Severity of ulnar deficiency and its relationship with lower extremity deficiencies

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To assess the characteristics of ulnar deficiency (UD) and their relationship to lower extremity deficiencies, we retrospectively classified 82 limbs with UD in 62 patients, 55% of whom had femoral, fibular, or combined deficiencies. In general, UD severity classification at one level (elbow, ulna, fingers, thumb/first web space) statistically correlated with similar severity at another. Ours is the first study to show that presence of a lower limb deficiency is associated with less severe UD on the basis of elbow, ulnar, and thumb/first web parameters. This is consistent with the embryological timing of proximal upper extremities developing before the lower extremities. *J Pediatr Orthop B* **28:62–66 Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.**

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Introduction

Ulnar deficiency (UD) represents a spectrum of pathology ranging from missing hand rays to complete absence of the ulna. Radiohumeral synostosis and hypoplastic upper extremities may also be seen. It occurs in one in 50 000–100 000 live births and is 4–10 times less common than radial deficiency [1–4]. Ninety percent of patients have missing or hypoplastic digits [3]. Unlike radial deficiency, anomalies of other systems and syndromes rarely occur and most cases are sporadic [4]. However, other musculoskeletal anomalies such as fibular and femoral deficiencies and scoliosis are frequently seen with UD. Defects in the so-called femoral–fibular–ulnar developmental field are believed responsible for this frequent association [5]. The pathogenesis of UD is thought to be related to a relative deficiency of sonic hedgehog (Shh) signaling in the developing limb bud [4].

Most of the literature on UD has concentrated on many classifications and treatments for the upper extremity anomalies. These studies make reference to associated lower extremity findings, but do not discuss them further. A recent review [6] specifically excluded those patients who had lower extremity deficiencies from their review because they were felt to be part of a syndrome. From an embryological standpoint, understanding the association of upper and lower extremity deficiencies may provide for a more comprehensive understanding of the development of UD.

The purpose of this study was to review the characteristics of UD and to determine their relationship with the lower extremity deficiencies. We will define the severity of each of the anatomical components of the UD, shoulder, elbow, forearm, fingers, and thumb/first web spaces, by their most accepted classifications, as there is no accepted unifying classification. We will classify the lower extremity deficiencies by their general anatomic location.

Patients and methods

An Institutional Review Board approved retrospective review of available patient charts and radiographs was undertaken for 940 patients with upper extremity and 976 with lower extremity congenital anomalies on the basis of a diagnostic database search. We selected those patients who met criteria for UD, namely shortening of the ulna or ulnar ray deficiency or hypoplasia with a normal appearing ulna as described by Havenhill *et al.* [7]. Epidemiologic data including sex and associated diagnoses as well as the number of missing digits per affected limb were recorded. Using radiographs and chart reviews, patients were grouped according to the classification systems of Al Qattan *et al.* [6] (shoulder), Kummel [8] (elbow), Ogden *et al.* [9] (ulna), Ogino and Kato [10] (fingers), and Cole and Manske [11] (thumb/first web deformity) (Table 1). In the absence of available radiographs of other parts of the upper extremity or other description in the medical record, we assumed that the other parts of the extremity were normal. We also did separate analyses in terms of the different UD classification categories and the number of absent digits.

Lower extremity involvement was classified by fibular only, femoral only, or combined fibular/femoral deficiency. As most limbs with fibular deficiency have some femoral shortening, femoral deficiency was defined for those cases where the limb shortening in the femoral segment exceeded that in the tibial segment. Statistics were computed using analysis of variance and χ^2 analyses to compare anomalies within the upper

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Table 1 Classification of 82 limbs with ulnar deficiency (62 patients)

Shoulder [6]	
I: Normal	82
II: Dysplastic	0
Elbow [8]	
I: Normal	28
II: Radial head dislocation	20
III: Radiohumeral synostosis	34
Ulna [9]	
O: Normal	19
I: Hypoplasia	13
II: Partial aplasia	23
III: Total absence	27
Fingers [10]	
A: Hypoplasia of the small finger	8
B: Absent small finger	6
C: Absent ulnar two digits	40
D: Absence of three digits	16
E: Complete absence of digits	12
Thumb/first web space [11]	
A: Normal	15
B: Hypoplastic thumb/mild deficiency of the first web space	26
C: Hypoplasia, malrotation and loss of thumb opposition	25
D: Complete thumb absence	16

extremities and between upper and lower extremities. Computations were performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corporation, Armonk, New York, USA) and significant findings were defined as a P value less than 0.05.

Results

There were 62 patients found with confirmed UD involving 82 limbs. There were 44 males and 18 females with a male to female ratio of 2.4. The rate of radiohumeral synostosis (elbow type III) was statistically higher for females than males (50 vs. 19%, respectively, $P = 0.004$).

Thirty-four (55%) patients had an associated lower extremity deficiency. Nineteen had fibular deficiency only, 13 had combined fibular/femoral deficiency (one of whom had phocomelia with contralateral fibular deficiency) and two had femoral deficiency alone. No other type of lower extremity deficiency was found. Of the 34 patients with lower extremity deficiencies, 21 (65%) had them bilaterally.

The limbs with UD in patients with lower extremity deficiencies, compared with those without, were less likely to have an abnormal elbow ($P < 0.0001$, elbow type II or III), especially radiohumeral synostosis (elbow type III, $P = 0.008$). They were also less likely to have severe ulna types II ($P = 0.008$) or III ($P = 0.001$) and more likely to have a normal thumb/first web (type A, $P = 0.008$). The number of absent rays or the Finger classification had no relationship with the presence or absence of lower extremity deficiencies ($P = 0.70$ and 0.69, respectively).

In 20 (32%) of the 62 patients, the ulnar deficiencies were bilateral. Twenty-four (57%) of 42 unilateral ulnar deficiencies occurred on the left and 18 were on the right. All upper extremity findings are listed in Table 1. We had no patient with documented shoulder anomaly [6], but only 30 patients had shoulder radiographs. Mean number of rays (including the thumb) on the involved upper extremity was 2.6.

Comparing the relationships in severity between the anatomic regions in ulnar deficiency

Elbow

Those limbs with normal elbows (elbow type I) are more likely to be associated with normal ulnas (type O, $P < 0.0001$), fewer absent rays ($P = 0.035$), and a normal type A thumb/first web space ($P = 0.011$).

Ulna

Limbs with normal ulna type O were more likely to be unilateral ($P = 0.003$), and be associated with a normal elbow (type I, $P < 0.0001$), fewer absent rays ($P < 0.02$) or less severe finger classification (not types D or E, $P \leq 0.02$), and less likely to have a severe thumb/first web type D ($P \leq 0.007$) than ulna types II or III.

Fingers

The number of absent rays directly correlated with severity of elbow ($P = 0.035$), ulnar ($P < 0.02$), and thumb/first web anomalies ($P \leq 0.001$). Severe finger classification types D and E were more likely to be associated with severe ulna type III ($P < 0.02$) and thumb/first web type D ($P \leq 0.005$).

Thumb/first web

A type A thumb/first web space, compared with type D, was more likely to be associated with a normal elbow (type I, $P = 0.011$), ulna (type O, $P < 0.007$), fewer absent rays (mean = 1 vs. 4.3 rays, $P \leq 0.001$) and less severe finger classification ($P \leq 0.005$). Thumb/first web types B and C were not significantly different from each other or types A and D with respect to other upper extremity anomalies.

Two patients with unilateral UD had other contralateral upper extremity anomalies. One had a congenital shoulder disarticulation and one had a transverse deficiency at the trans-humeral level. There were 24 patients with unilateral UD who had lower extremity deficiencies. Of these lower extremity deficiencies, 14 were bilateral, four were ipsilateral, and six contralateral to the UD. There were 10 patients with bilateral UD and lower extremity deficiencies. Of these, the lower extremity deficiencies were present bilaterally in seven patients, on the right in two patients, and one was on the left.

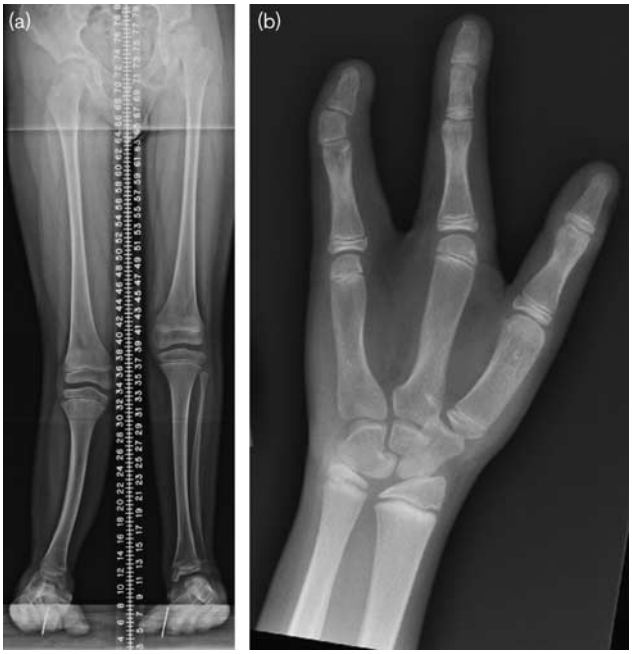
Discussion

Fibular and femoral deficiencies are found in 1–2/100 000 and 1/50 00–200 000 live births, respectively [12]. We found them in 55% of patients with UD. Other studies have reported the rate at 4.5–41.5% [6,13–16]. The observed higher incidence reported here may be attributable to the fact that our search was not limited only to patients being

seen in the upper extremity clinics. Many milder cases were being seen at our institution exclusively because of their lower extremities (Figs 1 and 2). While upper extremity anomalies were present, they were not requiring treatment. This correlates with our findings that ulnar deficiencies with lower extremity deficiencies are more likely to have a normal elbow, ulna, and thumb/first web space than UD in isolation. One explanation for this is the difference in embryological timing of upper extremity versus lower extremity development since emergence of the upper limb buds occurs prior to emergence of the lower limb buds. As skeletal elements of the limb are specified from proximal to distal during development, an insult would affect a more distally forming domain within the upper limb and a more proximal domain within the lower extremity, that is, the ulna in the upper limb and femur in the lower limb resulting in both limbs being affected but within different regions. Alternatively, an insult responsible for a proximal upper extremity anomaly could occur before the lower extremities have begun to develop.

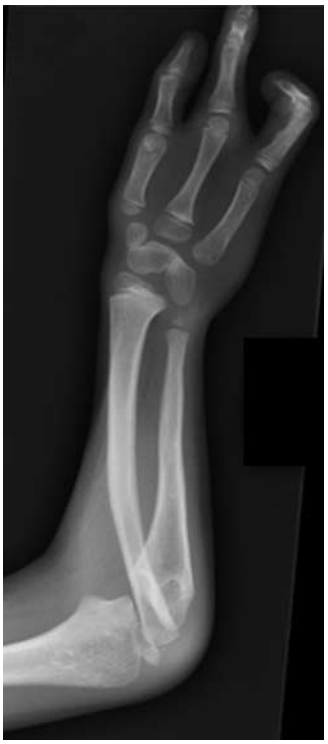
The lower extremities in our patients with UD are more frequently bilaterally involved (65%) compared with 22–28% reported for other studies involving fibular deficiency [5,17]. This suggests that there is some dose effect resulting in more severe (bilateral vs. unilateral) lower extremity involvement that also predisposes the embryo/fetus to upper extremity anomalies. In addition, isolated fibular or fibular with femoral combined deficiency is more commonly seen with UD than is isolated femoral deficiency. We could not categorize lower extremity severity for analysis further as so many patients had bilateral and asymmetrical lower extremity types. Tibial deficiency, a preaxial condition, was not found in our series. This is consistent with expected embryology since ulnar and fibular/femoral deficiencies are all postaxial conditions.

Fig. 1



(a) The lower extremity radiographs of an 11-year-old boy show bilateral fibular deficiency worse on the right with bilateral four-rayed feet. (b) Radiographs of his left hand at age 14 show three rays with a type III thumb and carpal coalitions. The ulna, elbow, and shoulder were normal.

Fig. 2



Radiographs show the right upper extremity of an 8-year-old boy with normal lower extremities. The hand has three rays, a type III thumb, carpal coalitions, type I ulnar hypoplasia with radial head dislocation (elbow type II). The shoulder was normal.

We found a 32% rate of bilaterality in UD compared with 0–35% reported in other studies [2,6,9,11,13–16]. This seems to be related to the definition of UD. Some other authors have not included contralateral ulnar ray deficiency, hypoplasia, or synotosis, if the ulna appeared normal in their rate calculations. We noted the presence of contralateral transverse deficiencies with unilateral UD. Other authors [14–16] have also noted the frequent presence of contralateral transverse deficiencies and phocomelia with UD. If we had included other contralateral anomalies, such as transverse deficiencies, within the spectrum of UD, our rate of bilaterality would be even higher.

In general, we found the severity of an anomaly in one region of the upper extremity was directly correlated with severity in another. For example, a normal ulna was more likely to be associated with a normal elbow and less severe finger and thumb/first web anomalies. And, severe

finger anomalies were more likely to occur with total absence of the ulna and the most severe thumb/first web anomalies. This suggests that a smaller dose effect throughout the upper limb creates less severe anomalies and a larger dose effect creates more severe deformities throughout. As we had no patients with known shoulder anomalies, we cannot comment on how they relate to the other anomalies in UD.

We found unilateral UD with a slight predilection (57%) for the left side. The reports in the literature show variable side preference [2,4,9,11,13,15,16]. In contrast, most studies show unilateral fibular deficiency more commonly on the right side [5,17]. We could not find any correlation between the side of the upper extremity involved to the side of the lower extremity involvement, as might be expected for a developmental field. However, the high number of bilateral cases in both the upper and lower extremity made this variable difficult to isolate. This does not exclude the possibility of the involvement of single gene genetic mutations as previously identified mutations in humans and mice frequently present preferentially in either the upper limb, lower limb, or with a left/right bias even though the genes are expressed within the same domain in all of the limb buds [18–21].

These clinical observations appear to support timing and dose-related insults to the developing limbs. However, the exact mechanisms are poorly understood. Normal development of the emerging limb bud is dependent upon the establishment of three key signaling centers: the apical ectodermal ridge (AER), the zone of polarizing activity (ZPA), and the dorsal/ventral ectoderm. The AER is a specialized structure in the limb bud apex producing fibroblast growth factors that support development of the underlying mesenchyme and maintain the ZPA. Signals from the dorsal/ventral ectoderm also contribute to ZPA maintenance [6,18,21,22]. The ZPA produces *Shh* and establishes a gradient of *Shh* signaling which is critical for normal anterior/posterior (radial/ulnar) patterning of the limb [23]. *Shh* signaling affects the levels and activity of downstream effectors like the transcription factor Gli3. In the presence of a *Shh* signal, zinc finger-containing factor 3 (*Gli3*) repressor formation at the tip of primary cilia is inhibited and the *Gli3* activator stimulates downstream target gene expression [6,24]. Primary cilia are organelles extending from the mammalian cell surface. They play an important role in cell signaling in the hedgehog and wingless pathways and are the site of complex formation between *Gli3* and stabilizing factors like T-box 3 (*Tbx3*) [25]. In humans, heterozygous *TBX3* mutations cause ulnar-mammary syndrome [26]. In addition, studies of ethanol and cadmium chloride limb toxicity have shown that mutations in the *Shh* signaling pathway predispose mice to induced limb anomalies [27]. Cadmium chloride and ethanol, have also been shown to alter signaling between the AER and ZPA leading to limb dysmorphogenesis [28–30]. Thus, radioulnar anomalies can likely be attributed to mutations in genes involved in maintenance or mediation of Shh signals or chemical insults that interfere with these key signaling centers within the developing limb.

Our study agrees with other studies that UD is found more frequently in males (55–70%) [9,11,13–16], as is fibular and femoral deficiency [5,17]. While they are less frequent in number, we did find that females are statistically more likely to have radiohumeral synostosis as part of their UD than are males. We could not find any other report that has found this association. Overall, we found no other differences between males and females with UD.

The limitations of this study are related to its retrospective design. Existing records and radiographs were used to determine what anomalies were present. These may not have been complete if there was limited impairment due to an anomaly and it went unnoticed by patient or physician. Not all patients were followed to maturity and subtle anomalies might have become more evident with age and growth. A multicenter prospective study would be the next step to improve completeness of documentation and increase the numbers of patients. Future studies from the standpoint of the lower extremities may reveal more correlations of those anomalies and the anomalies in UD.

Conclusion

We found that the severity of UD was less for those who also had lower extremity deficiencies. This is consistent with what is known about the timing of upper and lower, proximal to distal limb development. The rate of concomitant lower extremity deficiencies and bilaterality for UD depends on how inclusive you are with the definition of UD. We think these are important distinctions to make if we are to fully understand the embryology of these deficiencies.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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