LEOPARD Syndrome Caused by Tyr279Cys Mutation in the *PTPN11* Gene

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Key Words

Hypertrophic cardiomyopathy · LEOPARD syndrome · *PTPN11* · Sudden cardiac death · Tyr279Cys

Abstract

LEOPARD syndrome (LS) is an acronym consisting of lentiginos, electrocardiographic abnormalities, ocular hypertelorism, pulmonary valve stenosis, abnormal genitalia, retardation of growth and deafness. However, hypertrophic cardiomyopathy, the most frequent cause of sudden cardiac death in young people, is the most common cardiovascular manifestation in LS patients and the major determinant of mortality and morbidity. In approximately 85% of the patients with a definite diagnosis of LS, a missense mutation is found in the protein-tyrosine phosphatase non-receptor type 11 (*PTPN11*) gene located on chromosome 12q24.1. We report the case of an asymptomatic 17-year-old male with a missense mutation (c.836A>G) in exon 7 (Tyr279Cys) of the *PTPN11* gene and a non-obstructive asymmetric anteroposterior hypertrophic cardiomyopathy.

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LEOPARD syndrome (LS) is an acronym derived from its main features, i.e. lentiginos, electrocardiographic abnormalities, ocular hypertelorism, pulmonary valve stenosis, abnormal genitalia, retardation of growth and deafness.

Though it is not included in the acronym, hypertrophic cardiomyopathy (HCM) is the most frequent anomaly

observed, representing the only life-threatening problem in these patients. HCM, which is generally asymmetric involving the left ventricle, is detected in up to 80% of the patients with a cardiac defect and may associate with significant left ventricular outflow tract obstruction in up to 40% of the cases [Limongelli et al., 2007; Sarkozy et al., 2008].

HCM is regarded as the most common cause of sudden cardiac death (SCD) in young people including trained athletes. However, assessing SCD risk and identifying the most appropriate candidates for a prophylactic device is a complex process because of the unpredictability of the underlying arrhythmogenic substrate and the absence of a single dominant and quantitative risk marker for this heterogeneous disease.

In approximately 85% of the patients with a definite diagnosis of LS, a missense mutation is found in the protein-tyrosine phosphatase non-receptor type 11 (*PTPN11*) gene, located on chromosome 12q24.1 [Sarkozy et al., 2008], and encoding for the protein tyrosine kinase SHP-2, which exerts a role in RAS-mitogen-activated protein kinase (MAPK) signaling [Tartaglia et al., 2002]. Different *PTPN11* mutations in exons 7, 12 and 13 (Tyr279Cys/Ser, Ala461Thr, Gly464Ala, Thr468Met/Pro, Arg498Trp/Leu, Gln506Pro, and Gln510Glu/Gly) have been reported, the most frequent (65% of the cases) being those that occur in the Tyr279Cys and Thr468Met mutation [Sarkozy et al., 2004]. Furthermore, Pandit et al. [2007] identified in about one-third of *PTPN11*-negative LS patients the presence of missense mutations in the *RAF1* gene, encoding for a serine threonine kinase involved in the RAS-MAPK pathway.

Fig. 1. Multiple dark brown spots on the skin (lentiginosis) of chest, arms and neck.

Fig. 2. Twelve-lead ECG showing high R waves in the right pre-cordial leads with ST depression in the context of LVH and systolic ventricular overload.

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Results and Discussion

We report the case of an asymptomatic 17-year-old male, who presented with widespread lentiginosis (fig. 1), severe bilateral sensorineural hearing loss, bilateral valgus flat feet and hypertelorism. No abnormalities were observed in a genitourinary examination. The electrocardiogram (ECG) revealed a left ventricular hypertrophy (LVH) (fig. 2) and the echocardiogram showed a non-obstructive

asymmetric antero-septal HCM (interventricular septum of 24 mm) with a progressive increase since his first year of life to the present. No pulmonary stenosis was seen. Treadmill tests showed a good exercise capacity without arrhythmias or hypotensive response and periodic 24-hour ambulatory ECG monitorings were normal. The diagnosis of LS was made and a molecular analysis of the *PTPN11* gene was carried out, directly sequencing the coding region. The molecular analysis (not shown) revealed a

missense mutation (c.836A>G) in exon 7 (Tyr279Cys) of the *PTPN11* gene and a single nucleotide polymorphism in the intronic coding change of exon 8 (rs41279090).

Digilio et al. [2002] screened for mutations in the *PTPN11* gene in 9 patients with LS, between 4 and 39 years old, finding the Tyr279Cys mutation in 3 patients and the Thr468Met mutation in four. In those 3 patients with Tyr279Cys mutation only one of them, a 6-year-old patient, had obstructive HCM without associated arrhythmias. Similarly, Legius et al. [2002] reported 3 cases of LS with the Tyr279Cys mutation all of them having non-obstructive HCM without arrhythmias. Also, Limongelli et al. [2008] studied 24 LS patients with LVH. Sixteen of them were found to have mutations in the *PTPN11* gene (only one of them had the Tyr279Cys mutation), 2 had mutations in the *RAF1* gene, and the mutations in 6 of them could not be found. Patients without *PTPN11* mutations showed a significantly higher frequency of family history of SCD and an increased incidence of bradyarrhythmias, episodes of supraventricular tachycardias, atrial fibrillation, and non-sustained ventricular tachycardia at 24-hour ECG monitoring. During follow-up, 2 patients with *PTPN11* mutations (the first was a 17-year-old patient with Tyr279Cys mutation, no family history of SCD or heart failure and a non-obstructive severe LVH with non-sustained ventricular tachycardia in a 24-hour Holter ECG and the 2nd was 1 infant with Thr498Arg mutation and signs of heart failure) died suddenly. One patient with *RAF1* mutation received an implantable cardioverter defibrillator-pacemaker following resuscitated cardiac arrest and 2 siblings (*PTPN1* negative) received an implantable cardioverter defibrillator for primary prevention of sudden death due to an elevat-

ed clinical risk score for SCD, and an appropriate discharge was observed in one of them.

The ACC/AHA/ESC 2006 guidelines for SCD determine 5 major risk factors: family history of sudden death (under 45 years old), unexplained syncope, septal thickness ≥ 30 mm, non-sustained ventricular tachycardia on Holter (heart rate >120 bpm), and abnormal blood pressure response during activity (non-elevation or drop in systolic pressure >20 mm Hg during activity) [Zipes et al., 2006]. Left ventricular outflow tract obstruction could also be included in the overall risk profile of patients with a marked left ventricular outflow gradient under basal conditions [Christiaans et al., 2010]. Patients with two or more risk factors have an estimated overall sudden risk rate of about 3% per year, while patients with none of these risk factors show a significantly lower risk of sudden death [Elliott et al., 2004].

To date, it is unclear whether the genotype may influence the clinical course in LS patients with LVH, especially because many of the affected individuals described in the literature are children and there is not a clear risk figure available based on a follow-up study of a sufficient size patient cohort. However, anecdotal reports provide enough evidence to state that long-term prognosis seems benign in LS patients with only mild cardiac abnormalities, whereas HCM in LS is indeed associated with a risk of fatal cardiac events as seen in primary HCM. Therefore, it is very important to properly recognize, diagnose and undergo regular cardiovascular monitoring, including ECG, echocardiography, treadmill test and 24 Holter ECG testing in patients with LS, in order to detect potential predictors of adverse cardiac events during follow-up, independently of their genetic mutation.

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