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Brief Report

Is sudden cardiac death predictable in LEOPARD syndrome?

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Abstract We report the sudden cardiac death of a young male presenting with classic clinical features of LEOPARD syndrome, shown to be due to a mutation in the PTPN11 gene, and severe non obstructive hypertrophic cardiomyopathy. We also discuss briefly the usefulness of prophylactic risk stratification in patients with syndromic and non syndromic hypertrophic cardiomyopathy.

Keywords: Hypertrophic cardiomyopathy; PTPN11 gene; risk stratification

Sudden cardiac death is a catastrophic event, particularly in young and apparently healthy individuals.[1,2] It is known to occur frequently in the setting of hypertrophic cardiomyopathy,[1,2] and the potential to insert an implantable cardioverter defibrillator therapy as a prophylactic antidote has greatly stimulated the effort of clinicians and scientist to detect patients known to be at increased risk.[1–3]

Hypertrophic cardiomyopathy, nonetheless, represents the common phenotype for a wide group of disorders, such as Noonan or LEOPARD syndrome, Friedreich's ataxia, Barth syndrome, and metabolic and mitochondrial diseases.[4] Although rare, sudden cardiac death also occurs in these secondary forms of hypertrophic cardiomyopathy.[1,2,4] We report here the sudden cardiac death of a young patient presenting with classic clinical features of LEOPARD syndrome and severe non-obstructive hypertrophic cardiomyopathy.

Case report

The patient, a young male, was first referred to our Department at 9 years of age, after he was diagnosed with hypertrophic cardiomyopathy. He had previously undergone surgical repair of an infundibular pulmonary stenosis with right ventricular outflow tract patch at 2 years of age. The diagnosis of LEOPARD syndrome was then made at the age of 7 years on the basis of common dysmorphic features. The electrocardiogram showed sinus rhythm, incomplete right bundle branch block, and signs of left ventricular hypertrophy with abnormalities of repolarization (Fig. 1a). An echocardiographic examination showed severe but asymmetric left ventricular hypertrophy, with maximal thickness of the ventricular wall of 29 millimetres. He was seen on an annual basis. At 21 years of age, echocardiography showed an increased mural thickness, which then measured 33 millimetres at the midportion of the muscular ventricular septum (Fig. 1b). A treadmill exercise test showed normal response of blood pressure, and a 24-hour Holter recording revealed a 7 beat run of nonsustained ventricular tachycardia (Fig. 2). Molecular analysis revealed a missense mutation between 836A→G and Tyr279Cys in exon 7 of the PTPN11 gene, albeit that no mutations were found in the other members of the family.

Due to the presence of two recognized risk markers for sudden death, namely severe hypertrophy and non sustained ventricular tachycardia, we discussed the need for implantation of a cardioverter defibrillator. Unfortunately, the patient died suddenly prior to implantation of the device during moderate exercise while walking home from shopping.

Discussion

LEOPARD syndrome is an autosomal dominant disease, described for the first time by Gorlin and

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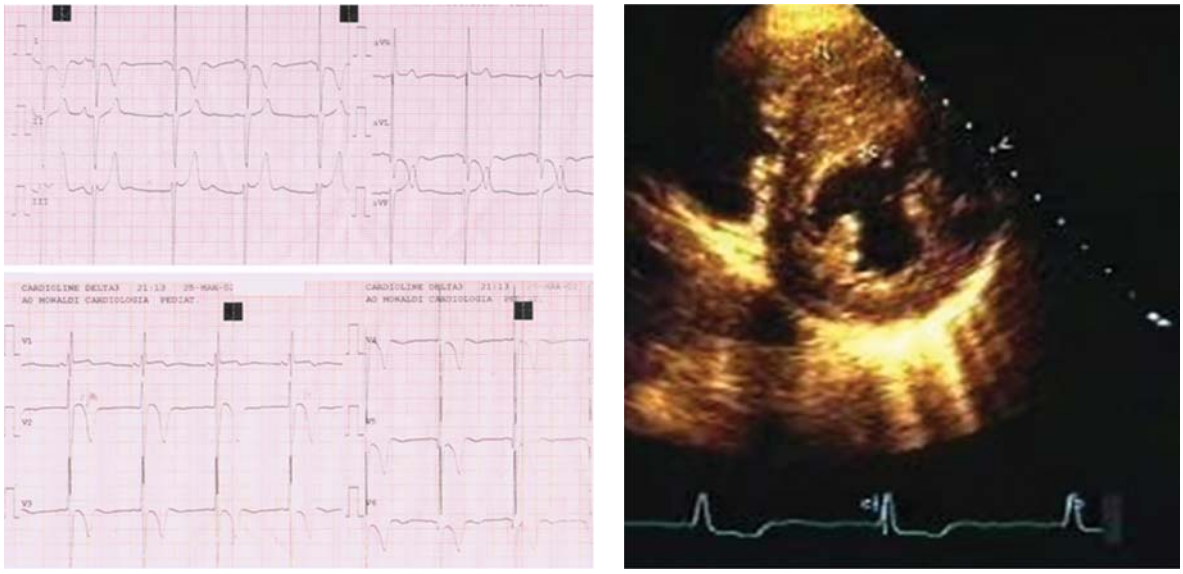

(**a**) (**b**)

Figure 1.
*The electrocardiogram (**a**) shows left ventricular hypertrophy and abnormalities of repolarization, specifically deep and negative T waves in leads DI, AVL, V2–V6. Echocardiography (**b**) shows severe left ventricular hypertrophy, with the maximal thickness seen at the midportion of the ventricular septum.*

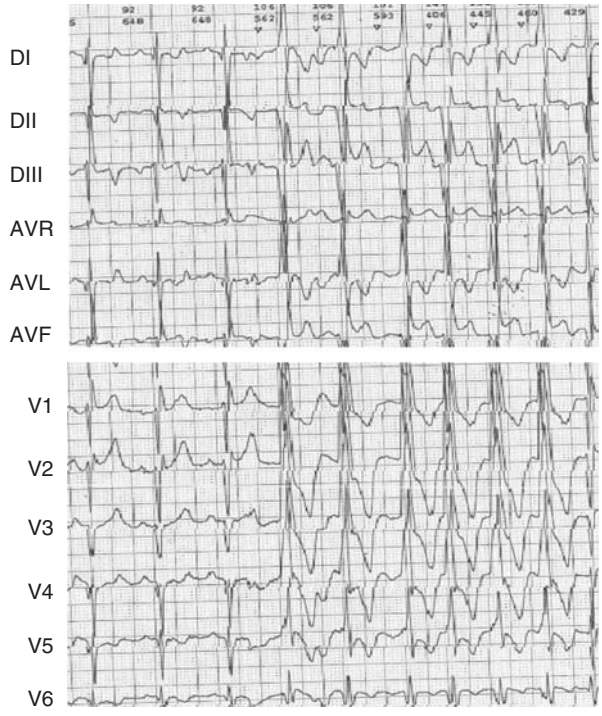

Figure 2.
24-hour Holter monitoring revealed a seven beat run of nonsustained ventricular tachycardia.

colleagues in 1969, and now known to be caused by mutations in the PTPN11 gene.[5,6] The most common cardiac abnormalities are pulmonary stenosis and hypertrophic cardiomyopathy, and they probably represent the major prognostic determinants.[5,7,8] Due to the rarity of the disease, nonetheless, there is little data available concerning the natural history, prognosis, and risk of sudden cardiac death.

In contrast, a family history of sudden death, syncope, severe hypertrophy, an abnormal response of blood pressure to exercise, and non sustained ventricular tachycardia on Holter monitoring have all been suggested as risk markers for sudden death in primary, or non syndromic, hypertrophic cardiomyopathy.[1–4] The presence of severe hypertrophy, or two or more risk factors, is now considered to represent sufficient increased risk to warrant consideration of implantation of a cardioverter defibrillator.[1–3]

It has also been suggested that the underlying genetic substrate, such as mutations of Troponin T, can identify a subgroup of patients with hypertrophic cardiomyoapthy at increased risk of sudden cardiac death.[9] Recently, Gln510Glu mutation of the PTPN11 gene have been reported in patients with LEOPARD syndrome and severe, biventricular obstructive cardiomyopathy, although little data regarding the combination of genotype and phenotype exists for LEOPARD syndrome, so far.[10]

Cardiac arrest has previously been reported in patients with cardiomyopathic lentiginosis.[7]

Woywodt et al reported the case of a 26 years-old male with LEOPARD syndrome and hypertrophic cardiomyopathy who collapsed during moderate effort and was successfully resuscitated from ventricular fibrillation.[7] Unlike our patient, however, this

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patient did not appear to have a severe phenotype or a profile of high risk. This indicates that an apparently favorable phenotype, such as absence of severe hypertrophy and arrhythmias, does not necessarily protect patients with cardiomyopathic lentiginosis, and underscores the lack of specific data on risk stratification for sudden cardiac death in the secondary form of hypertrophic cardiomyopathy.

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