

3.1. Headache types

Only a few types of headache according to the classification of the international headache society (IHS) (Table 1) have been described in MIDs [5]. These include migraine, cluster headache, tension-type headache, and headache secondary due to arterial hypertension, glaucoma, subarachnoid bleeding, infection, and central vein occlusion.

3.1.1. Migraine and migraine-like headache (MLH)

Migraine in MIDs refers to migraine with aura or to MLH. There are several features upon which migraine with aura in MIDs can be delineated from MLH. Some authors regard MLH exclusively as a manifestation of a stroke-like episode (SLE) but some authors use the term also in the absence of SLEs [6]. Thus, MLH can be primary or secondary. Some authors even use both terms synonymously [7]. According to the ICHD-II and ICHD-III [5,8], MLH is a symptomatic headache secondary to the MID. MLH may not only occur in association with a current or previous SLE but also in association with seizures or without other neurological compromise [9]. Duration of visual phenomena prior to headache may be prolonged compared to migraine with aura (prolonged aura) [3]. Prolonged aura is characterised by aura-like visual disturbance after the headache attack, which may last up to 6 months [10]. Interestingly, the prevalence of MIDs is not increased among migraine patients with prolonged aura [11]. MLH may be the initial manifestation of a MID [9]. MLH may be associated with a worse outcome as compared to MID patients with migraine with aura [9].

Among syndromic MIDs, migraine or MLH has been most frequently reported in MELAS syndrome (Table 2). However, migraine or MLH also occur in other MIDs, such as MERRF, chronic progressive external ophthalmoplegia (CPEO), Leigh syndrome, Leber's hereditary optic neuropathy (LHON), Alpers-Huttenlocher disease, and in non-specific MIMODS (Table 2). In a study of 40 patients with late-onset CPEO, 40% had a history of migraine [12]. Migraine was also reported in 52% of 34 patients carrying the m.8344A > G mutation [13]. In a study of four MELAS patients, migraine was the initial clinical manifestation in two [14]. Frequencies of migraine in MID patients in other studies are listed in Table 3. In patients carrying the m.3243A > G mutation, SLEs may be associated with MLH and homonymous hemianopsia [15]. MLH has been also reported in LHON due to the mutation m.14484T > C [16]. Complications of migraine may be adrenergic stimulation, cell stress, or ischemic stroke. Stress from migraine may even precipitate epilepsy [14].

3.1.2. Trigemino-autonomic headache

The term trigemino-autonomic headache includes cluster headache, the paroxysmal hemicranias, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), and hemicrania continua (Table 1). Trigemino-autonomic headache has been only rarely reported in MIDs. Only cluster headache has been described in a patient carrying a $tRNA^{(Leu)}$ mutation [17]. Additionally, cluster headache was described in patients carrying mtDNA deletions [18,19]. Some authors even regarded cluster headache exclusively as a manifestation of MIDs since they found P-MRS abnormalities in the brain and muscle in 14 patients with cluster headache [20].

3.1.3. Tension-type headache

Though myopathy affecting the axial muscles is frequent among the various MIDs [21], tension-type headache associated with axial