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A Case Report of Thromboembolic Stroke in a Patient with Holt-Oram Syndrome

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Abstract

Ischemic stroke associated with rare clinical syndromes represents less than 5% of etiologic factors. From those syndromes are Holt-Oram syndrome and Left ventricular non-compaction syndrome. We report a case of a 66 years old male with genetically confirmed Holt-Oram syndrome due to TBX5 mutation who presented with cryptogenic stroke most likely due to cardioembolic etiology. The patient has a history of moderate nonischemic cardiomyopathy due to an atypical pattern of left ventricular non-compaction confirmed by Cardiac Magnetic Resonance Imaging. The patient was treated appropriately with thrombolytic therapy and catheter-directed mechanical thrombectomy with minimal residual stroke symptoms. Holt-Oram syndrome is a genetic condition with variable clinical phenotypes, including cardiac manifestations. Left ventricular non-compaction syndrome is rare congenital cardiomyopathy defined as prominent left ventricular trabeculae, deep intertrabecular recesses, and a thin compacted layer. And only a few cases were reported with both conditions. Therefore, patients with the Holt-Oram Syndrome should get a comprehensive cardiac evaluation to exclude non-compaction cardiomyopathy, which may have significant prognostic implications.

Keywords: Holt-Oram syndrome, Left ventricular non-compaction syndrome, Stroke, Cardiomyopathy, Case report

1. Introduction

Holt-Oram syndrome (HOS) is characterized by congenital cardiac and forelimb musculoskeletal anomalies. It is caused by a mutation in the TBX5 gene located on chromosome 12q24.1. In addition, HOS can be associated with left ventricular non-compaction (LVNC), characterized by prominent left ventricular trabeculae, deep intertrabecular recesses, and a thin compacted layer. And only a few cases were reported with both conditions. Therefore, patients with the Holt-Oram syndrome should get a comprehensive cardiac evaluation to exclude non-compaction cardiomyopathy, which may have significant prognostic implications.

Learning objective

Ischemic stroke associated with rare clinical syndromes represents less than 5% of etiologic factors. From those syndromes are Holt-Oram syndrome and left ventricular non-compaction syndrome. Holt-Oram syndrome is an autosomal dominant congenital disorder characterized by upper extremity abnormalities, congenital heart defects, and conduction abnormalities. On the other hand, left ventricular non-compaction syndrome is rare congenital cardiomyopathy characterized by prominent left ventricular trabeculae, deep intertrabecular recesses, and a thin compacted layer. And, only a few cases were reported with both conditions. Therefore, patients with the Holt-Oram syndrome should get a comprehensive cardiac evaluation to exclude non-compaction cardiomyopathy, which may have significant prognostic implications.
ically confirmed HOS initially diagnosed at the age of 12 and showed TBX5 mutation. At the time of his diagnosis, he had presented with an ASD that reportedly closed spontaneously and pectus carinatum. However, he had no major limb deformity.

At age 59, he was noted to have left ventricular (LV) systolic dysfunction, and his left ventricular ejection fraction (LVEF) was 40–45%. Electrocardiogram findings were significant for a first-degree atrioventricular (AV) block and a QRS duration of 150 ms. Cardiac catheterization showed non-obstructive coronary artery disease confirming the nonischemic etiology. Cardiac Magnetic Resonance (CMR) showed anomalous muscle bands from the apex inserted into the interventricular septum. The muscle bands appeared to be in the shape of papilla, thick, compact muscle and lacked the typical muscular network appearance of non-compaction. Anticoagulation for primary stroke prophylaxis was not initially recommended. Serial echocardiograms showed a further reduction in LVEF (25–35% when he was 64 years old). However, He had been maintained on guideline-directed medical therapy (GDMT) for his cardiomyopathy. CMR at age 64 showed a reduced LVEF of 43%, a nonischemic pattern of delayed gadolinium enhancement, and the abnormal papillary muscle bands that were seen on the prior CMR. He had continued to have New York Heart Association class II symptoms for heart failure, and he underwent cardiac resynchronization therapy with an implantable cardioverter-defibrillator device (CRT-D) (the Supplemental Content can be found here: https://scholarlycommons.gbm.org/cgi/viewcontent.cgi?filename=0&article=1062&context=jchimp&type=additional&preview_mode=1).

During the index hospitalization for stroke, his laboratory workup showed a white blood cell count of 13.7 (4.5–1000 × 10^3/μL), hemoglobin of 12.9 (13–17 g/dL), with the rest of the routine lab work being within normal limits. Computerized tomography (CT) scan of the head revealed no intracranial process. CT angiography of the head and neck demonstrated an absence of opacification in the distal aspect of the M1 segment of the right middle cerebral artery, consistent with an intraluminal thrombus. There was an enhancement of the middle cerebral artery distally likely through the collateral flow. National Institute of Health stroke score was reportedly 12, and alteplase was administered. Transthoracic echocardiogram showed an LVEF of 40–45%, and the thick muscular bands in the left ventricle were re-visualized (Fig. 1) (Supplementary material 1). There was no intratrial septal defect and no carotid arterial occlusion identified on the imaging.

He underwent a successful emergent catheter-directed mechanical thrombectomy. Subsequent follow-up revealed evolving lacunar infarcts in the right basal ganglia and caudate nucleus without significant mass effect. CT scan of the head and Magnetic resonance imaging scan of the brain demonstrated foci of acute ischemia in the right caudate nucleus, right basal ganglia, and right cortical occipital lobe (Fig. 2 and Fig. 3). His CRT-D device was interrogated that did not show any atrial or ventricular arrhythmias; specifically, there was no evidence of atrial fibrillation (AF) or flutter.

His left-sided weakness and slurred speech improved, and he was discharged home on oral anticoagulation with apixaban 5 mg for secondary stroke prophylaxis.

3. Discussion

HOS is known as heart-hand syndrome type 1, is an autosomal dominant congenital disorder characterized by upper extremity abnormalities, congenital heart defects (CHD), and conduction abnormalities. Upper extremity malformation can present as aplasia/hypoplasia of the radius and/or thumb (radial defect is the most common presentation of the upper limb abnormalities 1:30000),5 carpal bones malformation, triphalangeal or absent thumb, polydactyly.6 Congenital heart defect can present most commonly as an ASD in 75% of the cases.1 Conduction abnormalities, including sinus bradycardia, AV block, AF, can also occur.6

Diagnosis is mainly clinical; diagnostic criteria include personal, family history of CHD, and conduction defect with preaxial radial abnormalities in at least one upper limb identified by an x-ray examination.3 In addition, molecular genetic tests can confirm the diagnosis, although the absence of mutation does not rule out HOS or change management.7

Management is a multidisciplinary approach, including genetics, orthopedics, cardiology, and possibly cardiac surgery.5 Genetic counseling should be offered to the family members of the patient with a confirmed mutation.8 Cardiac management is goal-directed therapy and depends on the severity and types of CHD and conduction abnormalities.

LVNC is characterized by prominent left ventricular trabeculae, thin compacted layer, and deep intertrabecular recesses and is best visualized by CMR.3,5,10 The prevalence of LVNC is reported as...
0.05% in adults. It can be associated with cardiomyopathies or congenital heart disease, and neuromuscular disorders.

Diagnosis can be made mainly by echocardiography and CMR. Stollberger et al. proposed the following diagnostic criteria for LVNC. Three or more trabeculations were protruding from the left ventricular wall, apically to the papillary muscles, visible in 1 echocardiographic image plane; intertrabecular spaces perfused from the ventricular cavity, as visualized on color Doppler imaging; and a double-layered structure of the myocardium, consisting of a trabeculated and a nontrabeculated layer, best visualized at end-systole. MRI has the advantage of better delineation between the compacted and non-compacted myocardial layers, visualization of the apex, false tendons, prominent papillary muscles, and apparent bands.

LVNC can have multiple complications, including arrhythmia, conduction disturbances, heart failure, and thromboembolism. There is no specific
treatment for LVNC syndrome. Instead, management is directed to associate conditions like heart failure therapy, antiarrhythmic therapy, antithrombotic therapy, and implantable cardiac devices. Cardiac transplantation can be considered in patients with heart failure refractory to medical management.9,10

Our patient had a confirmed diagnosis of HOS. He did have moderate nonischemic cardiomyopathy. However, the CMR findings did not show the typical hyper-trabeculation, crypts, and recesses of LVNC, indicating a significantly increased risk of thromboembolic phenomena and was consequently not on oral anticoagulation before the event. Moreover, he was not found to have any atrial arrhythmia on device interrogation hence ruling out atrial emboli as a cause of potential stroke. There was no interatrial septal defect and no carotid arterial occlusion identified on the imaging. Thus, the stroke was likely to be cardioembolic, with emboli possibly arising from the left ventricle related to his ventricular structural abnormality.

To our knowledge, there are only a few case reports of stroke and HOS; one of the cases was reported in a four-month-old male child with tricuspid atresia, pulmonary stenosis, a 3 mm Ostium Secundum ASD, and a fenestrated atrial septal aneurysm. He presented with ten days of abnormal movement on the right hand with loss of consciousness and was found to have had an ischemic stroke in the left parietal lobe. In contrast, our patient’s ASD had spontaneously closed, confirmed with an echocardiographic evaluation with agitated saline. One reported case described a 49 years old female with a significant family history of triphalangeal thumb, sinus node dysfunction, intermittent sinus pauses, and documented LVNC.13 She presented with chest tightness, not a stroke, and she does not have a pacemaker. Our patient was different as he had the ICD implementation, and he presented with a stroke.

4. Conclusion

HOS is a rare monogenic disorder characterized by musculoskeletal abnormalities and cardiac anomalies, including cardiac septal defects and conduction abnormalities, and it can be associated with LVNC. Early diagnosis is necessary to prevent complications in the patient and identify other family members at risk. Specialized multidisciplinary teams are required to facilitate appropriate diagnosis and management for these patients and their families.

Authors’ contributions

BA wrote the draft and final versions of the manuscript and edited it based on feedback. MK and NB assisted in the modification of the drafts and the final version of the manuscript. MH supervised the case and the write-up, making significant changes to the document, including the literature review. All authors read and approved the final manuscript.

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Ethics approval and patient’s consent

Informed consent was obtained from the patient, and approval was obtained from McLaren Health Care privacy officer.

Conflict of interest

None declared.

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