CLINICAL QUIZ (p243-244) ANSWER

What is the diagnosis?

The patient presented with upper limb defects and congenital heart disorder. There was no craniofacial dysmorphism and he had normal intelligence. The overall picture was compatible with Holt-Oram syndrome (HOS).

Exome sequencing found a heterozygous single base pair deletion variant in *TBX5* {NM_000192.3}:c.292del. This changed the 98th codon from Threonine to Arginine with subsequent frameshift and eventually to a premature STOP at the 123rd codon. Parental testing was negative for such variant demonstrating a de novo mutation. This variant has not been reported in the gnomAD, Clinvar, HGMD or literature. Loss of function is a known disease-causing mechanism for *TBX5*-related-disease with a pLI score of 1. By ACMG guideline, it is classified as pathogenic. The molecular diagnosis of Holt-Oram syndrome was substantiated.

What are the clinical features?

HOS is rare with an estimated prevalence between 0.7 and 1 per 100,000 births, but is the most common of the heart-hand syndromes.[1] It is characterized by upper limb deformity, congenital heart malformation and cardiac conduction disease. HOS should be suspected when an individual presents with radial ray anomaly with personal or family history of cardiac septation or cardiac conduction defects.

Upper limb preaxial radial ray anomalies are found in all patients with HOS though with varying severity and could be unilateral or asymmetrical. The upper limb involvement may range from isolated abnormal carpal bone to unequal arm length from aplasia of the radius. Most commonly seen are absent, hypoplastic, bifid or triphalangeal thumb, radial-ulnar and carpal bone anomalies.[2] The upper limb defects could be very mild resulting in individuals only being diagnosed when a more severely affected relative is born or when symptoms of cardiac conduction disease appear later in life.

Congenital heart diseases are found in 75% of HOS patients and most commonly involve the septum. The most commonly seen are ostium secundum atrial septal defect and muscular ventricular septal defect.[3] The severity and location of septal defects could vary. Some patients with severe congenital heart malformation may need early repair surgery.[4] High-resolution prenatal ultrasound may be used to detect fetal upper limb and congenital heart malformations. Patients with HOS are at risk of cardiac conduction disease irrespective of whether they have congenital heart malformations. At birth, babies should be monitored for any sinus bradycardia or atrioventricular block. The cardiac conduction disease can progress to complete heart block in some individuals which could be life-threatening. The prognosis and life expectancy of HOS patients are mainly determined by the severity of their cardiac conditions.

If body systems other than the heart and upper limbs are involved, other differential diagnoses e.g. VACTERL association or teratogenic effects should be considered.

What is the genetic basis of HOS?

It is inherited in an autosomal dominant pattern and around 85% resulted from de novo variants. Offspring of affected individuals has a 50% risk of inheriting the mutant allele. More than 70% of patients can have molecular confirmation by sequence analysis of the *TBX5* gene. Only <1% of cases involve deletions or duplications of *TBX5* which could be detected by multiplex ligation-dependent probe amplification (MLPA). The remaining clinically diagnosed HOS patients may have negative genetic test findings.[4]

For possible genotype-phenotype correlations, it has been reported that pathogenic variants near the 5' end of *TBX5* are associated with more severe cardiac disease. Whereas variants near the 3' end are associated with more pronounced upper limb deformity.[3] However, there is significant variable expressivity even among family members carrying the same *TBX5* variants. Therefore, the severity of upper-limb deformity and congenital heart malformation cannot be accurately predicted by genetic test alone.

What are the management issues for HOS?

Management of HOS requires multidisciplinary specialists including paediatricians, cardiologists and orthopedic surgeons.[5] Hand and upper-limb x-rays should be performed to assess the extent of upper-limb deformity. Physiotherapy and occupational therapy are effective in improving function. In cases of severe upper limb deformity, orthopedic surgeons could be consulted for possible surgery to improve quality of life.

All HOS patients are at risk of cardiac conduction disease, so annual ECG monitoring is recommended. If there are existing conduction defects, annual ECG combined with Holter monitoring should be performed to assess for any disease progression. Patients may also need follow-up ultrasound, medication or even early surgery for respective congenital cardiac conditions. Joint management is recommended with cardiologists.

Apparently asymptomatic at-risk relatives of an affected individual should be offered clinical and/or genetic screening as early identification of HOS could aid in monitoring of cardiac diseases and family planning. Such individuals could be referred to clinical geneticists for counseling before deciding on testing.

Acknowledgements

We would like to express our gratitude to the patient and his family for their contribution. Informed consent was obtained for publication.

References

1. Ingeborg Barisic, Ljubica Boban, Ruth Greenlees, et al. Holt Oram syndrome: a registry-based study in Europe. Orphanet J Rare Dis 20145;9:156.
2. Holt M, Oram S. "Familial heart disease with skeletal malformations." Br Heart J 1960;22:236-42.
3. Basson CT, Huang T, Lin RC, et al. Different *TBX5* interactions in heart and limb defined by Holt–Oram syndrome mutations. Proc Natl Acad Sci U S A 1999;96:2919-24.
4. Sletten LJ, Pierpont ME. Variation in severity of cardiac disease in Holt-Oram syndrome. Am J Med Genet 1996;65:128-32.
5. McDermott DA, Fong JC, Basson CT. Holt-Oram Syndrome. 2004 Jul 20 [Updated 2019 May 23]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022.