Brief Report

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Skeletal computed tomography findings of upper extremities in middle-aged persons with thalidomide embryopathy

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SUMMARY Individuals with thalidomide embryopathy are now approximately 60 years old. For years, they have been compensating for their hypoplastic limbs in various aspects of daily living, and they face secondary problems such as limb and back pain. Imaging analysis is beneficial for understanding the pathogenesis of these problems. However, previous studies on skeletal imaging were mainly radiographic studies conducted at young ages, and there are few studies on skeletal imaging after aging, with most of them being case reports. In this study, detailed analyses of the skeletons of the upper extremities were performed using three-dimensional computed tomography and multiplanar reconstruction images in five individuals with thalidomide embryopathy aged approximately 60 years. Each individual frequently complained of neck, shoulder, and/or back pain. Dislocation, subluxation, and osteoarthritis were observed in the shoulder joints in some individuals. Hypoplasia of the trochlea and/or capitulum of the humerus, coronoid fossa, olecranon, and coronoid processes was observed in the elbow joints. Fusion and hypoplasia of the carpal bones were frequently observed in wrist joints. Radiocarpal and ulnocarpal synostoses were also observed. The joint instability and osteoarthritis found in this study may have contribute to upper limb pain in individuals with thalidomide embryopathy.

Keywords skeletal imaging, 3D-CT, phocomelia

1. Introduction

Thalidomide embryopathy (TE) is a well-known drug-induced tragedy affecting over 10,000 infants worldwide. It is characterized by congenital limb malformations, auditory hypoplasia, and internal organ malformations. Phocomelia or radial longitudinal deficiency in the upper extremities is characteristic of TE.

Most individuals with TE are now approximately 60 years of age. In addition to symptoms associated with congenital malformations, they frequently complain of age-related secondary problems such as limb and back pain (*1*). The pathophysiology of TE needs to be understood through imaging analyses to address these secondary problems. However, previous reports on skeletal imaging were mostly based on radiographic findings at young ages, and there are few studies on skeletal imaging after the individuals had aged (*2-5*).

In this study, the computed tomography (CT) findings of the upper limbs in five individuals with TE after aging were analyzed using three-dimensional-CT (3D-CT) and multiplanar reconstruction (MPR).

2. Materials and Methods

From October 2022 to February 2023, five individuals with TE (age: 59–61 years, two men and three women) underwent CT from the head to the pelvis for internal medicine checkup, and we analyzed 3D-CT and MPR findings of the upper extremity skeletons. 3D medical imaging workstation "Ziostation2" (Ziosoft, Japan) was used in 3D-CT analysis.

This study was approved by the National Center for Global Health and Medicine Ethics Committee (NCGM-S-004260-02), and it conformed to the provisions of the Declaration of Helsinki. Written informed consent concerning this research was obtained from all participants.

3. Results and Discussion

Detailed findings and clinical manifestations of each upper limb in the five individuals (CaseA–E) are shown in Table 1. Regarding the clinical phenotypes, malformations were limited to the forearms and hands of all individuals. Clubhands with short forearms were present in seven limbs of four individuals. The degree of digit malformation differed among the limbs. Concerning clinical symptoms, three out of five individuals complained of a forward-leaning posture to compensate for their short upper limbs during daily activities, and they also suffered from neck and/or shoulder pain.

Regarding the CT findings of the shoulder joints, five of the ten upper limbs showed normal morphology. The other five limbs are shown in Figure 1. Abnormal humeral head position and/or osteoarthritis was seen in some limbs. In A-right, the humeral head was slightly elevated, and A-left showed downward subluxation of the humeral head and osteoarthritis. In A-left, the clavicle and acromion were long, and the acromioclavicular joint projected outward, exhibiting the so-called pointed shoulder. D-right and D-left show hypoplastic humeral heads. In D-right, the humeral head was dislocated anteroinferiorly. D-left and E-left also presented with osteoarthritis.

The characteristic CT findings of the elbow joints are shown in Figure 2. B-right and D-left, which did not have radial defects or proximal radioulnar synostosis, show normal elbow joint morphology. The other eight limbs showed hypoplasia of the trochlea and/or capitulum of the humerus, coronoid fossa, olecranon, and coronoid process: B-left showed typical features. D-right showed proximal radioulnar synostosis and the corresponding deformity of the humerus. E-left shows a radial defect, with a radius-remnant-like object attached to the coronoid process.

In the wrist joints, nine of the 10 upper limbs showed hypoplasia and fusion of the carpal bones. The wrist joint showed various morphologies, and Figure 3 shows the typical deformities. In A-right, the distal end of the ulna showed a bowl-shaped deformation. A-left showed ulnocarpal synostosis. In B-left and C-right, the carpal bones contacted the ulna only in a limited area. D-right showed radiocarpal synostosis.

Thalidomide was marketed as a sleeping pill and morning sickness medicine in the late 1950s and the early 1960s. Congenital malformations have been reported in children born to mothers receiving thalidomide; this condition was called TE. The most common malformations are congenital limb malformations, auditory hypoplasia, and internal organ malformations. In Japan, lower extremity malformations are rare and almost all extremity malformations are limited to the upper limbs (*6*).

People with TE are now approximately 60 years of age, and in addition to the symptoms associated with the original malformations, they complain of age-related secondary problems. In a scoping review of 25 relevant articles on age-related changes in TE, Newbronner (*1*) found that individuals with TE frequently reported joint pain, especially in the neck, shoulder, and back. Approximately 30–70% of individuals with TE experienced joint pain (*1,7-9*). Merkle (*2*) reported that 58% of individuals with TE experienced shoulder joint pain, and approximately one-third had osteoarthritis in the shoulder joints.

Imaging analysis is beneficial for investigating the pathogenesis of these secondary problems. However, previous reports on radiographic findings of TE mainly comprise reports of when the disease was first reported (*10-12*), and there are few studies on skeletal imaging after aging. Previous studies have included a few surgical reports of joint replacement for shoulder osteoarthritis (*2,3*), 31 cases of lower extremity CT analysis (*4*), and one case report on shoulder osteoarthritis using radiography, 3D-CT, and Magnetic Resonance Imaging (MRI) (*5*).

Henkel (*13*) classified congenital malformations of the upper extremities as 1. mildest to 4. the most severe; 1. distal ectromelia: malformation involving the radial ray of the hand and the radius; 2. axial ectromelia: malformation involving the radial ray of the hand, the radius, and the humerus; 3. phocomelia: absent humerus, radius, and ulna, and several ulnar hands connected to the shoulder girdle, 4. amelia: arm completely absent. In the present study, only case D showed humeral hypoplasia (axial ectromelia), while the other four cases exhibited malformations localized in the forearms and hands. (distal ectromelia)

According to Mansour (*14*), a pointed shoulder with long clavicle and acromion, and a prominent acromioclavicular joint is characteristic. Shoulder joint dislocation can also be caused by marked hypoplasia of the superior girdle muscles (*15*). In the present study, one of the 10 limbs had a pointed shoulder, and three limbs showed an abnormal position of the head of the humerus, which was consistent with previous studies. All three limbs also showed osteoarthritis, which is consistent with a previous study that reported shoulder osteoarthritis in TE after aging (*2*).

In the elbow joints, radial defects and proximal radioulnar synostosis were found in eight of the ten limbs. This result is consistent with a previous study that showed hypoplasia of the elbow joint, proximal radioulnar synostosis, and ulnohumeral synostosis as characteristic features (*15*). In this study, articular surface deformity was revealed by separating the humerus from the radius and/or ulna using 3D-CT imaging techniques. Hypoplasia of the trochlea and/or capitulum of the humerus, coronoid fossa, olecranon, and coronoid processes was observed. Articular surface deformation can be an age-related change corresponding to congenital bone loss or bone fusion.

Table1. Summary of the clinical phenotypes/symptoms and CT findings

	Case A		Case B		Case C		Case D		Case E	
	right	left	right	left	right	left	right	left	right	left
age(years),gender	60, female		60, female		61, male		59, female		60, male	
clinical phenotypes	short and bowed forearm, clubhand, deficient thumb	short and bowed forearm, clubhand, deficient thumb	hypoplastic thenar muscle	short and bowed forearm, clubhand, deficient thumb & digit II, hypoplastic digit III-V	short and bowed forearm, clubhand, hypoplastic thumb	short and bowed forearm, clubhand, hypoplastic thumb	deficient thumb	rudiment thumb	short and bowed forearm, clubhand, rudiment thumb	short and bowed forearm, clubhand, deficient thumb
clinical symptoms	pain in shoulders and upper limbs forward-leaning posture		pain in neck and shoulders forward-leaning posture poor posture balance		pain in neck, shoulders, back and knees forward-leaning posture		pain in both upper arms (left dominant)		pain in fingers	
CT findings shoulder joint	slightly elevated humeral head	osteoarthritis, downward subluxation, pointed shoulder	normal	normal	normal	normal	anteroinferior dislocation, hypoplastic humeral head	osteoarthritis, hypoplastic humeral head	normal	osteoarthritis
upper arm	normal	normal	normal	normal	normal	normal	short humerus	normal	normal	normal
elbow joint	hypoplasia of joint components*	hypoplasia of joint components*	normal	hypoplasia of joint components*	hypoplasia of joint components*	hypoplasia of joint components*	deformity of the trochlea and capitulum of humerus	normal	hypoplasia of joint components*	hypoplasia of joint components*
forearm	radial deficiency	radial deficiency	normal	radial deficiency	radial deficiency	radial deficiency	proximal radioulnar synostosis	normal	radial deficiency	rudiment radius
wrist joint	hypoplastic and fused carpus	hypoplastic and fused carpus ulnocarpal fusion	normal	hypoplastic and fused, carpus	hypoplastic and fused carpus	hypoplastic and fused carpus	hypoplastic and fused carpus, radiocarpal fusion	hypoplastic and fused carpus, radiocarpal fusion	hypoplastic and fused carpus	hypoplastic and fused carpus

*hypoplasia of the trochlea and capitulum of the humerus, coronoid fossa, olecranon, and coronoid process.

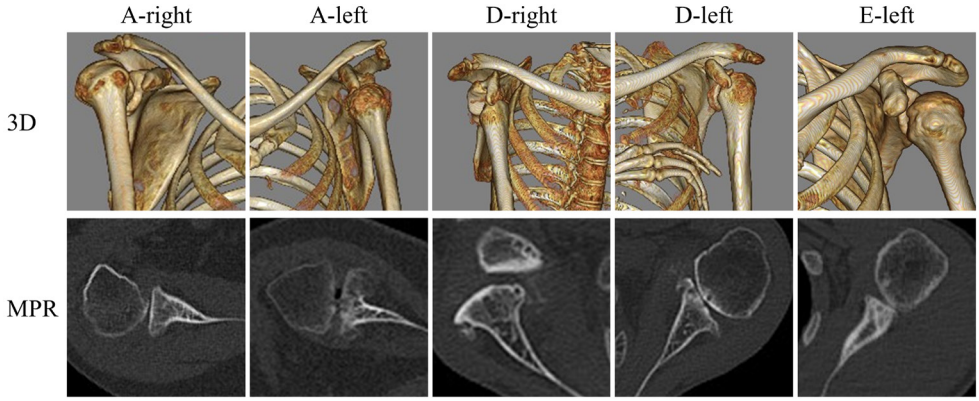

Figure 1. Abnormal findings of the shoulder joints. The humeral head is abnormally positioned in A-right (slightly elevated), A-left (downward subluxation), and D-right (anteroinferior dislocation). Osteoarthritis can be observed on A-left, D-left, and E-left. A-left also shows a pointed shoulder. D-right and D-left show hypoplastic humeral heads.

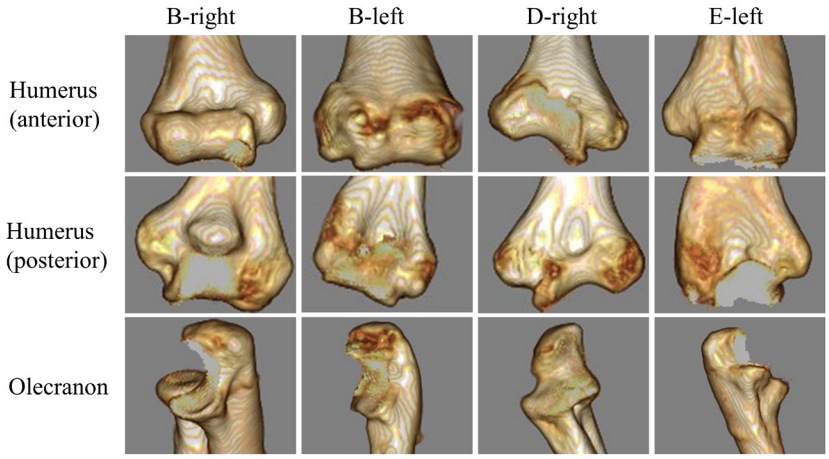

Figure 2. Characteristic findings of the elbow joints. B-right shows normal morphology. B-left shows hypoplasia of the trochlea and capitulum of the humerus, coronoid fossa, olecranon, and coronoid processes. D-right shows the proximal radioulnar synostosis and the corresponding deformity of the humerus. E-left shows a radial defect with a radius-remnant-like object attached to the coronoid process.

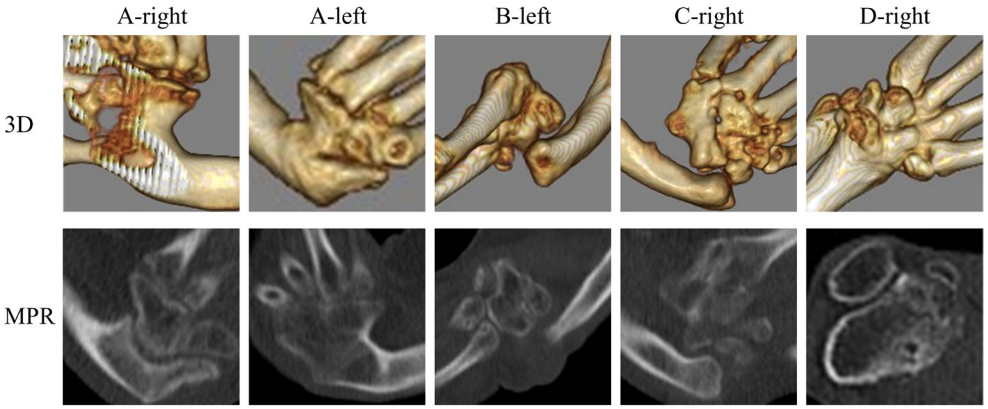

Figure 3. Typical deformities in the wrist joints. A-right shows a bowl-shaped deformation of the ulnar head. A-left shows ulnocarpal synostosis. B-left and C-right show club hands with carpal bones in contact with the ulna in only a limited area. D-right indicates radiocarpal synostosis.

In the wrist joints, 3D-CT elucidated the positional relationship between the carpal bones and the radius and/or ulna. In some cases, the carpal bones establish contact with the radius or ulna only in a limited area, suggesting joint instability. Previous studies on the carpal bones have shown radially predominant carpal bone defects or fusion as characteristic features. Longitudinal fusion is unique and is usually not seen in other diseases that show upper extremity malformations similar to TE (*14*). In this study, carpal bone hypoplasia and fusion were observed in nine of 10 limbs, which is consistent with previous studies.

In individuals with TE reported in this study, hypoplasia of the wrist and elbow joints was frequently observed. 3D-CT is particularly useful for analyzing the detailed morphology and 3D structure of articular surfaces. To the best of our knowledge, this is the first report on the morphology of the articular surface of the upper extremities in individuals with TE after aging. In addition, using 3D-CT, the three-dimensional relationship between the bones was clarified, suggesting joint hypoplasia and instability in each joint.

In this study, neck and shoulder pain were common complaints among individuals with TE. In addition to the pain caused by daily activities with a forward-leaning posture to compensate for the short upper limbs, joint instability and osteoarthritis observed in this study may have also contributed to pain.

One limitation of this study was the lack of documentation of imaging findings at young ages, which made it impossible to distinguish between congenital and post-aging findings. As individuals with TE age, the incidence of age-related secondary problems is expected to increase. The accumulation of imaging analysis studies in more cases and further understanding of the pathogenesis would be beneficial for improving joint protection and pain control. Although this study focused on skeletal CT findings, muscle hypoplasia is also known to occur in patients with TE. Studies involving the analysis of muscle mass can also be considered in future research.

In conclusion, skeletal CT analysis of the upper extremities of middle-aged individuals with TE revealed various bone deformities, including bone fusion and hypoplasia. Osteoarthritis was also frequently observed.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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