Familial Noncompaction In Holt-Oram Syndrome

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Keywords
non-compaction, hypertrabeculation, congenital heart defect, heart failure, sudden cardiac death

Letter to the Editor

In a recent article, Kapadia et al. reported about a family with Holt-Oram syndrome in four family members and symptomatic left ventricular hypertrabeculation / noncompaction (LVHT) in the index patient and his mother. We have the following comments and concerns.

The 36 years old index patient is reported to have developed atrial fibrillation at age 36 years. Which was the CHADS2 and the CHA2DS2 VASc scores? Which were the results of coronary angiography? Did the individual history show a previous embolic event? Did he ever undergo cerebral MRI to rule out asymptomatic embolic stroke? Why did he receive acetyl-saliclyc acid but no oral anticoagulation?

LVHT was diagnosed on cardiac MRI. Was LVHT also found on transthoracic echocardiography? Which was the reason why the patient initially underwent cardiac MRI and not echocardiography? Were previous echocardiographic investigations available and reviewed for the presence or absence of LVHT to rule out acquired LVHT?

LVHT was found in the index patient and his mother. Were other family members also investigated for LVHT? Did any of the other family members present with a history of heart failure, ventricular arrhythmias, or previous cardio-embolism? Is there any evidence that sudden cardiac death (SCD) in the index patient’s sister was attributable to a complication of LVHT? Did she ever undergo echocardiography before decease? Did autopsy detect LVHT in addition to myocardial fibrosis? Was myocardial fibrosis distributed in a vascular or non-vascular pattern?

In addition to the index patient, Holt-Oram syndrome was also found in the mother, a cousin from the mother’s side, and a second cousin. In the first cousin the TBX1 mutation p.T124K was detected. Were other family members presenting with Holt-Oram syndrome also tested for the mutation and how many carried this mutation? Were asymptomatic family members tested for the mutation?

It is misleading to classify LVHT as a genetic disorder. Though LVHT may be associated with mutations in >30 different genes and with a number of chromosomal defects, a causal relation with any of these mutations has not been proven so far. The only argument in favour of a causal relation is the occurrence of familial LVHT in Barth syndrome or mitochondrial disorders, which are the disorders most frequently associated with LVHT.

LVHT is reported to be associated with microvascular subendocardial perfusion defects and endocardial fibrosis. Were such abnormalities seen on cMRI? Were any other investigations, such as PET or thallium scintigraphy carried out to search for these abnormalities?

Why did the index patient only receive acetyl-saliclyc acid in the light of the SCD in his sister? Why did the authors not consider implantation of an implantable cardioverter defibrillator (ICD)? Did palpitations recur during follow-up? Which were the results of follow-up Holter investigations?

Overall, this interesting case could profit from a broader family history, and a more extensive family screening for LVHT and Holt-Oram syndrome. Furthermore, close Holter-monitoring, implantation of a loop recorder, or implantation of an ICD should be considered in the index patient.

There are no conflicts of interest

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