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Absent Left Main Coronary Artery and Separate Ostia of Left Coronary System in a Patient with Holt-Oram Syndrome and Sinus Node Dysfunction

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Male, 41
Final Diagnosis: Sick Sinus Syndrome and absent left main coronary artery • separate ostia of left anterior descending and circumflex arteries in Holt-Oram Syndrome
Symptoms: Conduction disturbance • seizure-like activity • upper extremity malformations
Medication: —
Clinical Procedure: Electro physiology study • coronary catheterization • pacemaker
Specialty: Cardiology

Objective: Congenital defects/diseases

Background: Holt-Oram syndrome (HOS) is a rare but significant syndrome consisting of structural heart defects, conduction abnormalities, and upper extremity anomalies. It was first described in the British Heart Journal in 1960 by Mary Holt and Samuel Oram as a report of atrial septal defect, conduction disturbances, and hand malformations occurring in family members. Patients can present with heart blocks or symptoms of underlying congenital heart defects.

Case Report: A 41-year-old man with Holt-Oram syndrome presented with seizure-like activity and was found to have an underlying conduction disturbance. Physical exam showed bilateral atrophic upper extremities with anatomic disfiguration, and weakness of the intrinsic hand muscles. Cardiovascular exam revealed a slow heart rate with irregular rhythm. EKG showed sinus arrest with junctional escape rhythm. Cardiac catheterization revealed coronary anomalies, including absent left main coronary artery and separate ostia of the left anterior ascending and left circumflex coronary artery. Coronary arteries were patent. Following electrophysiology study, sick sinus syndrome and AV block were diagnosed, and the patient received implantation of a permanent pacemaker.

Conclusions: This patient presented with a seizure-like episode attributed to hypoxia during asystole from an underlying cardiac conduction defect associated with Holt-Oram syndrome. Arrhythmias and heart blocks are seen in these patients, and conduction defects are highly associated with congenital heart defects. Holt-Oram syndrome rarely presents with coronary artery anomalies. There is no reported case of separate coronary ostia and absent left main coronary artery. Prompt diagnosis is important since anomalies in coronary and upper extremity vasculature might be challenging for invasive procedures.

MeSH Keywords: Coronary Vessel Anomalies • Hand Deformities, Congenital • Heart Defects, Congenital • Sick Sinus Syndrome

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/896474

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Background

Holt-Oram syndrome (HOS) is a rare but important syndrome consisting of structural heart defects, conduction abnormalities, and upper extremity anomalies. HOS was first described in the British Heart Journal in 1960 by Mary Holt and Samuel Oram as a report of an atrial septal defect, conduction disturbances, and hand malformations occurring in family members. Patients can present with heart blocks or symptoms of underlying congenital heart defects. Upper extremity deformity must be present to diagnose HOS. Coronary anomalies are extremely rare findings. In the existing medical literature only 1 report has detailed right coronary anomalies in Holt-Oram syndrome, and there have been no descriptions of an anomalous left system, as in this patient.

Case Report

A 41-year-old man with Holt-Oram syndrome (HOS) with repaired atrial septal defect (ASD), hypertension, hypercholesterolemia, and remote history of asthma presented to the emergency room following witnessed seizure-like activity. His wife witnessed him having muscle contractions and called the emergency medical service. He woke up in an ambulance and was confused for a short time. There was no urinary or bowel incontinence, and no tongue biting. He had never been diagnosed with a seizure disorder. The father's medical history was unknown. He reported prior use of cocaine and marijuana in the remote past.

The patient had been diagnosed with HOS soon after birth. He was diagnosed with an ASD which was repaired at 7 years old. Eight years ago, he had previous cardiac catheterization performed at a nearby hospital due to chest pain with elevated cardiac enzymes. Coronary arteries were patent at that time. The left main coronary artery was absent and he had separate ostia of the left anterior descending and left circumflex coronary artery (Figure 1). Left ventriculogram showed mild global hypokinesis with ejection fraction of 40–45%.

Physical exam showed decreased muscle bulk in bilateral upper extremities, which was more severe in distal muscles compared to proximal muscles (Figure 2). Upper extremity examination was limited due to congenitally underdeveloped bones and muscles (Figure 3). Range of motion at the shoulders and elbows was reduced. Bilateral arm strength was 5/5 proximally and 4/5 in forearm flexors and extensors. Intrinsic hand muscle strength was 2/5. Deep tendon reflexes were 1+ in bilateral biceps and triceps and 2+ reflexes at patellar and ankles. Plantar responses were equivocal. Neurologic examination showed normal cranial nerves and sensation. Finger-to-nose testing was limited bilaterally due to limited range of motion at the shoulders and elbows. His gait was intact.

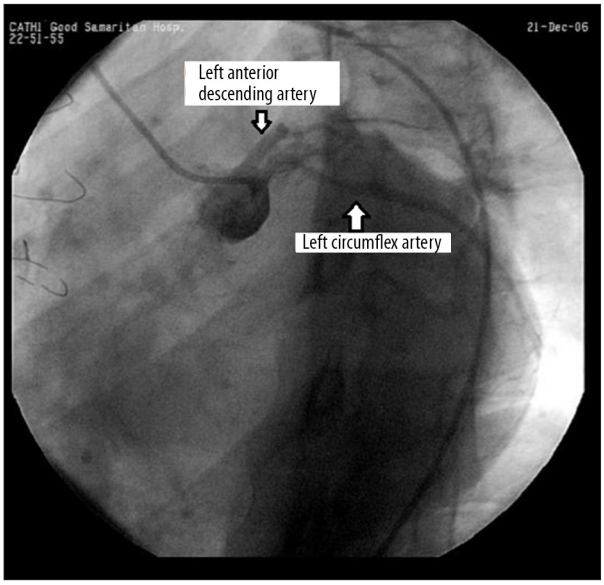

Figure 1. Coronary angiogram showing separate ostia for left anterior descending artery and left circumflex artery.

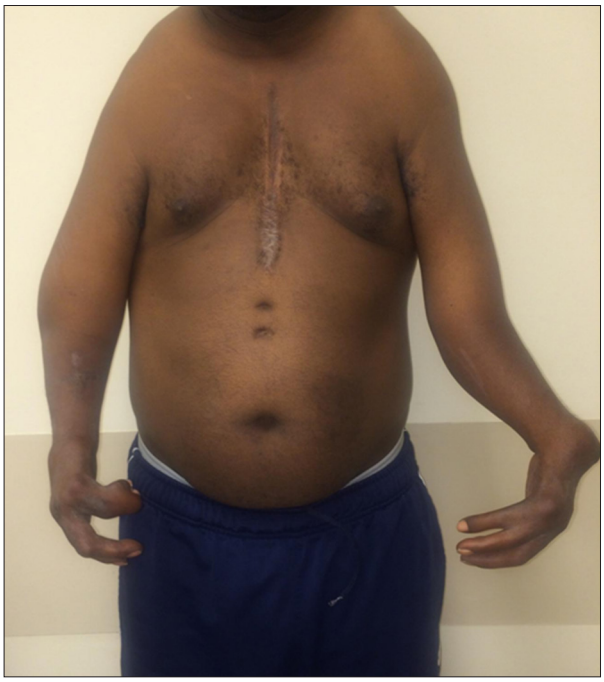

Figure 2. Deformity of bilateral upper extremities in Holt-Oram syndrome.

Head-CT and magnetic resonance imaging (MRI) revealed no acute intracranial process. Positive findings were diminished attenuation at the bilateral paramedian frontal lobes and left subcortical area encephalomalacia, which was suggestive of prior intracranial injury. Electro-encephalogram showed no epileptiform discharges or focal abnormalities. The patient had no recurrence of seizure during his hospitalization.

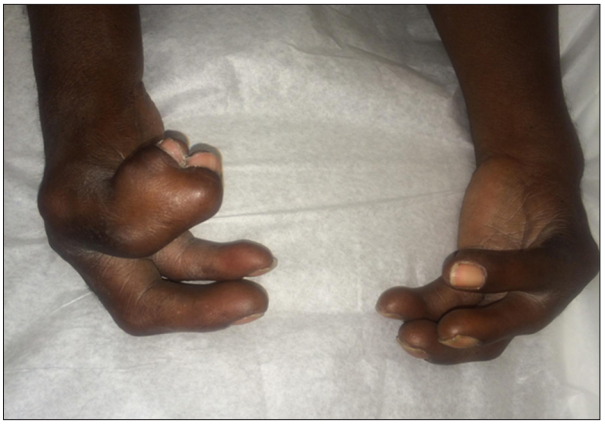

Figure 3. Absence of thumb on left upper extremity and fusion of first 3 digits on right upper extremity.

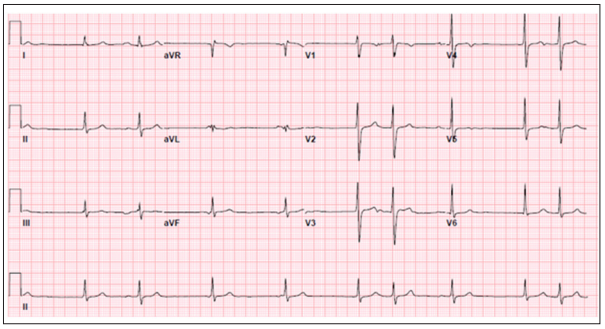

Figure 4. Twelve-lead EKG sinus rhythm showing underlying heart block and junctional escape rhythm.

Cardiovascular examination revealed a slow heart rate with irregular rhythm. EKG showed sinus arrest with junctional escape rhythm. Heart rate was 57 beats per minute. Rhythm was irregular due to skipped beats. QRS duration was 124 milliseconds (msec) and interventricular conduction delay was diagnosed. QT interval was not prolonged (corrected QT interval was 432 msec) (Figure 4). Telemetry showed frequent sinus arrest with junctional escape rhythm during the night. Echocardiography showed an enlarged left ventricle and global hypokinesis. Ejection fraction was estimated to be around 45%. The right atrium and ventricle were normal in size. No intracardiac shunt or significant valvular abnormalities were noted.

Cardiology was consulted for heart block. Considering the singular nature of the seizure with normal EEG and evidence of sinus arrest, there was a concern for the possibility of bradyarrhythmia, including asystole, leading to seizure-like activity. The patient received a transvenous temporary pacemaker as an emergency procedure. Additionally, the patient had history of syncope and LV systolic dysfunction; therefore, an electrophysiology study (EPS) was performed.

Sinus node recovery time at drive cycle length of 600 msec was 2070 msec. The corrected SNRT was 885 msec, which is

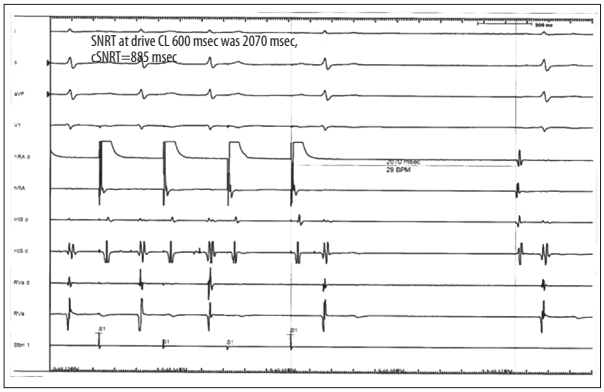

Figure 5. Electrophysiology study showing abnormal sinus node recovery time (SNRT). Corrected SNRT was 885 at cycle length of 600 msec.

clearly an abnormal finding (Figure 5). Sick sinus syndrome was diagnosed since the normal value for cSNRT was less than 550 msec. The AH interval was 55 msec, HV interval was 50 msec, and sinus cycle length was 1186 msec. AV conduction disease was also diagnosed due to AV Wenckebach block at 410 msec. Programmed ventricular stimulation did not induce ventricular tachycardia. Procainamide infusion was then started to stress the cardiac conduction system but was discontinued due to hypotension.

Based on sick sinus syndrome and AV block, the patient was directed to have an implantation of a permanent pacemaker.

Discussion

Holt-Oram syndrome (HOS) was first described in 1960 by Mary Holt and Samuel Oram in their case report of atrial septal defect, conduction disturbances, and hand malformations occurring in 9 family members spanning 4 generations. It was later classified as Online Mendelian Inheritance in Man No. 142900 [1,2].

It is also known as heart-hand syndrome type I and the most common of the rare heart-hand syndromes or atrio-digital dysplasia. It is a very rare condition, affecting 1 in 100 000 live births in an autosomal dominant pattern with complete penetrance and variable expression. The underlying genetic defect was believed to be mutations of TBX3 and TBX 5 genes located on the long arm of chromosome 12 (12q2). Mutations of these 2 TBX genes generate the orthopedic and cardiologic anomalies [3,4].

Clinical diagnostic criteria for Holt-Oram syndrome include pre-axial radial ray malformations in at least 1 upper limb and congenital heart defects and/or conduction defects. Therefore, all patients with Holt-Oram syndrome have upper extremity

anomalies by definition [5]. When a congenital heart defect is not present, there should be a family history of Holt-Oram syndrome consistent with an autosomal dominant inheritance pattern.

The largest study of Holt-Oram syndrome involved 73 patients and was published by Barisic et al. in 2014. The spectrum of upper extremity deformities ranges from abnormal carpal bone to bilateral phocomelia, including triphalangeal thumb, aplasia, hypoplasia, bifid digits, and syndactyly of thumb or fingers, radius, ulnar, humerus, or clavicle. The most common deformities are absence of thumb and humerus hypoplasia.

Congenital heart defects are noted in 75–90% of patients with Holt-Oram syndrome. Atrial septal defects (ASD) (45%) and ventricular septal defects (VSD) (37%) are the most common. Our patient had an atrial septal defect which was diagnosed early and underwent patch repair at the age of 7 years. Valvular and structural heart anomalies are also reported, such as pulmonary atresia, aortic valve stenosis or regurgitation, mitral valve anomalies, tetralogy of Fallot, double outlet right ventricle, right-sided aortic arch, dextrocardia [6].

Our patient is unique as he has separate coronary ostia of left anterior descending and left circumflex coronary arteries with absent left main coronary artery. Holt-Oram syndrome rarely presents with a coronary artery anomaly. There was 1 report, by Vianna et al. in 2011, regarding a patient with Holt-Oram syndrome with an anomalous right coronary artery. To the best of our knowledge, there is no reported case of separate coronary ostia and absent left main coronary artery in Holt-Oram syndrome [7].

Arrhythmias and heart blocks are common but not necessary for diagnosis of Holt-Oram syndrome. Most patients who presented with conduction disturbances had cardiac defects, especially in familial cases, and up to 95% of patients have cardiac anomalies. Cardiac rhythm disturbances can vary from asymptomatic rhythm disturbances to sudden death due to heart blocks [8,9].

Our patient presented with seizure-like activity, which was later attributed to the hypoxia due to presumptive asystole. This dramatic presentation warranted a temporary pacemaker placement followed by electrophysiology study the very next day, with placement of a permanent pacemaker. Proper diagnosis of Holt-Oram syndrome is important since most of the patients have structural heart defects and coronary anomalies can lead to challenges during electrophysiology study, pacemaker implantation, or cardiac catheterization.

Conclusions

Holt-Oram Syndrome is a rare but significant syndrome consisting structural heart defects, conduction abnormalities and upper extremity anomalies. Patients can present with heart blocks or symptoms from underlying congenital heart defects. Upper extremity deformity must be present for diagnosis.

Holt-Oram Syndrome rarely presents with coronary artery anomalies. There was one case report by Vianna, et al. in 2011 regarding an anomalous right coronary artery. Our patient has an absent left main artery with separate left anterior descending and left circumflex coronary ostia. There has not yet been a reported case in the medical literature to date. Thorough investigation with accurate diagnosis is important since anomalies in coronary and upper extremity vasculature can present unique difficulty during electrophysiology study, pacemaker implantation or cardiac catheterization.

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