

Holt-Oram Syndrome: Family Affected Without *TBX5* Mutation and Without Phenotype Manifestations in a Probable Mutation Carrier

Síndrome de Holt Oram. Descripción de una familia afectada sin mutación del gen *TBX5* ni manifestaciones en un probable transmisor

To the Editor,

Holt-Oram syndrome (HOS) is a disorder characterized by skeletal abnormalities in the upper limbs accompanied by cardiovascular defects. The diagnosis of HOS is based on these abnormalities and defects, both in the individual or in the parents, and is indicative of congenital transmission.¹

All those affected by this syndrome have upper limb skeletal abnormalities, which preferentially affect the thumbs. Of those diagnosed with this syndrome, 75% have cardiovascular defects, atrial septal defect being the most frequent. The lack of correlation between the severity of the skeletal and cardiac lesions is well known, as well as the heterogeneity of the syndrome in the affected relatives.

The causative gene *TBX5*, located on chromosome 12, was discovered in 1997. This has an autosomal dominant transmission with 100% penetrance. The location and type of mutation in *TBX5* are not predictive of phenotypic expression. The probability of finding the mutation in the *TBX5* gene is 74% in patients who fulfill the clinical criteria for HOS.²

We present the clinical case of a 14-year-old girl with hypoplastic thumbs who had been diagnosed with an ostium secundum atrial septal defect (Fig. 1). A maternal uncle has a similar thumb malformation. All those who were candidate for inheriting the mutation (Fig. 2) underwent Doppler echocardiography and electrocardiography study with no findings of note. As the mother was considered the probable transmitter of the genetic disorder, despite having no bone or cardiac defects, an x-ray of her hands was performed which ruled out any subclinical bone malformation.

After obtaining informed consent, genomic DNA from the patient was extracted and purified, followed by PCR amplification specific to all the exons and intron flanking regions of the *TBX5* gene. Finally, direct sequencing of all the purified double-stranded PCR fragments was performed. No variations in the nucleotide sequence were found such that HOS could be confirmed.

In 2006, Borozdin et al. detected deletions in one or several exons or even of the entire *TBX5* gene in around 2% of individuals with HOS who did not present mutations identified via sequencing.³ The study of this family was completed by MLPA (Multiplex



Figure 1. Hypoplastic thumb. Malformed distal phalanx.

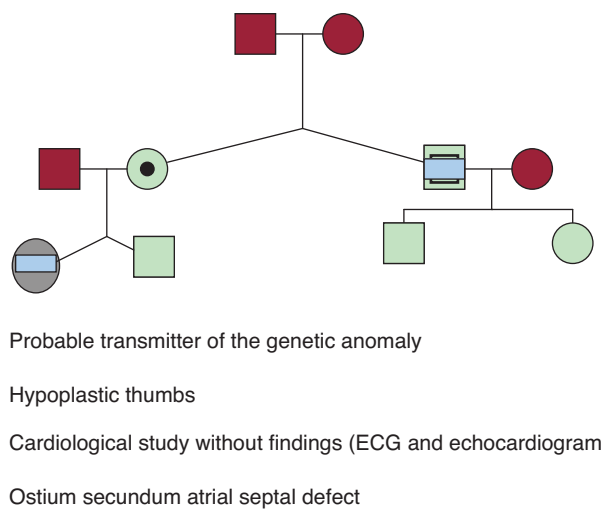


Figure 2. Family genogram. The probable carrier of the genetic anomaly is the patient's mother, who does not present phenotypic manifestations involving the thumbs or subclinical radiological findings suggestive of carpal bone abnormalities.

Ligation-dependent Probe Amplification) using the P180-B1 kit (MRC-Holland, Amsterdam, the Netherlands); duplications or deletions in the 10 exons of the *TBX5* gene were also ruled out and the existence of two copies of the gene checked.

De novo mutations or mosaicism were eliminated due to the presence of a first-degree relative affected by characteristic skeletal alterations. The absence of other abnormalities (deafness, anemia, renal, etc.) ruled out other syndromes (Okimoto and acro-renal-ocular) which are typically due to *SALL4* mutations. Within the range of abnormalities related to the *SALL4* gene, an exceptional case of classic HOS has been described.⁴ The low prevalence of these malformations makes such a coincidence exceptional. We consider that 25% of the family in whom the classic genetic anomaly was not detected were affected by HOS.

We draw attention to two relevant clinical aspects related to reports in the literature: the bone disorder is similar in the affected patients, and the probable transmitter (the patient's mother) has no bone or cardiac manifestations, which is exceptional in the families described in the literature.

In relation to *SALL4* gene abnormalities, incomplete penetrance and an identified mutation without clinical manifestations in members of 2 families have been described. This incomplete penetrance has not been described in *TBX5*-associated HOS or in families with clinical HOS.

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Recurrent Ventricular Fibrillation and ST Segment Elevation in the Right Precordial Leads Due to Acute Occlusion of the Conus Branch

Fibrilación ventricular recurrente y elevación del segmento ST en precordiales derechas por oclusión aguda de la arteria conal

To the Editor,

We present the case of a 79 year-old man diagnosed with high blood pressure and chronic liver disease due to hepatitis C virus. The patient was referred for surgery for severe mitral valve regurgitation associated with the prolapse of P2 and P3 through the spontaneous breakage of the chordae tendineae. The left ventricle (LV) and coronary arteries were normal.

Mitral valve reconstruction was undertaken using a Carpentier-Edwards Physion no. 28 annuloplasty ring and the implantation of two GoreTex cords attached to P2 and P3. No intraoperative complications were encountered. On arrival at the postoperative care unit the patient suffered several episodes of ventricular fibrillation. Advanced cardiopulmonary resuscitation was begun with multiple electrical defibrillations; the situation stabilized following the administration of amiodarone. Emergency bloodwork revealed no ion abnormalities, although an electrocardiogram showed a previously undescribed convex elevation of the ST segment in V1-V3 (Fig. 1). Emergency coronary angiography was performed, which revealed the complete occlusion of the conus branch of the right coronary artery (RCA); no such findings were

seen in pre-surgery coronary angiography (Figs. 2A and B). The left coronary artery tree was normal. After discussing the images with the surgical team it was concluded that the cause of this acute occlusion was a suture used to fix the cable of the epicardial pacemaker in place. Balloon angioplasty was performed and blood flow restored. Good coronary angiographic results were obtained (Fig. 2C).

The first artery arising from the RCA is the conus branch, although in 30%-50% of cases it may originate from the aorta.¹ Its function is to irrigate the pulmonary trunk (the outlet tract of the right ventricle [RV]). When very developed it can reach as far as the lateral wall of the RV. Its acute occlusion, either because of vasospasm (the most common cause), atherosclerotic disease or accidental injury during surgery in the region of the pulmonary infundibulum, etc., can give rise to myocardial ischemia in the latter area and in the RV lateral wall. This is manifested by two major events. The first is ST segment elevation in the right precordial leads, which has also been described in isolated ischemia of the RV. Geft et al.² concluded that, after inducing ischemia in experimental animals, the isolated involvement of the RV (i.e., with no LV involvement) gives rise to the displacement of the electrical forces towards the right, and thus ST segment elevation for these leads. However, when the LV is involved (generally the inferoposterior segments), left forces predominate and ST segment elevation is seen in the leg leads accompanied by ST segment depression in the right precordial leads. The second is a greater predisposition towards suffering polymorphic ventricular tachycardia and/or ventricular fibrillation. In animal models it has been shown that ischemia of the RV outlet tract leads to abnormal

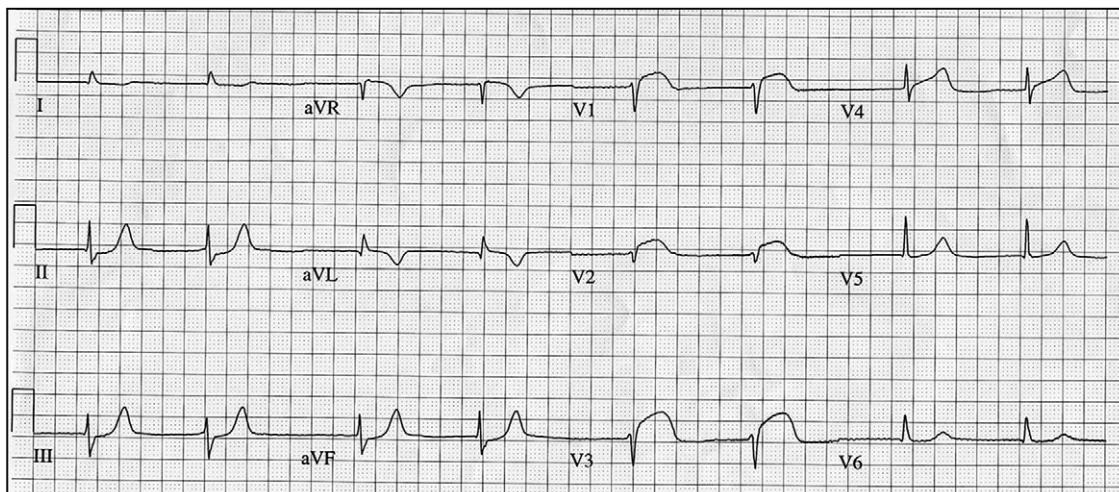


Figure 1. Convex elevation of the ST segment in the right precordial leads.