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Research Article

Relationships Between Seasonal Variation and Idiopathic Congenital Talipes Equinovarus in Northwest China

Running title: Relationship Between Season and Equinovarus

Yi-Jun Yang, Xiao-Wei Wang, Jun-Hu Mao, Kai-Hua Gou*

Department of Orthopedics, The Affiliated Children's Hospital of Xi'an Jiaotong University, Xi'an City, Shaanxi Province, China

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Abstract: ***Background:*** The purpose of this study was to determine whether the occurrence of neonatal idiopathic congenital talipes equinovarus (ICTEV) in Northwest China followed a seasonal pattern and to speculate the potential etiology of ICTEV. ***Methods:*** We collected data from 221 children with ICTEV who were born in Northwest China to investigate seasonal variations. We also analyzed seasonal variations in the month of birth and severity. ***Results:*** Among male infants with ICTEV, the constituent ratio of children born in May and October was statistically different from that of normal children (OR=1.674, 95%CI, 1.003-2.795, P=0.049; OR=0.041, 95%CI, 0.450-0.968, P=0.041). The months distribution of unilateral and bilateral limb was different (P=0.025). The constituent ratio of bilateral limb in March was higher than that in the other months(P=0.003). ***Conclusions:*** This study does not support an in-utero enterovirus infection as the etiology of ICTEV. However, the current research provides strong evidence in support of an unidentified environmental factor influencing the occurrence of ICTEV in the Northwest Chinese population.

Keywords: Equinovarus; Seasonal variation; Blood folate level

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Corresponding author: Kai-Hua Gou, orientdoctor@163.com

Abbreviations: ICTEV, Idiopathic Congenital Talipes Equinovarus Introduction; OR, odds ratio; ORL, The lower limit of OR value confidence interval; ORU, The upper limit of OR value confidence interval.

1 Introduction

Idiopathic congenital talipes equinovarus (ICTEV) is one of a kind of common orthopedic surgery disease. The global annual incidence is 0.6~1.5/1000[1]. The annual incidence in China was 0.51/1000[2]. Male: female ratio was 1.68:1[3]. For the past 50 years, the main treatment method adopted by physicians for ICTEV has been the Ponseti method.

Neonates with ICTEV demonstrate a seasonal pattern of birth, and current evidence suggests that exposure to risk-factors during pregnancy may play a significant role in ICTEV incidence. Previous studies have reported that the birth season of children with ICTEV in eastern and southeastern China has no effect on the incidence of ICTEV, and the gender-related birth season has no influence on ICTEV[4]. However, the incidence of ICTEV in babies born in Britain in winter months, March and April is higher than that in babies born in the other seasons[5-6]. Currently, there is no research on the correlation between ICTEV incidence and birth season in children in Northwestern China. To address this knowledge gap, we conducted a case-control study in nearly 2000 people living in Northwestern China. This study will improve our understanding of the mechanisms of the development of ICTEV.

2 Methods

2.1 Study population and design

The subjects of this study were 221 children with ICTEV born between January 2014 and December 2017 and who were admitted to the orthopedics department of the Affiliated Children's Hospital of Xi'an Jiaotong University. Inclusion criteria for the case group were as follows: 1) children conforming to the diagnosis of ICTEV; 2) children undergoing the Ponseti therapy and surgery in the department of orthopedics; 3) children born between January 2014 and December 2017; 4) children whose mothers lived in Northwest China during pregnancy, and the duration of pregnancy was 37 to 42 weeks; and 5) birthplaces of children included Shaanxi, Shanxi, Ningxia, Gansu, Qinghai, and Inner Mongolia. The exclusion criterion for the case group was children with other malformations. The date of birth, gender, and region of birth were collected from the hospital medical records system. The severity of the deformity was graded by the number of casts used. Children who were born between January 2014 and December 2017 and who were hospitalized in the orthopedics department were classified into the control group.

2.2 Statistical analysis

χ^2 test was used to compare the differences in the constituent ratios of number of birth in season or month between the ICTEV case group and the control group. When the theoretical frequency was less than 5, Fisher's exact probability method was adopted. Differences in severity at birth season or month in children with ICTEV were measured by the Student's t test or the rank sum test. The Kruskal-Wallis test was used for data from multiple groups of measurement. $P<0.05$ was considered statistically significant. This study was approved by the ethics committee of the Affiliated Children's Hospital of Xi'an Jiaotong University(No.:20190006).

3 Results

The study included 221 children with ICTEV, including 161 males and 60 females. Further, 82 cases had bilateral disease and 139 cases had unilateral disease (left-sided disease in 52 cases, right-sided disease in 87 cases), which was similar to that reported in previous studies.[4] The ratio of male to female patients was 2.68:1; which was the same as that reported in a previous study[3]. There were 1901 normal children in the control group, including 1101 males and 800 females, in the study, and the male to female ratio was 1.38:1.(Figure 1) There was no difference in the seasonal constituent during the four years(P=0.861), and there was no difference in the monthly constituent during the four years(P=0.437). There was no statistical difference in the birth season of children with ICTEV, but through the use of a combined grid, the constituent ratio of children born in May and those born in other months was different, and the ratio of children born in May was higher than that of children born in the other months (Table 1). There was a difference in the gender constituent between the case group and the control group($P<0.01$) (Table 5); therefore, a stratified analysis was required. There was no difference in the birth season of male infants with ICTEV, but the constituent ratio of children born in May and October was statistically different from that of children without ICTEV (OR=1.674, 95%CI, 1.003-2.795, P=0.049; OR=0.041, 95%CI, 0.450-0.968, P=0.041) (Table 2). The constituent ratio of children and women with ICTEV born in seasons and months was not statistically different from that of children in the control group (Table 3). The severity of malformation in children with ICTEV was different in spring and autumn, and the severity of malformation in children born in spring was greater than that in children born in autumn(p=0.023). There was no difference between birth months (P=0.810), and there was no difference in severity between sexes (P=0.630). There was no difference in severity between births (P=0.678). There was no difference in seasonal distribution between cases with unilateral and bilateral limb(P=0.294). The months distribution of unilateral and bilateral limb was different(P=0.025); and through the use of a grid combination, it was found that the constituent ratio of bilateral limb in March was higher than that in the other months(P=0.003).

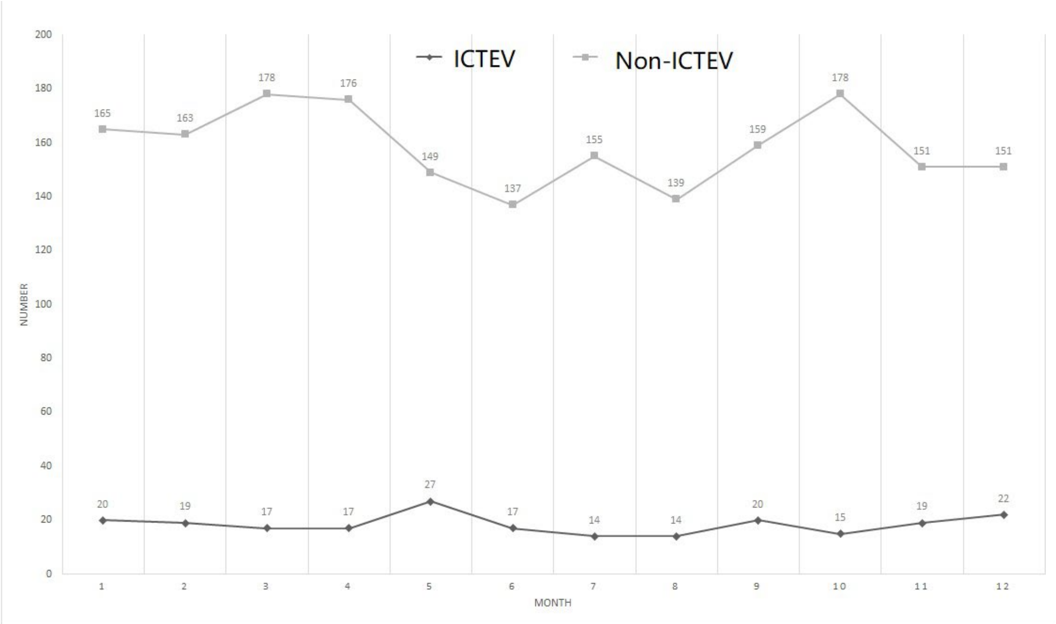

Figure 1. The graph showing the monthly distribution of children with ICTEV in the authors' department during the 4-year period and the monthly distribution of children from the same areas during the period between January 2014 and December 2017.

Table 1. Baseline Characteristics of the 2122 Person-trials Derived From The Affiliated Children's Hospital of Xi'an Jiaotong University (2014-2017), Comparing ICTEV Person-trials With Non-ICTEV Person-trials. And Odds Ratios For the Association Between ICTEV and Season/Month Variation in 2122 Person-trials.

	ICTEV		**Non-ICTEV**						
	n	**%**	**n**	**%**	**χ^2**	**P**	**OR**	**ORL**	**ORU**
Characteristic	**(n=221)**		**(n=1901)**						
Male sex	161	72.9	1101	57.9	18.319	**<0.001**	**1.950**	**1.436**	2.647
Season									
Spring	61	27.6	503	26.5	0.132	0.716	1.060	0.775	1.448
Summer	45	20.4	431	22.7	0.607	0.436	0.872	0.618	1.231
Autumn	54	24.4	488	25.7	0.159	0.690	0.936	0.677	1.294
Winter	61	27.6	479	25.2	0.603	0.437	1.132	0.828	1.547
Month									
January	20	9.1	165	8.7	0.034	0.854	1.047	0.643	1.704
February	19	8.6	163	8.6	0.000	0.991	1.003	-	-
March	17	7.7	178	9.4	0.663	0.416	0.807	0.481	1.353
April	17	7.7	176	9.3	0.587	0.443	0.817	0.487	1.371
May	27	12.2	149	7.8	4.992	**0.025**	**1.636**	**1.062**	**2.521**
June	17	7.7	137	7.2	0.069	0.792	1.073	0.634	1.815
July	14	6.3	155	8.2	0.893	0.345	0.762	0.433	1.339
August	14	6.3	139	7.3	0.283	0.595	0.857	0.486	1.512
September	20	9.1	159	8.4	0.121	0.728	1.090	0.670	1.773
October	15	6.8	178	9.4	1.589	0.207	0.705	0.409	1.214
November	19	8.6	151	7.9	0.115	0.735	1.090	0.662	1.795
December	22	10.0	151	7.9	1.070	0.301	1.281	0.801	2.049

Abbreviations: ICTEV, Idiopathic congenital talipes equinovarus; χ^2, Chi-square value; OR, Odds ratios; ORL, The lower limit of OR value confidence interval; ORU, The upper limit of OR value confidence interval

Table 2. Odds Ratios For the Association Between ICTEV and Season/Month Variation in 1262 Male Person-trials.

	ICTEV		Non-ICTEV		χ^2	P	OR	ORL	ORU
	n	%	n	%					
Characteristic	**(n=161)**		**(n=1101)**						
Season									
Spring	47	29.2	297	27.0	0.348	0.555	1.116	0.775	1.608
Summer	31	19.3	249	22.6	0.919	0.338	0.816	0.538	1.237
Autumn	39	24.2	269	24.4	0.003	0.954	0.989	0.659	1.483
Winter	44	27.3	286	26.0	0.133	0.715	1.072	0.739	1.555
Month									
January	14	8.7	99	9.0	0.015	0.902	0.964	0.535	1.735
February	16	9.9	102	9.3	0.075	0.784	1.081	0.620	1.884
March	12	7.5	102	9.3	0.468	0.494	0.789	0.400	1.557
April	15	9.3	109	9.9	0.054	0.816	0.935	0.531	1.648
May	20	12.4	86	7.8	3.882	**0.049**	**1.674**	**1.003**	**2.795**
June	13	8.1	81	7.4	0.105	0.746	1.106	0.601	2.036
July	9	5.6	95	8.6	1.715	0.190	0.627	0.312	1.261
August	9	5.6	73	6.6	0.250	0.617	0.834	0.409	1.700
September	16	9.9	85	7.7	0.938	0.333	1.319	0.753	2.310
October	7	4.3	101	9.2	4.180	**0.041**	**0.450**	**0.209**	**0.968**
November	16	9.9	83	7.5	1.118	0.290	1.353	0.772	2.372
December	14	8.7	85	7.7	0.185	0.667	1.138	0.631	2.055

Abbreviations: ICTEV, Idiopathic congenital talipes equinovarus; χ^2, Chi-square value; OR, Odds ratios; ORL, The lower limit of OR value confidence interval; ORU, The upper limit of OR value confidence interval

Table 3. Odds Ratios For the Association Between ICTEV and Season/Month Variation in 860 Female Person-trials.

	ICTEV		Non-ICTEV		χ^2	P	OR	ORL	ORU
	n	%	n	%					
Characteristic	**(n=60)**		**(n=800)**						
Season									
Spring	14	23.3	206	25.8	0.171	0.679	0.878	1.630	0.473
Summer	14	23.3	182	22.8	0.011	0.917	1.033	0.559	1.911
Autumn	15	25.0	219	27.4	0.159	0.690	0.884	1.618	0.483
Winter	17	28.3	193	24.1	0.536	0.464	1.243	0.694	2.228
Month									
January	14	23.3	99	12.4	0.223	0.637	1.236	0.513	2.974
February	16	26.7	102	12.8	*	0.613			
March	12	20.0	102	12.8	0.089	0.765	0.866	2.228	0.337
April	15	25.0	109	13.6	*	0.219	-	-	-
May	20	33.3	86	10.8	*	0.323	-	-	-
June	13	21.7	81	10.1	*	1.000	-	-	-
July	9	15.0	95	11.9	*	0.799	-	-	-
August	9	15.0	73	9.1	*	1.000	-	-	-
September	16	26.7	85	10.6	0.452	0.502	0.701	1.976	0.249
October	7	11.7	101	12.6	0.862	0.353	1.445	0.665	3.140
November	16	26.7	83	10.4	*	0.468	-	-	-
December	14	23.3	85	10.6	1.834	0.176	1.711	0.786	3.722

Abbreviations: ICTEV, Idiopathic congenital talipes equinovarus; χ^2, Chi-square value; OR, Odds ratios; ORL, The lower limit of OR value confidence interval; ORU, The upper limit of OR value confidence interval
*Theoretical frequency<1, using Fisher probabilities in 2*2 table data method

4 Discussion

Several reports have shown that that seasonality of birth plays an important role in ICTEV incidence[5-9]. The first research question in this study sought to determine the correlation between seasonality of birth and constituent ratio of ICTEV. The second research question in this research was to assess the correlation between seasonality of birth and severity of ICTEV. The current study found that the highest number of children with ICTEV were born in May. However, the fewest number of children with ICTEV were born in October. This finding is consistent with that in the study by Barker et al. who found that the incidence of ICTEV was increased in the months of March and April and there was a decrease in the incidence of ICTEV in the months of October and November[6]. The authors suggest that both environmental and genetic factors may play a role. Toxins, temperature, season, and infectious pathogens are the possible pathogenic factors in summer. These results reflect those of Robertson et al. who also found that a larger number of mothers who born the children with ICTEV were pregnant in June. The authors suggested that a limited enterovirus anterior horn cell infection could theoretically produce a clubfoot deformity. The peak time of enterovirus infection in temperate climates corresponds to the ideal time for the production of such an embryologic problem. This research seemed to support the intrauterine viral hypothesis of the cause of congenital clubfoot deformity. However, the epidemic pattern of hand foot and mouth disease in Shaanxi province has two peaks in May and November and the lowest incidence in December and February. Pryor et al. noted that in normal fetal life, the talus attains its correct alignment around 16 weeks of gestation and that environmental influences may have their maximum impact at that time[5]. The epidemiological pattern of enterovirus in Shaanxi province is different from that in our study.

Hyperthermia is a well-known animal teratogen, and maternal fever has been associated with birth defects in human studies[10]. The external and internal temperature in summer is higher than that in winter. In Northwest China, especially in Shaanxi province, the temperature is the hottest from July to August and the coldest from December to January[11]. Temperature-related factors may affect the embryos early in pregnancy. However, these factors were not consistent with the finding that children born in May whose mothers were pregnant in August formed the anterior horn of the spinal cord in October, and children born in October whose mothers were pregnant in January formed the anterior horn of the spinal cord in March[12].

The blood folate level of Chinese people is high in winter and spring and low in summer and autumn[13]. This is similar to the seasonal patterns that we noted. Moorthi et al. found that the prevalence odds ratios (PORs) for ICTEV before and after maternal folic acid fortification showed a very small decrease among infants born after fortification[14]. This may also explain why the severity of deformity and the side of affected feet in children with ICTEV were different in spring and autumn. However, the findings of the current study do not support the previous research. Pavone observed that patients with clubfoot were born most frequently during the period January to March[8]. The reasons may include temperature and food toxins. Furthermore, the Italian enterovirus epidemic occurs from April to June[15]. I It has previously been suggested that patients with clubfoot were born most frequently during the period December to February.5 This inconsistency in the finding may be due to the fact that the authors suggested that pregnancy at 16 weeks (July to October) is affected in some way, which is consistent with the enterovirus epidemic in the UK from July to December[16].

In this case control study, there is a potential for bias arising from the fact that many neonates born with clubfeet were not registered in Northwest China because of the limited source of healthcare registry in China. Our department is specialized in the field of clubfoot management using the Ponseti method across Northwest China, and thus a great number of patients visit our department for treatment. Although the sample size of 221 neonates was found to be adequate. Further multi-center investigations are required to identify the possible factors predisposing to clubfoot incidence in terms of seasonal variation. Seasonal variation in the incidence cannot be explained by heritable factors alone, and hence, this study provides strong evidence in support of an unidentified environmental factor influencing the incidence of ICTEV in the Northwest Chinese population.

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