

Clinical Features of Congenital Pseudarthrosis of the Tibia in Children—a Study Focusing on 514 Cases in China

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Abstract

Background: Congenital pseudarthrosis of the tibia (CPT) is a refractory and rare disease. Because of its extremely low incidence, little is known about its clinical features. In this retrospective study, the aim of this study was to analyze the clinical characteristics of patients with CPT.

Methods: This is a retrospective study of children with CPT identified by radiological review. Investigations of CPT included general condition, the characteristics of CPT, treatment methods and surgical complications.

Results: We have collected 514 CPTs from 1999 to March 2020 in our hospital, 317 (61.67%) boys, 197 (38.33%) girls; 330 (62.86%) in Crawford IV; 510 (97.14%) in mid and distal 1/3 tibia; 481 (93.58%) in less than 3 years of first appearance of symptom; 297 (57.78%) in less than 3 years of the first visit of outpatient. The most common postoperative complication was ankle valgus (101, 39.60%), followed by limb length discrepancy (91, 35.69%), refracture (38, 14.90%), osteomyelitis (15, 5.88%) and removal of internal fixation (10, 3.93%).

Conclusions: CPT with higher incidence of Crawford IV frequently occurs in boys and middle or distal part of the tibia; most patients have the first appearance of symptom and the first visit of outpatient before 3 years; the major surgical complications were ankle valgus and limb length discrepancy.

Background

Congenital pseudarthrosis of the tibia (CPT) is a rare disease of the skeletal system in children, with a prevalence of 1 in 140,000 or 300,000 [1, 2]. CPT related healthcare costs, work or study loss, and psychosocial problems result in a tremendous burden for children's family [3]. As the most populous country in the world, however, little information regarding CPT epidemiology is available in China.

Our clinical knowledge of CPT is still scarce and lacking unified understanding, because of its rare incidence. To this day, only three studies had more than 100 cases, two multi-center studies and one single-center study [4-6]. The incidence of CPT in the population was more recognized as 1 in 140,000, nonetheless, this data was reported in 1972 and only 13 patients were included [2]. The only large sample data is a multi-center study [7] organized by The European Pediatric Orthopedic Society (EPOS) in 2000, which collected 340 cases from 20 hospitals in 13 countries. However, the above data are all from European countries, the different findings are based on small sample sizes. Additionally, to date, there has been no population-based epidemiological study investigating the etiology or pathogenesis of CPT. Therefore, a retrospective study based on a large sample should be conducted to better explore and enrich the relevant clinical information and knowledge of CPT.

Since the first CPT patient was admitted in our department from 1998, through hard work for nearly 20 years, more than 600 patients with CPT have been treated in our unit [8-18]. Therefore, based on a large number of cases, we established a Hunan CPT study database. The Hunan CPT study, which is a cross-

sectional study of a general population sample of mainland Chinese, is designed to enhance current knowledge of CPT. As the previous studies have been constrained by the number of samples. In this study, the aims of the present paper are to introduce the clinical characteristics of patients with CPT.

Methods

Study design and procedures

We performed a retrospective CPT between 1998 and 2020, in the Human Children's Hospital. Patients who had CPT were identified by radiological review. The trial was conducted in accordance with the Declaration of Helsinki and approved by all local Ethics Committee (HCHLL-2019-37). All the patients provided written informed consent.

Investigations of CPT included patient's general condition (affected side, age of first appearance of symptom, age of the first visit of outpatient, age of first operation and whether combined with NF1 fibular cysts, definite injury and first visiting our hospital), the characteristics of CPT (Crawford classification, the location of the pseudarthrosis, the location of the pseudarthrosis, lateral proximal tibia angle (LPTA), lateral distal tibia angle (LDTA) and whether there be pseudarthrosis of the fibula or cystic changes of the fibula), treatment methods and surgical complications.

Inclusion and exclusion criteria

We included participants aged under 16 years and provided complete data radiological review measurements. We excluded participants aged older 16 years old and others caused by osteomyelitis, trauma and malignant tumor.

Measurements

The location of CPT was a record as proximal 1/3, mid 1/3 and distal 1/3. Briefly, we divided the tibial length into equal 3 parts and record the pseudarthrosis site in each of the proximal, middle or distal part in X-ray that named the proximal 1/3, mid 1/3 and distal 1/3. The measurement methods: at lateral X-rays, the length of the pseudarthrosis to the proximal tibial epiphyseal growth plate (a) and the length of the pseudarthrosis to the distal tibial epiphyseal growth plate (b), calculates $a / (a+b) = c$ ($0 < c < 1$). $C < 1/3$, the pseudarthrosis was recorded as proximal 1/3 of the tibia; $1/3 \leq C < 2/3$, the pseudarthrosis was recorded as mid 1/3 of the tibia; $C \geq 2/3$, the pseudarthrosis was recorded at the distal 1/3 of the tibia. The location of the pseudarthrosis of fibular was measured in the same way. They were recorded as proximal 1/3, mid 1/3 and distal 1/3 of the fibula.

Crawford classification recorded at anteroposterior or lateral X-rays of the tibia/fibula which was taken at the first visit. We referred Springer B et al method^[19] to define LDTA and LPTA. The CPT pathological classification we referred with the Crawford method^[20] and define them in 4 types.

Statistical analysis

The patients of CPT were numbered through the inpatient system and the imaging system, the general data of the corresponding children were entered into the EXCEL2019 form. All data was analyzed using STATA (Version 13.0, StataCorp LP, TX, USA). Two-sample t-tests were used to analyse continuous data, the chi-square test was used for categorical data.

Results

Patient's general condition

Between 1998 and 2020, 514 children with a recorded diagnosis of CPT. 317 (61.67%) boys, 197 (38.33%) girls; 253 (49.22%) in left, 250 (48.63%) in right and 11 (2.15%) in bilateral of affected side; 368 (71.60%) in birth-<1 year, 113 (21.98%) in ≥ 1 -3years and 33 (6.42%) in ≥ 3 years of first appearance of symptom; 66 (12.83%) in birth-<1 year, 231 (44.94%) in ≥ 1 -3years and 217 (42.23%) in ≥ 3 years of the first visit of outpatient; 51 (11.70%) in birth-<1 year, 170 (38.99%) in ≥ 1 -3years and 215 (49.31%) in ≥ 3 years of first treatment; 349 (67.90%) with NF-1, 165 (32.10%) without NF-1; 456 (88.72%) of first treatment in our hospital, 58 (11.28%) of first treatment not in our hospital; 388 (75.49%) without definite injury, 126 (25.51%) with definite injury which included 81 (64.29%) walking fall, 9 (7.12%) bruise with weight, 8 (6.35%) sprain, 4 (3.17%) aggravating activities and 24 (19.05%) falling accidents. (Table 1)

The radiologic features of CPT

Crawford type IV had the largest number of 276 cases, accounting for 53.70% of all types, and the other types were Crawford type I 33 (6.29%), Crawford type II 106 (20.19%) and Crawford type III 56 (10.67%) in turn according to the proportion. For the pseudarthrosis and fibular condition, 276 (53.70%) in CPT with pseudarthrosis of the fibula and 238 (46.30%) in CPT without pseudarthrosis of the fibula; 44 (8.56%) in CPT with cystic changes of the fibula and 470 (91.44%) in CPT without cystic changes of the fibula. For the location of CPT, main locations of the lesion were in the middle and distal tibia in the study, 14 (2.67%) in proximal 1/3 tibia, 191 (36.38%) in mid 1/3 tibia and 319 (60.76%) in distal 1/3 tibia. Genu valgum and ankle valgus had 101 (38.11%) which were the main manifestations of CPT. To explore the statistical difference, only pseudarthrosis of the fibula was statistically between boys and girls ($p=0.015$) (Table 2).

Treatment methods and surgical complications

In our database, 78 (15.18%) cases received conservative treatment and 436 (84.82%) cases received surgical operation. The incidences of surgical complications are the following: 101 (39.60%) cases occurred ankle valgus, 91 (35.69%) cases occurred limb length discrepancy, 38 (14.90%) cases occurred refracture, 15 (5.88%) cases occurred osteomyelitis, and 10 (3.93%) cases occurred displacement of internal fixation (Table 3).

The map of regional distribution

Regional distribution of patients was divided by province, autonomous region and direct jurisdiction cities. 514 cases came from 29 provinces or autonomous regions or direct jurisdiction cities, including 65 (12.67%) in Hunan province, 44 (8.58%) in Henan province, 34 (6.42%) in Shandong province, 28 in Jiangsu province, 27 (5.26%) in Guangxi Zhuang Autonomous Region, 27 (5.26%) in Hubei province, 26 (5.07%) in each Guangdong province, and Jiangxi province, 25 (4.87%) in Hebei province, 25 (4.87%) in Zhejiang province, 21 (4.09%) in Anhui province, 17 (3.31%) in each Gansu province, Liaoning province and Yunnan province, 14 (2.73%) in each Fujian province and Shanxi province, 13 (2.53%) in Jilin province, 12 (2.34%) in each Guizhou province and Sichuan province, 9 (1.75%) in Shanxi province, 8 (1.56%) in Xinjiang Uygur Autonomous Region, 6 (1.17%) in each Heilongjiang province and Nei Monggol Autonomous Region, 5 (0.97%) in each Beijing and Chongqing, 4 (0.78%) in Tianjing, 3 (0.58%) in Ningxia Hui Autonomous Region, 2 (0.39%) in each Hainan province and Shanghai (Figure 1).

Discussion

In this study, we first present a huge cases of CPT described retrospective study, and defined them clinical features from the parts of general condition, radiological and clinical characteristic. Thus, we bring a much more deep knowledge of CPT from Chinese aspect.

In this study, we have collected 514 cases which came from 29 provinces or autonomous regions and direct jurisdiction cities. Hunan province had the highest number of cases with 65 (12.67%), in the top 10 provinces with the largest number of cases, only Guangxi Zhuang Autonomous Region 27 (5.26%) and Jiangxi province 26 (5.07%) was not among the top 10 provinces or autonomous regions and direct jurisdiction cities with the largest population in China. Provinces or autonomous regions and direct jurisdiction cities with larger population had more cases, but Hunan provinces weren't the top one with the largest population in China, which may be related to the geographical location of our hospital.

CPT is a rare pathology occurring in between $1/140,000$ and $1/250,000$ births^[21-23] and is one of the most complex orthopedic situations in pediatrics. Based on the morbidity reported above, in recent 10 years, the number of newborns in China which from official data reports was 157.56 million, from this aspect, this may reflect the number of CPT patients was closed to 630-1125 cases. Of the 514 cases collected in our hospital, 424 cases were collected from 2011 to 2020, and 90 cases were collected from 1999 to 2010. It means that our one center has treated nearly 40% of the national CPT since 2011.

Currently, the timing of surgery for CPT is a controversial issue^[24]. EPOS recommend avoiding surgery for CPT in patients younger than 3 years old, operation should be postponed to the age of 5 years, otherwise, patients may have a worse prognosis^[7]. Hardinge^[25] had similarly recommended deferred surgery to the age of 4 years. However, Shah H^[26] reported that the achievement of bone union in young children can minimize the abnormal growth and lower limb shortening. Joseph^[27] reported that the bone union of CPT occurred in 12 out of 13 (92%) children treated before the age of 3 years. Liu^[14] reported 42 patients

with CPT which were recruited and analyzed, overall, the frequency of bone union was higher in children with CPT operated before reaching 3 years of age, Liu suggested that there is no need to defer surgery for CPT until the child is older than 3 years of age. Considering this controversial issue, in our study, age of first appearance of symptom, first visit of outpatient and first operation were divided into three groups which were birth-<1year, ≥ 1 -<3years and ≥ 3 years. In this study, the age of first appearance of symptom before 3 years had 481 (93.58%) cases and after 3 years had 33 (6.42%) cases; the age of the first visit of outpatient before 3 years had 297 (57.78%) cases and after 3 years had 217 (42.22%) cases ; 221(50.69%) cases had operation before 3 years old and 215 (49.31%) cases had operation after 3 years old; this phenomenon which operation before 3 years was as common as operation after 3 years may be related to the age of the first visit of outpatient.

Pseudarthrosis of the fibula (CPF) is frequently associated with CPT, but it becomes uncommon when it's isolated. Isolated CPF is usually considered a less severe condition than CPT. However, its site most frequently near the ankle leads to severe valgus and instability of this weight bearing joint^[24, 28]. In Liu's study^[10], patients with fibular pseudarthrosis had a high incidence of refracture and ankle valgus, he suggested that attention should be paid to the presence of fibular pseudarthrosis when managing CPT. There were 276 (53.70%) CPF treated in 514 cases of this study, meanwhile 44 (8.56%) cases with cystic changes of his fibula. There were statistical differences in the prevalence of CPF, but no statistical differences in cystic changes of his fibula.

We found that Crawford IV (330, 62.86%) CPT had the greatest cases, which may be associated with hyperactivity. We treated Crawford IV CPT and developed into Crawford IV CPT with operation. It has been well documented that external fixation in children and adolescents have a significant physical and physiological impact, with studies reporting pain and consequent sleeping problems in approximately half of the patients^[29]. The operation complications related primarily to the use of an external or internal device, residual limb-length discrepancy and valgus deformity are commonly reported with an overall complication rate of 30–100%^[30]. In our study, the complication also concluded ankle valgus, limb length discrepancy, refracture, osteomyelitis and removal of internal fixation. ankle valgus (101, 39.60%) and limb length discrepancy (91, 35.69%). The present study is a retrospective review limited by the heterogeneity of the available data and follow-up. Firstly, this study was a cross-sectional analysis and didn't provide prognostic or therapeutic recommendations for cohort studies. Secondly, this study was a single-centre analysis. Although our cases came from all over the country, there was still bias. We should combine The China Pediatric Orthopedic Association with expanding multi-center research in future studies, with further detailed documentation, it may be possible to clarify many more issues^[31].

Conclusion

Until now, we have collected 514 cases of CPT, which was the largest single-centre study. CPT with higher incidence of Crawford IV frequently occurs in boy and middle or distal tibia; the major surgical complications were ankle valgus and limb length discrepancy. In subsequent studies, we will further

report pathologic mechanism, surgical methods, complications, and prognosis of CPT through prospective studies.

Declarations

Author Contributions:

Conceptualization, Y.Z, G.Y. and H.M.; methodology, Y.Z, Y.L and Q.T; validation, K.L., G.Z. and Y.L.; formal analysis, Q.T and Y.Z.; investigation, Y.Z and Q.T.; resources, G.Y. and H.M.; data curation, Y.Z.; writing—original draft preparation, Y.Z.; writing—review and editing, Y.Z, G.Y. and H.M.; supervision, H.M. and G.Z.; project administration, G.Y. and H.M.; funding acquisition, G.Y. and H.M. All authors have read and agreed to the published version of the manuscript.

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Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Ethics Committee of Hunan Children's Hospital (protocol code HCHLL-2019-37). Written informed consent has been obtained from the patients to publish this paper.

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Consent for publication: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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Tables

Table 1 Patient' s general condition

	Male (n=317)	Female (n=197)	Statistical value	P value
Affected Side				
Left	146	107	3.5675	0.168
Right	163	87		
Bilateral	8	3		
Age of first appearance of symptom				
birth-1year	235	133	3.0079	0.22
≥1-3years	65	48		
≥3years	17	16		
Age of the first visit of outpatient				
birth-1year	38	28	1.537	0.464
≥1-3years	149	82		
≥3years	130	87		
Age of first operation				
birth-1year	31	20	1.21	0.54
≥1-3years	113	57		
≥3years	132	83		
NF-1 (Yes/No)				
yes	212	137	0.396	0.529
no	105	60		
First visit of outpatient in our hospital (Yes/No)				
yes	281	175	0.00612	0.9376
no	36	22		
With/without definite injury				
yes	72	54	1.4493	0.229
no	245	143		
walking fall	51	30		
bruise with weight	7	2		
sprain	7	1		

aggravating activities	3	1
falling accidents	4	20

Table 2 The characteristics of CPT

	Male (n=317)	Female (n=197)	Statistical value	P value
Crawford classification (n1+n2 means n1=lateral and n2 =bilateral)				
I	20	12+1	1.78	0.618
II	54+6	45+1		
III	33+3	18+2		
IV	202+7	119+2		
pesudarthrosis of the fibula (Yes/No)				
Yes	183	93	5.9228	0.015
No	134	104		
Cystic changes of the fibula (Yes/No)				
Yes	29	15	0.3653	0.546
No	288	182		
The location of the pesudarthrosis (n1+n2 means n1=lateral and n2 =bilateral)				
Proximal 1/3	6	7+1	3.9795	0.137
Mid 1/3	110+2	76+3		
Distal 1/3	192+14	111+2		
LPTA and LDTA				
LPTA	86.91±5.002	86.98±5.456	0.1437	0.8858
LDTA	87.573±10.928	87.079±10.432	-0.5088	0.6111

Table 3 Treatment methods and surgical complications

	Male	Female	Statistical value	P value
Treatment methods				
Non-operation	41	37		
operation	276	160	3.227	0.072
Surgical complication				
Ankle valgus	63	38	3.5205	0.475
Limb length discrepancy	56	35		
Refracture	18	20		
Osteomyelitis	8	7		
Removal of Internal fixation	7	3		

Figures

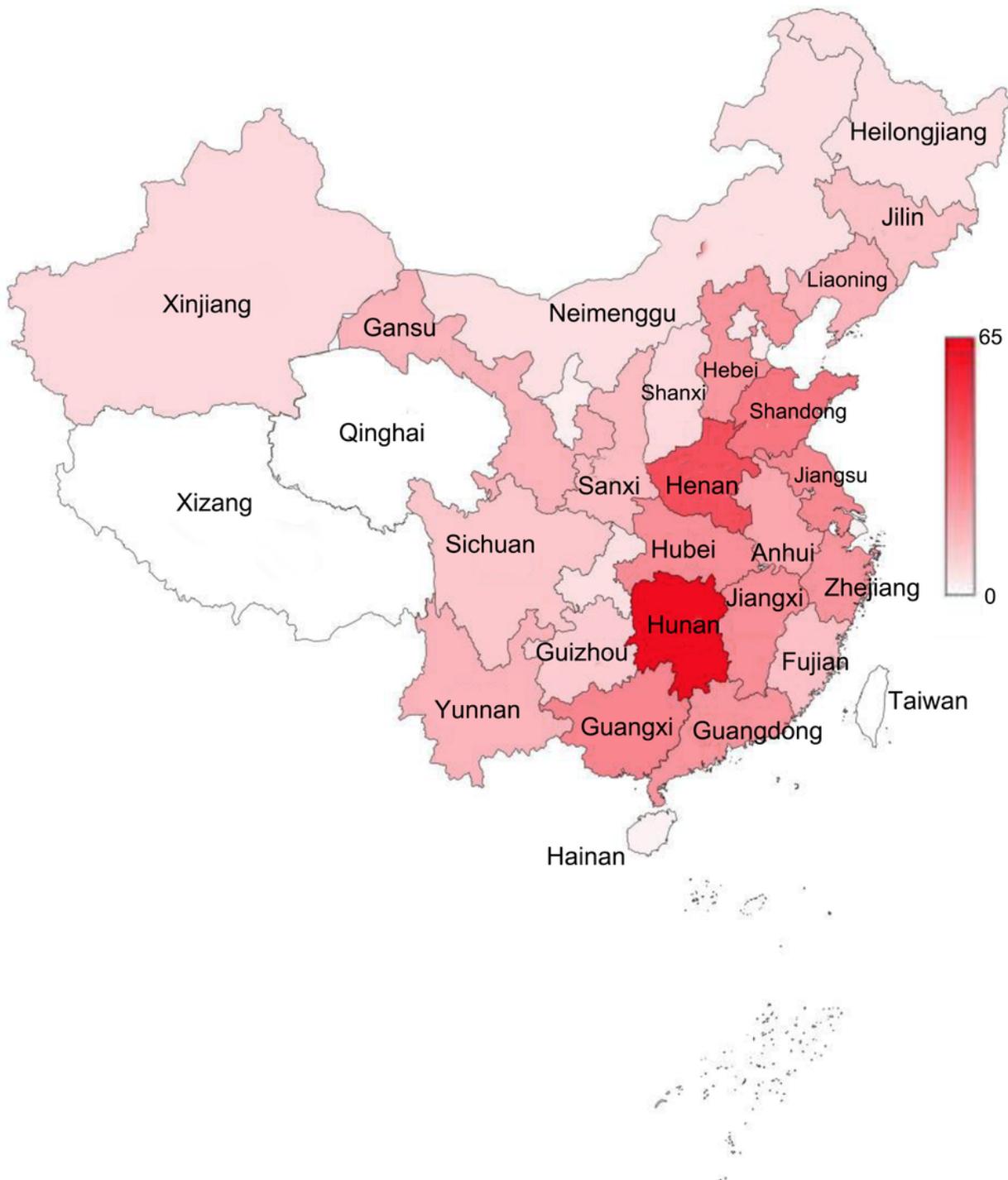


Figure 1

Regional distribution of patients was divided by province, autonomous region and direct jurisdiction cities. 514 cases came from 29 provinces or autonomous regions or direct jurisdiction cities, including 65 (12.67%) in Hunan province, 44 (8.58%) in Henan province, 34 (6.42%) in Shandong province, 28 in Jiangsu province, 27 (5.26%) in Guangxi Zhuang Autonomous Region, 27 (5.26%) in Hubei province, 26 (5.07%) in each Guangdong province, and Jiangxi province, 25 (4.87%) in Hebei province, 25 (4.87%) in

Zhejiang province, 21 (4.09%) in Anhui province, 17 (3.31%) in each Gansu province, Liaoning province and Yunnan province, 14 (2.73%) in each Fujian province and Shanxi province, 13 (2.53%) in Jilin province, 12 (2.34%) in each Guizhou province and Sichuan province, 9 (1.75%) in Shanxi province, 8 (1.56%) in Xinjiang Uygur Autonomous Region, 6 (1.17%) in each Heilongjiang province and Nei Monggol Autonomous Region, 5 (0.97%) in each Beijing and Chongqing, 4 (0.78%) in Tianjing, 3 (0.58%) in Ningxia Hui Autonomous Reigion, 2 (0.39%) in each Hainan province and Shanghai.