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LETTER TO THE EDITOR

Treatable mitochondrial diseases: cofactor metabolism and beyond

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Sir,

In the past, numerous articles related to disorders of mitochondrial cofactor metabolism have been published in *Brain* (Ozand *et al.*, 1998; Gempel *et al.*, 2007; Johnson *et al.*, 2012; Foley *et al.*, 2014; Haack *et al.*, 2014; Ortigoza-Escobar *et al.*, 2016). These studies not only facilitated our understanding of the underlying biochemical defects, but also paved the way to specific treatment options. As a consequence our clinical view on mitochondrial diseases has changed substantially during the last years.

The umbrella term 'mitochondrial disease' comprises a large group of inherited metabolic disorders caused by dysfunction of the pyruvate oxidation route. Our common understanding of mitochondrial diseases mainly refers to classical mitochondrial syndromes such as Leigh syndrome or MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes). However, the spectrum of mitochondrial diseases is much broader and the development of novel genetic tools has undeniably advanced our knowledge about this disease group. During the past 6 years more than 100 novel mitochondrial diseases have been identified via next generation sequencing (NGS) strategies leading to a total number of around 280 known disease genes, affecting diverse mitochondrial pathways. Accordingly, clinical management of affected individuals is challenging and diagnostic strategies are in flux.

Unfortunately, current therapeutic options for the majority of classical mitochondrial syndromes are limited to supportive care. Nevertheless, apart from these prognostically unfavourable diseases, there are several mitochondrial defects that are amendable by specific treatment strategies (Table 1). Among the group of these 'treatable mitochondrial diseases', defects of cofactor metabolism play a major role.

For normal functioning, the mitochondrial oxidative phosphorylation (OXPHOS) system requires a large number of organic and inorganic cofactors that facilitate these enzyme-catalysed reactions. Organic cofactors are mainly derived from vitamins such as thiamine, riboflavin, biotin or niacin but there are also non-vitamin cofactors such as coenzyme Q_{10} or heme. The group of inorganic cofactors comprises metal ions such as iron, magnesium, copper, zinc, and molybdenum. Most cofactors or its precursors are derived from food and intestinal absorption as well as tissue uptake requires specific transport mechanisms. However, in the cases of coenzyme Q_{10} or heme, endogenous biosynthesis is the main source for cellular supply.

In conditions with insufficient cofactor availability, mitochondrial energy metabolism might get severely disturbed, leading to tissue damage primarily affecting organ systems with high energy demand such as skeletal muscle and brain. The most common vitamin-related cofactor diseases caused by nutritional deficiency of thiamine (beriberi), niacin (pellagra), or riboflavin (pellagra sine pellagra) were elucidated

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Table 1 Inherited mitochondrial diseases with specific treatment options

Affected pathway	Clinical syndrome	Affected gene(s)	Clinical phenotype	Therapeutic substance	Treatment response
Primary disorders of mitochondrial vitamin cofactor metabolism	Brown-Vialetto-Van Laere syndrome / Fazio-Londe disease	*SLC52A2*, *SLC52A3*, *(SLC52A1)*[a]	Sensorineural hearing loss, cranial nerve palsies	Riboflavin (oral: 10–50 mg/kg/day)[b]	Generally good
	Biotin-thiamine-responsive basal ganglia disease	*SLC19A3*	Episodic encephalopathy, dystonia, seizures	Thiamine (oral: 10–20 mg/kg/day), biotin (oral: 10–15 mg/kg/day)[c]	Generally good
	Biotinidase deficiency	*BTD*	Dermatitis, muscular hypotonia, developmental regression	Biotin (oral: 5–10 mg/kg/day)[d]	Generally good
	Holocarboxylase synthetase deficiency	*HLCS*	Skin lesions, metabolic acidosis, seizures, developmental delay	Biotin (oral: 10–20 mg/kg/day)[e]	Variable but generally good
	Thiamine pyrophosphokinase deficiency	*TPK1*	Episodic encephalopathy, dystonia, spasticity	Thiamine (oral: ~20 mg/kg/day)[f]	Variable (<10 patients treated so far)
Disorders with indirect response to mitochondrial vitamin cofactor supplementation	ACAD9 deficiency	*ACAD9*	Encephalopathy, myopathy, hypertrophic cardiomyopathy	Riboflavin (oral: 10–20 mg/kg/day)[g]	Variable
	Multiple acyl-CoA dehydrogenase deficiency	*ETFA*, *ETFB*, *ETFDH*, *SLC25A32*, *FLAD1*	Early childhood multisystem disease or late-onset form with muscle weakness, hepatopathy, etc.	Riboflavin (oral: ~10 mg/kg/day)[h]	Generally good
	Thiamine-responsive pyruvate dehydrogenase deficiency	*PDHA1*	Neonatal lactic acidosis, seizures, developmental regression, spasticity	Thiamine (oral: 30–40 mg/kg/day)[i]	Variable
Disorders of mitochondrial non-vitamin cofactor metabolism	Coenzyme Q_{10} deficiency	*PDSS1*, *PDSS2*, *COQ2*, *COQ4*, *COQ6*, *COQ7*, *ADCK3*, *ADCK4*, *COQ9*	Variable phenotypes, ranging from adult-onset myopathy to fatal neonatal presentations	Coenzyme Q_{10} (oral: 10–30 mg/kg/day)[j]	Highly variable depending on the underlying defect
Disorders of mitochondrial inorganic cofactor metabolism	Cytochrome c oxidase deficiency	*SCO2*, *COA6*	Infantile encephalocardiomyopathy	Copper–histidine (dose unclear; subcutaneous injections of up to 500 μg daily were suggested)[k]	Unclear, only one *SCO2* patient treated; only *in vitro* evidence for *COA6*
	Molybdenum cofactor deficiency	*MOCS1*, *MOCS2*, *GPHN*	Infantile-onset epileptic encephalopathy, progressive brain damage	Cyclic pyranopterin monophosphate (intravenous: 80–320 μg/kg/day)[l]	Generally good in MoCD type A patients
'Inhibitors' of mitochondrial metabolism	3-Hydroxyisobutyryl-CoA hydrolase deficiency	*HIBCH*	Infantile Leigh-like phenotype	Valine-restricted diet[m]	Unclear, only few patients treated
	Enoyl-CoA hydratase deficiency	*ECHS1*	Infantile Leigh-like phenotype	Valine-restricted diet[n]	Unclear, only few patients treated so far
	Thioredoxin 2 deficiency	*TXN2*	Cerebellar atrophy, dystonia, seizures, peripheral neuropathy	Antioxidant treatment (e.g. Idebenone up to 20 mg/kg/day)[o]	Apparently good (only one patient reported)
	Ethylmalonic encephalopathy	*ETHE1*	Severe, multisystem infantile disorder	Metronidazole, *N*-acetyl cysteine as glutathione precursor, liver transplantation[p]	Variable

[a]Only a single case with postulated *SLC52A1* haploinsufficiency has been reported so far.

[b–p]The therapeutic regimens are suggestions based on the indicated references: [b]Foley *et al.*, 2014; [c]Haack *et al.*, 2014; [d]Jay *et al.*, 2015; [e]Donti *et al.*, 2016; [f]Banka *et al.*, 2014; [g]Gerards *et al.*, 2011; [h]Olsen *et al.*, 2007; [i]van Dongen *et al.*, 2015; [j]Hargreaves, 2014; [k]Freisinger *et al.*, 2004; [l]Schwahn *et al.*, 2015; [m]Soler-Alfonso *et al.*, 2015; [n]Haack *et al.*, 2015; [o]Holzerova *et al.*, 2016; [p]Dionisi-Vici *et al.*, 2016.

more than 70 years ago (Eijkman and Hopkins, 1965; Sebrell and Butler, 1939; Elvehjem *et al.*, 1973). These diseases are characterized by severe clinical phenotypes including progressive neurological deterioration that are highly responsive to supplementation of the lacking vitamin.

The first inborn errors of mitochondrial cofactor metabolism were already described in the 19th century (Brown, 1894; Londe, 1894). However, it took decades until advances in genetic diagnostic tools allowed the identification of the underlying inherited defects affecting the tissue-specific transport and metabolism of these cofactors. Classical examples of inherited vitamin-related disorders of cofactor metabolism are Brown-Vialetto-Van Laere syndrome (BVVLS1 and 2; OMIM #614707, #211530), biotin-thiamine-responsive basal ganglia disease (OMIM #607483) or biotinidase deficiency (OMIM #253260; Gompertz *et al.*, 1973; Brown, 1894; Ozand *et al.*, 1998). These disorders are autosomal recessive defects of specific transporter proteins, causing severe neurometabolic diseases with onset in childhood. In the case of BVVL, mutations in *SLC52A2* or *SLC52A3* impair cellular supply with riboflavin (Green *et al.*, 2010; Johnson *et al.*, 2012). This leads to sensorineural hearing loss and cranial nerve palsies. The progression of these neurological problems can be slowed down or even stopped by supplementation of high-dose riboflavin (Foley *et al.*, 2014). Apart from classical BVVLS, Fazio-Londe disease (OMIM #211500; Londe, 1894) caused by *SLC52A3* mutations is a recognized riboflavin-responsive clinical entity similar to BVVLS but without sensorineural deafness. Biotin-thiamine-responsive basal ganglia disease is characterized by episodes of encephalopathy, dystonia and seizures. The disease is caused by mutations in *SLC19A3*, leading to impaired thiamine transport into the CNS with subsequent mitochondrial dysfunction (Zeng *et al.*, 2005). Thiamine is beneficial in affected patients and prevents further neurological deterioration (Haack *et al.*, 2014). In addition, biotin supplementation is helpful via increasing the gene expression of *SLC19A3* (Debs *et al.*, 2010). During the past years, the spectrum of vitamin-related disorders of cofactor metabolism has broadened substantially. Treatable genetic defects include holocarboxylase synthetase deficiency (OMIM #253270), thiamine pyrophosphokinase deficiency (OMIM #614458) or inherited riboflavin deficiency (OMIM #615026). The recent reports of Schiff *et al.* (2016) and Olsen *et al.* (2016) add to this rapidly growing list of potentially treatable diseases affecting mitochondrial cofactor metabolism (Table 1). They illustrate that in some individuals, the clinical course can be alleviated with simple measures such as vitamin supplementation.

Importantly, beyond the field of such 'classical' cofactor-related mitochondrial diseases, there is also a growing group of treatable disorders that affect mitochondrial metabolic pathways via inhibitory/toxic mechanism. This involves, for example, 3-hydroxyisobutyryl-CoA hydrolase (HIBCH) deficiency (OMIM #250620) and enoyl-CoA hydratase (ECHS1) deficiency (OMIM #616277), both defects of the valine catabolic pathway. The disorders induce secondary OXPHOS deficiency, which is most likely caused by the accumulation of the toxic metabolites methacrylyl-CoA and acryloyl-CoA (Ferdinandusse *et al.*, 2013; Peters *et al.*, 2014). The diseases present with a severe infantile Leigh-like phenotype. Preliminary clinical evidence suggests that affected children might be responsive to a valine-restricted diet (Haack *et al.*, 2015; Soler-Alfonso *et al.*, 2015). Another example is the recently described disorder thioredoxin 2 deficiency (OMIM #616811), which affects an essential mitochondrial pathway that is protective against oxidative stress. The clinical phenotype is characterized by early-onset neurodegeneration, dystonia, and seizures. *In vitro* and *in vivo* studies indicated a benefit of high-dose antioxidant treatment (Holzerova *et al.*, 2016).

The studies mentioned above illustrate how the application of NGS technologies facilitates our understanding of the pathophysiology of mitochondrial diseases in general and potentially treatable disease subgroups in particular. Importantly, many of the above-mentioned treatable defects show clinical and neuroradiological similarities to classical mitochondrial disorders such as Leigh syndrome (e.g. *SLC19A3*, *ECHS1* or *HIBCH* mutations). Therefore, it is crucial to recognize that a subset of patients with a clinical diagnosis of 'mitochondrial disease' may suffer from a vitamin/cofactor-responsive condition. These disorders need to be urgently explored in patients with mitochondrial diseases. In our view, early empirical therapy in combination with rapid genetic diagnostic strategies should be applied to maximize treatment benefits and to avoid any delay in appropriate treatment. This especially holds true in critically ill patients. For example in neonates with severe lactic acidosis or children with acute neurological deterioration, a therapy regimen including thiamine (20 mg/kg/day), biotin (5 mg/kg/day), riboflavin (20 mg/kg/day) and coenzyme Q_{10} (15 mg/kg/day) might be considered. This approach covers the most important disorders summarized in Table 1. Importantly, empirical application of these cofactors is not expected to cause any serious side effects. In case of biotin, potential interaction with streptavidin-biotin laboratory methods should be kept in mind (Kummer *et al.*, 2016).

However, despite the scientific progress discussed above, it is important to realize that not all of the disorders summarized in Table 1 have an ideal treatment prognosis and caution should be emphasized against an overly enthusiastic approach. Moreover, clinical evidence for the suggested treatment options in some of the disorders remains limited, owing largely to the fact that these are rare and recently discovered genetic defects. This underlines the need of further clinical and genetic data collection, for example via international mitochondrial disease registries, to achieve generalizable recommendations regarding optimal treatment and long-term prognosis for these patients.

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