Severe, early onset hypertrophic cardiomyopathy in a family with LEOPARD syndrome

Giuseppe Limongelli1
Giuseppe Pacileo1
Maria Giovanna Russo1
Anna Sarkozy3
Maria Felicetti4
Giovanni Di Salvo1
Carmela Morelli1
Paolo Calabrò1
Dario Paladini4
Bruno Marino2
Bruno Dallapiccola3
Raffaele Calabrò1

1 Chair of Cardiology, Second University of Naples, Monaldi Hospital
2 “La Sapienza” University, Department of Pediatrics, Rome, Italy
3 IRCCS-CSS, San Giovanni Rotondo e CSS-Mendel Institute, Rome, Italy
4 Department of Gynecology, “Federico II”, Naples, Italy

Reprint requests to: Giuseppe Limongelli, MD, PhD
Chair of Cardiology, Monaldi Hospital
Second University of Naples, Naples, Italy
Tel. +39 081 7062852
Fax +39 081 7062683
E-mail: limongelligiuseppe@libero.it

Introduction

LEOPARD syndrome is an acronym (multiple Lentigines, Electrocardiographic conduction abnormalities, Ocular hypertelorism, Pulmonic stenosis, Abnormal genitalia, Retardation of growth, and sensorineural Deafness) describing an autosomal dominant disease due to mutations in the RAS-MAPK pathway (1-3). The PTPN11 gene, encoding the protein tyrosine phosphatase SHP-2, causes the disease in 80% of the patients affected (LEOPARD syndrome type 1) (2). Pandit et al. recently described RAF-1 mutations in 2 out of six patients with LEOPARD syndrome without PTPN11 mutations (LEOPARD syndrome type 2) (3). Clinical outcome is worse in patients with cardiovascular involvement, and a number of fatal events have been reported in patients affected by hypertrophic cardiomyopathy (HCM) associated with the syndrome (4, 5). Here, we describe a family (mother and daughter) with clinical and molecular diagnosis of LEOPARD syndrome 1 and HCM, and we report the prenatal diagnosis of HCM in a fetus at risk for LEOPARD syndrome.

Case Report

The family pedigree is showed in Figure 1. A 32-year-old woman with LEOPARD syndrome with multiple lentigines, facial dysmorphia, short stature, and mild, non obstructive HCM (asymmetric left ventricular hypertrophy, with maximal wall thickness of 14 mm at the mid-portion of the posterior interventricular septum, in absence of outflow tract obstruction) was referred to our Department for foetal echocardiography and genetic counselling during her second pregnancy. Her first pregnancy resulted in a daughter (the proband) who was born with a severe form of obstructive HCM, and pulmonary valvar and subvalvar stenosis. She had café au lait spots on her trunk, hypertelorism, broad nasal bridge, pterigium colli, pectus excavatum and short stature. She was administered with beta blockers (7 mg/kg/day) for her cardiomyopathy, but she died suddenly at 2 years of age. Clinical diagnosis of LEOPARD syndrome was confirmed by genetic analysis showing a mutation in exon 13 of the PTPN11 gene (codon 498), in both mother and daughter.

During the second pregnancy, prenatal scan at 22 weeks of gestation evidenced fetal growth restriction (about 3 weeks), and fetal echocardiography showed a significant hypertrophy of both ventricles (left and right ventricular wall thickness 9mm and 3 mm, respectively) (Figure 2). Systolic function was slightly depressed (ejection fraction measured by biplane Simpson method was 45%), and diastolic function was abnormal. The parents were counselled by a team of physicians

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HCM is the most common defect in patients with LEOPARD syndrome (about 70% of the cases) (6). Long-term prognosis seems benign in LEOPARD syndrome patients with only mild cardiac abnormalities (6, 7). On the other hand, patients with HCM may develop arrhythmias and other life-threatening complications (6, 7). The phenotype (a severe, obstructive left ventricular hypertrophy) may represent a risk factor for adverse clinical outcome (sudden death; as in the present case) in patients with LEOPARD syndrome and HCM. In addition, the genotype may represent a potential risk factor of adverse event in selected patients. We have recently reported 2 patients with an early onset obstructive HCM, associated with a high risk of heart failure and cardiac events. We showed a specific mutation in exon 13 of the PTPN11 gene (codon 510) (7). Of note, in the present report both the mother and her daughter had a mutation in exon 13 of the PTPN11 gene (codon 498). However, intrafamilial variability is clear in the present report (since the mother had a mild form of HCM, while the first daughter and the foetus showed a severe, early onset hypertrophic disease), representing a strong limitation to the potential use of the genotype (i.e. mutations in exon 13) as clinical predictor of malignant events in patients with HCM and LEOPARD syndrome.

In conclusion, HCM significantly worsen the prognosis in LEOPARD syndrome. However, lacking large population studies on HCM associated to the rare LEOPARD syndrome, the clinical and genetic heterogeneity of the disease warrant particular attention, especially in prenatal counselling, which should involve a multidisciplinary and experienced team (gynecologist, cardiologist, geneticist, and psychologist).

References


No conflict of interest declared.