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Case Report

Severe Dilated Cardiomyopathy in a Child with Pitt-Hopkins Syndrome

Jelena Hubrechts[1*], Eric Olinger[2], Claire De Halleux[3], Alain Poncelet[4], Stéphane Moniotte[1]

[1]Division of Congenital and Paediatric Cardiology, Department of Paediatrics, University Hospital Saint-Luc, Brussels, Belgium

[2]Center for Human Genetics, University Hospital Saint-Luc, Brussels, Belgium

[3]Department of Paediatrics, Grand Hôpital de Charleroi, Charleroi, Belgium

[4]Department of Cardiovascular and Thoracic Surgery, University Hospital Saint-Luc, Brussels, Belgium

***Corresponding author:** Jelena Hubrechts, Division of Congenital and Paediatric Cardiology, Department of Paediatrics, University Hospital Saint-Luc, Avenue Hippocrate 10, B-1200 Brussels, Belgium

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Abstract

A 6-months old girl presented with dilated cardiomyopathy (dCMP) with severe left ventricle dysfunction. Surgical pulmonary artery banding was performed, with successful weaning of ventilator despite persistent cardiac dysfunction. Despite the lack of extra-cardiac symptoms at initial presentation, the patient progressively developed marked global developmental delay, stereotypical hand and head movements, and growth retardation, initially thought to be related to the persistent cardiac condition. SNP-array and panel testing for cardiomyopathy and lysosomal storage diseases were noncontributing. Trio exome sequencing revealed a *de novo* likely pathogenic variant in *TCF4* establishing the molecular diagnosis of Pitt-Hopkins Syndrome (PTHS) and explaining the non-cardiac features. As far as we know, this is the first patient described with the association of dCMP and PTHS. We did not detect other known genetic etiologies for dCMP on targeted panel analysis nor in the exome. Systematic unbiased assessment of infantile dCMP patients in the future will therefore be crucial to confirm a possible relationship between *TCF4* variants and dCMP. In conclusion, multidisciplinary approach in patients with dCMP contributes to novel insights. With a genetic diagnosis, precision medicine approaches including major therapeutic decisions such as heart transplantation are clearly considered differently. This makes an important difference for the patient, parents, and medical team.

Keywords: Dilated Cardiomyopathy; Heart Failure; Developmental Delay; Exome Sequencing; Pitt-Hopkins Syndrome

Introduction

In contrast to other types of cardiomyopathies, such as hypertrophic cardiomyopathy, the complexity of dilated cardiomyopathy (dCMP) genetic architecture challenges its diagnosis. In very young patients, associated clinical signs may present later than the cardiac features and etiological diagnosis on clinical grounds is therefore often challenging. We present a case of an infant presenting with severe dCMP, secondarily diagnosed with Pitt-Hopkins syndrome (PTHS).

Case Report

A 6-months old girl, born from consanguineous parents, was transferred to our hospital for decompensated respiratory distress despite non-invasive ventilation. She had normal growth parameters at birth. Echocardiography on admission showed a very dilated left ventricle (LV), with an end-diastolic diameter of the LV of 52mm (Z-score +9, 8 following the Boston Children's Hospital reference values) and a compressed right ventricle (RV) (Figure 1).

Mitral regurgitation was important (grade ¾) with major dilatation of the left atrium. This was associated with a severe dysfunction of the LV with an ejection fraction (EF) of 10% and a fractional shortening of 6% on motion mode (M-mode). Electrocardiogram showed normal sinus rhythm. N-Terminal Pro-B-Type Natriuretic Peptide (NT Pro-BNP) level was 20142pg/ml at that time. Lactic acid levels were low (1.0mmol/L), suggesting a sub-acute onset of the heart failure. There were no ionic perturbations, nor increased infectious blood parameters. Chest X-ray showed a major cardiomegaly and pulmonary vascular overload (Figure 2). Anatomic causes of dilated LV, including anomalies of the coronary arteries, were ruled out by angiography.

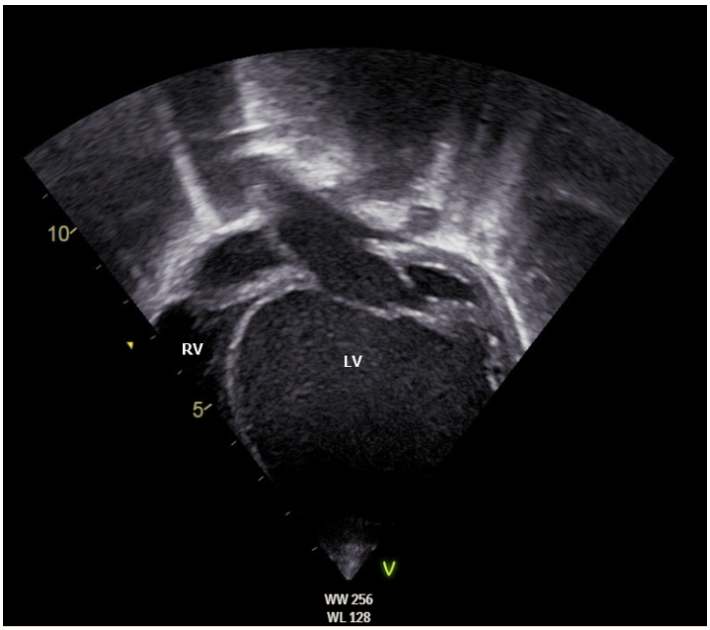

Figure 1: Echocardiographic four chamber view at diagnosis, showing a very dilated LV of 52mm (Z-score +9,8 following the Boston Children's Hospital reference values) and compression of the right ventricle; LV: left ventricle, RV: right ventricle.

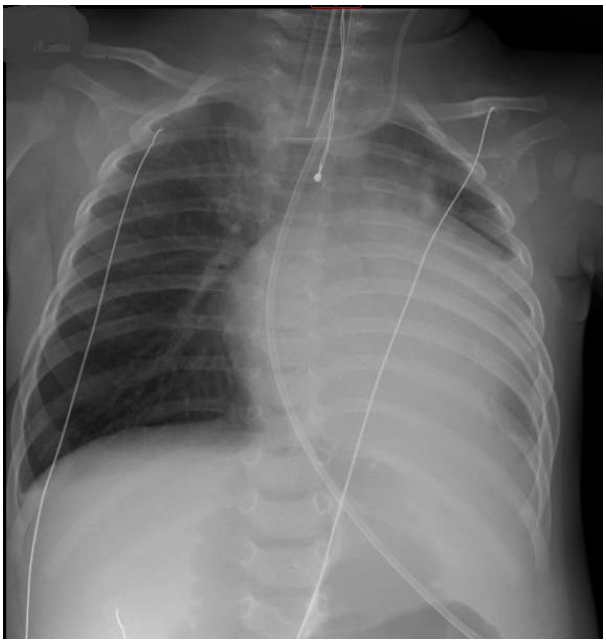

Figure 2: Chest X-ray at diagnosis, showing an important cardiomegaly and perihilar vascular overload. Note the projection of cardiac monitoring leads, endotracheal tube, endo-esophageal thermal probe, and nasogastric feeding tube. D: right.

Our patient was initially treated by inotropics (milrinone 0.8µg/kg/min, dobutamine 5µg/kg/min and levosimendan 0.2µg/kg/min) and ventilatory support. In the absence of improvement after 12 days, a surgical pulmonary artery banding was performed, with successful weaning of ventilator after 3 weeks. Nevertheless, cardiac dysfunction remained severe with a maximum EF of 24%.

She was discharged home under full heart failure treatment (captopril 1.5mg/kg/d, carvedilol 1mg/kg/d, hydrochlorothiazide 2mg/kg/d, spironolactone 2mg/kg/d, tinzaparine 180U/kg/d according to anti-FXa level), with no extra-cardiac symptoms at the initial stage. Exhaustive metabolic screening was negative. All

infectious samples remained negative too. Toxic and endocrine causes were yet excluded. Vitamine B1 and B2 supplementation did not have any effect. Initial Single Nucleotide Polymorphism (SNP) array and panel testing for cardiomyopathy and lysosomal storage diseases were noncontributing.

She was re-admitted several times in the following months, for cardiac decompensation, often in the context of intercurrent viral infections. LV dilatation worsened and EF decreased to 12% since the age of 9 months. NT pro-BNP levels were increasing (Figure 3), troponins remained negative over time. We discussed exhaustively for heart transplantation but this approach was refused by the parents. She could be fed orally, with a hypercaloric diet and was fully vaccinated.

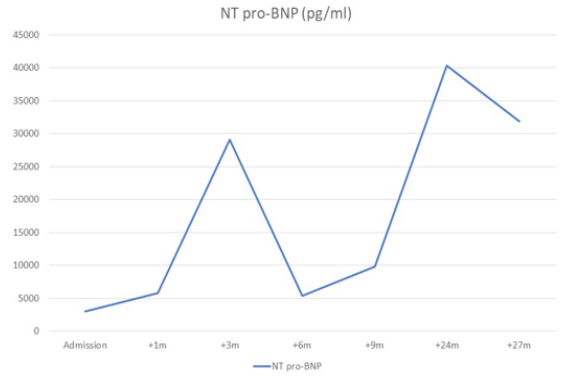

Figure 3: Evolution in time of N-Terminal Pro-B-Type Natriuretic Peptide serum levels, in pg/ml.

During later follow-up, she developed marked global developmental delay, stereotypical hand and head movements, and growth retardation, initially thought to be related to the persistent severe cardiac condition. She acquired a wide-based ataxic gait at the age of 22 months. At that age, she was babbling without any concrete words. Her parents reported sleep problems. She also showed dysmorphic facial features (small forehead, plump horizontal eyebrows with synophrys, short philtrum and small chin).

Genetic testing was intensified and finally, trio exome sequencing revealed a *de novo* likely pathogenic (class 4/5) variant (NM_001243226.3: c.638_642delCTTAT; p.(Ser213Ilefs*11)) in *TCF4* establishing the molecular diagnosis of Pitt-Hopkins Syndrome. Palliative care with chronic heart failure therapy was continued at home. She died at the age of 3 years and 7 months. Shortly before, echocardiography showed that LV dilatation was still very important (LVEDD 73mm, + 18,4 Z-score) as was the LV dysfunction (LVEF 10%).

Discussion

PTHS is a rare neurodevelopmental disorder caused by loss of function of one allele of the TCF4 gene [1]. TCF4 encodes a ubiquitous transcription factor mainly involved in cellular differentiation, proliferation, and lineage commitment. Motor delay, speech delay, intellectual disability, stereotypical behavior, and sleep problems, are very commonly reported as neurological features of PTHS in the current literature [2, 3]. Seizures, microcephaly, distinctive facial gestalt, breathing abnormalities and constipation are other characteristics. So far, there were no cardiac features described [1-3]. PTHS is an autosomic dominant disease, *de novo* in our patient. Probably, PTHS is under-diagnosed as the knowledge of this syndrome in general practice is poor and genetic testing not standardized worldwide. Moreover, both clinical variability and genetic heterogeneity exist within PTHS. Diagnosis of PTHS on clinical ground is very difficult; the current scoring tools have several limitations [4-5].

Our patient presented at a very young age with severe dCMP. Well-conducted heart failure therapy, including pulmonary artery banding, did not permit recovery. Etiological work-up included broad infectious and metabolic testing. Initial genetic testing consisted in SNP-array and routine panel for cardiomyopathy. All results were negative. The development of extra-cardiac features became evident only later during the patient's evolution and motivated exome sequencing.

We believe that genetic testing and counseling should be repeated if initial DNA microarray and routine panels are negative in patients with dCMP. Innovative techniques such as exome sequencing should be discussed with the geneticist because they are an important tool for further clinical management of the patient. The same rationale is true for patients with developmental delay lacking a clear underlying etiology. As our scientific interest and understanding of rare diseases grow, considering second or third tier genetic testing with exome sequencing seems reasonable [3].

In this case, exome sequencing was performed revealing the diagnosis of PTHS. This genetic finding explained the non-cardiac features (developmental delay, stereotypies, sleep disturbances) and helped us to rule out invasive approaches such as Left Ventricular Assist Device (LVAD) and heart transplantation. This was also of major importance for the parents to accept palliative care. As far as we know, this is the first patient described associating dCMP and PTHS. Yet, we have to be careful not to imply definitive causal association. PTHS is well characterized and to our knowledge, no dCMP has ever been reported. So, it is very well possible that both presentations are independent in this consanguineous pedigree. Of note, we did not detect other known genetic etiologies for dCMP on targeted panel analysis nor in the exome. Systematic unbiased

assessment of infantile dCMP patients in the future will be crucial to confirm a possible relationship between *TCF4* variants and dCMP.

Regarding the treatment of dCMP, this is well-established [6], also in the pediatric population even if large pediatric studies are lacking [7]. Medical treatment consisted in Angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and diuretics. Treatment was monitored by blood pressure measurements, repeated electrocardiograms, and blood samples (renal function, electrolytes, lactate, troponins, and NT pro-BNP). In addition to the medical treatment and as published in recent series [8,9], the surgical approach with pulmonary artery banding is nowadays standardized in our center. This case also illustrates the effectiveness of well-conducted heart failure therapy. Despite a very severe heart condition with an EF below 20% since 6-months of age, this girl was living at home with her family and reached the age of 3 years and 7 months.

The treatment of PTHS being only supportive for this time, appropriate therapies including speech and physical therapy were set up. We highlight the necessity of a multidisciplinary approach in children with medical complexity. Developmental delay should be investigated early and not be considered as "collateral damage" of a severe cardiac condition. With a genetic diagnosis, precision medicine approaches including major therapeutic decisions such as heart transplantation are clearly considered differently. This makes an important difference for the patient, parents and medical team.

Conclusion

Advanced genetic testing in children with dCMP contributes to novel insights. This is the first patient published associating a severe dCMP with PTHS. Therapeutic strategies were adapted and heart transplantation was considered not reasonable. Systematic unbiased assessment of infantile dCMP patients in the future will be crucial to confirm a possible relationship between *TCF4* variants and dCMP.

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