HOLT-ORAM SYNDROME: A RARE CASE REPORT

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ABSTRACT

Holt-Oram syndrome (HOS) is a heart-upper limb malformation complex with an autosomal dominant inheritance and near-complete penetrance but variable expression. Holt and Oram first described this syndrome in 1960. Approximately 40% of cases represent new mutations. The syndrome is associated with defective development of cardiac structures that results in atrial septal defect (ASD), most commonly the secundum type; heart block of varying degree; or both.

The syndrome is characterized by cardiac malformations and aplasia or hypoplasia of the thumb. The incidence of HOS is estimated at 1:100,000 live births. In the literature, it is also known as atriodigital syndrome, heart-hand syndrome, upper limb-cardiovascular syndrome, cardiac-limb syndrome, or cardiomelic syndrome. Herein, we report a 22-year-old female case of HOS presenting with the absence of the right radius of the upper limb and ulnar dysplasia, hypoplasia, and kyphoscoliosis along with a large secundum type ASD and carotid artery abnormalities. We present this case of holt-oram syndrome with cardiac surgery and postoperative neurological complication and its successful treatment.

Keywords: Holt- Oram, Atrial Septal Defect, Surgery.

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Introduction

Holt-Oram syndrome (HOS) is a congenital autosomal hereditary condition, characterized by skeletal abnormalities of the upper limbs and cardiac malformations. It was first described by Mary Clayton Holt and Samuel Oram in 1960 in members of four generations of a family as the triad of ASD, conduction disturbances, and hand malformations associated with a congenital anomaly of the thumbs laying in the same plane as the fingers with their terminal phalanges being curved inward. In the literature, it is also known as atriodigital syndrome, heart-hand syndrome, upper limb-cardiovascular syndrome, cardiac-limb syndrome, or cardiomelic syndrome. Herein, we report a 22-year-old female case of HOS presenting with the absence of the right radius of the upper limb and kyphoscoliosis along with a large secundum type ASD whose neurological symptoms persisted despite surgery and in whom carotid angiography showed vascular abnormalities.

Case report

A 22-year-old female patient was admitted to our cardiology outpatient clinic with a complaint of palpitation for a year. The patient who was diagnosed with ASD was hospitalized and scheduled for surgery. Her medical history was non-specific, except palpitation. Her family history was also non-remarkable. Physical examination revealed a grade 3/6 ejection murmur loudest at
the anterior sternal border and splitting of the second heart sound. The other findings were normal. Musculoskeletal findings indicated hypoplasia of the thenar muscles, absence of radius, ulnar dysplasia and hypoplasia, a thumb hypoplasia, an inwardly deviated hand from the wrist and a functionally inactive hand (Figure 1a).

Electrocardiography demonstrated a normal sinus rhythm (77 bpm) with right axial deviation and right bundle branch block. Chest X-ray showed levocardia, a significantly increased cardiothoracic ratio due to the right ventricular hypertrophy, and pulmonary parenchymal changes secondary to mild pulmonary hypertension. Laboratory test results were within reference ranges.

Plain radiographs of both upper limbs showed no pathology of the left upper limb; however, the absence of radius, ulnar dysplasia and hypoplasia, severe hypoplasia of the first metacarpal bone, and hypoplasia and dysplasia of the phalangeal bones (Figure 1b). In addition, thoracic X-ray images showed severe kyphoscoliosis and pectus carinatum (Figure 1c).

Two-dimensional transthoracic echocardiography revealed an ejection fraction of 55% with a large secundum type ASD (38 mm) in the interatrial septum, severe tricuspid regurgitation, severe right atrial and ventricular dilation, a pulmonary artery pressure of 75 mmHg, and a pulmonary to systemic flow ratio of 6. Cardiac catheterization results were as follows: RA: 6 mmg, PA: 61-17-32/50-17-29 mmHg, Ao:115-78-93 mmHg, and LA:5 mmHg. Saturation values were as follows: SVCmax: 59%, SVCmin: 8%; PV: 96%, PA1: 84, PA2: 79; Ao: 90, IVC: 65%, and Qp/Qs: 1.9. Based on these findings, cardiovascular surgeons and cardiologists decided that the patient was ineligible for percutaneous intervention and was scheduled for a complete correction surgery.

A written informed consent was obtained from the patient. Surgery was performed through median sternotomy, followed by aortic bicaval cannulation under moderate hypothermia and cardiopulmonary bypass. Antegrade blood cardioplegia was used and diastolic arrest was achieved. Then, right atriotomy was performed and the defect was closed using a small pericardial patch. De-Vago annuloplasty was performed for the repair of tricuspid valve. The right atrium was shrunk during the closure. Finally, sternal revision was done and carinatum sternum was corrected through resection and fixed using steel wires.

Following surgery, the patient was taken into the intensive care unit. She was in junctional rhythm (75 bpm). On Day 1, she returned to sinus rhythm. However, pleural fluid was detected in the right and left lungs, and thoracentesis was performed through the junction of the fifth intercostal space and mid-axillary line. A thoracic tube was inserted after serous aspiration and underwater drainage system was activated. During the intensive care unit stay, the patient with bilateral atelectasis was under continuous positive airway pressure (CBAP) on a regular basis, which reduced atelectasis. Fingertip saturation value was above 95%. On Day 4, a sudden-onset, left-sided hemiplegia, hemiparesis, and central facial paralysis developed with visual disturbances. The patient, therefore, was referred to a neurologist.
Cerebral angiography was performed in the radiology department. It showed early bifurcation of the carotid artery with normal internal carotid artery (ICA) and external carotid artery (ECA) fillings. The left middle cerebral artery (MCA) and anterior cerebral artery (ACA) filling were detected, as well as the right MCA and ACA fillings due to ACoA and PCoA patency (Figure 1d).

In addition, a poor filling was observed in the end branches of the right MCA. A totally obstructed ICA at the distal part was also detected (Figure 1e).

The left vertebral artery directly originated from the arcus aorta (Figure 1f).

During the examination of the right vertebral artery, the carotid system was filled through dilated VA and PCoA. A diluted 0.1 mg gliserol trinitrate as administered to the right ICA for the management of stroke. A catheter was advanced toward the distal right ICA and an intraatrial 10 mg tPA was intermittently administered.

Repeated examinations showed no complete resolution of the ICA obstruction; however, ophthalmic artery improved with partially filled anterior perforating arteries. The patient had left-sided motor symptoms due to the insufficient filling of the end branches of the right MCA. However, ACoA and PCoA were patent, and the right MCA and ACA were filled mostly through the right VA. Therefore, 5 mg tPA was intermittently administered to the right VA. Repeated examinations showed an improved right MCA filling volume.

During the intensive care unit stay, repeated echocardiography showed normal findings during. At eight hours of tPA administration, her neurological symptoms regressed with progressively improved clinical condition. At 24 hours, visual disturbances completely resolved with neurologically improved muscle strength and tone, as before. No tPA-related complication was observed. On Day 6 of surgery, the patient was transferred to the ward. Repeated echocardiography and teleradiography showed no additional problem. On Day 12 of selective tPA, cerebral computed tomography angiography revealed normal flow of the right ICA, which was previously totally occluded, without any occluded vein (Figure 1g). No thrombolytic treatment-related complication was observed. The patient was discharged with complete recovery.

Discussion

Holt-Oram syndrome is characterized by skeletal abnormalities of the upper limbs and cardiac malformations. The incidence of HOS is estimated at 1:100,000 live births\(^7\). The syndrome has a complete penetrance due to the autosomal-dominant nature of the disease, which can be inherited from one generation to another. Therefore, all family members of the patient should be scanned. In patients whose family members are negative are considered to have a new gene mutation, based on the literature data\(^8\).
In our case, family history was negative and no component of the syndrome was detected. Therefore, we considered a new gene mutation.

HOS is inherited in an autosomal dominant manner. Approximately 85% of affected individuals have HOS as the result of a de novo pathogenic variant. Offspring of an affected individual are at a 50% risk of being affected. In pregnancies at 50% risk, detailed high-resolution prenatal ultrasound examination may detect upper-limb malformations and/or congenital heart malformations. Prenatal molecular genetic testing may be used to confirm a diagnosis if the TBX5 pathogenic variant has been identified in an affected relative.

The responsible gene has been mapped to band 12q24.1, which encodes the human transcription factor TBX5. Prognosis in patients with Holt-Oram syndrome (HOS) is dictated by the severity and type of cardiac and limb malformations. Because the most common defect in HOS is atrial septal defect (ASD), the prognosis is excellent.

The syndrome may present in a wide range of symptoms from dysplasia of the upper limbs, thumb hypoplasia, clinodactyly, brachydactyly, triphalangeal thumb, dysmorphic carpal bones, ulnar shortness, humerus shortness or hypoplasia, and the absence of radius, as in our case, to phocomelia, the most severe form of the disease. Congenital cardiac malformations are the other components of the syndrome, which are determinant factors in the mortality and morbidity. These include ASDs at a rate of 60%, although about 18% have a broad-range of complex congenital cardiac diseases. On the other hand, there is no association between the severity of cardiac disease and severity of the upper limb deformity.

Holt and Oran first reported undefined atrial arrhythmias in this patient population. Later, sinus arrest, atrioventricular blocks at varying degrees, right bundle branch block, sinus node dysfunction, supraventricular tachycardia, and Wolf-Parkinson-White syndrome were reported in the literature.

Similarly, our case had right bundle branch block and right axial deviation. Furthermore, the incidence of arrhythmia in patients with HOS has been shown to increase following cardiac correction surgery, suggesting an underlying chromosome abnormality.

In our case, we performed right bundle branch block correction surgery and she returned to sinus rhythm, although she was in pace-dependent junctional rhythm for a short-time period after surgery. She did not develop any arrhythmia later.

Furthermore, HOS can be misdiagnosed as thrombocytopenia and radius aplasia (thrombocytopenia-absent radius, TAR). Roberts syndrome, thalidomide embryopathy, and Fanconi anemia. The differential diagnosis includes the absence of hematologic abnormalities, absence of hypoplasia of the thumb, and family history.

In conclusion, we believe that other vascular structures and variations should be examined through catheterization in patients with multiple defects, such as HOS. In particular, cardiac surgery should be well-tailored and a multidisciplinary approach including experienced surgeons should be implemented to minimize postoperative complications. For the welfare of the patient, we recommend performing surgery only by well-equipped institutions to manage such complications. In addition, family history should be well-documented and family members should be informed on hereditary diseases, such as HOS.

References


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