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Association of Radial Longitudinal Deficiency and Thumb Hypoplasia

An Update Using the CoULD Registry

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Background: Deficiency of the radial aspect of the forearm and hand is the most common congenital longitudinal deficiency of the upper limb. Radial longitudinal deficiency is associated with several named syndromes. The purpose of the present study was to explore patterns of radial longitudinal deficiency and thumb hypoplasia in syndromes and to examine the severity of these differences across various syndromes.

Methods: Data were collected from the Congenital Upper Limb Differences (CoULD) registry. Congenital differences are classified in the registry with use of the Oberg-Manske-Tonkin (OMT) classification system. Diagnosis of a syndrome by a physician as noted in the CoULD registry was recorded. Thumb deficiency and radial deficiency were classified according to the modified versions of the Blauth criteria and the Bayne and Klug criteria, respectively.

Results: We identified 259 patients with 383 affected limbs with radial deficiency. Eighty-three of these patients had a diagnosed syndrome. The severity of radial deficiency was correlated with the severity of thumb deficiency. The Kendall tau coefficient indicated significant correlation between radial severity and thumb severity (tau = 0.49 [95% confidence interval = 0.40 to 0.57]; $p < 0.05$). Subjects with a syndrome were twice as likely to have bilateral deficiency and 2.5 times more likely to have both radial and thumb deficiency compared with subjects without a syndrome. Subjects with VACTERL syndrome (vertebral defects, anal atresia, cardiac anomalies, tracheoesophageal fistula, renal anomalies, and limb defects) had patterns of thumb and radial deficiency similar to the general cohort, whereas subjects with Holt-Oram syndrome, TAR (thrombocytopenia absent radius) syndrome, and Fanconi anemia demonstrated varied presentations of thumb and radial deficiency.

Conclusions: The present study investigated the characteristics of patients with radial longitudinal deficiency and thumb hypoplasia. Our results support the findings of previous research correlating the severity of radial deficiency with the severity of thumb deficiency. Furthermore, we identified characteristic features of patients with radial longitudinal deficiency and associated syndromes.

Radial longitudinal deficiency is the most common congenital longitudinal deficiency of the upper limb, occurring in as many as 1 in 5,000 live births[1]. Radial longitudinal deficiency and thumb hypoplasia are complex congenital anomalies with a spectrum of clinical presentations affecting the radial side of the extremity[2]. The Oberg-Manske-Tonkin (OMT) system, which is based on embryological development, classifies radial longitudinal deficiency and thumb hypoplasia as malformations involving a failure of formation and differentiation along the anteroposterior axis[3]. In 2015, the OMT system was adopted by the International Federation of Societies for Surgery of the Hand (IFSSH) to replace the older Swanson system, which was morphologically rather than embryologically based[4]. Under the Swanson system, radial deficiency had been considered a failure of formation. Genetic factors play a known role in Holt-Oram syndrome[5-8], thrombocytopenia absent radius (TAR) syndrome[9-11], and Fanconi anemia[12-14]. The association of vertebral anomalies, anal atresia, cardiac anomalies, tracheoesophageal fistula, renal anomalies, and limb defects (VACTERL) is a spectrum of congenital

*A list of the CoULD Study Group members is given in a note at the end of the article.

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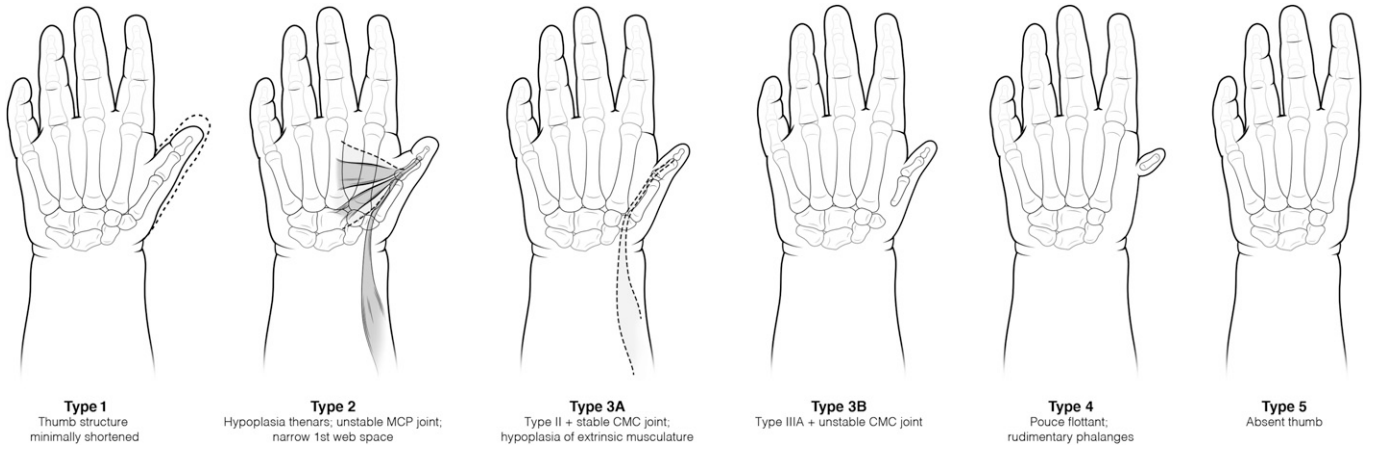

Fig. 1

Illustrations depicting the modified Blauth system for the classification of thumb deficiency used by the CoULD registry. MCP = metacarpophalangeal, and CMC = carpometacarpal. (Reproduced with permission from the Children's Orthopaedic Surgery Foundation.)

malformations linked to radial defects without any clearly responsible gene (or genes) having been identified[15-17].

James et al., in 2004, retrospectively explored the relationship between anomalies affecting the radial side of the limb[18]. Those authors observed that the severity of thumb deficiency was proportional to the severity of radial deficiency and could be used to predict treatment and prognosis. Goldfarb et al. showed that conditions including cardiac anomalies, TAR syndrome, Fanconi anemia, Holt-Oram syndrome, and VACTERL were present in two-thirds of patients with radial longitudinal deficiency and that these conditions were more prevalent in patients with severe cases of radial longitudinal deficiency[19]. A recent study of patients with Holt-Oram syndrome showed a high prevalence of the most severe types of radial longitudinal deficiency[20]. Likewise, in a cohort of 25 patients with VACTERL, Carli et al. found that one-third had absent radii and all had thumb hypoplasia; 79% of thumbs were severely hypoplastic[21].

The current understanding of genetics and clinical presentations of radial deficiency have been based on single-institution studies in which information was collected over decades of evolving knowledge and practice. The Congenital Upper Limb Differences (CoULD) registry currently contains data on 2,825 subjects from 8 institutions and offers a wider, up-to-date perspective on radial longitudinal deficiency, thumb deficiency, and associated syndromes than previous studies have offered[22]. The purpose of the present study was to reexamine the relationship of radial longitudinal deficiency and thumb hypoplasia in a large, multicenter cohort of children. Specifically, we aimed to perform an in-depth evaluation of whether the relationship between thumb and radial deficiency described by James et al. in 2004[18] holds true in the context of various genetic syndromes. We hypothesized that subjects with syndromes would have characteristic combinations of thumb and radial deficiency that differed from the

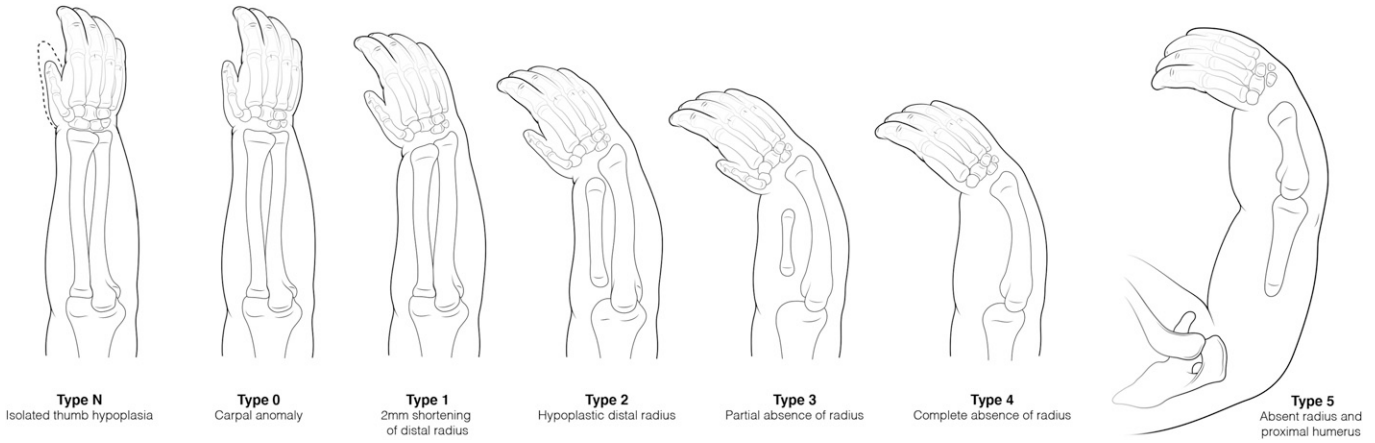

Fig. 2

Illustrations depicting the modified Bayne and Klug system for the classification of radial longitudinal deficiency used by the CoULD registry. For illustrative purposes, type-N through 3 radial longitudinal deficiencies are shown with a type-2 thumb hypoplasia, and type-4 and 5 radial longitudinal deficiencies are shown with a type-5 thumb. (Reproduced with permission from the Children's Orthopaedic Surgery Foundation.)

TABLE I Demographic Characteristics (N = 259)

Age at enrollment* *(yr)*	2 (1-6)
Female sex *(no. of patients)*	113 (44%)
Hispanic *(no. of patients)*	28 (11%)
Race *(no. of patients)*	
White or Caucasian	194 (75%)
Black or African American	19 (7%)
Asian	30 (12%)
American Indian or Alaska Native	2 (1%)
Native Hawaiian or Other Pacific Islander	2 (1%)
Refused/unknown/other	26 (10%)
Hand dominance *(no. of patients)*	
Right	69 (27%)
Left	31 (12%)
Ambidextrous	4 (2%)
Not determined yet	155 (60%)
Side enrolled in CoULD *(no. of patients)*	
Right	67 (26%)
Left	65 (25%)
Both	127 (49%)
Family history of upper-extremity condition† *(no. of patients)*	38 (16%)
History of radial-sided deficiency	20 (9%)
History of syndrome	10 (4%)
History of other upper-extremity condition	8 (3%)
Detected in fetal ultrasound† *(no. of patients)*	54 (23%)

*The values are given as the median and the interquartile range. †Only recorded for 232 patients (90%) who consented to follow-up and to supplying additional demographic information.

pattern found in the general population of patients with nonsyndromic radial longitudinal deficiency.

Materials and Methods

Data Source

Data were collected from the CoULD registry, an ongoing prospective database initiated in 2014 that includes data on subjects from multiple pediatric tertiary-care centers across the United States[22]. Children from birth through 17 years of age with a congenital upper-extremity difference who have not previously had surgery on the affected limb are eligible for enrollment. Congenital differences are classified by the treating surgeon with use of the OMT system[3]. The OMT system involves the use of a modified version of the Blauth classification[23,24] for thumb hypoplasia and a modified Bayne and Klug classification[2,25] for radial longitudinal deficiency (Figs. 1 and 2). In addition, the CoULD registry includes thumbs that are unclassifiable with the Blauth system as "Type 6 (unclassifiable);" this classification includes 5-fingered hands and those with digits of indiscernible morphology. Data for the present study were collected with use of the Research Electronic Data Capture (REDCap) tool[26]. Parents provided consent for their children to participate in CoULD; children aged 7 years and older were also asked for their consent to participate. The institutional review board at each participating center approved the CoULD registry for retrospective review for the present study.

Study Population

All patients with documented thumb hypoplasia and/or radial deficiency who were entered into the CoULD registry from 2014 to 2019 were selected for analysis. Two hundred and fifty-nine patients (383 affected limbs) were available for review. The demographic characteristics of this population are shown in Table I. The CoULD registry records OMT classification data for all patients with upper-limb differences at participating institutions. However, some patients do not consent to prospective data collection or do not speak English; for such patients, we can report only basic demographic information and OMT classification data. Twenty-seven (10%) of the 259 patients in the present study fell into that category; these 27 patients are included in the table on demographic data (Table I) as well as in our analysis of radial longitudinal deficiency and thumb hypoplasia (Table II).

Outcome Measures

We examined the OMT classifications of the thumb and the radius as primary outcome measures (Table II). Classification of radial longitudinal deficiency differentiates between type N (limited to thumb hypoplasia) and type 0 (carpal anomaly), but this difference is difficult to ascertain at a young age because normal radiographic ossification of the scaphoid does not begin until approximately 8 years of age[27,28]. Because of the young age of most of our patients, types N and 0 were combined for the purpose of statistical analysis. Furthermore, our modified Bayne and Klug criteria included an additional category (type 5) to classify the most severe type of radial longitudinal deficiency in which the proximal part of the humerus is absent.

Diagnosis of a syndrome was used as our secondary outcome measure. VACTERL is considered a "syndrome" for

TABLE II Occurrence of Radial and Thumb Types*

	Radial Type						
Thumb Type	N/0	1	2	3	4	5	Total
1	14	2	1	0	0	1	18
2	90	11	1	1	2	0	105
3A	46	13	3	0	0	0	62
3B	24	12	4	1	9	0	50
4	15	13	2	5	11	2	48
5	18	6	5	7	42	7	85
6 (unclassifiable)	2	7	2	1	2	1	15
Total	209	64	18	15	66	11	383

*The values are given as the number of limbs.

TABLE III Syndrome Summary

Syndrome	No. of Patients (N = 259)
Fanconi anemia	4 (2%)
Holt-Oram syndrome	17 (7%)
TAR syndrome	5 (2%)
VACTERL syndrome	36 (14%)
Other syndromes	21 (8%)
Total	83 (32%)

the purposes of the registry. For the present study, subjects who exhibited ≥2 characteristics of VACTERL in addition to the radial and/or thumb deficiency were included in the VACTERL cohort[21,29]. The presence of a medical syndrome was documented by the treating surgeon on the basis of available patient records; no additional genetic testing or documentation was collected in the CoULD registry or as part of the present study. However, it is routine practice to perform renal ultrasound, echocardiography, and a complete blood-cell count for all children with radial or thumb deficiency and to refer them for genetic testing or consultation if these tests are abnormal or if other concerning phenotypic differences are present. While some patients presented with diagnosed syndromes at the time of enrollment, many patients were noted to have syndromes at the time of follow-up visits that were later added to the registry. For the present study, we reviewed the charts of patients who had pending diagnoses or who presented to the initial visit with other congenital anomalies that were suspicious for syndromes and updated the data accordingly.

Statistical Analysis

To evaluate the association between radial longitudinal deficiency and thumb hypoplasia, the Kendall tau rank correlation coefficient and the Somers delta coefficient were estimated along with 95% confidence intervals (CIs). The Somers delta coefficient provides a more specific quantification for the relationship between variables, namely, an estimate of the proportional reduction in error for a relationship between an independent variable and a dependent variable. For the present study, the Somers delta coefficient gives the proportional reduction in error of the expected severity of thumb hypoplasia when information on the severity of the radial longitudinal deficiency was available as compared with

TABLE IV Genetic Loci of Syndromes*

Syndrome	Cytogenic Location	Inheritance	OMIM Number†
TAR syndrome	1q21.1	AR	274000
Nager syndrome	1q21.2	AD	154400
Popliteal pterygium syndrome	1q32.2	AD	119500
Lacrimo-auriculo-dento-digital syndrome	4p16.3/5p12/10q26.13	AD/AD/AD	149730
Williams-Beuren syndrome	7q11.23	AD	194050
CHARGE syndrome	7q21.11/8q12.2	AD/AD	214800
Rothmund-Thomson syndrome	8q24.3	AR	268400
Trisomy 9 mosaic syndrome	9	NA	
Holt-Oram syndrome	12q24.21	AD	142900
Oculoauriculovertebral syndrome (Goldenhar syndrome)	14q32	AD	164210
Fanconi anemia A/B/C/D1/D2	16q24.3/Xp22.2/ 9q22.32/13q13.1/3p25.3	AR/XLR/AR/AR/AR	227650/300514/ 227645/605724/227646
Pierre Robin syndrome	17q24.3-q25.1	AR	261800
Mosaic trisomy 18 (Edwards syndrome)	18	NA	
Partial trisomy 18/monosomy 21	18, 21	NA	
Diamond Blackfan anemia	19q13.2	AD	105650
Goltz syndrome	Xp11.23	XLR	305600
Melnick-Needles syndrome	Xq28	XLD	209350
Gershoni Baruch syndrome	Unknown	AR†	609545
Hunter-McAlpine syndrome	Unknown	AD†	601379
VACTERL syndrome	Unknown	NA	192350
Fetal valproate syndrome	NA	NA	609442

*AD = autosomal dominant, AR = autosomal recessive, XLD = X-linked dominant, XLR = X-linked recessive, and NA = not applicable. †OMIM = Online Mendelian Inheritance in Man. ‡Suspected.

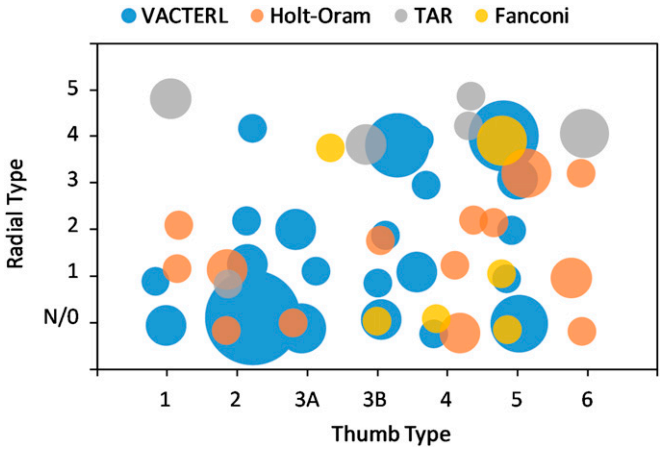

Fig. 3

Bubble plot depicting the combinations of radial and thumb deficiencies found in subjects with VACTERL, Holt-Oram, TAR, and Fanconi anemia syndromes. The frequency of each combination is denoted by the size of the bubble.

when such information was not available. The association between the presence of a syndrome and the occurrence of bilateral deficiency was assessed with use of logistic regression analysis. The odds ratio (OR) along with the 95% CI was estimated for the effect of the presence of a syndrome on the likelihood of bilateral deficiency. Subgroup analyses were conducted on subjects with Holt-Oram and VACTERL syndromes.

Power analysis demonstrated that a minimum sample of 122 subjects would be required for a Kendall tau coefficient of as small as 0.4 to estimate 95% CIs with no wider than 0.2 unit about the tau coefficient. As the Kendall tau and Somers delta are algebraically related, we can expect comparable necessary sample sizes for both the Kendall tau and the Somers delta. Our sample of 383 limbs in 259 subjects provided sufficient power for primary and secondary analyses.

Results

Association Between Radial and Thumb Deficiency

Two hundred and nine (55%) of the 383 extremities had thumb deficiency with no radial deficiency. The severity of radial deficiency was correlated with the severity of thumb deficiency. Seventy-one (92%) of the 77 limbs with complete absence of the radius (types 4 and 5) had severely affected thumbs (Blauth types 3B, 4, and 5). One hundred and fifty (72%) of the 209 limbs with normal radii had mildly affected thumbs (types 1, 2, and 3A) (Table II). The Kendall tau coefficient indicated a correlation between radial severity and thumb severity of 0.49 (95% CI, 0.40 to 0.57; $p < 0.05$). Moreover, the Somers delta coefficient indicated that there was a 55% proportional reduction in error of the expected severity of thumb hypoplasia given the information on the radial longitudinal deficiency (delta = 0.55 [95% CI, 0.48 to 0.62]; $p < 0.05$).

Associated Syndromes

Nearly one-third of the cohort (32%; 83 of 259) had concomitant syndromes, with 21 unique syndromes identified (Table III). Subjects with syndromes were twice as likely to have bilateral deficiency compared with subjects without syndromes (OR = 2.10 [95% CI, 1.23 to 3.57]; $p < 0.05$). Furthermore, patients with syndromes had 2.5 times the odds of having radial and thumb deficiencies as opposed to thumb deficiency alone (OR = 2.48 [95% CI, 1.44 to 4.27]; $p < 0.05$). Genetic information from the Online Mendelian Inheritance in Man (OMIM)[30] database was obtained for each syndrome (Table IV). No patterns of genetic loci were identified.

VACTERL syndrome (n = 36), Holt-Oram syndrome (n = 17), TAR syndrome (n = 5), and Fanconi anemia (n = 4) were the most common syndromes. The patterns of severity found in patients with VACTERL syndrome, Holt-Oram syndrome, TAR syndrome, and Fanconi anemia are illustrated in Figure 3.

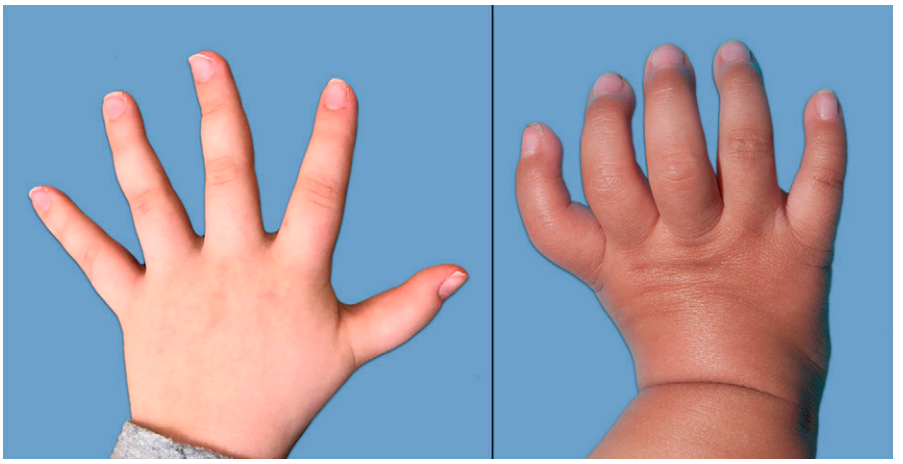

Fig. 4

Photographs of 5-fingered hands. The photograph on the left shows a classic type-2 thumb deficiency, and the photograph on the right shows a type-6 or "unclassifiable" 5-fingered hand.

VACTERL Syndrome

Fifty-two limbs were analyzed in the 36 patients with VACTERL syndrome. The Kendall tau coefficient indicated a correlation between radial severity and thumb severity of 0.38 (95% CI, 0.16 to 0.61; $p < 0.05$) (Fig. 3). The Somers delta coefficient indicated a 40% proportional reduction in error of the expected severity of thumb hypoplasia given the information on the radial longitudinal deficiency (delta = 0.40 [95% CI, 0.20 to 0.61]; $p < 0.05$). There was no significant difference in the likelihood of bilaterality ($p = 0.55$) or the likelihood of having both radial and thumb deficiency ($p = 0.15$) for patients with VACTERL syndrome compared with those without ($p = 0.55$).

Holt-Oram Syndrome

Twenty-nine limbs were analyzed in the 17 patients with Holt-Oram syndrome. The Kendall tau coefficient indicated a correlation between radial severity and thumb severity of 0.32 (95% CI, 0.03 to 0.62; $p < 0.05$) in the Holt-Oram cohort. The Somers delta coefficient indicated that there was a 31% proportional reduction in error of the expected severity of thumb hypoplasia given the information on the radial longitudinal deficiency (delta = 0.31 [95% CI, 0.05 to 0.57]; $p < 0.05$). There was no difference in the likelihood of bilaterality ($p = 0.08$) for patients with Holt-Oram syndrome versus those without. However, patients with Holt-Oram syndrome were 5 times more likely to have both radial and thumb deficiency than the general cohort (OR = 5.11 [95% CI, 1.43 to 18.25]; $p = 0.01$). Five thumbs (17%) in the Holt-Oram cohort were unclassifiable (type 6). Three of these were in patients with 5-fingered hands (Fig. 4). The degree of radial deficiency tended to be more severe in subjects with Holt-Oram syndrome than the overall cohort, but this finding did not reach significance. Ten (34%) of the 29 limbs in the Holt-Oram cohort had type-4 and 5 radii, compared with 20% in the general cohort ($p = 0.08$). Three (18%) of the 17 patients with Holt-Oram syndrome had bilateral radioulnar synostosis. Only 5% of the nonsyndromic population had radioulnar synostosis in any limb.

TAR Syndrome

Five patients with 10 affected limbs were diagnosed with TAR syndrome. Six of the 10 affected limbs were classified as having type-4 radii, 3 were classified as having type-5 radii, and 1 was classified as having a type-1 radius. Although all patients with TAR syndrome had thumbs, they presented with thumb deficiencies of varying severity. Three thumbs in this cohort (30%) were unclassifiable (Fig. 3).

Fanconi Anemia

Four patients with 8 affected limbs were diagnosed with Fanconi anemia; all were affected bilaterally. Five limbs (63%) had type-5 thumbs, and 4 limbs (50%) had type-4 radii (Fig. 3).

Discussion

To our knowledge, the present study of 259 patients with 383 affected limbs is the largest of its kind to investigate the presenting characteristics of patients with radial longitudinal deficiency and thumb hypoplasia. The size of the CoULD registry allowed us to contrast syndrome-specific characteristics of thumb and radial deficiency and to elucidate how these patterns differ from the classic pattern of radial longitudinal deficiency found in the nonsyndromic population. Our results support the findings of previous research correlating the severity of radial longitudinal deficiency with the severity of thumb deficiency[18]. Furthermore, we identified characteristic features of patients with radial longitudinal deficiency and associated syndromes. Subjects with a syndrome were twice as likely to have bilateral deficiency and 2.5 times more likely to have both radial and thumb deficiency compared with subjects without a syndrome. While patients with Holt-Oram, TAR, and Fanconi anemia syndromes presented with patterns of radial longitudinal deficiency that differed from the nonsyndromic cohort, patients with VACTERL presented very similarly to nonsyndromic patients with radial longitudinal deficiency and thumb hypoplasia. This finding, in combination with the inability to accurately identify a specific genetic locus in cases of VACTERL, supports the concept that VACTERL is an association rather than a true genetic syndrome[31].

Conversely, patients with Holt-Oram syndrome had a higher proportion of unclassifiable thumbs than the rest of the study population (17% versus 4%). Patients with Holt-Oram syndrome also were more likely to have both radial and thumb deficiency and radioulnar synostosis than the general cohort. Radioulnar synostosis is an established finding among patients with Holt-Oram syndrome[20]. Established features of TAR syndrome, including complete absence of the radius and the presence of thumbs[32], were confirmed in our cohort. Similar to the findings in a recent series of 34 patients with TAR syndrome[33], all patients with TAR syndrome in our series demonstrated some element of thumb hypoplasia. Patients with Fanconi anemia tended to have severely affected radii, with 50% of affected limbs having an absent radius. However, we caution against the assumption that all subjects with Fanconi anemia have "more severe" radial and thumb deficiency as 3 (38%) of the 8 limbs in our Fanconi population had only thumb involvement. We continue to recommend that all patients with radial-sided deficiencies undergo testing for Fanconi anemia because of the devastating consequences of this condition[34].

Our study also examined the "unclassifiable thumb." We found that many patients had 5-fingered hands or hands with fewer than 4 digits. The addition of the aforementioned hand anomalies in the modified Blauth classification system may help to better identify these atypical presentations of thumb deficiency. Furthermore, 10 of the 15 unclassifiable thumbs were found in patients with syndromes such as Holt-Oram or TAR syndrome, supporting the findings of previous studies on the prevalence of unclassifiable thumbs in these syndromes[19,20]. These findings may be useful for the detection of such syndromes by hand surgeons when atypical presentations of thumb hypoplasia appear in the clinical setting. Additional studies are needed to examine atypical presentations of thumb deficiency and their association with radial longitudinal deficiency across various syndromes.

Previous investigations of radial longitudinal deficiency have been retrospective studies spanning multiple decades, largely from single institutions. It is conceivable that earlier studies underestimated the presence of syndromes as genetic diagnosis was not available[16,17]. For instance, James et al. reported on a cohort of 55 patients with 12 unique associated syndromes[18], compared with the 25 unique syndromes that we identified among 83 patients. At our participating centers, it is routine practice to refer patients with concerning phenotypic findings to appropriate specialists for cardiac, renal, and/or hematological evaluation and for genetic testing or consultation. The present study, therefore, reflects a reasonably accurate estimate of syndromes within this population of children presenting with radial deficiency to tertiary pediatric hospitals. However, the CoULD registry is limited by exclusion of follow-up data for patients who do not consent to follow-up or do not speak English. For these patients, constituting approximately 10% of our series, diagnosis of a syndrome was only recorded if it was present at the time of the first appointment. Therefore, the presence of syndromes in the current study may be underestimated. One of the strengths of the present study is its multicenter design, which enables inclusion of a geographically diverse population. However, as all participating study sites were large specialty pediatric institutions, it is possible that we overestimated the prevalence of rare syndromes such as Fanconi anemia and Holt-Oram syndrome.

Although the present series represents modern practice regarding genetic evaluation of patients with radial longitudinal deficiency, we could not identify any clear commonality among the 25 unique syndromes in our population. In addition, over two-thirds of patients in the present study with radial deficiency and/or thumb hypoplasia had no documented syndrome. Future studies may include a detailed genomic investigation of patients without documented syndromes. Using the CoULD database to examine this large population of nonsyndromic patients with radial deficiency may prove useful for determining genetic and embryological causes of this condition. ■

NOTE: In addition to the authors listed in the byline, members of the CoULD Study Group include Donald S. Bae, MD, Children's Hospital Boston, Boston, Massachusetts; Charles A. Goldfarb, MD, Department of Orthopaedic Surgery, St. Louis Children's Hospital, Washington University School of Medicine, St. Louis, and Shriners Hospitals for Children–St. Louis, St. Louis, Missouri; and Patricia E. Miller, MS, Children's Hospital Boston, Boston, Massachusetts.

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