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Defining Features of The Upper Extremity in Holt-Oram Syndrome

Lindley B. Wall, MD[1], **Samantha L. Piper, MD**[3], **Rolf Habenicht, MD**[2], **Scott N. Oishi, MD**[3], **Mary Beth Ezaki, MD**[3], and **Charles A. Goldfarb, MD**[1]

[1]Shriner's Hospital for Children and St. Louis Children's Hospital at Washington University School of Medicine, Department of Orthopaedic Surgery St. Louis, Missouri

[2]Catholic Children's Hospital Wilhelmstift, Hamburg, Germany

[3]Texas Scottish Rite Hospital for Children, Dallas, Texas

Abstract

Purpose—To investigate the distinguishing morphologic characteristics of children with radial longitudinal deficiency (RLD) in Holt-Oram Syndrome (HOS).

Methods—One hundred fourteen involved extremities in 62 patients with a diagnosis of HOS were identified at 3 institutions. Medical records and radiographs were evaluated. RLD and thumb hypoplasia were classified according to the modified Bayne and Klug classification and Blauth classifications respectively, when possible. Other unusual or distinguishing characteristics were catalogued.

Results—There was bilateral involvement in 84% of patients. The forearm was involved in 81% of the extremities and a shortened distal radius (Bayne and Klug type I RLD) was the most commonly identified forearm anomaly (40%). Radioulnar synostosis was present in 15% of the extremities, all in the proximal forearms with reduced radial heads. Thumb aplasia (Blauth type V hypoplastic thumb) was the most common type of classifiable thumb abnormality and occurred in 35% of involved thumbs. 27% of abnormal thumbs affected were not classifiable according to the Blauth classification, and 19% of involved thumbs (hypoplastic or absent) had first web syndactyly.

Conclusions—The upper extremity in Holt-Oram Syndrome differs from the typical presentation of radial longitudinal deficiency. The forearm is more often involved and may demonstrate radioulnar synostosis. The thumb is frequently unclassifiable by the Blauth classification and has first web syndactyly. The presence of radioulnar synostosis and syndactyly of the radial 2 digits in RLD should prompt the hand surgeon to obtain a cardiac evaluation and consider genetic testing for HOS.

Corresponding Author: Lindley B. Wall, MD, Washington University, Department of Orthopaedic Surgery, 660 S. Euclid Ave, St. Louis, MO 63110, wallli@wudosis.wustl.edu, phone: 314-362-9369, fax: 314-747-2599.

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Keywords

Holt-Oram Syndrome; Thumb; Syndactyly; Synostosis

INTRODUCTION

Holt-Oram Syndrome (Online Mendalian Inheritance of Man #142900) is one of the heart-limb conditions and is characterized by a congenital heart defect and radial longitudinal deficiency. The incidence of Holt-Oram Syndrome (HOS) is estimated to be about 0.7 in 100,000 live births.[1] The cardiac and limb anomalies vary in presentation.

HOS is autosomal dominant and is associated with over 70 mutations in the gene for the transcription factor TBX5, located on the chromosome 12q24.1. Mutations in the gene, described as missense, deletion, or truncation, affect the protein's ability to dimerize with other proteins that are necessary for cardiac and limb development.[2–4]

While hand and forearm involvement in HOS have been previously described,[1,5] the specific characteristics have not been compared to other forms of RLD. Barisic et al.[1] reported on from a European database in 2014, and Newbury-Ecob et al.[5] reported from the United Kingdom in 1996, but neither specifically classified the thumb and forearm characteristics in HOS. HOS patients have findings that are not typically seen in RLD, such as syndactyly of the thumb and index finger and forearm synostosis. The characteristics of the upper limb in HOS patients challenge the accepted classification schemes for RLD involvement of the forearm[6–8] and thumb[9].

This investigation sought to characterize the upper limb involvement in individuals with HOS.

METHODS

Institutional review board approval for this investigation was obtained at 3 institutions: St. Louis Shriners Hospital for Children, Texas Scottish Rite Hospital, and Catholic Children's Hospital Wilhelmstift; all are specialized pediatric referral centers. We reviewed the medical records and radiographs from the hand clinics of each institution to characterize all patients with upper extremity anomalies in addition to cardiac defects. The diagnosis of HOS was based on the presence of RLD with cardiac anomaly and no other syndromes. If cardiac involvement was not present,[10] then the diagnosis was confirmed with a positive family history of HOS or genetic testing (gene sequencing). We confirmed the diagnosis of HOS from the medical record or, if this was not possible, we consulted cardiology notes or spoke directly with the family to confirm family history.

Unilateral or bilateral involvement was documented. We evaluated the thumb deficiency and, when possible, classified hypoplasia by the Blauth system[9]. Additionally, we assessed for the presence of a triphalangeal thumb and syndactyly of the radial 2 digits. We classified

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the forearm involvement by the modified Bayne and Klug system[6,7] and noted the presence and type of forearm synostosis.

RESULTS

We identified 62 patients with HOS with 114 involved extremities. An atrial septal defect was the most commonly noted cardiac anomaly, present in 33 patients, and a ventricular septal defect was noted in 30 patients; other anomalies were less common. Some patients had more than one cardiac anomaly. In the 6 patients with no detected cardiac abnormality, there was a positive family history in 3 patients and positive genetic testing in the others.

There was bilateral involvement of the upper limbs in 52 individuals (84% of the cohort). There was proximal arm involvement in 26 extremities (23%) including a hypoplastic scapula or proximal humerus. The forearm was classified with the modified Bayne and Klug classification[7] (Table 1). Two forearms could not be classified. The most common type of forearm involvement was type I. There was a forearm synostosis in 17 of 114 extremities involved (15%). The extent of synostosis ranged from 25–100% of the length of the forearm. Two forearms had 25% length, 6 had 30%, 1 had 75%, and 5 had 100% length of the forearm synostosed. One patient was seen to have a radial head dislocation not associated with synostosis.

There was a thumb anomaly associated with 108 of 114 affected extremities (95%). Type V, absent thumb, was the most common classifiable thumb, seen in 36 extremities. (Table 2). Twenty-nine thumbs (27%) could not be classified by the Blauth classification. Thumbs, or the most radial digit, that were syndactylized to the adjacent digit were not considered classifiable because assessment of intrinsic and extrinsic muscle function and joint stability was not possible. Twenty-one radial digits (19% of 108 affected thumbs) were syndactylized to the adjacent finger. Fourteen of these consisted of a triphalangeal most radial digit, 4 were biphalangeal radial digits, and 3 hands had syndactyly of the second web space, specifically thumb aplasia with the index finger (most radial digit) syndactylized to the long finger. Three thumbs were in the plane of the hand,[12] 2 patients had triphalangeal thumbs, and 3 had radial polydactyly.

DISCUSSION

HOS is one of the more common syndromes seen in patients with RLD.[12,13] The clinical upper extremity characteristics of RLD in HOS, however, are dissimilar to those of non-HOS deformities or associations. While the prevalence of a Blauth type IV or type V hypoplastic thumb was quite high in this population, seen in 47% of the affected thumbs in this cohort, which is similar to the general RLD population,[12,15] most other findings were inconsistent with other presentations of RLD. First, 84% of the patients in this cohort were affected bilaterally in contrast to previous reports of bilateral RLD involvement, which ranged between 61–72%.[6,12,14] In addition, with regards to the forearm, type I involvement of the forearm (shortened radius) in HOS was the most common type, affecting 42% of extremities, while type I presentation in RLD in general was seen in 15%.[7] In previous reports on RLD, radial aplasia (type IV) was most common, in 27% of the population, and

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type 0 (only thumb affected) and type N (thumb and carpus affected) together comprised approximately 50% of the population.[7] This is in contrast to the HOS cohort, which revealed type IV to be second most common at 19%, while types 0 and N compromised 16% of the population.

Radioulnar synostosis occurred in 15% of the involved forearms. The synostosis in HOS is a Clary and Omer type 2,[16] characterized by a synostosis with a reduced radial head. Clary and Omer[16] noted that type 2 congenital radioulnar synostosis was the least frequent, present in 3 of 36 elbows. In addition, the synostosis in HOS extends further distally in the forearm, ranging from 25–100% of its length, as compared to the more common presentation of a limited bony link between the proximal radius and ulna (Figure 1). This extended synostosis does not fit well into the Clary and Omer classification and seems to be characteristic of this population because 6 forearms in our study had a synostosis which extended >75% the length of the forearm.

The thumb may also be different from the typical hypoplastic thumb in RLD. We found that 27% (n = 29) of the thumbs affected in this cohort could not be classified according to Blauth's hypoplastic thumb classification. Specifically, 19% of the affected thumbs in this study had syndactyly of the radial 2 digits, a finding rarely seen in RLD (Figure 2). Additionally, thumbs were triphalangeal in 17% of the thumbs affected, a cohort including ones found to be in the plane of the hand. These findings are unusual in the RLD thumb and should prompt suspicion of a diagnosis of HOS.

When considering the thumb and forearm together, the thumb was more severely affected and the forearm less affected in this HOS cohort compared with the typical presentation of RLD. James et al. previously demonstrated in a general RLD population that the severity of the thumb involvement was directly proportional to the severity of the forearm involvement.[17]

Barisic et al. reported involvement of all thumbs in 73 HOS patients[1], and Newbury-Ecob et al.[5] reported 84% of 55 patients with HOS had thumb involvement. We found an intermediate incidence of 95%. The difference between our results and those of Newbury-Ecob et al. may reflect the fact that our cohort was from hand surgery clinics, whereas their patients came from cardiology and genetics clinics and an upper limb support group. We also found a higher incidence of thumb-index syndactyly compared with the previous reports, 19% vs 5%–11%[1,4]. Newbury-Ecob et al. reported 64% of patients had forearm involvement, but details were not provided, and radioulnar synostosis was not mentioned (although limited forearm supination was noted). While Barisic et al. did identify forearm synostosis in 20%, similar to our prevalence of 15%, they did not characterize the radiographic presentation.

There are several limitations to this type of retrospective evaluation. First, we only included patients seen in our clinics. This may have contributed to the difference in prevalence of characteristics compared to the cardiac clinic population. Nonetheless, our sizeable cohort, drawn from 3 institutions, is likely representative of the distribution of the atypical anomalies for RLD. A second limitation is that we depended on recorded differences in the

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medical record; some differences, such as limited forearm motion, may not have been clearly documented and thus were not included in this study. Additionally, the Blauth classification[18] of thumb hypoplasia was not used because of limited data on thumb stability to distinguish type IIIA from type IIIB was available in the medical records. Lastly, this study contains the inherent limitations associated with retrospective studies for rare conditions, including limited statistical analysis and limited capacity to generalize from the patients available. There is also the potential that some patients with HOS were missed secondary to a lack of documentation in the medical records. Given limited resources we did not contact every RLD patient but identified those with documented RLD and cardiac anomaly, family history, or diagnosis of HOS. And finally, there was a potential recall bias related to confirming the family history from family members.

The hand surgeon is in a privileged position to diagnose HOS in patients with RLD. Unusual findings including an unclassifiable thumb, such as a syndactylized thumb and index web, and atypical forearm synostosis in RLD should prompt a cardiac evaluation with consideration of HOS. While an atrial septal defect is the most common cardiac anomaly, conduction anomalies can also be present[1,4] and need full evaluation prior to any general anesthetic for surgical intervention for an upper extremity abnormality. Additionally, genetic testing may be considered to allow for counseling given the autosomal dominant nature of HOS.

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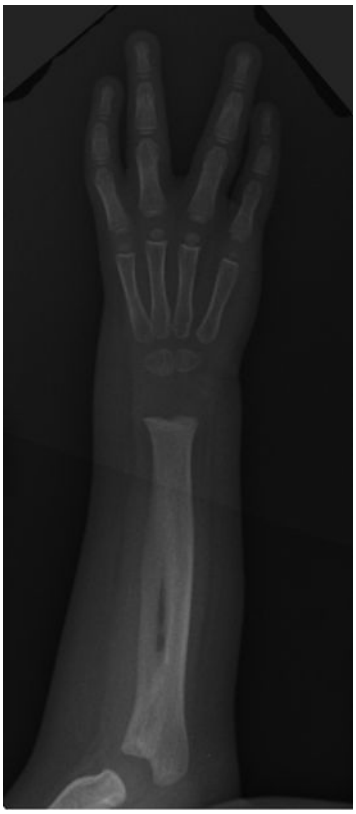

Figure 1.
Anteroposterior radiograph of a forearm in a patient with Holt-Oram syndrome. The image depicts the congenital radioulnar bony synostosis with reduced radial head and involvement extending nearly the entire length of the forearm.

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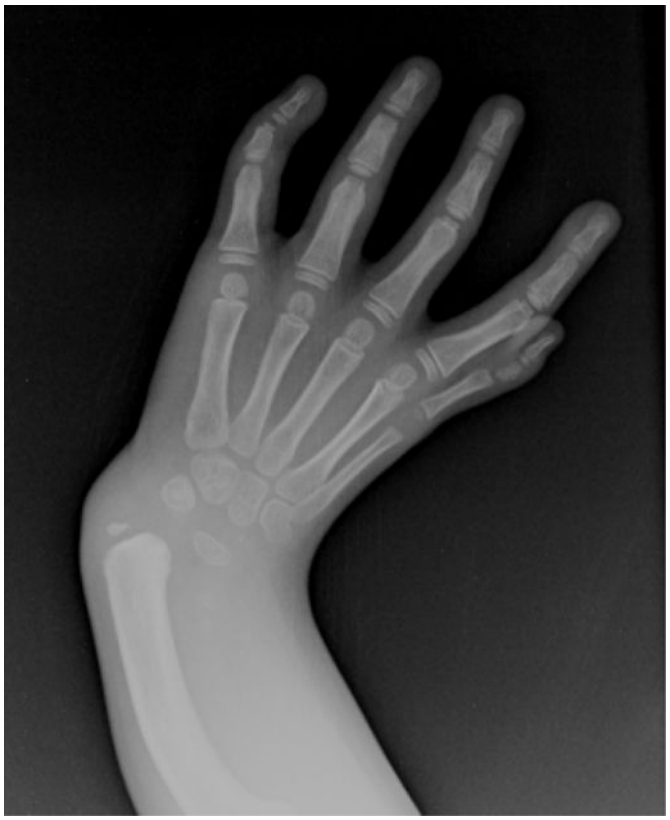

Figure 2.
Posteroanterior radiograph of a hand in a patient with Holt-Oram syndrome. The thumb is quite thin, triphalangeal, and webbed to the index finger, a unique finding in HOS.

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Table 1

Forearm classification according to modified Bayne and Klug classification.

Classification Type	Brief Description	Number	Prevalence
N or 0	N = normal; 0 = Carpus hypoplastic, absence, coalition	18	16%
I	Radius >2mm shorter than ulna	47	42%
II	Hypoplastic Radius	15	13%
III	Hypoplastic radius with absent distal physis	11	10%
IV	Absent Radius	21	19%

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Table 2

Thumb classification according to the Blauth classification.

Classification Type	Brief Description	Number	Prevalence
I	Small thumb with hypoplastic intrinsic muscles	4	5%
II	Small thumb with narrowed first web, hypoplastic intrinsic muscles, and laxity of the MP joint ulnar collateral ligament	10	15%
III	Small thumb with narrowed first web, hypoplastic intrinsic and extrinsic muscles, MP joint instability	14	18%
IV	Floating thumb, pouce flottant	13	16%
V	Absent thumb	38	48%