Sea food consumption for improving cardiac and cerebral manifestations of mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes

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Since the initial description >30 y ago, therapeutic options for mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome, the most well-known of the mitochondrial disorders (MIDs), remain limited due to the complexity of its genetic background and its clinical manifestations (1,2). MELAS is a maternally inherited, progressive MID, usually affecting people <40 y of age, with a prevalence ranging from 18.4 to 236/100,000 individuals (1-6). Clinically, MELAS manifests with cerebral, psychiatric, muscular, cardiac, renal, gastrointestinal, endocrine, auditory, dermatological, or visual abnormalities (2,3,7). Cardiac and neurological involvement has the strongest impact on the prognosis and outcome of these patients. One of the cerebral manifestations of MELAS is epilepsy, which may be linked or unlinked to stroke-like episodes. Cardiac involvement includes cardiomyopathy, pulmonary hypertension, conduction defects, or arrhythmias, possibly complicated by sudden cardiac death (SCD). Treatment of epilepsy and cardiac disease in MIDs is challenging. Whether intake of omega-3 highly unsaturated fatty acids (O3-HUFAs) has a beneficial effect on epilepsy or cardiac disease in MELAS or MIDs in general is unknown but this letter is dedicated to considerations about the usefulness of O3-HUFAs in the treatment of mitochondrial epilepsy and cardiac disease.

MELAS may be associated with partial or generalized seizures, including convulsive or non-convulsive status epilepticus (3,8). The pharmacological treatment of epilepsy in MIDs is usually not at variance from therapy of epilepsy due to other causes (8). However, mitochondrion-toxic AEDs such as valproic acid (VPA), carbamazepine (CBZ), phenytoin (PHT), or barbiturates should be avoided if possible (8-10). Treatment of epilepsy in MIDs relies on classical AEDs, the ketogenic diet, L-arginine, pyruvate, or ketamine (8,11-13). Death from epilepsy in MIDs has been only rarely reported (8) and sudden unexpected death in epilepsy (SUDEP), the most common cause of death in people with intractable epilepsy (14), is unreported in MELAS.

Cardiac dysfunction represents an important cause of disability in MELAS patients and MIDs in general (15-17). Cardiac involvement in MIDs, including MELAS, needs to be recognized by comprehensive cardiovascular screening protocols and needs to be carefully monitored and adequately treated, to reduce the risk of morbidity and mortality (17). Currently, there is a lack of clinical and experimental studies evaluating cardiac complications and preventive and curative strategies in MELAS (17,18). Though cardiac abnormalities can be a major problem in MELAS patients, our understanding of the best way to prevent cardiac compromise is still unknown. Accordingly, MELAS patients live with a chronic intractable disorder, which reduces the quality of life with a subsequent burden on the caregiver, the family, and the society (19).

About 10 years ago a debate about the dietary management with O3-HUFA supplementation for epilepsy, SUDEP, and cardiovascular disease evolved (20-22). It was proposed to develop new methods or actions, other than classical medical therapies, to prevent or treat it. Already the Old Testament book of Tobias proclaimed the benefits of consuming O3-HUFAs as a possible type of medical therapy ("*Then the angel said to him: Take out the entrails of*

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the fish, and lay up his heart, and his gall, and his liver for thee; for these are necessary for useful medicines") (23,24). Since Bang and Dyerberg reported in 1972 that Greenland Eskimos on a diet rich in O3-HUFAs have a lower incidence of cardiovascular disease, a series of translational studies were conducted in order to evaluate the beneficial effects promoted by O3-HUFAs on human diseases and health systems in general (25,26).

O3-HUFAs have been shown to be effective in preventing stroke and myocardial infarction. Particularly in individuals with high cardiovascular risk, moderate-to-high consumption of fish lowered the prevalence of chronic diseases associated with obesity, diabetes, and some types of cancer and displayed neuroprotective properties and exerted beneficial effects on neurological and psychiatric disease (20-22,27-34). In a meta-analysis of patients with arterial hypertension O3-HUFAs reduced high blood pressure values (35). There are also indications that O3-HUFAs have an anti-arrhythmic effect and positively influence atrial fibrillation (36). In a study of 205 patients with chronic heart failure, intake of O3-HUFAs significantly improved left ventricular diastolic dysfunction and reduced proBNP levels (37). The beneficial effect of O3-HUFA on heart failure was also confirmed by other studies (38). In a study of pediatric patients with dilated cardiomyopathy, O3-HUFA supplementation during 6 months resulted in improvement of various echocardiographic parameters (39). O3-HUFA may also cause adverse reactions. In animals but not in humans O3-HUFA has been shown to reduce insulin-resistance. However, intake of O3-HUFA appears to carry an increased risk for developing diabetes (40).

O3-HUFAs, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are essential fatty acids (41,42), which exert their beneficial effect via anti-inflammatory, anti-oxidative, or anti-fibrotic mechanisms. Since the human body cannot synthesize O3-HUFAs, an appropriate diet represents an important source of these essential fatty acids (25,43,44). Evaluating these considerations, advantages and nutritional benefits of a diet rich in fish or other seafood are particularly due to the content of high-quality protein and high concentrations of EPA and DHA in various marine species (45-47). The most appropriate fish choices for consumption, particularly with regard to the amount of O3-HUFAs, the predatory characteristics, and the concentrations of contaminants (e.g., methylmercury, polychlorinated biphenyls and dioxins), are anchovies, atlantic herring, salmon, trout, and sardines (27,45-48). For subjects who prefer a diet with safe concentrations of contaminants and would like to enjoy the benefits of O3-HUFAs, fish oil supplements or intake of foods such as walnuts or oils from flax, canola, or soybean, can be alternatively given (49,50). According to national and international guidelines containing recommendations for the general population on the prevention of chronic diseases, consumption of at least 250 mg/day of long-chain O3-HUFAs or at least 2 servings/week of oily fish is recommended (51).

Overall, MELAS is a currently incurable genetic disorder with cardiac and cerebral involvement and although our proposal is speculative, there is a strong need that thought is given to new considerations and that studies are carried out if O3-HUFAs are effective regarding the cardiovascular and CNS compromise in MELAS or other MIDs. Until new therapeutic options are available, MID patients should undergo comprehensive diagnostic work-up and monitoring, particularly of neurological and cardiac abnormalities, not to miss application of effective treatment and prophylaxis. Regular intake of O3-HUFA-rich fish is a good option, because it is healthy and relatively inexpensive. Moreover, prescribing non-contaminated fish to MID and MELAS patients is recommendable since it has no adverse effects and may exhibit a beneficial effect on epilepsy and cardiac complications in these patients.

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Footnote

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