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Letter to the Editor

After the Diagnosis of Hypertrophic Cardiomyopathy, A Genetic Work-Up and Counselling Should be Carried Out Before Further Family Planning

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We read with interest the article by Dubcus *et al*. who reported on two patients with prenatal hypertrophic cardiomyopathy due to variants c.1204G>A (maternally inherited) and c.1628T>G (paternally inherited) in *ACAD9* [1]. Hypertrophic cardiomyopathy was associated with intrauterine growth retardation (IUGR), and resulted in stillbirth in patient-1 and death in patient-2 a few hours after birth [1]. The parents of both children were non-consanguineous [1]. It was concluded that searching for *ACAD9* mutations should be considered in fetuses with hypertrophic cardiomyopathy and IUGR, [1]. The study is impressive, but it has limitations that should be discussed.

It has been reported that ACAD9 variants to not only cause hypertrophic cardiomyopathy, but rather is a multisystem disease additionally affecting the optic nerve (atrophy), brain (intellectual disability), liver (hepatopathy), skeletal muscle (myopathy), endocrine organs (ovarian failure), and kidneys (renal insufficiency) [2]. We should know which organs other than the heart were affected particularly in patient-2. Was patient-2 also autopsied?

The list of disorders presenting intrauterine hypertrophic cardiomyopathy is incomplete. Hypertrophic cardiomyopathy not unique to patients with the disorders listed in Table 1, but has also been reported in Donohue syndrome (leprechaunism) [3], *RAF1* mutation carriers [4], *NEXN* mutation carriers [5], *INSR* mutation carriers [6], *NDUFB7* mutation carriers [7], *SCO1* mutation carriers [8], *ALPK3* mutation carriers [9], MYH7 mutation carriers [10], TMEM70 mutation carriers [11], and acantholytic epidermolysis bullosa due to DSP deletion [12].

Basal ganglia calcifications, as found in patient-1, are a common phenotypic feature of mitochondrial disorders (MIDs) and has been reported with or without calcifications in other cerebral regions. It would be interesting to know the pathophysiological explanation of basal ganglia calcification.

A limitation of the study is that the parents were not prospectively screened for cardiac involvement. In particular, the mother, who presented with junctional tachycardia should have been thoroughly evaluated for malignant ventricular arrhythmias (MVAs) through long-term ECG recordings. Nothing is reported about the father. Was he asymptomatic?

Another caveat is that patient-1 was not genetically tested at autopsy. In addition, following stillbirth of patient-1, the parents apparently did not undergo genetic counselling. The first trimester miscarriage (3rd child) was apparently not further investigated. Only after the death shortly after birth of the fourth child was genetic investigation initiated.

In summary, the interesting study has limitations that call the results and their interpretation into question. Addressing these issues would strengthen the conclusions and could improve the status of the study. Patients carrying ACAD9 variants, require thorough autopsy or if they survive, a comprehensive evaluation for clinically overt or subclinical multisystem disease.

Keywords: hCMP, ACAD9, Respiratory Chain, Complex-I, Stillbirth

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