Incidence and Genetics of Legg-Perthes Disease (Osteochondritis Deformans) in British Columbia: Evidence of Polygenic Determination*

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Legg-Perthes disease (osteochondritis deformans) is an aseptic necrosis of the capital femoral epiphysis. The clinical and radiographic features of Legg-Perthes disease have been well documented (Goff, Shutkin, and Hersey, 1954; Kemp and Boldero, 1966) but apart from Molloy and MacMahon's Massachusetts study (1966) few epidemiologic investigations have been reported. A genetic component to the disease has been suggested by many authors (Goff *et al*, 1954; Goff, 1962) but the extent of familial occurrence and mode of inheritance have not been defined.

The objectives of this study were twofold: firstly, to determine the incidence of Legg-Perthes in the Province of British Columbia, Canada, by identifying all children in whom the diagnosis was made for the first time during the period 1952-67 inclusive; secondly, to analyse for possible genetic factors.

Methodology

The patients were ascertained from three sources: (1) The British Columbia Registry for Handicapped Children and Adults. This Registry has multiple sources for obtaining information (Miller, 1969) including public health units, private physicians, special diagnostic clinics, and recently hospital discharge forms. (2) Hospital records, based on the admission and discharge diagnoses of the 9 major hospitals in British Columbia which admit paediatric patients. (3) Office records of the 29 orthopaedic surgeons in the Metropolitan Vancouver area.

A total of 434 patients were identified and their sources of ascertainment are shown in Table I. Since children with this disease are usually referred to orthopaedic surgeons and are admitted to hospital at some

TABLE I
ORDER AND SOURCE OF ASCERTAINMENT OF
LEGG-PERTHES PATIENTS*

1. Registry for Handicapped Children and Adults	299
2. Hospital records	125
3. Orthopaedic surgeons	10
Total	434

* Multiple ascertainment is not shown.

time during their illness it is estimated that ascertainment was reasonably complete.

With the assistance of the Provincial Public Health Staff an attempt was made to contact or enlist cooperation of parents whose children were known to the Registry. A breakdown on the amount of information obtained on the total case load is seen in Table II.

TABLE II
INFORMATION OBTAINED ON LEGG-PERTHES
CASE LOAD

Full family, sex, age and diagnostic information	267
No family history, but sex, age and diagnostic information	112
Diagnostic information only	55
Total	434

Some of the interviews were performed by the senior author (I.M.G.) but the majority were done by public health nurses using a specially prepared questionnaire. From the total case load of 434 enough information was obtained on 379 (87%) to include them in the age and sex specific incidence rate tabulations.

A patient was considered to have Legg-Perthes disease only if a definitive diagnosis had been made on the basis of a radiological examination. Doubtful cases and cases of avascular necrosis secondary to congenital dislocation of the hip were not included. Relatives of index patients were recorded as affected if a definitive diagnosis of Legg-Perthes had been made with radiological

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proof and a clinical picture consistent with the disease existed.

Estimates of the British Columbia population under 15 years by single years of age for the 16-year period, 1952-67, were derived from the Division of Vital Statistics, Department of Health Services and Hospital Insurance, Government of British Columbia, Canada.

Results

Age and Sex Specific Incidence. Minimal annual incidence rates of Legg-Perthes disease, according to age and sex, are shown in Table III. The term 'minimal' incidence is used because the results are based on 379 of the known 434 patients diagnosed in the period 1952-67. The age and sex distribution is also shown in Table III. The age in years is the age when the diagnosis was first made.

Several features of the disease are illustrated in Table III and Figure 1. The male/female ratio of the annual incidence rates for children under 15 years is 5.2/1.0. The incidence of the disease is observed during a relatively restricted age group, from 2-12 years. The minimal annual incidence for children under 15 years was 5.1:100,000 while the peak incidence rate is observed between 4 and 5 years. The age distribution for children under 15 years shows a mode of 4 years, mean of 5 years, and a median between 4 and 5 years. For males the peak incidence rate is observed at 4 years (24.5:100,000); for females it is between 5 and 6 years (4.3:100,000).

The frequency of Legg-Perthes disease can be expressed as an annual incidence rate, which we have done, ie, new cases appearing in a year or as an attack rate (cumulative incidence) which Molloy and MacMahon (1966) have done, ie, cases appear-

FIG. 1. Minimal annual incidence of Legg-Perthes disease according to sex and to single years of age (under 15 years) in British Columbia, 1952-67.

ing in a cohort of children followed to age 15 (the period of risk). We have computed our results both ways for purposes of comparison. We have not computed the prevalence rate which is the number of cases present in a population at a point in time. The minimal attack rate in our study is 1:820 for males and 1:4500 for females giving a combined rate of 1:1400.

It is always of interest to determine if the incidence of a particular condition is changing. Table IV shows the incidence rates for 4 periods of 4 years. There is no appreciable difference among the last 3 periods and the lower rate in 1952-55 can probably be explained by the fact that the Registry, where 70% of the cases were ascertained, began in 1952 and reporting was less likely in that early period.

TABLE III

MINIMAL ANNUAL INCIDENCE OF LEGG-PERTHES DISEASE ACCORDING TO SEX AND SINGLE YEARS OF AGE (UNDER 15) IN BRITISH COLUMBIA (BC), 1952-67

Age (yr)	Number of Cases			BC Population (in thousands) 1952-67			Minimal Incidence per 100,000		
	Males	Females	Total	Males	Females	Total	Males	Females	Both Sexes
< 1	0	0	0	284.0	272.6	556.6	0	0	0
1	0	0	0	281.0	271.3	552.3	0	0	0
2	10	5	15	279.8	268.4	548.2	3.6	1.9	2.7
3	37	6	43	278.7	266.9	545.6	13.3	2.2	7.9
4	67	5	72	273.1	263.5	536.6	24.5	1.9	13.4
5	56	11	67	271.0	260.5	531.5	20.7	4.2	12.6
6	42	11	53	267.0	255.2	522.2	15.7	4.3	10.2
7	43	6	49	261.6	249.7	511.3	16.4	2.4	9.6
8	28	6	34	254.7	244.4	499.1	11.0	2.5	6.8
9	22	3	25	250.4	238.9	489.3	8.8	1.3	5.1
10	8	1	9	241.6	230.9	472.5	3.3	0.4	1.9
11	5	3	8	233.5	222.9	456.4	2.1	1.4	1.8
12	4	0	4	222.7	213.5	436.2	1.8	0	0.9
13	0	0	0	214.7	205.3	420.0	0	0	0
14	0	0	0	205.4	196.7	402.1	0	0	0
0-14	322	57	379	3819.2	3660.7	7479.9	8.4	1.6	5.1

TABLE IV

MINIMAL ANNUAL INCIDENCE OF LEGG-PERTHES DISEASE DURING 4 PERIODS OF 4 YEARS ACCORDING TO SEX

Period	Minimal Incidence per 100,000 (under 15)		
	Male	Female	Both Sexes
1952-55	6.5	1.8	4.2
1956-59	9.2	1.8	5.6
1960-63	9.0	1.2	5.2
1964-67	8.5	1.6	5.1

Clinical Findings. In this series the interval between onset of symptoms and diagnosis as reported by the patients or parents was less than one month in 23% of the patients, within 2 months in 52%, and within 6 months in 82%. The interval ranged from a few hours to 4 years. Four were incidental findings on radiological examination. The side involved was known for 377 patients (321 males, 56 females). Sixty (58 males, 2 females) or 16% of the patients were affected bilaterally (18% of males, 3% of females). Of the 317 patients with unilateral involvement 150 (47%) were in the right hip and 167 (53%) in the left.

Of the 267 patients who were interviewed only one recurrence was reported. Right Legg-Perthes disease was diagnosed in a male at 3 years of age and was treated for 3 years. At 9 years of age symptoms recurred and the same process was observed radiologically in the right hip. The patient was again treated for approximately 2½ years.

Genetics. A total of 267 index patients, 223 males and 44 females, were included in the genetic study. Adopted or foster children with no known family history were not included. Numbers of first cousins in large families were often not recalled,

so that the total number of cousins is an underestimate. The rates of occurrence of Legg-Perthes disease in relatives of male and female index patients were calculated and the results are shown in Table V. The rates of occurrence of Legg-Perthes disease in relatives of the total index patients were: sibs 28/729 (3.8%); parents 4/530 (0.8%); uncles and aunts 6/2043 (0.3%); first cousins 13/4534 (0.3%). Of the first-degree relatives a significantly ($p = < 0.001$) smaller proportion of parents than sibs were affected. Of the male index patients the percentage occurrence in male sibs was 5.9% and in female sibs 1.4%. Of the female index patients the percentage occurrence in male sibs was 7.3% and in female sibs 1.6%. No mothers, aunts, or female first cousins of male or female index patients were affected.

The rate of occurrence in relatives can be compared directly with the total attack rate, since, as Molloy and MacMahon (1966) state, the attack rate approximates the rate which would be obtained if a cohort was followed through the entire age period of risk. The minimal attack rate in this study was 1:1400. In first-degree relatives, parents, and sibs combined, the rate of occurrence was 1:39; for sibs alone 1:26; for parents alone 1:132. In second-degree relatives—uncles and aunts—the rate of occurrence was 1:340. In third-degree relatives—first cousins—the rate of occurrence was 1:350. There is a significant difference between the rates of occurrence in first-degree relatives compared with second- and third-degree relatives.

Discussion

This study has provided a direct estimate of average annual age and sex incidence rates of Legg-Perthes disease in British Columbia during the

TABLE V

PROPORTIONS OF AFFECTED AND TOTAL FIRST-, SECOND-, AND THIRD-DEGREE RELATIVES OF INDEX PATIENTS WITH LEGG-PERTHES DISEASE

	Sibs		Parents		Uncles and Aunts		First Cousins	
	Brothers	Sisters	Fathers	Mothers	Uncles	Aunts	Male	Female
Male index patients (223) Affected/total x Population incidence	19/321 (5.9%) 49x	4/291 (1.4%) 62x	4/221 (1.8%) 15x	0/222 (0%) —	3/834 (0.4%) —	0/841 (0%) —	12/1918 (0.6%) —	0/1829 (0%) —
Female index patients (44) Affected/total x Population Incidence	4/55 (7.3%) 60x	1/62 (1.6%) 71x	0/43 (0%) —	0/44 (0%) —	3/193 (1.6%) —	0/175 (0%) —	1/398 (0.2%) —	0/389 (0%) —
Total index patients (267) Affected/total x Population incidence	23/376 (6.1%) 50x	5/353 (1.4%) 62x	4/264 (1.5%) 12x	0/266 (0%) —	6/1027 (0.6%) 5x	0/1016 (0%) —	13/2316 (0.6%) 5x	0/2218 (0%) —
x Population incidence	28/729 (3.8%) 52x		4/530 (0.8%) 11x		6/2043 (0.3%) 4x		13/4534 (0.3%) 4x	

TABLE VI
MINIMAL ANNUAL INCIDENCE RATES AND ATTACK RATES: COMPARISON
BETWEEN BRITISH COLUMBIA AND MASSACHUSETTS
(Molloy and MacMahon, 1966)

	British Columbia			Massachusetts		
	Male	Female	Total	Male	Female	Total
Sample size	322	57	379	72	14	86
Minimal attack rate	1:820	1:4500	1:1400	1:740	1:3700	1:1200
Minimal annual incidence per 100,000	8.4	1.6	5.1	—	—	5.7

FIG. 2. Annual incidence of Legg-Perthes disease according to single years of age (under 15 years) in British Columbia, 1952-67 compared with Massachusetts, 1969.

period 1952-67 inclusive. Our results are in remarkable agreement with those of Molloy and MacMahon (1966) despite the differences in sample size (Table VI and see Fig. 2).

Other than Molloy and MacMahon's study (1966) few population studies of this nature have been reported. Goff *et al* (1954) stated that Legg-Perthes syndrome occurs in 1:20,000 living individuals of all ages. As Molloy and MacMahon suggested this would appear to be more of a prevalence estimate from the manner in which Goff defined it. Later Goff (1962) estimated that there are 75 new cases per year in the State of Connecticut, from which Molloy and MacMahon calculated an average annual incidence of 10:100,000 in children under 15 years, and an attack rate of 1:670. These figures differ from the present results and from those of Molloy and MacMahon by a factor of 2, however Goff does not describe his methods of ascertainment. Helbo (1953) reported that in Denmark the disease is present in 0.44/1000 children (1:2300) between the ages of 6 to 14 years

but this is really an estimate of prevalence. Emr (1966) reported an annual incidence of 9 new cases in a population of 302,000 (1:34,000) in a survey of the three districts of the East Bohemian region. This result cannot be directly compared to our study for our population was under 15 years.

The ratio of the incidence rates in male and females (5.2:1.0) in this study is in agreement with Molloy and MacMahon's of 5:1, and with several other authors (Goff *et al*, 1954; Goff, 1962).

Bilateral Legg-Perthes disease was observed in 16% of our cases. Molloy and MacMahon reported 7:87 (8%) bilateral at the time of first diagnoses. This discrepancy may be explained by the fact that our study covered a 16-year period, and the interval between onset of the disease process in the first and second hip may vary considerably. Goff *et al* (1954) in a study of 103 cases of Legg-Perthes reported 18:103 (18%) bilateral cases of Legg-Perthes disease. Wansbrough *et al* (1959) reported 23:129 (20%) bilateral cases. Kemp and Boldero (1966) in a study of 220 cases for radiological changes reported 10% bilateral cases. It is important to remember that multiple epiphyseal dysplasia may resemble Legg-Perthes disease and should be thought of particularly in bilateral cases and those with a positive family history (Barrie, Carter, and Sutcliffe, 1958).

Evidence for Polygenic Inheritance. The rate of occurrence of Legg-Perthes disease in first-, second-, and third-degree relatives has been determined and tests for polygenic inheritance applied. The rate of occurrence in first-degree relatives, parents and sibs combined, was 1:39, 35 times the attack rate in the general population. For sibs alone the rate of occurrence was 1:26, almost 50 times that of the general population.

For parents alone the rate was 1:132 or 10 times the general population rate. This is less than would be expected since in polygenic inheritance the rate in sibs is usually comparable to that of parents.

TABLE VII
RELATIVE INCIDENCE IN SIBS OF LEGG-PERTHES DISEASE IN BRITISH COLUMBIA

	Incidence in General Population	Observed Relative Incidence	Expected Relative Incidence in Sibs		
			Dominant ($\frac{1}{2}p^{-1}$)	Recessive ($\frac{1}{4}p^{-1}$)	Multifactorial ($p^{-\frac{1}{2}}$)
Male	0.001212	6.1/0.1212 = 50.3	412.5	206.3	28.7
Female	0.000225	1.4/0.0225 = 62.2	2222.2	1111.1	66.7
Both sexes	0.000729	3.8/0.0729 = 52.1	685.9	342.9	37.03

The paucity of affected parents possibly reflects memory bias and unawareness of a specific diagnosis for events 30 or more years previously. It is also possible that some cases of Legg-Perthes disease may be so mild as to be self limiting and this would underestimate the rates in parents and in uncles and aunts. It would be preferable to study the rate in the offspring of affected persons but since none of our index patients have reproduced yet this could not be tested. The rates of occurrence in both second- and third-degree relatives (see Table V) were both approximately 3-4 times the general population rate. As mentioned earlier, the number of normal first cousins is probably an underestimate thus over-estimating the occurrence rate.

These results suggest a polygenic or multifactorial mode of inheritance in which a gradual reduction is expected in the incidence of the disease from first-through to third-degree relatives, the incidence in third-degree relatives not being very different from that of the general population. Edwards (1960 and 1963) stated that in polygenic inheritance the incidence in first-degree relatives approximates $\sqrt{p}$, where p is the incidence in the general population. Our incidence gives a value of $\sqrt{p}$ of 1:35 to 1:37 which is in good agreement with the observed value of 1:39. However, for sibs alone 1:26 is greater than expected. Edwards (1960) states that when p is less than about 16% the incidence in first-degree relatives exceeds $\sqrt{p}$. If polygenic inheritance is hypothesized with a sex differential an increased rate of occurrence would be expected in first-degree relatives of female index patients as was found in pyloric stenosis by Carter (1965). In this study there is an increased rate in the brothers of female index cases but this is not significant.

Polygenic inheritance has been observed in many congenital malformations such as cleft lip and palate, spina bifida, clubfoot, and congenital dislocation of the hip (Smith and Aase, 1970), however this mode of inheritance has not previously been suggested for Legg-Perthes disease. Goff *et al*

(1954) stated that heredity played a part in at least 20% of those affected, and suggested that the mechanism was usually recessive yet sometimes dominant with variable penetrance. Later Goff (1962) calculated a 12% family history which he does not discuss further. In our study 37:267 (14%) had a positive family history.

Wansbrough *et al* (1959) analysed sibs born subsequently to 124 probands. They found the frequency of occurrence of Legg-Perthes disease among sibs was 1:35 and suggested that the mode of inheritance was sex-influenced autosomal dominant with reduced penetrance, and varying expressivity. If dominant inheritance is postulated we would expect to find the incidence in sibs being ($\frac{1}{2}p^{-1}$) and for recessive inheritance ($\frac{1}{4}p^{-1}$). Our observed value fits more closely with a polygenic model (Table VII).

Summary

An epidemiologic and genetic study of Legg-Perthes disease in British Columbia was carried out primarily using the records of The Registry for Handicapped Children and Adults. Annual incidence and sex specific rates were enumerated and the data analysed for modes of inheritance. It is suggested that a polygenic mode is the most likely.

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