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Letter to Editor

NDUFB11 Mutations Causing Histiocytoid Cardiomyopathy and Allelic Microphthalmia with Skin Defects

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In a recent article, Rea., *et al*. reported about a 13 months old female with histiocytoid cardiomyopathy (HCCMP), arrhythmias, left ventricular hypertrabeculation/noncompaction (LVHT), intermittent squint (ophthalmoparesis), bulbar palsy with poor feeding, gastroesophageal reflux, and histiocytoid cells in the thyroid gland, the lungs and the choroid plexus due to a biallelic mutation in the *NDUFB11* and *FAM135A* genes respectively [1]. We have the following comments and concerns.

In addition to HCCMP, the patient presented with LVHT [1]. LVHT has been repeatedly reported as an associated cardiac abnormality in HCCMP but is also a frequent cardiac manifestation of MIDs [2]. According to which diagnostic criteria was LVHT diagnosed, the Vienna criteria or the Swiss criteria? Was LVHT confirmed on cardiac MRI? Were supraventricular and ventricular arrhythmias attributed to LVHT or HCCMP, or unrelated to both? In addition to ventricular arrhythmias, LVHT may be complicated by heart failure or cardioembolism [2]. Did the patient ever develop any of these complications?

The patient presented with a syndromic, multisystem mitochondrial disorder (MID) affecting the central nervous system (bulbar palsy, histiocytoid cells in choroid plexus), the muscle (ophthalmoparesis), the heart (HCCMP, LVHT, arrhythmias), the gastrointestinal tract (reflux), the thyroid gland (histiocytoid cells), and the lungs (histiocytoid cells) [1]. Were any other typical phenotypic features of MID, such as epilepsy, ataxia, stroke-like episodes, short stature, hypoacusis, ptosis, cataract, renal insufficiency, neuropathy, anemia, or skin lesions, detected in the index case [3]?

The authors explain the female preponderance of HCCMP with its X-linked transmission, suggesting that male are more severely clinically affected than females and thus die prenatally [1]. Is the prevalence of spontaneous abortions truly increased in families with HCCMP? How can the female preponderance be explained in cases where there is no X-linked transmission of the disease?

Evidence that HCCMP is a cardiac manifestation of a MID comes from previous reports describing an association of HCCMP with cytb gene mutations [4], with the m.8344A>G mutation, with lactic acidosis, with COX-negative fibers on muscle biopsy, with an increased number of abnormally shaped mitochondria in cardiomyocytes, and with reduced activity of complexes I and II of the respiratory chain [5].

The index case underwent heart transplantation at age 13 months [1]. Immunosuppressive treatment may be mitochondrion-toxic [6]. Did the patient's condition further deteriorate after transplantation?

Overall, this interesting case provides further evidence that HCCMP is indeed a cardiac manifestation of a MID. However, there is a need of further investigating the broad clinical and genetic heterogeneity of HCCMP.

Local Excision

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Author's Contribution

Both authors contributed equally. JF: Design, literature search, discussion, first draft, SZ-M: Literature search, discussion, critical comments.

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