INFORME DE CASO

Holt-Oram syndrome associated with esophageal atresia. Presentation of a case

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ABSTRACT

Introduction: Holt-Oram syndrome is a low frequency hereditary disease, with wide clinical heterogeneity. Characterized by skeletal defect in the upper limbs of variable and asymmetric degree, associated with congenital heart disease.
Case presentation: a four-year-old boy was presented, a male with a clinical diagnosis of Holt-Oram Syndrome, who presents shortening of the left upper limb, congenital heart disease and esophageal atresia, the first affected in his family, so it was considered that it occurred by new mutation.
Conclusions: due to the unusual occurrence of this syndrome associated with digestive malformation, it was difficult to reach the clinical diagnosis, where the clinical or pattern method was of great value to define the case. It was necessary to consult the case with other researchers, without being able to carry out a molecular study. Considering it is important to reach the clinical diagnosis of the genetic disease to provide adequate genetic counseling to this family.
Key words: Holt-Oram Syndrome; hand-heart syndrome; atrio-digital syndrome; congenital heart disease; cardiomyel syndrome; atrioventicular dysplasia; esophageal atresia

RESUMEN

Introducción: el síndrome de Holt-Oram es una enfermedad hereditaria de baja frecuencia, con amplia heterogeneidad clínica. Se caracteriza por el defecto esquelético en los miembros superiores, de grado variable y asimétrico, asociado a cardiopatías congénitas.
Información del paciente: se presenta un niño de cuatro años, con diagnóstico clínico de síndrome de Holt-Oram, que presenta acortamiento del miembro superior izquierdo, cardiopatía congénita y atresia esofágica; es el primer afectado en su familia, por lo que se consideró que se produjo por nueva mutación.
Conclusiones: por lo poco usual de la presentación de este síndrome asociado a malformación digestiva resultó difícil llegar el diagnóstico clínico, para el que fue de gran valor el método clínico o de patrón. Resultó necesaria la interconsulta del caso con otros investigadores; no se pudo efectuar el estudio molecular. Es importante llegar al diagnóstico clínico de la enfermedad genética para poder brindar un adecuado asesoramiento genético a la familia.
Palabras clave: Síndrome Holt-Oram; síndrome mano-corazón, síndrome atrio-digital; cardiopatía congénita; síndrome cardiomélico; displasia atrio-venticular; atresia esofágica

INTRODUCTION

Holt-Oram syndrome is a genetically determined developmental disorder with an autosomal dominant inheritance pattern, high penetrance and highly variable expressivity; however, several cases have been documented as new de novo mutations. This disease presents with great clinical heterogeneity in its phenotypic expression, making it difficult to identify clinical forms with milder variants. It is characterized clinically by an association of skeletal abnormalities in the upper extremities of variable and asymmetric shape, with cardiovascular abnormalities. It has an estimated incidence of 1/100 000 live births.[1,2]

In this syndrome skeletal anomalies affect the upper extremities and shoulder girdle with a great diversity ranging from phocomelia to minimal limitation of movement of the thumbs, elbows and shoulders. Alterations of the thumbs are the most common and consist of hypoplasia of the thenar eminence, lack of thumb opposition, partial syndactyly, triphalangeal/digitalized thumbs and hypoplasia or absence of thumbs. Other skeletal anomalies that have been described include hypoplasia of the radii, clavicular anomalies, narrowing of the shoulder girdle or hypoplasia of the musculature.[2]

In the cardiovascular system, among the most frequent alterations, *ostium secundum* type atrial septal defect, ventricular septal defect, truncus arteriosus or common atrioventricular canal are described. Electrocardiographic alterations without structural alteration, mitral valve anomalies, cardiomyopathies or normal cardiological examination have been described as minor cardiac anomalies.[3]

To make the clinical diagnosis of this syndrome, the characteristic alterations of the upper extremity and cardiac involvement must be present in the same individual; defects of variable degree may appear in their progenitors and show evidence of genetic transmission, otherwise it can be considered as a new mutation. There is usually no correlation between the severity of skeletal and cardiac anomalies.[4,5]

In 1997 the responsible gene was discovered, called TBX5, which has been mapped and cloned in 12q24.1. This is the first chromosomal localization of a gene responsible for congenital heart septal defects in humans. TBX5 belongs to a family of genes (T-box transcription factor family) involved in the development and differentiation of the mesoderm and because the beginning of cardiac and upper limb development takes place between the third and fourth weeks of embryonic life.[6]

This patient, in addition to the alteration in the left upper extremity and the atrial septal defect, was born with another congenital defect, an esophageal atresia that has been the cause of several operations. Due to the particularity of the case, its description is considered interesting, emphasizing the variable expressivity of this disease; it is necessary to keep it in mind in order to make the clinical diagnosis.

PATIENT INFORMATION

Male patient who was born at 37.2 weeks, euthyroid delivery by induction due to decreased amniotic fluid, weight 2,980 grams, size 51 cm and an Apgar test

of 7-9; immediately the Neonatology Specialists diagnosed esophageal atresia and he was sent to the "Octavio de la Concepción de la Pedraja" Provincial Genetics Center of the University Pediatric Hospital, reference hospital for neonatal surgery, in the city of Holguín, in the province of the same name; four hours later he underwent surgery and a gastrostomy was performed, which he still has to this day. The esophageal atresia section was extensive, with very distant edges, and requires, for its normal reposition, a complex operation, with intestine graft, which could not be performed yet. Subsequently, in the operating room, he was examined again and it was observed that the left arm was smaller in the mesomelic portion (corresponding to the ulna and radius) and a grade II-III/VI murmur was auscultated; an echocardiogram was indicated which showed an atrial septal defect in the form of ostium secundum. He remained hemodynamically stable, without treatment, until it closed spontaneously around the age of one year.

He was malnourished for the first six months of life and thin until he was three years old, with delayed motor development that improved when his nutritional status was corrected; he managed to walk, without support, at the age of three, with good language development.

Currently, at four years of age, he has good pondostatural development and maintains between the 10th and 25th percentile, with language development in accordance with his age.

The physical examination revealed shortening of the left arm at the expense of the radial region, with hypoplasia of the radial region, as well as the first joint of the left hand, which also has high implantation (Figure 1).

The defect of the limbs is asymmetrical, as shown in Figure 2, with shortening of the left upper limb, as a result of radial hypoplasia. In this same figure the extensive scar in the abdominal region can be seen as a result of the operations to correct the congenital defect, esophageal atresia, which has not yet been achieved and it was necessary to perform a gastrostomy, which is still present.

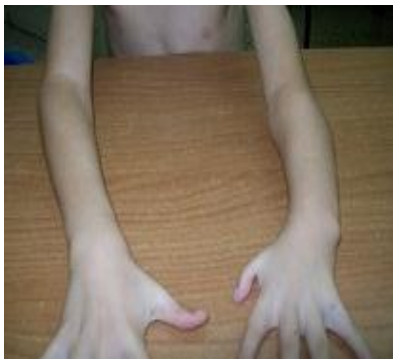

Figure 1. Characteristics of hands with hypoplasia of the first finger

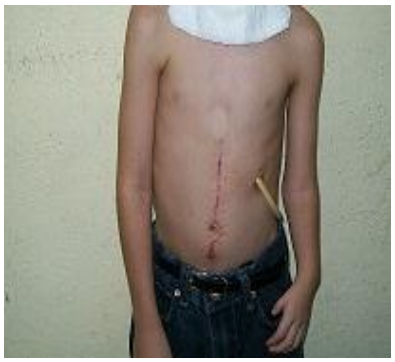

Figura 2. Particularidades de los miembros superiores

Due to the unusual occurrence of this syndrome associated with digestive malformation, tests were indicated for differential diagnosis with other pathologies.

Cervical, thoracic and lumbar radiographs were normal and abdominal ultrasound was performed, ruling out other malformations. A peripheral blood

sample was taken for conventional karyotyping with 400 bands that showed 18 metaphases, resulting in a chromosomally normal male 46, XY.
The family was asked for informed consent to examine him and to perform all the other studies, as well as to take photographs and publish them in scientific journals, to which his parents agreed.
After these studies, due to the dysmorphic and malformative pattern, a collective discussion and interconsultation with more experienced specialists took place and the clinical diagnosis of Holt-Oram syndrome was reached.

DISCUSSION

Cardiomyelic syndromes include congenital heart disease and skeletal malformations of the upper limbs and are related to mutations in transcription factors with T-Box domains. Probably producing a splicing alteration of the gene and resulting in a truncated protein at its C-terminal end. Holt-Oram syndrome is caused by a dominant mutation in the TBX5 gene that alters the three-dimensional structure of the protein and its DNA-binding function. Several point mutations and deletions in TBX5 have been found in these patients.[1,2,3]
The parents of this affected patient do not present any alteration, so it was considered as a new mutation, although a possible gonadal mosaicism is not ruled out.[3]
This disease with significant clinical heterogeneity but also genetic heterogeneity hinders the diagnosis, since the location and type of mutation in TBX5 are not predictors of phenotypic expressivity and the probability of finding the mutation in the TBX5 gene is only 74%. Thus, several studies report mutations of the duplication type, partial deletions in other chromosomes such as chromosome 14, pericentric inversion of chromosome 20.[3,4]
In 1997 it was studied and proved that the mutation of the human TBX5 gene is a critical factor for the development of limbs and heart, suggesting that the haploid insufficiency of the TBX5 gene is the molecular etiology of this disease. It was demonstrated in 1999 that the TBX5 mutation causes substantial anomalies in the heart and thumbs, observing different phenotypes in the exchange of glycine for arginine (gly 80 arg), which cause severe cardiac malformations, but only minimal alterations in the skeleton; whereas when two mutations occur, arginine to glycine (237, arg237 to gly) and arginine to tryptophan (arg to trp), there are extensive upper extremity lesions, but less significant lesions in the heart. This could partly explain the variability and severity of some presentations, and the latter could be what happened in this case.[5,6]
The differential diagnosis should be made with entities such as VACTERL association, which exhibits vertebral malformations, anal atresia, congenital heart disease, tracheoesophageal fistula, esophageal stenosis, as well as renal malformations, with dysplasia of the extremities, where the alterations in vertebrae are of great importance, which this patient does not have. Fanconi pancytopenia, which has limb alterations and hematological alterations, which this case does not present. With Poland syndrome, which presents agenesis of the pectoralis major of one side of the body, with variable degree of

involvement of the upper limb of the same side. Another differential diagnosis is made with thrombocytopenia-absence of radius, which this case does not have, and embryopathy due to thalidomide, which is discarded because it does not exist in our environment and has been withdrawn since the seventies worldwide because its teratogenic effect was proved. Other researchers have reported cases associated with aortic atresia, anorectal malformation, also association with microcephaly, crystalline lens opacity.[7,8]

However, renal and digestive malformations are not as common, as well as esophageal atresia as presented by this patient, only one other previously reported in addition to renal malformation also presented gastroesophageal atresia that was the cause of emergency surgery.[9]

This disease exhibits clinical and genetic heterogeneity with wide phenotypic variability, which could have prenatal ultrasonographic diagnosis, in cases with severe expression of the defect in limbs and in those in which it is sought by the existence of another affected person in the family. It can be found as a finding when a cardiovascular defect is associated in the genetic ultrasound with malformation of the upper limbs, which makes us think of this syndrome.[10]

In Cuba we do not have molecular diagnosis for this malformation syndrome, so it is of vital importance to study each case in particular, as well as their relatives using the clinical or pattern method to delineate the phenotype well. Reaching a clinical diagnosis allows us to take timely actions and inform families of the possible morbidity and mortality of these patients, depending on the severity of the congenital heart disease, most of whom require emergency intervention. Adequate genetic counseling is considered necessary for each affected family, explaining the risk of recurrence for the offspring, which is high at 50%.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.