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A CLINICAL, GENETIC AND EPIDEMIOLOGIC STUDY OF CONGENITAL CLUB FOOT[1]

Haruyasu YAMAMOTO

Department of Orthopedics, Tokyo Medical and Dental University, Tokyo, Japan

Summary Among 16,100 infants born from 1973 to 1976 at Tokyo Medical and Dental University and its affiliated hospitals, there were 14 patients with congenital club foot, an incidence of 0.87 per 1,000 live births. A family study was made based on 185 patients with this deformity diagnosed in these hospitals from 1960 to 1976. The male to female ratio was 2 : 1. Bilateral and unilateral affected cases were observed in equal numbers. The proportion of the probands who had other malformation was 10.3%. A sharp fall in the incidence among the relatives was observed, paralleling the remoteness of the blood relation. This suggests that congenital club foot is compatible with the model of multifactorial inheritance.

Heritability of the liability to the abnormality was estimated to be 72± 18%.

INTRODUCTION

Many hypotheses have been proposed concerning the etiology of congenital club foot; these include arrest of the embryologic development of the foot, muscle paralysis or spasm, mechanical distorsion and the effects of a germ plasm defect. Adams (1873) was the first to report that the disease tended to be familial. Family surveys of congenital club foot were made with contradictory conclusions such as autosomal recessive inheritance (Fetscher, 1921; Idelberger, 1939b), sex-linked recessive inheritance (Isigkeit, 1927) and autosomal dominant inheritance with reduced penetrance (Palmer, 1964). Idelberger (1939a) carried out a survey of twins and found that congenital club foot was concordant in 4 out of 134 (2.9%) dizygotic twin pairs and in 13 out of 40 (32.5%) monozygotic twin pairs. This result indicated that genetic factors had etiological implications in congenital club foot, although other factors were also involved. Recent observations by Wynne-Davies

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(1964), Carter (1965), Chung *et al.* (1969) and Palmer *et al.* (1974) suggest that many loci may be involved in the pathogenesis of the disease.

Little is known about the epidemiology and genetics of this defect in Japan. The present study was undertaken to investigate the incidence of congenital club foot in general population of the Kanto district, Japan, and the role of genetic factors in the etiology of this defect.

MATERIALS AND METHODS

Congenital club foot denotes a deformity characterized by adduction, varus, equinus and cavus of the foot. Club foot secondary to cerebral palsy, spina bifida, arthrogryposis or other neurological defects is not normally included.

The general incidence of congenital club foot here reported is based on the author's examination of the records on 16,100 consecutive deliveries (male 8,519, female 7,581) from January 1973 to December 1976 at the Tokyo Medical and Dental University and its affiliated hospitals. Probands for the genetic study were 185 patients with congenital club foot diagnosed in the above mentioned University and hospitals from January 1960 to December 1976. Family histories were taken from the parents of these proband children. Confirmation was obtained in all secondary cases from the physicians treating those affected relatives whom the author could not examine.

RESULTS

Incidence among live births

There were 9 male patients and 5 female patients with this deformity among 8,519 and 7,581 live births, respectively. Indicence in the males was 1.06 and in the females was 0.66 per 1,000 live births. The incidence in the sexes combined was 0.87 per 1,000.

Table 1. Numbers of probands with congenital club foot, by sex and the laterality of the affection.

Sex		Laterality			Total
		Right	Left	Bilateral	
Males	No.	33	32	59	124
	%	26.1	25.8	47.6	67.0
Females	No.	10	15	36	61
	%	16.4	24.6	59.0	33.0
Total	No.	43	47	95	185
	%	23.2	25.4	51.4	100.0

Sex ratio, laterality and associated malformations in 185 probands

Table 1 shows 185 probands by sex and the foot affected. The ratio of males to females was 2 : 1. Bilateral and unilateral cases were nearly equal in number. Among the 185 probands, 19 cases (10.3%) were complicated with other malformations which were: two cases with hand defects, two with toe defects, two with retentio testis, three with cleft lip with or without cleft palate and thirteen cases with various connective tissue defects, including congenital heart disease, congenital dislocation of the hip, inguinal hernia and torticollis. The proportion of patients with other malformations was 14.8% in females and 8.1% in males.

Table 2. Numbers of probands with congenital club foot by birth order.

Birth order	Males			Females		
	Observed	Expected	χ^2	Observed	Expected	χ^2
1	61	55.65	0.51	30	27.38	0.25
2	49	47.03	0.08	23	23.17	0
3	12	17.27	2.51	7	8.45	0.57
4-	2	4.05		1	2.00	
Total	124	124.00	3.10 (d.f.=2)	61	61.00	0.82 (d.f.=2)

Control data were obtained from Vital Statistics for 1972 in Japan.

Table 3. Maternal ages and birth orders in the probands.

Male

Maternal age in years	Liver birth order								
	1			2			3-		
	Obs.	Exp.	χ^2	Obs.	Exp.	χ^2	Obs.	Exp.	χ^2
-19	1	2.64	2.23	0	0		0	0	
20-24	24	31.02		2	9.88	1.13	0	0.52	0.52
25-29	33	27.02	0.92	27	25.45		3	4.51	
30-34	7	4.40	1.35	13	10.01	3.42	8	4.92	0.69
35-	1	0.92		5	1.66		0	1.05	
Total	66	66.00	4.50 (d.f.=2)	47	47.00	4.55 (d.f.=1)	11	11.00	1.51 (d.f.=1)
Female									
-19	2	0.56	2.38	0	0		0	0	
20-24	6	13.16		3	4.08	0.22	0	0.36	0.81
25-29	15	11.76	0.89	13	13.93		2	3.38	
30-34	2	1.96	2.44	8	5.03	0.67	5	4.08	0.58
35-	3	0.56		0	0.96		2	1.18	
Total	28	28.00	5.71 (d.f.=2)	24	24.00	0.89 (d.f.=1)	9	9.00	1.39 (d.f.=1)

Control data were obtained from Vital Statistics for 1972 in Japan.

Table 4. Proportions of affected first, second and third degree relatives of probands with congenital club foot.

Probands with congenital club foot	First degree relatives				Second degree relatives		Third degree relatives (1st cousins)		
	Father	Mother	Brothers	Sisters	Uncles	Aunts	Males	Females	Total
Male 124	1/124	1/124	0/64	0/36	1/368	0/412	2/539	1/515	6/2182
Female 61	1/61	0/61	1/57	1/26	1/194	1/210	0/302	0/270	5/1181
Total		3/370 (0.81%)		2/183 (1.09%)		3/1184 (0.25%)		3/1626 (0.18%)	

Birth order, maternal age and perinatal factors

Table 2 shows the number of probands by birth order along with the expected numbers based on the Birth Statistics 1972 of Japan. No significant differences were found. Table 3 shows the maternal ages and birth orders of the probands. Compared with the expected numbers based on the Birth Statistics 1972 of Japan, there was no significant effect of maternal age in any birth rank. Breech delivery was reported in 5.4% of probands, whereas caesarian sections occurred in 4.9% of cases. These figures were not significantly different from those among the 200 babies who were born at Tokyo Medical and Dental University in 1976 ($\chi^2=0.41$, $p>0.05$ and $\chi^2=0.48$, $p>0.05$). The birth weight of the probands was 3,098$\pm$ 327 g, again not differing from normal babies ($p>0.05$).

Correctability

Correctability of congenital club foot was studied in 131 probands who were over 2 years of age and who were treated to obtain adequate correction. The cases were divided in two groups; 1) those successfully treated utilizing conservative treatments alone, and 2) those requiring operative treatments. There was no difference in correctability between females and males ($\chi^2=1.18$, $p>0.05$), and between the cases with a positive family history and those with a negative family history ($\chi^2=2.31$, $p>0.05$). Bilaterally affected cases were surgically treated more often than unilateral cases ($\chi^2=4.41$, $0.02<p<0.05$).

Genetic analysis

No instance of consanguineous marriage was encountered among parents of the probands. The parents were normal except in three families. In two of the latter the father was affected and in one the mother was affected. The frequency of affected siblings in sibships in which both parents were normal was 1.10$\pm$0.77%. It was 0% for siblings in sibships with one affected parent.

The frequencies of congenital club foot among various relatives of the probands are shown in Table 4. The proportion of first degree relatives affected was 0.90$\pm$0.40%, in second degree relatives 0.25$\pm$0.14%, and in third degree relatives (first cousins) 0.18$\pm$0.10%. The proportion of affected relatives of male probands

was $0.27\pm0.11\%$ and that of female probands was $0.42\pm0.19\%$. No significant difference was found in the frequency between relatives of male and female probands ($\chi^2=0.58$, $p>0.05$). Compared with the incidence in the general population (0.087%), the incidence was increased 10-fold in first degree relatives, 3-fold in second degree relatives, and 2-fold in third degree relatives. The incidence declined sharply from first degree relatives to third degree relatives, towards the figure for the general population incidence.

Edwards (1960) indicated that in multifactorial inheritance with threshold the expected incidence of the trait among first degree relatives was approximately $p^{1/2}$ and among first cousins $p^{4/5}$, where p was the incidence in the general population. Applying this model to the present data, the expected incidences among first degree relatives were 3.26% ($\sqrt{0.00106}$) in males and 2.57% ($\sqrt{0.00066}$) in females, and among first cousins were 0.42% ($0.00106^{4/5}$) in males and 0.29% ($0.00066^{4/5}$) in females. Using F-distribution for the test of observed and expected incidence in each family class, the observed incidences among first degree relatives (fathers, $1.08\pm0.76\%$; mothers, $0.54\pm0.54\%$; male siblings, $0.83\pm0.82\%$; female siblings, $1.61\pm1.60\%$) were not significantly different from each expected incidence ($F_0=2.06$, $p>0.05$; $F_0=2.43$, $p>0.05$; $F_0=2.02$, $p>0.05$; $F_0=0.80$, $p>0.05$) and among first cousins (male, $0.24\pm0.17\%$; female, $0.13\pm0.13\%$) were not also significant ($F_0=1.18$, $p>0.05$; $F_0=1.14$, $p>0.05$).

DISCUSSION

The incidence of congenital club foot in Japan was reported to be 1.24 per 1,000 live and still births by Mitani (1953). Neel (1958), who studied major congenital defects in Japanese infants in the Hiroshima and Nagasaki areas, reported a value of 0.92 per 1,000 live and still births. The present study, which is based on live births only, revealed the rate to be 0.87 in the Kanto district.

Chung *et al.* (1969) found racial differences in the incidence of congenital club foot in Hawaii. Hawaiians had the highest incidence, 6.81 per 1,000, followed by Caucasians, 1.12. The Oriental group had the lowest incidence of 0.57. Japanese in Hawaii had an incidence of 0.54 per 1,000. which is comparable with the figure in Japan.

Palmer (1964) reported that congenital club foot was twice as common in males as in females and that roughly half of the cases was bilaterally affected and that the unilateral cases were rather evenly divided between the right and the left side. Similar results were obtained from the present data.

It is well known that congenital club foot is often associated with other malformations. Wynne-Davies (1964) found a high frequency of connective tissue disorders such as hernia, congenital dislocation of the hip, congenital heart disease and generalized joint laxity. Chung *et al.* (1969) observed a high frequency of hand deformities and toe defects. They pointed out that Japanese cases of congenital

club foot in Hawaii were the highest in the incidence of harelip with or without cleft palate, among all racial groups. The present data show a high frequency of connective tissue disorders and also a relatively high frequency of hand deformities, toe defects and harelip. In 90% of these patients with other malformations, congenital club foot had to be treated surgically.

Wynne-Davies (1972) pointed out that it was extremely difficult to evaluate the severity of congenital club foot as poor results following treatment might be due to extrinsic factors other than the severity of the initial deformity. While Chung *et al.* (1969) recognized this, they evaluated the degree of difficulty in treatment and classified their patients into four categories and found no significant differences between less and more easily treatable patients in sex, laterality and correctability. In this study no significant difference was found in correctability between cases with a positive family history and those with a negative family history, and between male and female patients. Bilaterally affected cases were treated more often surgically than unilaterally affected cases, suggesting that the former were more severe than the latter.

Idelberger (1939a) found that 67.5% of monozygotic twin pairs were discordant for congenital club foot. This suggests that environmental factors play a considerable role in the etiology in addition to genetic factors. Mechanical factors and intrauterine compression are seen examples of such environmental factors. In this study maternal illness during pregnancy and abnormal labor were evaluated in addition to birth order, maternal age and birth weight. All the factors were not associated with congenital club foot. Wynne-Davies (1964) and Chung *et al.* (1969), also, found that these factors were not related to the birth of a child with congenital club foot.

Carter (1965) analyzed Wynne-Davies' data (1964) and found that the incidence fell rapidly from first degree relatives to second and then to third degree relatives and that the incidence in the latter approached the general incidence. He suggested that congenital club foot accorded with the model of multifactorial inheritance. Chung *et al.* (1969) and Palmer *et al.* (1974) also analyzed their own data and agreed with Carter's results. In the present study the family patterns of congenital club foot were not compatible with recessive inheritance because of an almost equal incidence in parents and siblings. X-linked inheritance could be ruled out because affected fathers transmitted the same disorder to their sons. Of the remaining possibilities, dominant inheritance with reduced penetrance and multifactorial inheritance, the former was rejected because of the ridiculous paucity of affected parents and siblings. On the other hand, the incidence of congenital club foot fell sharply from first degree to third degree relatives, to the level in the general population. This fitted well with the expectation under the model of multifactorial inheritance. And applying Edwards' hypothesis to the present data, observed incidences among first degree relatives and first cousins were not significantly different from each expected incidence. From these results congenital club foot is com-

patible with the model of multifactorial inheritance. The finding of lower observed incidences in first and third degree relatives than figures expected from Edwards' model might be due to non-inclusion of milder cases in family taken from parents, while the figure in general population was based upon author's criteria which included milder cases.

The recurrence rate in the subsequent siblings was 2.86±1.99%, a 33-fold increase compared with the general incidence. Wynne-Davies (1964) reported a figure of 2.86% in England, and Palmer *et al.* (1974) 2.96+0.75% in the United States. These rates are very close to one another.

Applying the recurrence rate in siblings and the incidence in the general population to the model proposed by Falconer (1965), the heritability of liability to congenital club foot in Japan is estimated to be 72±18% (male, 67±26%; female, 79±27%). This value is very similar to Falconer's estimate for Caucasians (70± 8%) based on the data of Wynne-Davies (1964).

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