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Letter to the Editor

Novel Phenotypes and Cardiac Involvement Associated With DNA2 Genetic Variants

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In a recent article, Gonzalvez-del Angel *et al*., reported three patients with phenotypically heterogeneous multisystem mitochondrial disorder (MID) due to the heterozygous variants c.2346delT (patients-1 and 2) respectively c.578T>C (patient-3) in *DNA2 (*González-del Angel, A. *et al*., 2019*)*. Patient-1 presented with intrauterine hypotonia, failure to thrive, episodes of weight loss, delayed motor milestones, limb weakness due to myopathy with myalgia, frequent falls, scoliosis, and gait disturbance, Mobitz-2 block requiring pacemaker implantation, gestational diabetes, and preeclampsia, and multiple dysmorphisms (González-del Angel, A. *et al*., 2019). Patient-2 presented with neonatal hypotonia, failure to thrive, confusion and weight loss during episodes of febrile infections, delayed motor skills, facial, ocular, and limb weakness, supraventricular tachycardia, and facial dysmorphism (González-del Angel, A. *et al*., 2019). Patient-3 presented with ischemic cardiomyopathy, chronic obstructive pulmonary disease (COPD), hypoacusis, rhabdomyolysis, and transient facial and limb weakness following surgery under general anesthesia, and neck lipomatosis (González-del Angel, A. *et al*., 2019) We have the following comments and concerns.

MIDs are generally multisystem disorders, with affection not only of a single organ/tissue but multiple organs/tissues. Multisystem involvement may be present already at onset or may become evident with progression of the disease. Patient-1 manifested in the skeletal muscle, smooth muscle, heart, pancreas, and bones (González-del Angel, A. *et al*., 2019). Patient-2 manifested in the muscle, heart, and bones (González-del Angel, A. *et al*., 2019). Patient-3 manifested in the ears, muscle, and skin (González-del Angel, A. *et al*., 2019).Affection of various organs may be mild or subclinical why MID patients need to be prospectively investigated for multisystem involvement. Subclinical in patient-1 was the diabetes and epilepsy requiring the trigger pregnancy to become clinically evident. Subclinical in patient-3 was myopathy requiring the trigger general anesthesia to manifest clinically. The central nervous system (CNS) is the second most frequently affected organ in MIDs after the skeletal muscle, why it is crucial to initiate work-up for CNS involvement. Missing in this respect is the cerebral MRI of patient-1. Particularly we should be informed if muscle hypotonia in patient-1 was due to brainstem involvement or due to myopathy. It is also crucial to be informed if the stroke was truly ischemic on MRI or rather metabolic in the sense of a stroke-like episode (SLE). Concerning pre-eclampsia in patient-1 we should know the results of the EEG recordings during or after pregnancy. In patient-1 it is crucial to differentiate between myopathy and neuropathy as the cause of reduced tendon reflexes. Since MIDs are frequently associated with primary or secondary neuropathy (Finsterer, J. 2011), we should be informed about the results of nerve conduction studies.

Concerning the cardio-embolic stroke during pacemaker implantation we should be informed about the pathomechanism and nature of the stroke, particularly if there was a patient foramen ovale, if atrial fibrillation occurred, if thrombi within the left atrial appendage were detected, if there was a coagulation disorder, or if there was transient heart

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failure during the intervention. Missing in this respect are results of echocardiography, particularly the exclusion of cardiomyopathy, values of proBNP and troponin, and the results of long-term ECG recordings. Concerning coronary heart disease in patient-3 we should know which of the classical risk factors were present. Since hyperlipidemia may be a manifestation of a MID (Finsterer, J. *et al*., 2013), we should know if hyperlipidemia was interpreted as dietary or metabolic,

Concerning the trigger of rhabdomyolysis in patient-3, it should be discussed if it was a compound given during general anesthesia, the previous corticosteroid therapy for COPD, or rosuvastatin. Even beta-blockers have been reported to trigger rhabdomyolysis (Aihara, M. *et al*., 1990). We should know if rosuvastatin and steroids were discontinued after detection of the MID or not. From corticosteroids it is well known that they may have beneficial no, or adverse effects in patients with a MID (Finsterer, J., & Frank, M. 2015). Particularly patients with Kearns-Sayre syndrome may experience severe side effects from steroids (Finsterer, J., & Frank, M. 2015). From statins it is well appreciated that they cause myopathy in about 1% of the cases taking statins, most likely in patients with a subclinical MID.

Though DNA2 is an mtDNA maintenance protein and though patient-3 had multiple mtDNA deletions on long-range PCR (González-del Angel, A. *et al*., 201), none of the three patients was tested for depletion of mtDNA. Several MIDs due to mutations in nuclear genes involved in the replication of the mtDNA have been shown to present with mtDNA depletion (mitochondrial depletion syndromes) (El-Hattab, A. W. *et al*., 2017).

Overall, this interesting case series could be more meaningful if the points raised above were addressed. Phenotypic diversity may increase if MID patients are prospectively investigated for subclinical manifestations or if they are exposed to triggers of MID manifestations.

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