The mechanism of genetic predisposition in congenital dislocation of the hip

A. CZEIZEL, G. TUSNÁDY, G. VACZÓ, and T. VIZKELETY

Laboratory of Human Genetics, National Institute of Public Health; Mathematical Institute of the Hungarian Academy of Sciences; and Department of Orthopaedics, Semmelweis University of Medical Sciences, Budapest, Hungary.

Summary. The important role of polygenic acetabular configuration and monogenic joint laxity has again been proved in the aetiology of congenital dislocation of the hip. According to the findings reported these two genetic predispositions seem to be unrelated. The time of diagnosis in acetabular dysplasia type and joint laxity type did not differ, thus the neonatal and late-diagnosed cases do not seem to be two clear-cut entities.

Congenital dislocation of the hip (CDH) seems to be the most common congenital malformation in Hungary (Czeizel, Vizkelety, and Szentpéteri, 1972). Carter and Wilkinson (1964) have postulated that there are two gene systems acting in the aetiology of CDH: one relates to dysplasia of the acetabulum and is polygenic, while the other controls the capsule round the hip joint and is probably dominant. Wynne-Davies (1970a) has found that there is a preponderance of the joint laxity type in neonatal CDH and of the acetabular dysplasia type in late-diagnosed CDH. The purpose of this survey was (1) to study the connection of these two genetic predisposing factors; (2) to study the differences between neonatal and late-diagnosed CDH; and (3) to study the role of the sex hormone of mothers in the triggering of the genetic predisposition.

Material and methods

The sample was 3000 children treated for CDH, born in Budapest between 1962 and 1967 and ascertained in an epidemiological survey. A family study involving 1767 index patients was made by questionnaires (Czeizel *et al*, 1975). One hundred and fifty boys and 150 girls were randomly selected from index patients with sibs; these 300 subjects were seen personally.

Parents not planning more children were persuaded to undergo pelvimetry. Thus radiographic examination (antero-posterior view) was carried out in 84 fathers and 90 mothers and the Wiberg angle (Wiberg, 1953) was

determined using Müller's ischiometer. Data from one father and three mothers with CDH were discarded. A control group was studied which consisted of age-matched individuals who had suffered accidents and had pelvimetry which failed to show any damage of pelvis, hip, and femur (Vaczó, Schwáb, and Czeizel, 1974).

Index patients were examined for undue joint laxity in five joints (second metacarpophalangeal joint, carpometacarpal + first metacarpophalangeal joint, elbow, knee, and ankle) and first-degree relatives in one joint (second metacarpophalangeal). Finally 90 girls and 138 boys were evaluated. The age- and sex-matched child and adult control groups were examined in five joints (Fehér *et al*, 1975). Due to the laxity correlations existing among the joints examined and because measurements of the second metacarpophalangeal joint taken with angle-meter were the most exact, calculations were based on the latter.

Special case histories were taken of sex hormone disturbances in general (duration, appearance, course of menses), of the special events of pregnancy, and of the liver functions of mothers of index patients. Data were obtained from the mothers of patients with congenital pyloric stenosis (Czeizel, 1972) to serve as a control group.

Results and discussion

Acetabular configuration of parents. Wiberg angle measurements made on the parents of the index patients and on a control group covering the same age range (see Table I and Fig. 1) yielded a significantly lower mean angle for the fathers of affected boys than for the adult male control group ($n = 181$, $t = 2.40$; $p < 0.05$). On the other hand no

TABLE I
VALUES OF WIBERG ANGLE IN PARENTS OF INDEX PATIENTS AND IN AGE-MATCHED CONTROLS

Group	Parents	Wiberg Angle							Total	Significance		
		0-20	21-25	26-30	31-35	36-40	41-45	46-50		$\bar{x}$	SD	SE
Controls	—	2 (2.0%)	4 (4.0%)	21 (21.0%)	29 (29.0%)	38 (38.0%)	3 (3.0%)	3 (3.0%)	100	33.88	5.7	0.6
Females	—	2 (1.5%)	3 (2.2%)	32 (23.7%)	46 (34.1%)	34 (25.2%)	17 (12.6%)	1 (0.7%)	135	34.06	5.5	0.5
Males	—	4 (1.7%)	7 (3.0%)	53 (22.6%)	75 (31.9%)	72 (30.6%)	20 (8.5%)	4 (1.7%)	235	33.97	5.6	0.5
CDH												
Boys												
Mothers	3 (6.7%)	11 (24.4%)	13 (28.9%)	11 (24.4%)	6 (13.4%)	1 (2.2%)	0	45	28.93	6.1	0.9	
Fathers	1 (2.1%)	8 (16.6%)	11 (22.9%)	18 (37.6%)	8 (16.6%)	1 (2.1%)	1 (2.1%)	48	31.20	6.0	0.8	
Total	4 (4.3%)	19 (20.4%)	24 (25.8%)	29 (31.2%)	14 (15.1%)	2 (2.1%)	1 (1.1%)	93	30.10	6.1	0.6	
Girls												
Mothers	2 (4.8%)	14 (33.3%)	13 (30.9%)	6 (14.3%)	6 (14.3%)	1 (2.4%)	0	42	28.30	6.1	0.9	
Fathers	—	2 (5.7%)	7 (20.0%)	13 (37.1%)	7 (20.0%)	5 (14.3%)	1 (2.9%)	35	34.28	6.0	1.0	
Total	2 (2.6%)	16 (20.8%)	20 (25.9%)	19 (24.7%)	13 (16.9%)	6 (7.8%)	1 (1.3%)	77	31.02	6.7	0.7	
Total												
Mothers	5 (5.8%)	25 (28.7%)	26 (29.9%)	17 (19.5%)	12 (13.8%)	2 (2.3%)	—	87	28.63	6.0	0.6	
Fathers	1 (1.2%)	10 (12.0%)	18 (21.7%)	31 (37.4%)	15 (18.1%)	6 (7.2%)	2 (2.4%)	83	32.50	6.1	0.6	
Total	6 (3.5%)	35 (20.6%)	44 (25.9%)	48 (28.2%)	27 (15.9%)	8 (4.7%)	2 (1.2%)	170	30.52	6.4	0.5	

significant difference was found between the value of the fathers of index girls and the control group ($n=168$, $t=0.20$; $p>0.10$). In the mothers of index boys as well as of index girls the Wiberg angles were considerably smaller than in control females ($n=143$, $t=4.66$; $p<0.001$ and $n=140$, $t=3.86$; $p<0.001$, respectively). Thus, in the mothers of all the affected children and in fathers of affected boys the frequency of a shallower acetabulum is much greater. The papers of von Torklus (1967),

Rott (1968), and Wynne-Davies (1970a; 1970b) reported a significantly more frequent shallow acetabulum only in parents of late-diagnosis CDH cases.

Laxity of joint. In the index patients the average of quantitative measured extension in some joints was greater than in the age-matched controls. There was a close correlation in the laxity among joints for both index patients and controls (Fehér *et al*, 1975). The average extension of the second

TABLE II
THE DEGREE OF EXTENSION IN THE SECOND METACARPOPHALANGEAL JOINT IN INDEX PATIENTS, IN THEIR FIRST-DEGREE RELATIVES, AND IN AGE-MATCHED CONTROLS

Group	Average Age	Extension								Significance		
		15 (8-22)	30 (23-37)	45 (38-52)	60 (53-67)	75 (68-82)	90 (83-97)	105 (98-112)	120 (113-127)	$\bar{x}$	SD	Skewness
Child controls												
Girls ($n=100$)	5.0	13	24	34	24	2	3	—	—	43.0	17.3	0.29
Boys ($n=100$)	5.1	5	24	43	19	7	2	—	—	45.8	15.6	0.43
Index patients												
Girls ($n=90$)	5.0	7 (7.8%)	19 (21.1%)	31 (34.3%)	16 (17.8%)	4 (4.5%)	8 (8.9%)	2 (2.2%)	3 (3.4%)	51.3	24.6	0.95
Boys ($n=138$)	4.6	12 (8.7%)	28 (20.3%)	37 (26.8%)	17 (12.3%)	10 (7.3%)	15 (10.9%)	8 (5.8%)	11 (7.9%)	57.7	30.5	0.62
Sibs												
Sisters ($n=37$)	8.0	18.9 (7%)	21.6 (8%)	29.7 (11%)	8.1 (3%)	13.5 (5%)	5.4 (2%)	2.7 (1%)	—	45.4	23.8	0.61
Brothers ($n=62$)	9.2	21.0 (13%)	32.3 (20%)	37.1 (23%)	4.8 (3%)	—	1.6 (1%)	—	3.2 (2%)	37.7	20.8	2.03
Adult controls												
Females ($n=100$)	30.9	16	54	23	4	3	—	—	—	33.6	13.1	0.96
Males ($n=100$)	38.6	12.7 (14%)	43.6 (48%)	30.0 (33%)	12.7 (14%)	0.9 (1%)	—	—	—	36.8	13.5	0.32
Parents												
Mothers ($n=154$)	30.9	14.9 (23%)	44.2 (68%)	31.2 (48%)	45 (7%)	1.9 (3%)	1.9 (3%)	—	1.3 (2%)	37.1	17.6	1.89
Fathers ($n=139$)	34.3	19.4 (27%)	45.3 (63%)	29.5 (41%)	1.4 (2%)	1.4 (2%)	1.4 (2%)	—	1.4 (2%)	34.7	17.2	2.19

FIG. 1. Percentage of Wiberg angles in parents of index patients and in age-matched controls.

FIG. 2. Percentage distribution of extension in the second metacarpophalangeal joint in index patients and in age-matched controls.

metacarpophalangeal joint, which had been chosen as an indicator joint, was greater in boys and girls with CDH, than in controls ($n=236$, $t=3.51$; $p<0.001$; $n=188$, $t=5.98$; $p<0.001$, respectively). This is shown in Table II. This can be attributed mainly to a higher frequency of values beyond a 'threshold' of 1.65 standard deviations above the mean[†](in children $\leq 75^\circ$) as can be seen in Fig. 2. In this range both male and female index patients appeared significantly more often (24.6% and 14.4%, respectively; $\chi^2_1=23.14$; $p<0.001$; and $\chi^2_1=8.04$; $p<0.01$). Our material confirms that joint laxity occurs more frequently in boys with CDH ($\chi^2_1=$

3.46; $0.10>p>0.05$) (Lorenz, 1920; Massie and Horworth, 1951; Carter and Wilkinson, 1964).

First-degree relatives of index patients do not show remarkable differences when compared with matched control groups. Yet even in their case the frequency distributions are more often above the threshold and accordingly, the curves are skewed to the right. First-degree relatives of the 47 above-threshold index patients showed the following rates of joint laxity: 35.7% of the sibs (five out of 14) and 25.0% of the parents (eight out of 32) were above threshold value.

Sex hormone disturbances of mothers. In the mothers of index patients the appearance, dura-

TABLE III

RELATION OF ACETABULAR CONFIGURATION IN PARENTS AND JOINT LAXITY IN INDEX PATIENTS

Index Patients with Joint Laxity	Parents with Shallow Acetabulum								Unknown	Total
	Mother		Father		Both Parents					
	Present	Absent	Present	Absent	Present	Present Only in Mother	Present Only in Father	Absent		
Boys										
Present	2	0	3	3	0	1	2	1	22	34
Absent	3	4	1	2	8	13	3	8	62	104
Unknown	0	0	3	0	0	0	0	0	0	3
Girls										
Present	2	1	0	1	0	2	1	0	6	13
Absent	2	2	2	4	5	11	1	8	42	77
Unknown	7	0	0	0	0	0	0	0	0	7
Total	16	7	9	10	13	27	7	17	132	238

TABLE IV
INDEPENDENCE OF ACETABULAR CONFIGURATION
OF PARENTS AND JOINT LAXITY OF INDEX
PATIENTS

Joint	Shallow Acetabulum			
	Mothers		Fathers	
	Present	Absent	Present	Absent
Boys Lax Not lax	3 24	3 15	5 12	5 23
χ^2_1	0.29		0.82	
Girls Lax Not lax	4 18	2 11	1 8	3 23
χ^2_1	0.05		0.001	

tion, and course of menses, the events during pregnancy as well as the frequency of signs indicating previous liver diseases or pathological liver functions were the same as in the control group.

Connection of acetabular configuration and joint laxity. The joint laxity in the index patients and the shallow acetabulum in their parents—apart from the fathers of girls—are significantly more frequent than in the controls. Both these factors may have an important role in determination. The relationship of joint laxity in the patients and a shallow acetabulum ($\leq 30^\circ$) in one or both parents is shown in Table III. According to the statistical calculations (Table IV) these two genetic predispositions seem to be unrelated events. The so-called exact test of Fischer also showed no significant association (Finney *et al*, 1963).

Difference between neonatal and late diagnosed CDH. The time of diagnosis and so the proportion of cases diagnosed before the third month did not differ in acetabular dysplasia and joint laxity groups (Table V). Of the CDH cases, 41.2% were diagnosed during the first three months and 72.4% during the first six months. From these findings neonatal and late-diagnosed cases do not seem to be two clear-cut entities. Owing to the extensive neonatal screenings the number of diag-

nosed CDH cases has increased at least four-fold, and must include mild cases that would recover spontaneously. Neonatal and late-diagnosed cases of CDH may differ also in their manifestations, for example that at early diagnosis joint laxity still predominates, while in late-diagnosed cases the sign of acetabular dysplasia predominates.

Our studies have confirmed the important role of the polygenic acetabular configuration and monogenic joint laxity in the etiology of CDH. These two genetic predispositions seem to be unrelated. From these findings, however, the neonatal and late diagnosed cases do not seem to be two clear-cut entities.

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TABLE V
TIME OF DIAGNOSIS

Group	Age at Diagnosis (mth)							Total
	0–3	4–5	6–7	8–9	10–11	12+	Unknown	
All CDH	727 (42.2%)	551 (31.9%)	307 (17.8%)	73 (4.2%)	26 (1.5%)	43 (2.4%)	(40)	1727 (1767)
CDH with joint laxity	24 (51.1%)	14 (29.8%)	6 (12.8%)	1 (2.1%)	1 (2.1%)	1 (2.1%)	0	47
CDH with shallow acetabulum of mother	25 (44.6%)	18 (32.1%)	8 (14.3%)	3 (5.4%)	1 (1.8%)	1 (1.8%)	0	56