Diversity of congenital cardiac defects and skeletal deformities associated with the Holt–Oram syndrome

Gregory Chryssostomidis a, Meletios Kanakis a, Vassiliki Fotiadou b, Cleo Laskari c, Theofili Kousi d, Christos Apostolidis d, Prodromos Azaridis a, Andrew Chatzis a,∗

a Department of Paediatric and Congenital Cardiac Surgery, Onassis Cardiac Surgery Centre, Athens, Greece
b Athinaiki Mediclinic, Athens, Greece
c Department of Paediatric Cardiology, Onassis Cardiac Surgery Centre, Athens, Greece
d Department of Anaesthesiology, Onassis Cardiac Surgery Centre, Athens, Greece

ABSTRACT

INTRODUCTION: The Holt–Oram syndrome is a rare congenital disorder involving the skeletal and cardiovascular systems. It is characterized by upper limb deformities and cardiac malformations, atrial septal defects in particular.

PRESENTATION OF CASE: Four consecutive patients 1–15 years old with the Holt–Oram syndrome presented over a 10 year span for surgical treatment of their cardiac maladies. The spectrum of the heart defects and skeletal deformities encountered in these patients are described and discussed.

DISCUSSION: The Holt–Oram syndrome is an autosomal dominant condition; however absence of the morphological features of the trait in close family members is not rare. Although patients are known to predominately present with atrial septal defects, other cardiovascular anomalies, including rhythm abnormalities, are not uncommon. Skeletal disorders vary as well.

CONCLUSION: Cardiovascular disorders, skeletal malformations and familial expression of the Holt–Oram syndrome, vary widely.

© 2014 The Authors. Published by Elsevier Ltd. on behalf of Surgical Associates Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).
syndactyly of the left thumb and index finger and forward displacement of the right thumb were noted (Fig. 2). The ECG showed SR, ventricular premature complexes and abnormal right axis deviation. Echocardiography revealed a large VSD, aortic overriding, right ventricular outflow tract obstruction, RVH and also a secundum ASD. The patient underwent standard surgical correction, made a good overall recovery and was discharged home in good clinical condition.

2.4. Case 4

A 2-year-old girl presented with a canal type VSD, concomitant mitral cleft and a history of a pulmonary artery banding at the age of 1 month. Physical examination revealed syndactyly of the left thumb and index finger and forward displacement of the right thumb (Fig. 3). Her father exhibited similar skeletal abnormalities. ECG showed SR. Echocardiography revealed a large perimembranous VSD and a mitral cleft without a primum septal defect (Figs. 4 and 5). Currently, she is on the list for total repair.

Fig. 1. Case #1. Right thumb and middle finger.

Fig. 2. Case #3. (A) Right thumb forward displaced. (B) Left thumb-index finger syndactyly.

Table 1

| Case 1 | Case 2 | Case 3 | Case 4 |
|--------|--------|--------|--------|
| Gender | Male   | Female | Male   | Female |
| Age (years) | 15     | 4      | 1      | 2      |
| Family trait | No     | No     | Kyphosis, scoliosis, hypoplastic clavicles, pectus excavatum, thumb and index syndactyly (L), short and forward displacement of thumb (R) |
| Skeletal disorders | Kyphosis, absent fingers of the (R) hand | Bilateral upper limb dysplasia, short ring fingers | Kyphosis, scoliosis, hypoplastic clavicles, pectus excavatum, thumb and index syndactyly (L), short and forward displacement of thumb (R) |
| CHD | TOF/PA | TOF/ASD | ASD | VSD, mitral cleft |
| Psychomotor disorders | No | No | Yes – mental retardation, epilepsy | No |
| ECG | SR, RAE, LAE, right axis, RVH, T abnormality | Sinus atrial tachycardia, incomplete RBBB, RVH | SR, PVC, right axis | SR |
| Operation | Aorta to pulmonary artery shunt | ASD patch closure | TOF repair/ASD patch closure | Pulmonary artery banding |
| ICU/hospital stay (days) | 1/8 | 3/8 | 6/9 | 5/9 |

CHD, congenital heart disease; ECG, electrocardiogram; TOF, tetralogy of Fallot; PA, pulmonary atresia; ASD, atrial septal defect; VSD, ventricular septal defect; ICU, intensive care unit; SR, sinus rhythm; PVC, premature ventricular contractions; RBBB, right bundle branch block; RAE, right atrial enlargement; LAE, left atrial enlargement; RVH, right ventricular hypertrophy; (R), right; (L), left.
3. Discussion

The Holt–Oram syndrome is an autosomal dominant condition first described in 1960 by Mary Holt and Samuel Oram and was named after them a year later by Victor McKusick, when describing a similar case.2,3 Multiple transcription factors regulate specific programs of gene expression in heart development.4 Of these, TBX5, member of a family characterized by a highly conserved DNA binding motif (T-box) participates in the specification of left/right ventricles and ventricular septum position during cardiogenesis.5,6 The Holt–Oram syndrome is caused by the mutation of a gene residing on the long arm of the chromosome 12q24.7 It is argued, however, that heart-limb syndromes are expressed by mutation in different genes suggesting a genetically heterogeneous disease with just one locus mapping on this chromosome.8 TBX5, nonetheless, directly or indirectly, alters the transcription of different genes in heart and limb.1,5,9

Inward directed thumb as in the original description by Holt and Oram was found in 3 of our patients.2 However, a large number of different skeletal abnormalities have been reported. In particular, distally displaced, triphalangeal thumbs, hypoplastic thenar eminences, hypoplastic, absent or extra fingers, anomalies of the carpus, radial aplasia, phocomelia, hypoplasia of the clavicles and shoulders and pectus excavatum have been described. Upper extremity deformity is in the preaxial radial ray distribution, usually bilateral, yet may be asymmetrical in severity, the left side usually being the worst.2,8,10–13

The most frequent cardiac abnormalities are ASDs, followed by VSDs.1,12–16 Nonetheless 17.5% of patients have severe cardiac disorders.15 Persistent ductus arteriosus, anomalous coronary arteries, mitral valve prolapse, persistent left superior vena cava, tetralogy of Fallot, double outlet right ventricle and total anomalous pulmonary venous return have been described in patients with the Holt–Oram syndrome.10,14–20 Interestingly, numerous individuals with familial Holt–Oram syndrome showed only ECG abnormalities
without structural cardiac anomalies. Conduction disorders may occur, mostly affecting the atrioventricular node. Also sinus node dysfunction, bradycardia, atrial fibrillation, atrioventricular block, RBBB, Wolf-Parkinson-White syndrome and even sudden cardiac death have been reported. Hypoplastic and ectopic peripheral vessels are common, posing as a serious challenge in getting vascular access in these patients.

A variety of morphological and anatomic criteria in conjunction of genetic analyses have led to the recognition of multiple heart-limb syndromes, with Holt–Oram being the most common. Diversity in the expression of abnormalities both skeletal and cardiovascular in the Holt–Oram syndrome seems to be attributed to different gene mutations.

4. Conclusions

The association of a canal type VSD and mitral valve cleft with the Holt–Oram syndrome (case #4) has not been reported before to our knowledge.

Obviously, longevity of individuals with Holt–Oram syndrome depends upon the identification and treatment of their cardiac maladies. In our case series, nevertheless, morbidity was minimal.

Since the majority of the clinical information available is provided mostly by isolated reports, further epidemiological and genetic analyses are required to determine the incidence and categorize the different types of heart limb syndromes.

Conflicts of interest

None.

Funding

None.

Ethical approval

Written informed consent was obtained from the patients for publication of these case reports and accompanying images. A copy of the written consent for each one separately is available for review by the Editor-in-Chief of this journal on request.

Author contributions

Gregory Chryssoptomidis MD performed the literature review and drafted the manuscript. Meletios Kanakis MD performed the literature review and helped to draft the manuscript. Vassiliki Fotiadou MD, Theophili Kousi MD, Christos Apostolidis MD, and Prodromos Azariadis MD collected the data. Cleo Laskari MD helped for data analysis and interpretation; Andrew C. Chatzis MD involved in study concept and design, data analysis and interpretation, writing and editing the paper and is the guarantor of the work.

Key learning points

- The Holt–Oram syndrome exhibits a variety of congenital cardiac anomalies and not only atrioventricular septal defects.
- Although the syndrome affects predominately the upper limbs, it is also associated with other skeletal malformations.
- The trait may not be expressed in other family members.

References

1. Basson CT, Solomon SD, Weissman B, MacRae CA, Poznanski AK, Prieto F, et al. Genetic heterogeneity of heart-hand syndromes. Circulation 1995;91:1326–9.

2. Holt M, Oram S. Familial heart disease with skeletal malformations. Br Heart J 1960;22:236–42.

3. McKusick VA. 1959. Medical genetics, J Chronic Dis 1960;12:1–202.

4. Srivastava D, Olson EN. A genetic blueprint for cardiac development. Nature 2000;407:221–6.

5. Basson CT, Huang T, Lin RC, Bachinsky DR, Weremowicz S, Vaglio A, et al. Different TBX5 interactions in heart and limb defined by Holt–Oram syndrome mutations. Proc Natl Acad Sci USA 1999;96:2919–24.

6. Hobb M, Thomsen GH. Tbx5 is essential for heart development. Development 1999;126:1739–51.

7. Terrett JA, Newbury-Ecob R, Cross GS, Fenton I, Raeburn JA, Young ID, et al. Holt–Oram syndrome is a genetically heterogeneous disease with one locus mapping to human chromosome 12q. Nat Genet 1994;6:401–4.

8. Basson CT, Cowley GS, Solomon SD, Weissman B, Poznanski AK, Trail TA, et al. The clinical and genetic spectrum of the Holt–Oram syndrome (heart-hand syndrome). N Engl J Med 1994;330:885–91.

9. Yu Q, Shen Y, Chatterjee B, Siegfried BH, Leatherbury L, Rosenthal J, et al. ENU induced mutations causing congenital cardiovascular anomalies. Development 2004;131:6211–23.

10. Sinha R, Nema D. Rare cardiac defect in Holt–Oram syndrome. Cardiovasc J Afr 2012;23:e3–4.

11. Bohn M. Holt–Oram Syndrome. Circulation 1998;98:2636–7.

12. Brockhoff CJ, Rober H, Tsilimingas N, Dapper F, Munzel T, Meinertz T. Holt–Oram Syndrome. Circulation 1999;99:1305–5.

13. Frota Filho JD, Pereira W, Leiria TL, Vallenas M, Leães PE, Blacher C, et al. Holt–Oram syndrome revisited. Two patients in the same family. Arq Bras Cardiol 1999;73:429–34.

14. Shono S, Higa K, Kumano K, Dan K. Holt–Oram syndrome. Br J Anaesth 1998;80:856–7.

15. Sletten LJ, Pierport MEM. Variation in severity of cardiac disease in Holt–Oram syndrome. Am J Med Gen 1996;65:128–32.

16. Singh B, Kariyappa M, Vijyalakshmi IB, Nanjappa MC. Holt–Oram syndrome associated with double outlet right ventricle: a rare association. Ann Pediatr Cardiol 2013;6:90–2.

17. Kumar V, Agrawal V, Jain D, Shankar O. Tetralogy of Fallot with Holt–Oram syndrome. Indian Heart J 2012;64:95–8.

18. Vianna CB, Miura N, Pereira AC, Jatene MB. Holt–Oram syndrome: novel Tbx5 mutation and associated anomalous right coronary artery. Cardiol Young 2011;21:351–3.

19. Miller AB, Salcedo EE, Bahler RC. Prolapsed mitral valve associated with the Holt–Oram syndrome. Chest 1975;67:230–2.

20. Thai S, Boyella R, Arsanjani R, Thai H, Juneman E, Movahed MR, et al. Unusual combination of Holt–Oram Syndrome and persistent left superior vena cava. Congenit Heart Dis 2011;7:E46–9.

21. Basson CT. Holt–Oram syndrome vs. heart-hand syndrome. Circulation 2000;101:E191. Comment on Holt–Oram syndrome.