Family studies of relation between Perthes disease and congenital dislocation of the hip

SANNA DAHL NICLASSEN

From Landssjúkrahúsid, Tórshavn, The Faroe Islands

SUMMARY A family study of Perthes disease and congenital dislocation of the hip was made in the Faroe Islands, with a population of 40 000. The examination included 1123 sibs and first cousins of 43 probands with Perthes disease, 1942 sibs and first cousins of 59 dislocation probands, and 5205 sibs and first cousins of 172 unaffected matched controls. Both conditions occur with exceptionally high incidences in this population. Thus the incidence of Perthes disease was found to be 41:10 000 males and 7:10 000 females, of congenital dislocation of the hip 7:10 000 males and 59:10 000 females. These figures are 3 to 4 times higher than those commonly observed in Caucasian populations.

Among the 1123 relatives of Perthes probands, we found 10 cases of Perthes disease and 9 cases of dislocation; among the 1942 relatives of dislocation probands, there were 11 cases of Perthes disease and 23 cases of dislocation. Thus both disorders show an accumulation within the same families. On the other hand among the 5205 relatives of probands selected because the hips were unaffected, we found only 3 cases of Perthes disease and 10 cases of dislocation.

Considering the conspicuously low familial accumulation of Perthes disease seen in a low-risk population elsewhere (South Wales), the high incidence of the two disorders and the simultaneously strong intrafamilial accumulation in the Faroe population seem to indicate that the search for exogenous influences, specific to this area, should be intensified.

In the Faroe Islands with a population of about 40 000 inhabitants practically all radiological service has for many years been centralised at the Department of Radiology of Landssjúkrahúsid in Tórshavn. This gives us a unique opportunity to survey the total population. A conspicuously high incidence of two disorders, both involving the hip joint, has been noted, that is congenital dislocation of the hip and Perthes disease; furthermore, these disorders often seem to occur in the same families (Niclasen, 1974). This has prompted a systematic study of the relation between these two disorders. Few case reports of concurrent appearance of both disorders in the same patient or in the same family have been published so far, but no previous investigation seems to have been devoted to a more detailed study of the extent or nature of this relation.

Received for publication 27 June 1977

Material and method

The present analysis has been based on the incidences of Perthes disease and congenital dislocation of the hip in relatives of three different groups of probands, that is (1) patients with Perthes disease, (2) patients with congenital dislocation of the hip, and (3) a matched control group.

The 43 Perthes probands (37 males, 6 females) comprise *all* active cases diagnosed in the Faroe Islands in the period 1948 to 1968. The radiological and clinical criteria of the diagnosis have been described previously (Niclasen, 1974). No case of multiple epiphyseal dysplasia or previously diagnosed dislocation of the hip was included.

The 59 probands with dislocation of the hip (6 males, 53 females) comprise *all* cases diagnosed radiologically in persons born in the Faroe Islands

during the period 1942 to 1962. No case was based on a neonatal diagnosis. Subluxations have been disregarded.

In order to get control material of a size sufficient for valid estimates to be made, 4 unaffected controls matched for sex and age were selected for each of the Perthes probands among the inhabitants of the same village or its immediate surroundings. Altogether 172 control individuals (148 males, 24 females) were selected.

For the three proband groups information concerning personal and clinical data was collected for sibs, parents, sibs of parents, and first cousins. In all families, information was obtained through interviews with the parents and, as a rule, also with several other family members. Whenever there was a suspicion of hip disorder the person was x-rayed in Tórshavn. In the Perthes group nearly all sibs had a radiological examination irrespective of the clinical findings. Three previously unknown cases were discovered in this way; they were, for methodological reasons, counted as unaffected in the present analyses.

In the statistical analysis only sibs and first cousins have been taken into account because of the diagnostic difficulties in relatives belonging to the older generation, in whom x-ray examinations do not permit a definite classification. Similarly, because of diagnostic uncertainty, relatives born in 1970 or later and relatives who had died before attaining the age of 16 were disregarded.

Results

The 43 diagnosed active cases of Perthes disease originate from the years 1948 to 1968, a 21-year period during which there were about 18 000 births. This means a minimal attack rate of 24:10 000 in the

Table 2 Incidence of Perthes disease

	Minimal attack rate per 10 000		
	Males	Females	Total
Faroe population (18 000)	41	7	24
Sibs of Perthes probands (132)	869	318	606
First cousins of Perthes probands (991)	20	20	20
Sibs of dislocation probands (207)	265	106	193
First cousins of dislocation probands (1735)	81	0	41
Sibs of unaffected controls (526)	0	0	0
First cousins of unaffected controls (4679)	8	4	6

Table 3 Incidence of congenital dislocation of hip

	Minimal attack rate per 10 000		
	Males	Females	Total
Faroe population (18 000)	7	59	33
Sibs of dislocation probands (207)	0	212	97
First cousins of dislocation probands (1735)	81	162	123
Sibs of Perthes probands (132)	145	317	227
First cousins of Perthes probands (991)	0	122	61
Sibs of unaffected controls (526)	36	0	19
First cousins of unaffected controls (4679)	4	33	19

total material (41:10 000 in males and 7:10 000 in females).

The 59 cases of congenital dislocation of the hip diagnosed in the period of 1942 to 1962 likewise relate to roughly 18 000 births, giving a minimal attack rate of 33:10 000, that is 7:10 000 in males and 59:10 000 in females.

The main findings in the families are summarised in Table 1. Comparisons between incidences in various groups are given in Tables 2 and 3. The incidence of Perthes disease is increased both among the relatives of Perthes probands and among the relatives of probands with congenital dislocation of the hip. Similarly,

Table 1 Occurrence of Perthes disease and congenital dislocation of the hip among relatives of three groups of probands

	Male relatives			Female relatives			Male + female relatives		
	Total no. studied	Perthes disease	Dislocation of hip	Total no. studied	Perthes disease	Dislocation of hip	Total no. studied	Perthes disease	Dislocation of hip
Proband with Perthes disease (n = 43)									
Sibs	69	6***	1	63	2	2	132	8***	3
First cousins	502	1	0	489	1	6	991	2	6
Proband with Congenital dislocation of hip (n = 59)									
Sibs	113	3	0	94	1	2	207	4	2
First cousins	862	7**	7	873	0	14**	1735	7	21***
Unaffected Control probands (n = 172)									
Sibs	278	0	1	248	0	0	526	0	1
First cousins	2391	2	1	2288	1	8	4679	3	9
Total no. of relatives	4215			4055			8270		

, *: significantly different from relatives of control probands at the 1 per 100 and 1 per 1000 level, respectively.

the incidence of congenital dislocation of the hip is increased both among the relatives of dislocation probands and among the relatives of probands with Perthes disease. The discrepancy between incidences in the total population and in the relatives of the unaffected control probands may well be explained by the method of selection of control probands; thus, all individuals with hip disorders were deliberately discarded. This procedure is likely to lead to lower incidences among relatives, irrespective of whether the familial accumulation is caused by environmental or genetic factors.

Among 4215 male relatives of all types of probands, 19 cases of Perthes disease were found compared with 5 cases among 4055 female relatives, giving a sex ratio of 4:1, which is in reasonable agreement with the 6:1 ratio among the probands.

The number of male relatives with congenital dislocation of the hip was 10, the number of female relatives 42; thus, the sex ratio was 1:4, which is not significantly different from the sex ratio in the probands.

Among the parents of the 43 probands with Perthes disease 1 first-cousin marriage was encountered. The parents of the 59 dislocation probands also included 1 first-cousin marriage. This is not much different from the finding of 2 first-cousin marriages among the parents of the 172 control probands.

Discussion

No reasonable doubt seems to exist about the fact that the incidence of Perthes disease in the Faroe Islands is far higher than has been reported from any previous study. This is apparent from the following comparison of data from published reports (Table 4).

There is no satisfactory explanation at present for this very conspicuous excess morbidity in the Faroe Islands.

With respect to congenital dislocation of the hip, the incidence in the Faroe Islands exceeds previously published figures. Carter and Fairbank (1974) have recently surveyed earlier reports from which it appears that the incidence generally observed in Western Europe is less than one-third of that in the present study of the Faroe population.

Table 4 Data from published reports

	Attack rate per 10 000		
	Males	Females	Total
Molloy and MacMahon (1966), Massachusetts	13	3	8
Gray <i>et al.</i> (1972), British Columbia	13	2	7
Harper <i>et al.</i> (1976), South Wales	3	1	2
Niclasen, Faroe Islands	41	7	24

Gray *et al.* (1972) considered Perthes disease to be hereditary, with a polygenic mode of inheritance. The Faroe investigation is to some extent in agreement with this suggestion: it shows the expected steep decline of the rate of occurrence from first to third degree relatives of Perthes probands. The 14 probands with bilateral affection have relatively more affected sibs than the 29 probands with unilateral affection only, but the difference is not significant. On the other hand, the risk to relatives of probands of the less frequently affected sex is not higher in the present material which, however, only includes 6 female probands with a total of 23 sibs out of which 1 was affected.

The family study published by Harper *et al.* (1976) from South Wales did not support the assumption of any major genetic component in the aetiology, as only a very slight accumulation of Perthes disease was seen among the close relatives; as the population incidence was very low, one would, under a polygenic hypothesis, have expected a distinct excess morbidity among the relatives.

According to Falconer (1965) the relative importance of hereditary factors in the case of threshold characters may be estimated when the incidence of the trait in the population and in the relatives of probands is known. If these principles are applied to the two family studies mentioned above and to the present investigation, the following results appear:

	q_g	q_r	$h^2 \pm SE$
British Columbia	0.07%	3.8%	0.82 ± 0.05
South Wales	0.02%	0.6%	0.55 ± 0.14
Faroe Islands	0.24%	6.1%	0.82 ± 0.11

where q_g stands for the population incidence, q_r the incidence in sibs, and h^2 is the 'broad' heritability estimate which will be inflated if genes with dominance play a major role. It should be kept in mind that the effects of common, familial, non-genetic influences cannot be separated and also enter the estimate; thus if environmental conditions or factors are important, this estimate of the genetic proportion of the total phenotypic variation will of course exceed the true value, and a high h^2 value is, therefore, no proof of a substantial genetic component.

The fact that the heritability estimate based on the incidence in first cousins of Perthes probands in the Faroe Islands is of the same magnitude as the one given above suggests that dominance effects may be considered of minor importance.

The causes of the conspicuous variation between the 3 studies are thus difficult to disentangle, as they may be based on gene frequency differences as well as on differences in the environment. The high population incidence in the small Faroe population could be the

result of genetic drift or a founder effect. The low heritability in the South Wales study seems, on the other hand, to point to environmental factors specific to this population, as this heritability estimate is so much lower than the other two, though not significantly so. In the search for possible exogenous factors, comparable studies in the Orkney and Shetland Islands as well as in Iceland would be useful, as the living conditions and the ethnic background in these localities are similar to those of the Faroe Islands.

The present study does not contribute substantially to the genetics of congenital dislocation of the hip as the incidence among sibs of probands does not seem to be increased to any significant extent, whereas the incidence among third degree relatives is clearly raised. This could be the result of chance and the findings do not in any way contradict the generally accepted hypothesis of polygenic inheritance. The expected higher incidence among the relatives of the less frequently affected sex, in the present case the males, is seen in this material. Thus 6 male probands had a total of 12 living sibs and 175 living first cousins, out of which 6 first cousins (321 : 10 000) had congenital dislocation of the hip.

No explanation of the association found in the Faroe Islands between Perthes disease and congenital dislocation of the hip can be given at present. Previous studies of Perthes disease have paid no special attention to this relation. As a contribution to the elucidation of this problem an analysis would be desirable of the habits and conditions of daily life, with special regard to child care, in families with a heavy load of one or both of these disorders in comparison with families living in the same localities in whom hip affection is unknown.

Conclusions

(1) The population of the Faroe Islands constitutes an isolate with a conspicuously high incidence of two disorders of the hip joint: Perthes disease and congenital dislocation.

(2) In the Faroe population a significant intra-

family association has been found between these two disorders. Among the relatives of probands with either Perthes disease or dislocation an accumulation of both disorders is observed.

(3) Genetic as well as environmental factors have to be taken into consideration in order to explain the differences of incidences and family patterns of Perthes disease observed between high-incidence and low-incidence regions.

This work has been financially supported by 'Murer-mester Holms legat' and by 'Videnskabsfonden for Storkøbenhavn, Færøerne og Grønland'. Many thanks are due to Ina Tavsén, secretary, and Annika Olsen, medical student, who participated in the collection of the material. Dr Johs. Meyer, former chief of 'The Refsnaes Seaside Hospital', Denmark, has given diagnostic aid in evaluating the x-rays of the Perthes probands and their relatives. The epidemiological analysis has been performed by Professor Mogens Hauge and Professor Bent Harvald at the Institute of Clinical Genetics, Odense University.

References

- Carter, C. O., and Fairbank, T. J. (1974). *The Genetics of Locomotor Disorders*. Oxford University Press, London.
- Falconer, D. S. (1965). The inheritance of liability to certain diseases, estimated from the incidence among relatives. *Annals of Human Genetics*, **29**, 51–76.
- Gray, J. M., Lowry, R. B., and Renwick, D. H. G. (1972). Incidence and genetics of Legg-Perthes disease (osteochondritis deformans) in British Columbia: evidence of polygenic determination. *Journal of Medical Genetics*, **9**, 197–202.
- Harper, P. S., Brotherton, B. J., and Cochlin, D. (1976). Genetic risks in Perthes' disease. *Clinical Genetics*, **10**, 178–182.
- Molloy, M. K., and MacMahon, B. (1966). Incidence of Legg-Perthes' disease (osteochondritis deformans). *New England Journal of Medicine*, **275**, 988–990.
- Nielsen, S. D. (1974). Incidence of Legg-Calvé-Perthes' disease in the Faroe Islands. *Annales Societatis Scientiarum Færoensis*, **22**, 9–65.

Requests for reprints to Dr Sanna Dahl Nielsen, Department of Radiology, Landssjúkrahúsid, DK-3800 Tórshavn, The Faroe Islands.