East African Scholars Journal of Medical Sciences
Abbreviated Key Title: East African Scholars J Med Sci
ISSN: 2617-4421 (Print) & ISSN: 2617-7188 (Online)
Published By East African Scholars Publisher, Kenya

Volume-3 | Issue-3 | Mar-2020 | DOI: 10.36349/EASMS.2020.v03i03.008

OPEN ACCESS

Letter to Editor

Comprehensive Clinical and Genetic Work-Up in Carriers of the Variant C.1228G>A In *DNM1L* Is Warranted

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Article History
Received: 18.02.2020
Accepted: 20.03.2020
Published: 25.03.2020

Journal homepage:
https://www.easpublisher.com/easjms

Quick Response Code

Abstract:

Keywords: DNM1L, cardiomyopathy, heart failure, mitochondrial disorder, multisystem.

LETTER TO THE EDITOR

In a recent article, Vandeleur *et al.*,., reported about an 8 months-old female carrying the variant c.1228G>A in *DNM1L* which phenotypically manifested with microcephaly, failure to thrive, poor feeding, exsiccosis, cardiomyopathy (CMP), developmental motor delay, truncal hypotonia, exaggerated startle reaction, reduced visual tracking, myopathy, and lactic acidosis (Vandeleur, D. *et al.*, 2019). We have the following comments and concerns.

We do not agree that cardiac involvement in *DNM1L*-related disease "is undescribed" (Vandeleur, D. *et al.*, 2019). The *DNM1L*-gene encodes the dynamin-related protein-1 (DRP1). It is well known that DRP1 stimulates mitochondrial respiration, bioenergetics, and ROS-signalling in cardiomyocytes (Zhang, H. *et al.*, 2017). In mice with Drp1 deficiency disassembly of the protein impairs mitophagy, leading to reduction of the mitochondrial membrane potential, aberrant calcium handling, reduced ATP synthesis, myocardial inflammation, and lastly heart failure (Cahill, T. J. *et al.*, 2015).

There is a discrepancy concerning the cerebral myelination of the index patient. On the one hand the authors describe that myelination was normal for age (at age 6 months) on MRI and later in the case description they mention that there was hypomyelination (at age 8 months) at autopsy. We should know what is true and if the discrepancy results from evaluation at two different time points, is attributable to the disease course, or due to different types of investigation.

Missing is the specification of the CMP. It is described that the left ventricle was hypertrophic and dilated at the same time (Vandeleur, D. *et al.*, 2019). However, no information is provided if CMP was hypertrophic CMP with secondary dilatation, if CMP was primary dilative with secondary hypertrophy, if there was left ventricular hypertrabeculation (LVHT) / noncompaction, or if it was recurrent Takotsubo syndrome (TTS). Specifying the type of CMP is crucial as it may strongly determine the type of treatment and

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the outcome. Arguments for the presence of LVHT are the subendocardial fibrosis (Stöllberger, C., & Finsterer, J. 2019), frequently found in LVHT, and the mitochondrial disorder (MID), as LVHT is most frequently associated with MIDs (Finsterer, J. 2009). Missing are the troponin and proBNP values, long-term ECG recordings, and the information about the course of heart failure. We should know if heart failure completely resolved after the first episode or not. Was pulmonary embolism excluded as a cause of clinical deterioration during blood transfusion?

Missing is the information if the parents were consanguineous or not and if the siblings and the parents were genetically tested for the culprit mutation.

Since the patient had myopathy we should know if respiratory insufficiency was truly only due to heart failure or if there was additional or exclusive muscular respiratory failure.

We should know if the increased startle reaction was attributable to seizure activity, thus, if the EEG showed epileptiform discharges or not.

Overall, this interesting case report has a number of shortcomings which need to be addressed before drawing final conclusions. We should know if the mutation was inherited or occurred spontaneously and evaluation of the phenotype needs to be reinforced.

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