East African Scholars Journal of Medicine and Surgery
Abbreviated Key Title: EAS J Med Surg
ISSN: 2663-1857 (Print) & ISSN: 2663-7332 (Online) |
Published By East African Scholars Publisher, Kenya

OPEN ACCESS

Volume-1 | Issue-5 | July-Sept-2019 | DOI: 10.36349/EASJMS.2019.v01i05.003

Letter to the Editor

Kawasaki Disease in a *LDB3* Mutation Carrier with Subclinical Myopathy and Noncompaction

Josef Finsterer, MD, PhD

Krankenanstalt Rudolfstiftung, Messerli Institute, Vienna, Austria

*Corresponding Author
Josef Finsterer, MD, PhD

Keywords: myopathy, non-compaction, hypertrabeculation, mutation, gene, congenital muscular dystrophy.

In a recent article, Hachiya *et al.*, reported about a 6 months-old male with Kawasaki disease (KD) who also carried a *LDB3* mutation and presented with noncompaction(LVHT) (Hachiya, A. *et al.*, 2016). We have the following comments and concerns.

LDB3 is one of the six cardinal genes (*DES*, *CRYAB*, *LDB3/ZASP*, *MYOT*, *FLNC*, *BAG3*), of which mutations cause myofibrillar myopathy(MM), characterised by focal abnormal accumulation of intra-sarcoplasmic proteins, the presence of vacuoles, and disorganisation of the inter-myofibrillar network beginning at the Z-disk (Béhin, A. *et al.*, 2015). In addition, structural and functional abnormalities of mitochondria have been described (Jackson, S. e al 2015). Recently, it has been shown that mutations in the *DNAJB6*, *FHL1*, *PLEC*, or *TTN* gene, encoding for Z-disc proteins as well, may also cause MM (Jackson, S. *et al.*, 2015). Did the index case or any of his relatives present with clinical features of MM, such as slowly progressive diffuse weakness of the limb muscles, weakness of the distal muscles, or respiratory failure due to affection of the respiratory muscles? Did any of the mutation-carriers report muscle stiffness, aching, or cramps (Selcen, D. *et al.*, 2005 Jan 28). Were there indications for peripheral neuropathy occurring in 20% of the cases (Selcen, D. *et al.*, 2005 Jan 28). Which were the results of nerve-conduction studies, muscle MRI, and muscle biopsy?

We should be informed about those first-degree relatives who also carried the LDB3 mutation. In which relatives was the LDB3 mutation detected? Which of those who carried the mutation were symptomatic and which were asymptomatic? Which subjects had developed only cardiac manifestations and which presented with muscle disease and cardiac involvement? Did transmission of the mutation follow an autosomal dominant or autosomal recessive trait?

Mutations in *LDB3/ZASP*/cypher may not only be associated with LVHT but also with arrhythmogenic right ventricular dysplasia. Did the patient ever develop phenotypic features such as hepatomegaly, palpitations, syncope, dyspnoea, exercise-intolerance, or coma? Did endomyocardial biopsy show right ventricular fibro-fatty replacement, predisposing for premature ventricular contractions, sustained or non-sustained re-entrant ventricular tachycardia, supra-ventricular ectopic beats, supra-ventricular tachycardia, atrial flutter, atrial fibrillation, or sick sinus syndrome?

LVHT is frequently complicated by heart failure, ventricular arrhythmias, including sudden cardiac death, or cardiac embolism. Was heart failure and systolic dysfunction attributed to KD rather than LVHT or was it a complication of another type of cardiomyopathy, occurring in 15-30% of the cases (Selcen, D. *et al.*, 2005 Jan 28)?

Since cardiac disease in MM may go along with severe ventricular arrhythmias and conduction disturbances (Celestino-Soper, P. B. *et al.*, 2015), we should be informed about the results of long-term ECG recordings and if the individual or family history was positive for palpitations or syncopes. Did any of the first-degree relatives require a pacemaker or an ICD?

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Journal homepage:
http://www.easpublisher.com/easms/

Article History
Received: 12.09.2019
Accepted: 28.09.2019
Published: 10.10.2019

We do not agree with the notion that mutations in *LDB3* cause LVHT [1]. Though LVHT is associated with mutations in >40 different genes and a number of chromosomal defects, a causal relation has never been proven.

Overall, this interesting case would profit from a more clearcut delineation between manifestations of KD and those of the *LDB3* mutation. Relatives need to be investigated for the mutation and LVHT. Muscle manifestations of the *LDB3* mutation, including hyper-CKemia, need to be encountered.

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