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Letter to the Editor

The Causes of Headaches in Mitochondrial Disorders are more Diverse than Previously Thought

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Letter to the Editor

We read with interest the article by Azzimonti *et al*., a narrative review covering the epidemiology, clinical features, pathophysiology, and therapeutic approaches regarding primary and secondary headaches associated with primary mitochondrial disorders (MIDs) [1]. The authors noted that 50–70% of patients with an MID suffer from headaches, that migraine is the most common cause of headache in MIDs, and that prolonged migraine aura, accompanying multisystem manifestations, and temporal associations with stroke-like episodes aid in differentiating headaches within the context of MIDs [1]. While the study is interesting, certain aspects warrant further discussion.

A first point is that it is unlikely that migraine represents the most common type of headache in MIDs [1]. Given the multisystem nature of most MIDs, tension-type headaches or cervicogenic headaches are presumably far more common than migraine or migraine-like headaches; the latter are reported only occasionally by patients with specific syndromic MIDs. Since many patients with an MID suffer from myopathy that can also affect axial musculature - including the neck muscles - weakness of the neck extensors can lead to a "head-drop" phenomenon: the weakened neck extensors may become overloaded, secondarily causing tension-type headaches.

Another point is that the review article did not adequately consider various causes of secondary headaches associated with MIDs. These include all causes listed in the classification of secondary headaches.

Since MIDs frequently manifest as arterial hypertension [2], headaches in these patients can occur secondarily as a result of poorly controlled or undiagnosed arterial hypertension. Therefore, patients with MID must be carefully examined for elevated blood pressure, left ventricular hypertrophy, and hypertensive retinopathy.

Furthermore, patients with MID experience head trauma more frequently than healthy individuals, for instance, as a result of generalized seizures, extrapyramidal symptoms with gait disturbances, cerebellar involvement, pyramidal tract lesions, or myopathies causing muscle weakness that leads to uncontrolled falls. Thus, traumatic brain injury represents a common cause of secondary headache in MID patients; this must be considered particularly in patients with severe myopathy, generalized epilepsy, and gait disturbances resulting from involvement of the extrapyramidal system, the cerebellum, or the pyramidal tract.

Another aspect is the frequent ophthalmological manifestation of MIDs, such as ophthalmoparesis, myopia, keratoconus, glaucoma, refractive errors, or endocrine orbitopathy. Since ophthalmoparesis, strabismus, or glaucoma can cause ocular pain radiating to the frontal and temporal regions, affected patients may complain of frontal or temporal headaches resulting from ocular involvement.

Malalignment of the cervical spine due to myopathy of the head extensors can lead to chondrosis, osteochondrosis, spondylosis, spondylarthrosis, uncovertebral arthrosis (C3-7), Baastrup syndrome, or scoliosis. These changes can secondarily cause neck pain that radiates to the back of the head and may be mistakenly interpreted as a headache.

MIDs can also manifest in the heart through dilated or hypertrophic cardiomyopathy, arterial hypertension, and supraventricular or ventricular arrhythmias [3]. Since cardiac complications associated with such cardiac involvement can cause embolic or hypotension-induced ischemic strokes, and since strokes can, in turn, trigger headaches, it is essential to include secondary headaches resulting from embolic stroke in the analysis. Heart failure may cause cerebral hypoperfusion and thus headache from cerebral hypoxia.

MIDs can also manifest in the arteries as mitochondrial arteriopathy [4]. This, in turn, may be associated with atherosclerosis, vasospasms [5], dissection [6], reversible cerebral vasoconstriction syndrome [7], or aneurysm formation [8]. Mitochondrial

macroangiopathy in MIDs can therefore be complicated by arterial stenoses, occlusions, and cerebral hypoxia or hemorrhage. Aneurysm rupture can lead to subarachnoid hemorrhage, which typically presents with severe headache.
Lactic acidosis has not previously been considered a cause of headache in MIDs [1]. Given that lactic acidosis is a common complication of MIDs, affecting the brain and potentially causing headaches, it is crucial to include this type of headache in a review of headaches associated with MIDs.
Finally, patients with MIDs are often severely ill and require medications that can lead to secondary headaches. Medications known to cause headaches include pain killers, nitrates, epoprostenol, selexipag, and hormone replacement therapy preparations used for secondary or primary hormonal dysfunction.

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