Difference between affected and unaffected sides of forearm bone length in children with congenital terminal transverse deficiencies at the level of carpal bone

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The forearm of the affected sideis often shorter than that of the unaffected side in children with congenital terminal transverse deficiencies at the level of proximal or distal carpals. The aim of this study is to clarify the characteristics of forearm bone length in those children, especially to quantify the difference in forearm bone length between affected and unaffected sides. The subjects were children with carpal partial transverse deficiencies. The lengths of the radius and the ulna were measured in the radiographs. The lengths of affected and unaffected sides (A/U) were compared in order to quantify the discrepancy. The A/U ratio was defined as the length of the affected side divided by that of the unaffected side. The A/U ratios ranged from 77.1 to 99.0% in the radii and from 74.1 to 99.6% in the ulnae. In both the radius and ulna, the A/U ratios were significantly lower than the left/right ratios of normal adults. Additionally, the A/U ratios of the ulna were significantly lower than the A/U ratios of the radius. The forearm bones of affected side are significantly shorter than those of unaffected side. Although the cause remains unclear, it is possible that not only congenital factors but also acquired factors such as infrequent use of the affected upper limb are involved. A future longitudinal study is necessary to investigate whether length discrepancies can be reduced by using prostheses to increase the frequency of use on the affected limb. ***J Pediatr Orthop B*** **33: 76–82 Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Introduction

Congenital limb defect is a group of congenital anomalies featuring significant hypoplasia or aplasia of one or more bones of the limbs [1]. It is a rare disease, and the prevalence is reported to be 0.31–0.59 per 1000 live births or 0.56–0.79 per 1000 total births [2–6].

Gold reported that the most common apparent cause of congenital limb defect is vascular disrupting defects such as amniotic band-related limb deficiency and there are more cases where the cause is unknown [7]. Additionally, Fanconi anemia, chromosomal abnormalities (e.g. trisomy 18), environmental exposures (thalidomide and misoprostol), prenatal diagnostic procedures, and fetoscopic laser therapy for twin-twin transfusion syndrome are also reported to be associated with congenital limb defect [7–12]. It is also possible to be a symptom of syndromes such as Poland syndrome and Holt-Oram syndrome [13,14].

Deficiencies of the upper limbs are twice as common as those of the lower limbs [15]. In upper limbs, transverse deficiencies are the most prevalent [5]. Almost half of the patients are deficient only in the digits, and their arms and forearms are normal [7]. Most children with lower limb deficiencies use prostheses, which enhance their ability to participate in everyday activities [16]. In contrast, there is less evidence to indicate that children with upper limb deficiencies benefit from prosthetics. The demand for prostheses/orthoses depends on the level of deficiency and potential functional gain [15, 16]. In pediatric patients, prostheses are most often prescribed for those with unilateral transversal defects of the forearm, whereas few are prescribed for children with unilateral defects of the upper arm or the hand. In addition, prosthetics are rarely prescribed for children with longitudinal forearm defects [17–19].

According to the International Organization for Standardization (ISO)/the International Society for Prosthetics and Orthotics (ISPO) classifications, transversal defects involve a limb, which has developed only to a certain point, beyond which no skeletal elements exist [20]. For example, in carpal partial transverse deficiencies, the radius and ulna are present in their totality. The carpal bone is only partially present, and there is no skeletal element beyond. Clinically, however, it is often observed that the forearm is shorter on the affected side, although the shapes of its radius and ulna are preserved.

Even in normal adults, it is known that the right forearm is longer than the left forearm due to the difference in the frequency of use between both arms [21]. A study that measured the lengths of the radii and the ulnae in normal adults reported that the left radii measure 98.5–99.7% of the right radii and the left ulnae measure 98.4–99.6% of the right ulnae [22–26].

There has been no report on the length discrepancies between the affected side and the unaffected side of the forearms in children with congenital upper limb defects. The aim of this study is to identify the morphological features and length of the radius and the ulna in children with congenital terminal transverse deficiencies at the level of proximal or distal carpals to further understand why such limb length discrepancies arise and find a way to reduce the difference in length between the unaffected side and the affected side.

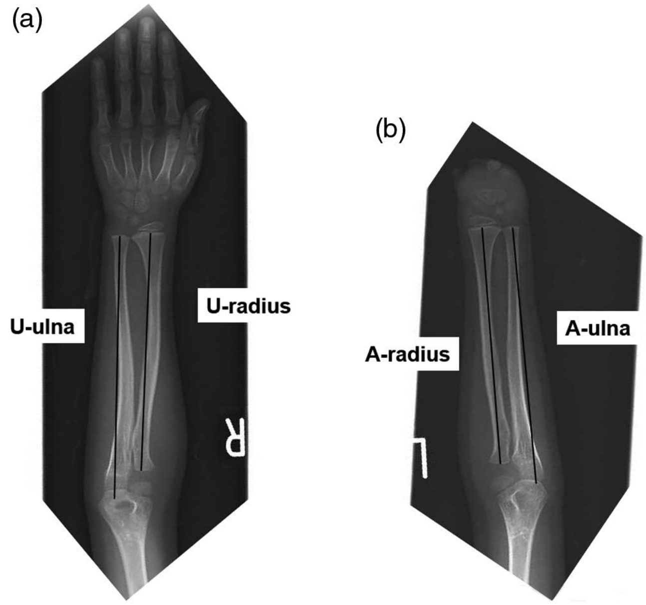
Methods

This study was approved by the Ethics Committee of the Faculty of Medicine, the University of Tokyo (approval number 2018148NI).

The subjects were patients classified as carpal partial transverse deficiency, according to ISO/ISPO classification, who had visited our hospital and had radiographs of both upper limbs taken. Patients with only one limb defect were included, and patients with two or more limb defects were excluded. Patients who were suspected as longitudinal defect from the morphology of the radius and ulna on the radiograph were excluded. The presence of their carpal bones and passive movement of the wrist joint was confirmed by palpation and inspection by multiple rehabilitation physicians and occupational therapists. In cases where palpation was uncertain, the presence or absence of carpal bones was confirmed by an ultrasonic diagnostic device, and children with congenital terminal transverse deficiencies absent of carpal bone were excluded. From the latest radiographs prior to prosthesis use, morphology of the radius and the ulna were confirmed. In addition, measurements were taken between the midpoint of the proximal epiphyseal line to the midpoint of the distal epiphyseal line of the radius and the ulna. To compare the lengths of affected and unaffected sides (A/U), the A/U ratio was defined as the length of the affected side divided by that of the unaffected side (Fig. 1). We compared the A/U ratios of the radius with the A/U ratios of the ulna. We further compared the pediatric A/U ratios with the left/right ratios of normal adults. Former research has shown that average L/R ratios of normal adults are 98% or higher; therefore, 98% was adopted as the control L/R ratio in the present study. We also examined the correlation between the radius A/U ratio and the ulna A/U ratio, as well as the correlation between the age of the subject and the A/U ratios of the affected bones.

We performed normality tests using the Anderson Darling statistic prior to the selection of the statistical test. The A/U ratios of the radius and ulna were compared using the Wilcoxon signed-ranks test to compare the pediatric A/U ratios with the L/R ratio of normal adults, we performed the Wilcoxon signed-ranks test. Spearman's rank correlation coefficient was used to examine the correlation between radial A/U ratio and ulnar A/U ratio, and between the subject's age and the A/U ratio of the affected bone. We divided the subjects into two groups, 0–2 years and 3–6 years, and tested for differences in radial and ulnar A/U ratios between the two groups using the Wilcoxon signed-ranks test. Statistical analysis was performed with JMP Pro 14.2.0 (SAS Institute, Tokyo, Japan), and $P < 0.05$ was considered significant.

Fig. 1



Radiographs of the upper limbs of a patients classified as carpal partial transverse deficiency. (a) Unaffected side (U) and (b) affected side (A). The radius and the ulna are present in their totality, the carpal bone is only partially present, and there is no skeletal element beyond. We measured the length of the radius and ulna from the proximal epiphyseal line to the distal epiphyseal line on the radiographs and calculated the ratio of the affected side length to the unaffected side length. A/U ratio of radius = A-radius/U-radius × 100 (%), A/U ratio of ulna = A-ulna/U-ulna × 100 (%). A/U, affected and unaffected sides.

Results

Table 1 shows the characteristics of the pediatric patients in this study. Of the 16 subjects (12 male and 4 female), eight were affected on the right side, and the other eight were on the left side. The subjects' ages ranged from 3 to 75 months, with a median of 18.5 months. No child had any comorbidity other than congenital terminal transverse deficiency and none had an obvious amniotic band. Additionally, there was no family history of congenital terminal transverse deficiency nor were any of the mothers taking oral medication during pregnancy. In all patients, the carpal bones were confirmed by palpation and the movement of the wrist was possible voluntarily.

Table 1 Characteristics of the pediatric patients

Case	Age	Sex	Affected side	Carpal bone (palpation)	Passive wrist joint movement	Carpal bone (radiograph)		Ossification in the distal epiphysis of the radius (radiographs)	
						Affected side	Unaffected side	Affected side	Unaffected side
1	3 months	Female	Left	O	O	×	O	×	×
2	4 months	Male	Right	O	O	×	O	×	×
3	5 months	Male	Left	O	O	×	O	×	×
4	6 months	Male	Right	O	O	×	O	×	×
5	10 months	Female	Left	O	O	×	O	×	×
6	1 year	Male	Left	O	O	×	O	×	×
7	1 year 5 months	Male	Right	O	O	×	O	×	×
8	1 year 5 months	Male	Left	O	O	×	O	×	O
9	1 year 8 months	Male	Right	O	O	×	O	O	O
10	1 year 11 months	Male	Left	O	O	×	O	×	O
11	2 years 2 months	Male	Right	O	O	×	O	×	O
12	3 years 2 months	Male	Left	O	O	×	O	O	O
13	4 years 8 months	Female	Right	O	O	×	O	O	O
14	4 years 10 months	Male	Left	O	O	O	O	O	O
15	5 years 3 months	Female	Right	O	O	O	O	O	O
16	6 years 3 months	Male	Right	O	O	O	O	O	O

Furthermore, in all 16 patients, the radius and ulna were visible on radiographs. When comparing the morphology of the respective bones, no clear difference was observed between the affected and the unaffected sides. Radiographs of the unaffected side confirmed carpal bones in all 16 patients. Of these patients, nine of the older children presented ossification in the distal radial epiphysis. On radiographs of the affected side, we were able to identify at least one carpal bone in three children, and ossification in the distal radial epiphysis in six children. In three children, the ossification in the distal radial epiphysis was observed on the unaffected side only.

Table 2 shows the lengths and the A/U ratios of each subject. Both the radius and ulna were significantly shorter on the affected side than on the unaffected side (radius: $P < 0.0001$, ulna: $P < 0.0001$). The A/U ratios ranged from 77.1 to 99.0% (median, 90.1%) in the radius, and from 74.1 to 99.6% (median, 89.5%) in the ulna. These pediatric A/U ratios were significantly lower than the L/R ratios of the radius and the ulna in normal adults (radius: $P = 0.0002$; ulna: $P < 0.0001$). The A/U ratios of the ulna were significantly lower than the A/U ratio of the radius ($P = 0.0008$). There was a positive correlation between the A/U ratios of the radius and those of the ulna ($\rho = 0.974$; $P < 0.0001$) (Fig. 2). There was a negative correlation between the patients' age and the A/U ratios of the radius and the ulna: however, this was not found to be significant (radius: $\rho = -0.454$, $P = 0.077$; ulna: $\rho = -0.485$, $P = 0.056$). There were no significant differences in both radial and ulnar A/U ratios between the 0–2 age group and 3–6 age group (radius: $P = 0.254$; ulna: $P = 0.254$).

Discussion

Subjects in this study were classified as terminal transverse deficiencies at the level of proximal or distal carpals rather than that of the forearm. The carpal bones were found by palpation in all subjects and the movement of the wrist joint was confirmed.

On the radiograph, there were 13 children whose carpal bones could be seen on the unaffected side but could not be confirmed on the affected side. It is possible that the cause of this is that the ossification of the affected side is delayed compared with that of the unaffected side. However, another possibility is that they are born with a terminal transverse carpal deficiency, so they have a deficient capitate and hamate bone, both of which can be confirmed by radiograph from an early stage [27,28]. This alone does not mean that there is a difference in the speed of ossification between the healthy side and the affected side. There were three children for whom we confirmed the presence of a distal radial epiphysis by radiograph on the unaffected side but not on the affected side. Since it has been confirmed that the radius was completely present in all subjects of this study, this suggests that the appearance of the distal epiphysis on the

Table 2 Lengths and A/U ratios of each subject

Case	Radius length (mm)			Ulna length (mm)		
	Affected side	Unaffected side	A/U ratio of radius (%)	Affected side	Unaffected side	A/U ratio of ulna(%)
1	61.6	62.9	97.9	69.0	69.3	99.6
2	61.3	61.9	99.0	68.0	69.8	97.4
3	71.5	74.0	96.6	80.4	83.9	95.9
4	69.3	75.4	91.9	79.3	85.7	92.5
5	63.0	73.8	85.4	70.2	84.4	83.1
6	64.9	84.1	77.1	70.8	95.3	74.3
7	75.6	84.4	89.5	80.7	93.1	86.7
8	96.5	102.4	94.1	105.4	114.0	92.4
9	86.3	88.7	97.2	95.6	100.2	95.3
10	83.7	94.9	88.1	92.8	107.4	86.4
11	99.9	103.0	97.0	106.5	115.0	92.6
12	107.6	121.0	88.8	117.3	134.5	87.2
13	101.8	121.1	84.1	111.5	136.2	81.9
14	119.1	131.4	90.6	129.3	144.3	89.6
15	113.2	126.5	89.4	125.3	139.8	89.5
16	116.7	144.9	80.4	114.9	155.0	74.1

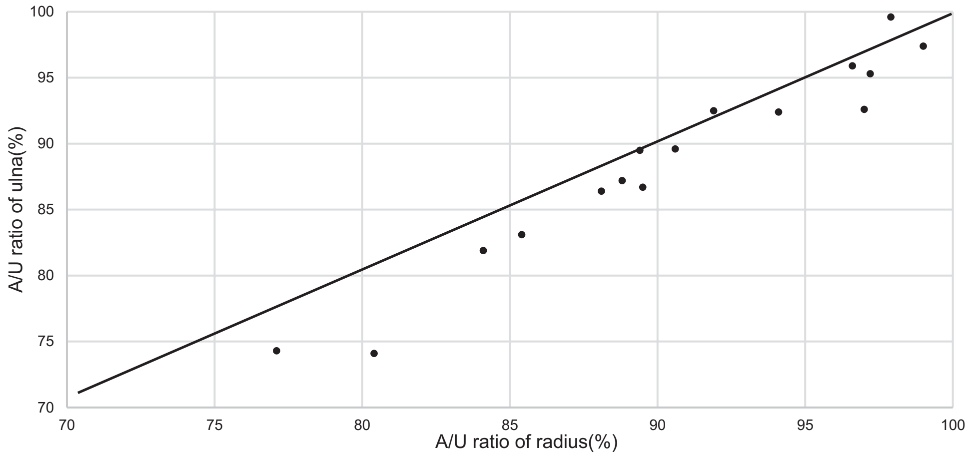
A/U, affected and unaffected sides.

affected side is delayed compared with the unaffected side. However, the possibility of morphological changes at the distal end of the radius or ulna cannot be ruled out.

This study revealed that the affected forearms of pediatric patients with congenital terminal transverse carpal deficiency were significantly shorter than the unaffected ones, and the difference was greater than the L/R differences of normal adults. Although all subjects were classified as having carpal partial transverse deficiency, there was variation in forearm length (radial A/U ratio: 77.1–99.0%; ulnar A/U ratio: 74.1–99.6%). The classification used in this study is based on morphology and not on cause. It is possible that the variation in length is a result of individual differences, and it is also undeniable that the cause of the defect may be related to the cause of the defect. However, in many cases, it is not possible to identify the cause, and even among the children in this study, no one has been able to identify the cause. Regardless of the cause of the congenital defect, there are two possible causes of the postnatal difference in forearm length between the affected and unaffected sides: congenital and acquired factors.

Congenital factors may involve embryological abnormalities during the fetal period, such as malformation and disruption. Malformation is one of the most prevalent types of limb dysplasia among other subtypes based on the type of tissue formation [29]. Malformation starts from specific localized tissue dysplasia that occurs during the first 7 weeks after embryonic limb formation. It is diagnosed by a maternal ultrasonic diagnostic device with an average gestational age of 20.5 ± 5.4 weeks, and is known to be associated with poor perinatal outcomes, including high rates of preterm delivery and stillbirth [30]. It is known that the development of human limbs during the fetal period starts from proximal and extends to distal through transmission of numerous gene signals [31], and the anterior–posterior limb bud axis, such as a guide to radial/ulnar differentiation, is associated with the zone of polarization activity and associated cell signaling, especially sonic hedgehog activity and many others [32]. During the fetal period, the human hand only increases in size without much morphological change as it completes most of its morphology during the embryonic period. Any abnormality that occurs in these gene signals, which gradually affects limb formation from proximal to distal, could cause malformation. In contrast, disruption is the collapse of the limb tissues after they have been formed by external mechanical forces, impaired blood flow or infection. Amniotic band-related limb deficiency is one of the most prevalent types of disruption. Disruption cannot be completely denied in these subjects, but at least none of the children had an obvious amniotic band. If there are children with amniotic band-related limb deficiency, they will need to be investigated separately from children with malformation because the cause, therefore the

Fig. 2



Positive correlation between the A/U ratios of the radius and those of the ulna: The straight line represents A/U ratio of radius (%) = A/U ratio of ulna (%). The points below the line indicate A/U ratio of radius (%) > A/U ratio of ulna (%), and the points above the line indicate A/U ratio of radius (%) < A/U ratio of ulna (%). A/U, affected and unaffected sides.

predicted outcome and growth of their affected forearms, will be different. In the future, advances in embryology and molecular biology may clarify the causes of dysplasia, phenotypic differences between individuals, and intraindividual differences such as L/R differences.

Acquired factors may involve infrequent use of the affected limb, thereby reducing load stimulus and mechanical stress to the limb. Without using prostheses, children with congenital terminal transverse carpal deficiency compensate for upper limb functions by using the upper limb on the unaffected side, the stump or elbow on the affected side, foot, chin, etc., and can perform almost all daily activities independently [33]. However, due to the difference in length between the left and right upper limbs, when the weight is applied, for example, when the baby crawls on the floor, the unaffected upper limb first touches the floor and more weight is applied. Moreover, they cannot hang on a horizontal bar with both hands. There are reports that mechanical stimulation such as weight-bearing is crucial for bone growth [34–36]. When a child with congenital terminal transverse carpal deficiency uses the affected limb less frequently, this may, therefore, result in insufficient forearm growth. In the case of brachial plexus birth palsy, it has been reported that the paralyzed side has shorter upper limb length than the nonparalyzed side, and the degree of growth retardation is related to the degree, extent and localization of the paralysis [37–39]. There is no congenital factor in brachial plexus birth palsy. Whether paralysis itself is a factor or the paralyzed side is used less frequently is not known, but it is clear that acquired factors alone can produce growth retardation of the upper limb. It is possible that the brain is also associated with growth retardation, but the size of the hand cortical representation of the brain in children with congenital upper limb defects and its effect on growth retardation has not been elucidated.

It is noteworthy that the A/U ratio of the ulna was significantly lower than the A/U ratio of the radius, indicating that the ulna grows even less than the radius on the affected side. Embryologically, the ulna is formed first, followed by the radius [40]. If any abnormalities occur during the embryonic or the fetal period, it is likely that the radius will be affected more than the ulna, because it is formed later. Abnormalities during the embryonic or fetal period should result in a shorter radius, but not a shorter ulna. Since it is the A/U ratio of the ulna that is significantly lower in our study, this phenomenon cannot be explained solely by congenital factors. It is known that when a distal load is applied to the forearm, about 80% of the load is distributed to the radius and about 20% to the ulna [41]. Therefore, children with congenital terminal transverse carpal deficiency have very little chance of applying load stimulation to the ulna on the affected side. This may, therefore, indicate that the slower growth of the ulna compared with the radius may be caused by reduced weight-bearing opportunity. However, it cannot be denied that other potential explanations, such as a component of longitudinal deficiency, may also be involved. A significant positive correlation was found between the A/U ratio of the radius and that of the ulna. This indicates that the radius and ulna are balanced. If we consider congenital factors such as interruptions of cell signaling associated with anterior–posterior axis of the limb bud, the balance between the radius and ulna should be different depending on the child. Since the radius and ulna were balanced in all the children, we presumed that the development of the radius and ulna was completed to some extent. The nonsignificant, negative correlation between children's age and the A/U ratios of the radius and the ulna calls for a longitudinal survey to clarify whether insufficient use of the affected forearm results in its shortness. Evaluation of the two groups, 0–2 and 3–6 years of age, also showed no significant differences in radial A/U ratio or ulnar A/U ratio between the two groups. Further studies with larger numbers of subjects are needed. There is a debate about the length of the affected side. In the case of a lower limb defect, the balance between the length of the prosthesis side and the unaffected side of the foot is very important because legs serve a major purpose in standing and walking. Also, if the lower limb stump is too long, it is difficult to use more advanced prosthetic parts [42]. In the case of the upper limbs, there are aesthetic problems, but an exact balance in length is not as important as in the lower limbs. In addition, since many activities of daily living can be undertaken without an upper limb prosthesis, the total time dependent on a prosthesis is relatively limited. Considering the difference in weight between the left and the right because the prosthesis is mostly not used and the balance of muscles in the entire body, it would be more favorable to focus on the deficient limb itself and promote the growth of children. Separation movements of fingers develop at the age of 1–2 years, and simultaneous use of both hands begins in a complementary manner. By the age of two, the fingers and arms will become more and more separated in various functional skills, controlling the stability and motility of the arms and hands at the same time, and being able to perform a series of two-handed movements [43,44]. By introducing upper limb prostheses before the time to acquire two-handed movements, it is expected that children will naturally acquire two-handed movements using upper limb prostheses, and it is expected that this will lead to an increase in the frequency of use on the affected side. Further study is recommended to corroborate this. There is also a report that the first prosthesis should be introduced between 6 and 24 months from the viewpoint of reducing the rejection of the prosthesis and improving the skill [45]. We hope that issues related to extraneous lengthening of the affected side with the prosthesis attachment due to growth of the limb with the prosthesis attachment can be managed through innovations of the prosthesis parts and improved technology of their mechanism.

As a limitation, this study was a cross-sectional single-center study at a single point in time before the subjects were started on upper limb prostheses. Furthermore, the number of participants in this study was small due to the rarity of this disease. We have not yet followed the subjects until they reach a sufficient age in bone growth. To investigate how the use or nonuse of prosthesis will impact the growth difference between the affected side and the unaffected side, longitudinal research will be desired in future. It was a comparison between the subject and a normal adult, and it was not possible to compare it with the right/left ratio of a normal child. This is because it was not recommended to take radiographs of healthy children for the sake of comparison from the viewpoint of radiation exposure. As for the effect of weight-bearing, we would like to investigate the growth of the lower limb length in children with lower limb deficiencies who walk using prostheses. More thorough discussion is needed on the possibility of patients with transverse limb deficiencies having components of longitudinal deficiencies.

In conclusion, our study has revealed that children with congenital terminal transverse carpal deficiency develop forearm bones that exist fully to the distal side, although are shorter on the affected side. Moreover, the length discrepancy between the unaffected side and the affected side is larger in the ulna than in the radius. The causes of these length discrepancies remain unclear, although congenital and acquired factors seem to be involved. Intervention is difficult if only congenital factors are involved, but if acquired factors are involved, rehabilitation intervention may be possible for that part. We hypothesize that using upper limb prostheses during the growth period and, thereby, increasing weight-bearing opportunity for the affected limb may potentially reduce the length discrepancy. Further comparative prospective studies are needed to examine this hypothesis.

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Conflicts of interest

There are no conflicts of interest.

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