*Cardiology in the Young*

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# Mitochondrial cardiomyopathy: a puzzle for the final diagnosis

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**Brief Report**

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## Abstract

Hypertrophic cardiomyopathy in children has diverse causes. Mitochondrial diseases, a rare aetiology leading to cardiomyopathy in 20–40% of affected children, predominantly present as hypertrophic cardiomyopathy. Diagnosis is challenging due to inconsistent genotype-phenotype correlation, resulting in various clinical presentations. We present a case of a one-month-old infant with severe hypertrophic cardiomyopathy and cardiac tamponade. Genetic diagnosis revealed a Valyl-tRNA synthetase 2 (VARS2) gene mutation, linking it to mitochondrial encephalopathy-cardiomyopathy. This case highlights novel variants and expands the understanding of hypertrophic cardiomyopathy aetiology in infants.

Paediatric cardiomyopathies present a diagnostic challenge due to their diverse aetiologies, with a significant proportion remaining idiopathic.[1] Although rare, mitochondrial diseases can cause cardiomyopathy in 20–40% of cases, often presenting as hypertrophic cardiomyopathy, with inconsistent genotype-phenotype correlations making diagnosis difficult.[2–4] Valyl-tRNA synthetase 2 (VARS2) gene variants result in oxidative phosphorylation deficiency, linked to mitochondrial encephalopathies and cardiomyopathies.[5] We present a unique case of a one-month-old infant with severe hypertrophic cardiomyopathy and cardiac tamponade in whom two VARS2 variants were detected, namely c.1100C>T (p.(Thr367Ile)) and c.1258G>A (p.(Ala420Thr)). This is the first case of compound heterozygosity for these two variants and documents their correlation with cardiac manifestations.

## Case report

A full-term male, macrosomic newborn presented with early respiratory distress, hypotonia, metabolic acidosis, and fluctuating hyperlactatemia. Initial treatment included mechanical ventilation due to maintenance of stridor and respiratory distress, mixed acidosis, and fluctuating hyperlactacidemia. Diagnostic hypotheses of myasthenic syndrome and metabolic disease were proposed, and echocardiography evaluation was normal at this time. At one month of age, his condition suddenly deteriorated with increasing respiratory distress, poor peripheral perfusion, hepatomegaly, muffled heart sounds, and acidemia. Cardiomegaly was detected on chest radiography with elevated cardiac markers (N-terminal pro-beta Natriuretic Peptide > 35,000 pg/mL and Troponin I 258.7 pg/mL). The ECG showed extreme axis deviation (QRS +154°) and right ventricular hypertrophy (Fig. 1) and the echocardiogram showed concentric left ventricular hypertrophy—interventricular septum 8.5 mm, z-score + 5.8 and posterior wall 11.5 mm, z-score + 11 (Boston z-scores) with severe systolic dysfunction (ejection fraction 10%, shortening fraction 5%), without obstruction of the left ventricular outflow tract. A large circumferential pericardial effusion (12 mm) was also present. Emergency pericardiocentesis led to clinical improvement.

Whole-exome genetic testing identified two variants in compound heterozygosity in the VARS2 gene: c.1100C > T (p.(Thr367Ile)) classified as pathogenic and c.1258G > A (p.(Ala420Thr)) classified as likely pathogenic. Parental segregation confirmed that the variants were in *trans*. Other genetic variants known to be associated with hypertrophic cardiomyopathy were excluded. This result supported the diagnosis of combined oxidative phosphorylation deficiency 20 (COXPD20, OMIM#61917). Treatment with riboflavin and ubidecarenone was initiated. The child was followed up as an outpatient (follow-up period of 24 months), showing a progressive reduction in left ventricular hypertrophy, recovery of systolic function, and improvement in respiratory function.

## Discussion

Mitochondrial diseases are a range of disorders resulting from mitochondrial respiratory chain dysfunction, affecting energy-dependent organs like the myocardium, which relies on oxidative metabolism for its functions.[6] They exhibit a highly variable phenotype-genotype correlation with different organs affected and with a wide range of severity. Cardiac involvement may

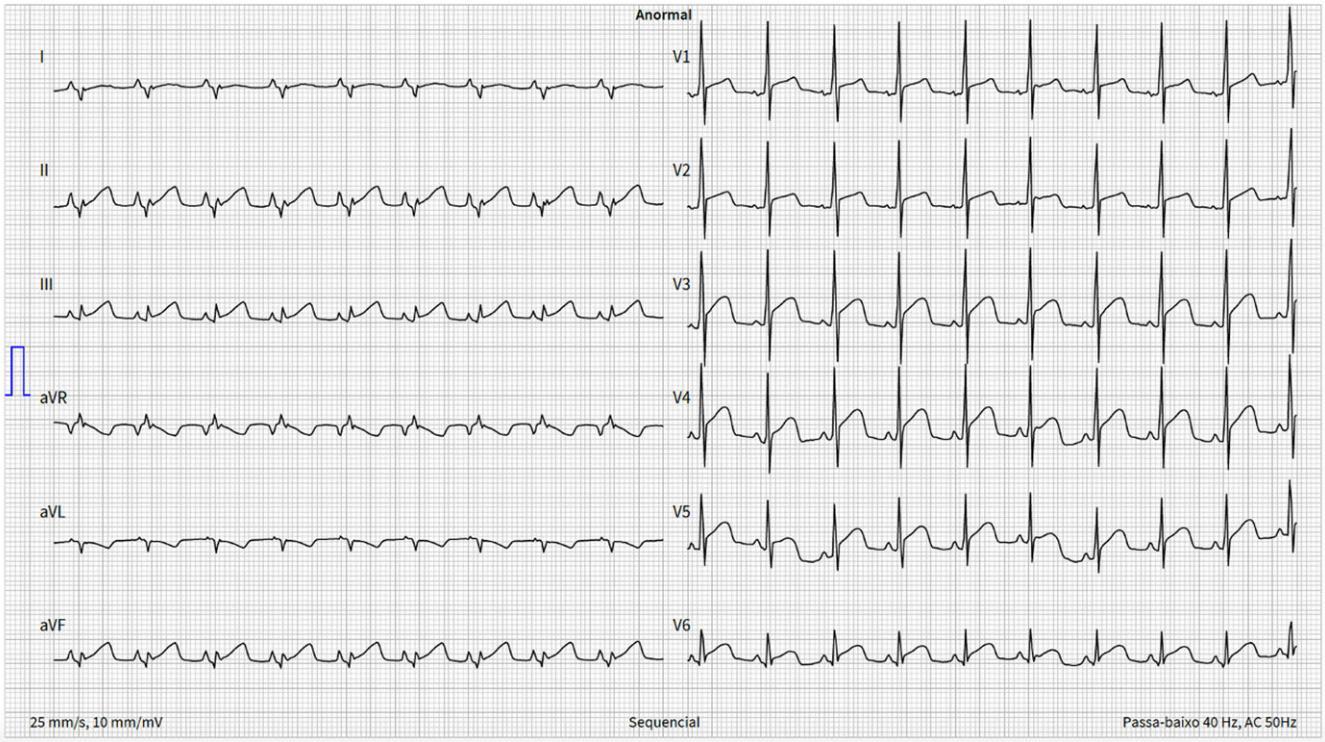


**Figure 1.** ECG at admission showing extreme axis deviation (QRS + 154°) and right ventricular hypertrophy.

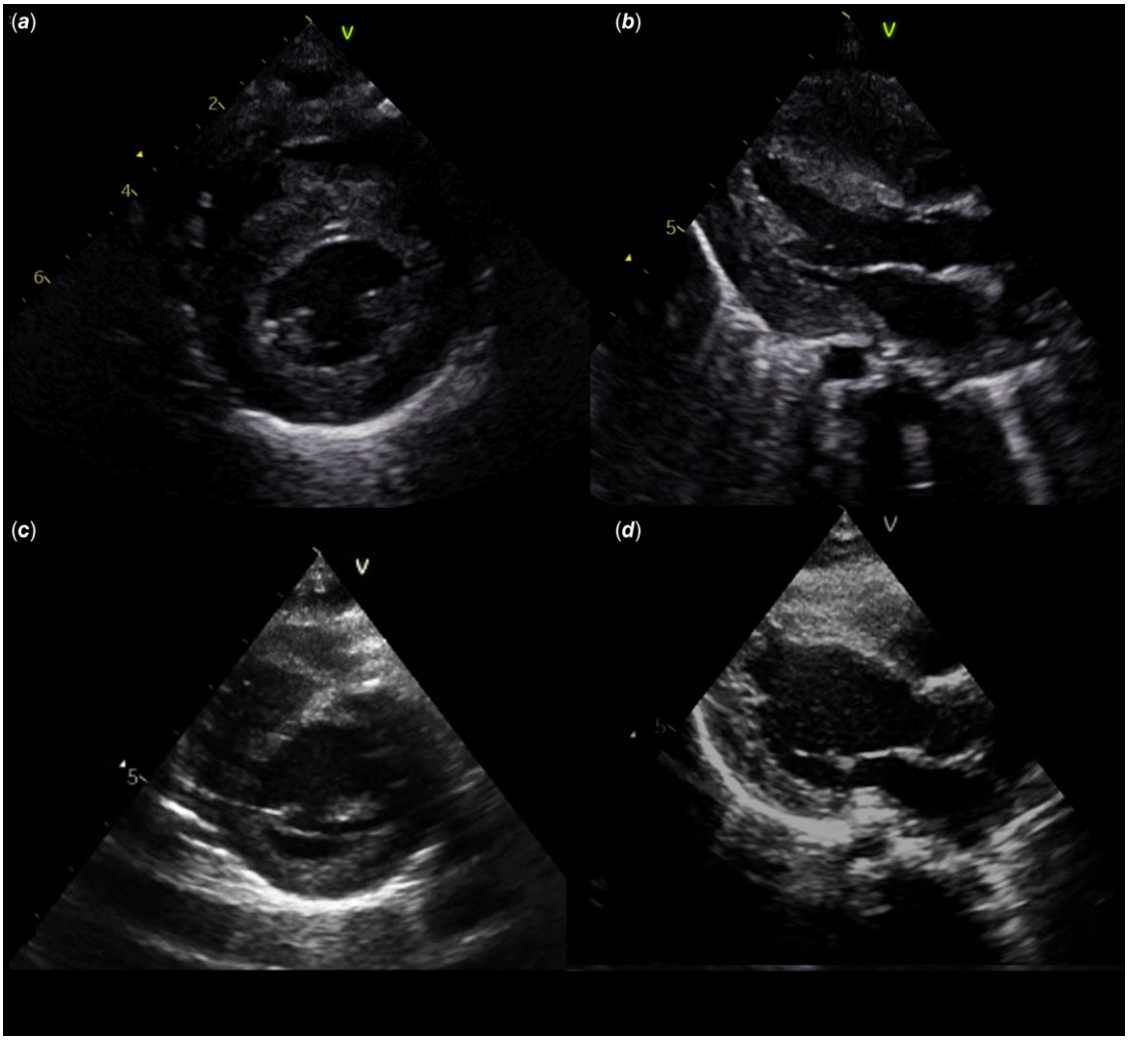


**Figure 2.** ***a*** and ***b*** – left ventricular (LV) hypertrophy (parasternal short axis and parasternal long axis, respectively); c and d – normal LV dimensions (PSAX and PLAX, respectively).

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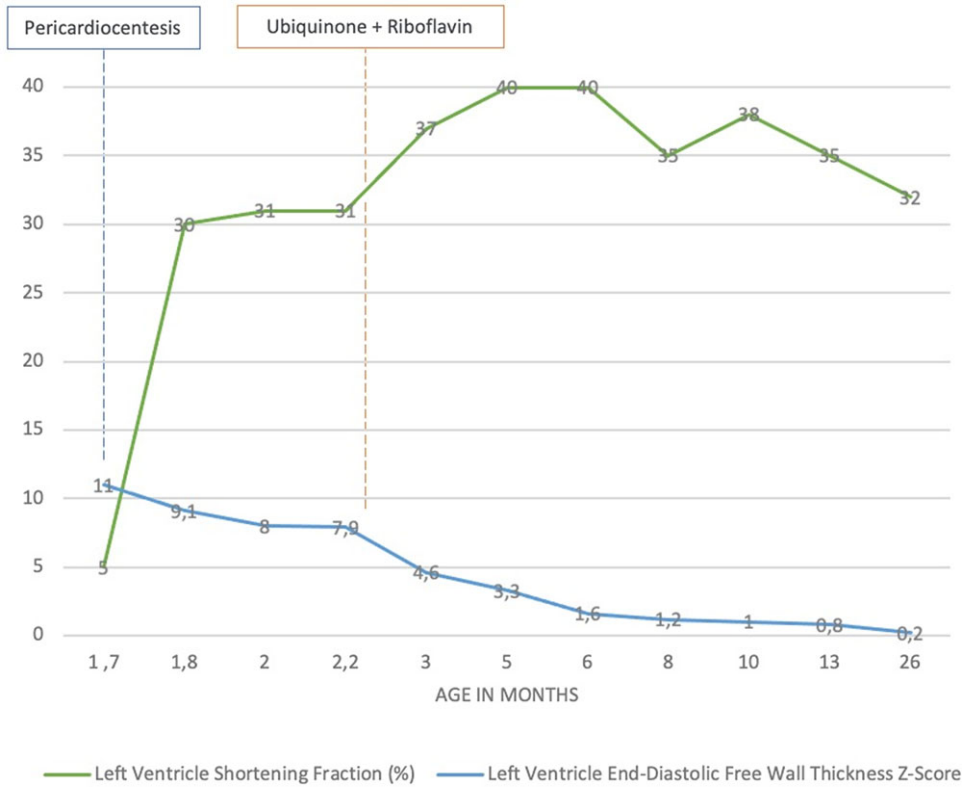


**Figure 3.** Graphic representation of left ventricular (LV) function (Shortening fraction) and LV free wall Z-score (Boston Z-scores) with the timing of medical therapy initiation.

include not only the hypertrophic expression but also dilated, restrictive, and arrhythmogenic forms of cardiomyopathy.[6,7]

Our patient's unique clinical picture, which was associated with severe cardiac symptoms, was associated with biallelic variants in the VARS2 gene, a rare cause of mitochondrial diseases, that has been linked to several clinical phenotypes, including mitochondrial encephalopathy, encephalocardiomyopathy, and isolated cardiomyopathy. This nuclear gene encodes a mitochondrial aminoacyl-tRNA synthetase that catalyses the binding of valine to tRNA for mitochondrial translation. This constitutes the first described case harbouring both [c.1100C > T (p.(Thr367Ile)) and c.1258G > A (p.(Ala420Thr))] in compound heterozygosity, as well as the association with hypertrophic cardiomyopathy. It is still unclear why genetic defects in transfer Ribonucleic acids (tRNAs) involved in mitochondrial DNA replication and expression can result in such different phenotypes. The role of mitochondrial tRNAs (mt-tRNAs) genetic variants in heart muscle disease is still poorly understood but may affect the 5' or 3' processing of tRNAs and induce structural and chemical modifications affecting respiratory chain complexes and consequently mitochondria, which in turn affects cardiomyocytes.[8]

The literature reports 24 cases of variants in VARS2 gene, including 18 pathogenic variants, with the most commonly described variant being the homozygous c.1100C > T (p. Thr367lle).[5,9,10] Kušíková and colleagues in 2021 accounted for 19 families with more than 23 affected individuals, 13 of whom were diagnosed with hypertrophic cardiomyopathy. They found that hypertrophic cardiomyopathy was present in 14 out of 15 cases in compound heterozygotes including the variant c.1100C > T (p. Thr367Ile). It was also shown that all homozygous for c.1258G > A variant had hypertrophic cardiomyopathy, but not the compound heterozygotes for this variant. Our patient presented a combination of both variants most commonly associated with Hypertrophic Cardiomyopathy suggesting that they may contribute to the pathological expression of cardiac disease and the severity of the involvement.

Three aspects of this case stand out from previously reported VARS2 gene variants: (1) a severe cardiac presentation with pericardial effusion and tamponade which has not yet been described; (2) complete regression of left ventricular hypertrophy with medical treatment; and (3) survival with no apparent deterioration of neurological, respiratory, or cardiovascular status to date.

The management of mitochondrial diseases is based on the treatment of symptoms and prevention of crisis, as well as dietary supplements such as coenzyme Q10, α-lipoic acid, vitamin C and vitamin E, vitamin B2 (riboflavin), l-arginine and l-citrulline, and creatine. Strategies and dosing vary greatly between institutions, and evidence about the benefit of using vitamins and supplements, besides the specific case of coenzyme Q10 deficiency disorders, is scarce.[7,11,12] Coenzyme Q10 supplementation in heart failure patients has also been used on the premise of energy depletion, so medications that can prevent this may have a role in their treatment. Nonetheless, data of moderate quality support the impact of coenzyme Q10 on lowering all-cause mortality, cardiovascular mortality, and heart failure hospitalisations.[13,14] The literature also mentions the use of standard heart failure therapy with β-blockers and angiotensin-converting enzyme inhibitors to treat cardiomyopathy in mitochondrial diseases.[7]

Our patient was treated with riboflavin (50 mg/day), ubidecarenone (10 mg/kg/day), and tapered diuretic therapy and showed a favourable course with normalisation of left ventricular dimensions and function without recurrence of pericardial effusion (Figs. 2 and 3).

Cardiomyopathy indicates poor prognosis in mitochondrial diseases, with a higher mortality rate compared to patients without cardiac involvement (72% versus 25%) demonstrating that this subgroup of patients needs to be closely monitored.[10,15]

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Cardiomyopathies are a very dynamic field and the genetic diagnosis of these diseases has proven to be valuable as it sometimes enables the development of targeted therapies.

## Conclusions

The diagnosis of early-onset cardiomyopathy is challenging. This case expands our understanding of the aetiology of early-onset hypertrophic cardiomyopathy and emphasises the need to consider mitochondrial disease in such cases. Mitochondrial diseases, particularly those associated with VARS2 gene variants, are rare but important causes of hypertrophic cardiomyopathy as the presentation can be severe. Prompt diagnosis and targeted therapies are crucial for better outcomes in these complex conditions.

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