CONGENITAL ABNORMALITIES AND PERTHES' DISEASE

CLINICAL EVIDENCE THAT CHILDREN WITH PERTHES' DISEASE MAY HAVE A MAJOR CONGENITAL DEFECT

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This paper reports a high incidence of minor congenital anomalies in boys and girls with Perthes' disease compared with that in a control population. There is a similarity of the incidence of minor anomalies in the children with Perthes' disease to that in babies with a single major congenital defect. Multiple major defects were more numerous and more severe than in the control children. It is speculated that there may be a congenital abnormality affecting skeletal development which in some way makes the hip susceptible to Perthes' disease at a later date.

Perthes' disease has long been regarded as a focal disorder of the hip in an otherwise normal child. In previous reports, however, we have demonstrated the association of delayed skeletal maturation as well as impaired and disproportionate growth with Perthes' disease (Harrison, Turner and Jacobs 1976; Burwell *et al.* 1978). This paper reports a study of congenital abnormalities in children with Perthes' disease and provides a further example of abnormal development revealed by careful clinical examination.

Children with congenital abnormalities have been regarded by some workers as not conforming to the diagnosis of classical Perthes' disease. Thus, Molloy and MacMahon (1966), in their analysis of the incidence of Perthes' disease in Massachusetts, excluded forty-one children as atypical, including three with an absent tibia, out of a total of 128 reported cases. Fisher (1972) in his epidemiological study of Perthes' disease excluded twenty-three atypical cases out of 211, among whom was one patient with Klinefelter's syndrome and one who was a "bird-headed dwarf". In this connection it is well known that changes in the hip similar to those in Perthes' disease are associated with certain congenital malformation syndromes including multiple epiphyseal dysplasia, Morquio-Brailsford chondro-osteodys-trophy, peripheral dysostosis, Down's syndrome and the trichorhinophalangeal syndrome (Fairbank 1947; Brailsford 1952; Goff 1962; Vaughan 1962; Wilk 1965; Gorlin, Cohen and Wolfson 1969). Less commonly, fragmentation of the femoral capital epiphysis is associated with other congenital syndromes including achondroplasia, Trevor's disease, chondrodystrophia

calcificans congenita, poikiloderma congenitale and Ollier's disease (Dunn 1965; Greenfield 1975).

The association of congenital abnormalities with typical Perthes' disease has been reported by several workers. In the skeleton, congenital abnormalities have been sought in radiographs of the spine and hands. In the spine, Katz (1959) found a high incidence of spina bifida occulta (82 per cent) in 178 children with Perthes' disease. Examination of a control series of eighty-nine patients with "all varieties of orthopaedic disorders other than Legg-Calvé-Perthes disease", showed the incidence of spina bifida occulta to be 67 per cent. Katz concluded that there was no evidence to prove a relationship between spina bifida occulta and Perthes' disease. Wilk (1965) revealed some lumbosacral abnormality in 139 of 171 patients (81 per cent); the abnormalities were spina bifida occulta and transitional vertebrae. The radiological findings were not compared with a control group of children. In the hands, Adams (1937) reported anomalies of the lunate, metacarpals and phalanges in a boy with Perthes' disease.

In the anterior chamber of the eye, Noorden and Burian (1961) found anomalies in nineteen of twenty-two patients with Perthes' disease; but their findings were not compared with normal children. Wilk (1965) evaluated 186 patients with Perthes' disease and found cases of haemophilia, cleft lip, undescended testicle and hypospadias. Catterall, Lloyd-Roberts and Wynne-Davies (1971) stated that in boys with Perthes' disease, the incidence of inguinal hernia was approximately eight times the expected figure; and that in patients with Perthes' disease, a definite disorder of the genito-

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urinary tract was present in 4.3 per cent, suggesting a higher prevalence than in the normal population. Similar anomalies of the genito-urinary tract were also claimed to be unexpectedly common amongst the first-degree relatives of these patients. Their survey did not disclose any further associated disorders in numbers larger than would be expected from any random survey. Harper, Brotherton and Cochlin (1976) were unable to confirm an association between Perthes' disease and congenital genito-urinary abnormalities. Matsoukas (1975) in a study of sixty children with Perthes' disease found patients with patent ductus arteriosus, inguinal hernia, renal disease, hypospadias, spina bifida occulta, dental anomalies and dermatoglyphic alterations. His data were not compared with a control population. Matsoukas raised the possibility of a causal correlation between prenatal rubella and Perthes' disease. Most recently, Wynne-Davies and Gormley (1978) have reported several congenital abnormalities associated with Perthes' disease: pyloric stenosis, radio-ulna synostosis, branchial fistula, talipes equinovarus, talipes calcaneovalgus, mental retardation, inguinal hernia and congenital defects of the kidney and ureter. The numbers of close relatives with genito-urinary tract anomalies and with congenital dislocation of the hip were higher than expected. The possible relationship between congenital dislocation of the hip and Perthes' disease has recently been discussed (Burwell 1978; Lindholm *et al.* 1978).

In this clinic also we have built up the impression over the years that major congenital abnormalities were more commonly found in children with Perthes' disease than would be expected. Such major abnormalities

Table 1. Major congenital abnormalities in 127 children with Perthes' disease (1973-1976)

Year	Major congenital abnormalities
1973	Cervical hemivertebra+strabismus
	Petit mal+multiple anomalies of the hands
	Hypercholesterolaemia+deafness
	Rubinstein-Taybi syndrome
	Imperforate anus+hydronephrosis
1974	Epilepsy
	Parathyroid hyperplasia+deafness
	Pyloric stenosis
	Congenital heart disease (? pulmonary stenosis)
1975	Goldenhar's (oculo-auriculo-vertebral) syndrome
	Undescended testicle
	Spondylo-epiphyseal dysplasia with kyphoscoliosis
1976	Haemophilia
	Gaucher's disease
	Congenital short tibia+ichthyosis
	Congenital heart disease+pyloric stenosis+strabismus

include phocomelia, ichthyosis, Fanconi's anaemia with vestigial thumbs, Down's syndrome, congenital dislocation of the hip, infantile idiopathic scoliosis, port-wine haemangioma of the face, thyroglossal cyst, congenital deafness, and cleft palate with hare lip. Since 1973, the congenital abnormalities in new patients attending the Perthes' Clinic at the Royal Orthopaedic Hospital, Birmingham, have been recorded and the major abnormalities are shown in Table 1.

Estimates of the incidence of congenital abnormalities in the general population vary considerably due to differences in the source of the primary information (examination of children, hospital records and death certificates), inclusion or exclusion of minor abnormalities and of stillbirths, and the duration of follow-up (Motulsky, Lenz and Ebling 1973). For this reason we felt it essential to compare our findings in children with Perthes' disease with those in a local control population.

Marden, Smith and McDonald (1964) evaluated the incidence of both major and minor abnormalities in 4412 consecutive births in Wisconsin, paying particular attention to the incidence of minor anomalies. Their finding that the presence of two (and particularly three or more) minor congenital anomalies in the same newborn baby was unusual except in those who had a major congenital defect (Fig. 1), has led us to study minor as well as major abnormalities in children attending our clinic, and to compare the incidence with that in the control population.

Major and minor congenital abnormalities are structural aberrations that have developed during

Fig. 1

The percentage of newborn infants with and without a major defect related to the number of minor anomalies present. Note that the babies with a single major defect have more minor anomalies and especially more multiple anomalies than do normal babies. (Drawn from the data of Marden *et al.* 1964.)

Table II. Major congenital defects in consecutive children with Perthes' disease and in the control children

	Boys		Girls	
	Perthes' (90)	Controls (90)	Perthes' (40)	Controls (40)
Single major defects	Epilepsy	Epilepsy	Epilepsy	Strabismus
	Undescended testicle	Strabismus	Pulmonary stenosis	
	Haemophilia	Pyloric stenosis	Inguinal hernia	
	Pyloric stenosis	Inguinal hernia		
Multiple (two or more) major defects	Congenital heart disease + pyloric stenosis + strabismus + odd facies	Idiopathic scoliosis + undescended testicle + deformity hallux	Spondylo-epiphysial dysplasia with kyphoscoliosis + odd facies	Nil
	Imperforate anus + hydronephrosis	Hypoplasia thumb + odd facies	Rubinstein-Taybi syndrome + mental retardation	
	Parathyroid hyperplasia + congenital deafness + undescended testicles + odd facies		Cervical scoliosis + strabismus + laryngeal stridor	
	Goldenhar's syndrome		Congenital dislocation of the hips + petit mal	

embryonic differentiation. A major defect is one that has an adverse effect on either the function or so-called acceptability of the individual and a minor anomaly is one that is of neither medical nor cosmetic consequence to the patient (Marden *et al.* 1964; Smith 1976). Such minor anomalies are most common in areas of complex and variable features such as the face, auricles, hands and feet, and often give the child a slightly odd appearance.

In this paper the word "anomaly" is reserved for minor congenital abnormalities, and "defect" for major abnormalities. The children with Perthes' disease will be referred to as the affected children.

A preliminary report of our findings has been published (Hall and Harrison 1978).

CLINICAL MATERIAL

The patients. All children in whom a radiological diagnosis of Perthes' disease was made between January 1, 1973, and December 31, 1976, at the Perthes' Clinic of the Royal Orthopaedic Hospital, Birmingham, were examined by one of the authors (DJH). A full paediatric history was taken by interviewing the parents. Low or uncertain birth weights were checked with the maternity hospital or the family doctor.

Ten boys and one girl were excluded from the series because they were living outside the Birmingham area at the time of diagnosis. Two of these had major congenital defects and were referred because they presented problems of management: one boy had hypercholesterolaemia and congenital deafness, the other had a congenital short tibia on the unaffected side and ichthyosis. Only two atypical patients were excluded. One had already been diagnosed as having Gaucher's disease before the radiological changes appeared in the hips; and the other showed radiological changes six months after an osteomyelitis of the upper end of the femur. This process of exclusion left a consecutive group of ninety boys and twenty-four girls, all resident in the Birmingham area at the time of diagnosis. In order to increase the number of girls in the study, sixteen girls diagnosed in 1971, 1972 and 1977 were also examined, making a group of forty consecutive girls.

Three non-Caucasian children were included: one West Indian

boy (with an Indian grandfather), one Indian boy, and one Indian girl. None of these children had any known Caucasian ancestry. Thirteen of the boys and ten of the girls had a family history of Perthes' disease in first, second or third-degree relatives. There were three pairs of related children.

The control subjects. A control series of ninety boys and forty girls with injuries was examined by the same observer at the nearby Birmingham Accident Hospital. Their parents were questioned about previous illnesses in order to disclose abnormalities which had already been treated. Only Caucasian children were included.

The children had attended hospital on account of injuries which fell into three approximately equal groups: minor injuries, mostly lacerations; head injuries requiring an overnight stay in hospital; and major injuries from road accidents or falls. No children with burns were included.

The controls were not consecutive, but were selected by age and by the nature of the injury, taking care not to look at the child first. It was found to be impossible by this method to make matching pairs of one child with Perthes' disease and one control child. Instead, details of birth weight, maturity, birth order, family size, parental age and father's occupation were obtained from the parents by questionnaire, for comparison with similar data for the children affected by Perthes' disease. The parents of eight boys and four girls in the control series failed to return the questionnaire. Details for the remaining controls were compared with those for the affected children in order to detect any difference in socio-economic status between the two groups.

The congenital abnormalities. Major congenital defects in the affected and the control children were recorded. Abnormalities reported by the parents, such as pyloric stenosis and epilepsy, were included in this group.

Minor anomalies were sought by surface examination only, using the criteria of Smith and his colleagues (Marden *et al.* 1964; Smith 1976). These writers listed the individual minor anomalies found in 4412 consecutive births, and also specified normal variants which should not be classed as anomalies. As their work included an evaluation of the incidence of minor anomalies in normal babies, and as there is no comparable survey of minor anomalies in childhood, we made an assessment of our data in order to divide the anomalies into two groups: those which would have been recognisable at birth, and those which would only be recognised in childhood. By this means we have attempted to compare our findings for both the affected and the control children with the results published by Marden *et al.*

RESULTS

Major congenital defects. The various major congenital defects found in the affected and the control children are shown in Table II.

There were four boys with single major defects in each of the two groups. The multiple major defects, on the other hand, were both more numerous and more severe in the boys affected by Perthes' disease than in the control boys. The first three of the boys with Perthes'

Table III. Minor congenital anomalies considered to be recognisable at birth (children without major defect)

Minor anomalies	Boys		Girls	
	Perthes' (82)	Controls (84)	Perthes' (33)	Controls (39)
Strabismus*	4	1	0	1
Ptosis	0	1	0	0
Epicanthic folds	7	8	1	5
Hypertelorism	2	0	0	0
Upslanting palpebral fissures	3	0	2	1
Short palpebral fissures	2	0	0	1
Bicoloured iris	0	1	0	0
Stenosed nasolacrimal duct	1	0	1	0
Bat ears	0	1	0	0
Pre-auricular tag	0	1	0	0
Ear asymmetry	6	2	1	1
Microstomia	1	0	0	0
Simian palmar crease	1	0	0	0
Cryptorchidism	2	0	0	0
Pilonidal sinus	1	0	0	0
Deep sacral dimple	1	0	0	0
Short great toe	0	0	1	0
Short recessed fifth toe	2	0	0	0
Syndactyly of the fourth and fifth toes	1	0	0	0
Hypoplastic toe nails	0	1	0	0
Raised haemangioma (>1 cm diameter)	1	0	0	0
Non-elevated haemangioma (other than face or neck)	0	0	2	0
Café-au-lait spots (>1 cm diameter)	3	1	0	2
Pigmented naevi (large or numerous)	0	0	2	1
Totals	38	17	10	12

*Observed in the children but for which the parents had not sought treatment.

disease and multiple defects were severely physically handicapped, though they had an apparently normal intelligence; each had undergone surgical correction of certain of their defects. Neither of the two control boys with multiple defects was severely handicapped. The difference in both number and severity of major defects was even more marked in the girls than in the boys. Four of the girls with Perthes' disease had multiple defects, the first two being severely handicapped; the girl with the Rubenstein-Taybi syndrome was mentally retarded. None of the control girls had multiple major defects, and only one had a single major defect.

Minor congenital anomalies. In this analysis we have excluded the fifteen affected and the seven control children who had one or more major defects; this is because five of the affected children had so many minor

Table IV. Minor congenital anomalies considered to be recognisable only in childhood (children without major defect)

Minor anomalies	Boys		Girls	
	Perthes' (82)	Controls (84)	Perthes' (33)	Controls (39)
Fair forelock	1	0	0	0
Eyebrows meeting	0	1	0	0
Shallow orbits	1	0	0	0
Absent permanent incisor	0	0	1	0
Short neck	2	1	0	0
Pectus excavatum	1	3	1	0
Pectus carinatum	0	0	1	0
Cubitus valgus	1	0	0	0
Flexion contracture of elbow	3	1	0	0
Clinodactyly	8	2	3	0
Inguinal hernia*	1	0	0	0
Undescended testicles*	3	3	0	0
Body hirsutism	2	1	0	0
Totals	23	12	6	0

*Observed in the children but for which the parents had not sought treatment.

anomalies as to distort any comparison between the affected and the control groups. Moreover, by excluding the children with major defects from both the affected and the control groups, our data were made comparable with those of Marden *et al.* (1964).

In the children without a major defect, the nature and incidence of the minor anomalies which we consider would have been recognisable at birth are shown in Table III; and those only recognisable in childhood in Table IV.

Incidence observed in the children. After excluding those children with major defects (single and multiple) there were eighty-two affected boys and eighty-four control boys, and thirty-three affected girls and thirty-nine control girls (Table V). Figure 2 shows the percentages of boys with minor anomalies observed in the two groups, the difference being statistically highly significant ($\chi^2=34.34$, $P<0.001$). A significant difference was also found for the girls ($\chi^2=6.20$, $0.02<P<0.05$).

Incidence which would have been recognisable at birth. Figure 3 shows the percentage of boys with minor anomalies which would have been recognisable at birth. The difference between the affected and the control groups was statistically highly significant ($\chi^2=43.38$, $P<0.001$, Table V). The similarity to the results of Marden *et al.* (1964) can be seen by comparing Figure 3

Table V. The numbers of children with minor congenital anomalies (children without major defect)

Number of minor anomalies	Boys		Girls	
	Perthes' (82)	Controls (84)	Perthes' (33)	Controls (39)
<i>Observed in the children*</i>				
0	41	63	21	29
1	27	16	9	9
2	10	3	2	0
3 or more	4	2	1	1
<i>Recognisable at birth</i>				
0	53	68	25	29
1	22	15	6	9
2	5	1	2	0
3 or more	2	0	0	1

*Including those recognisable at birth

with Figure 1. There was no significant difference in the incidence of minor anomalies between the eighty-two boys with Perthes' disease and Marden's fifty-eight babies with a single major defect nor between the eighty-four control boys and Marden's 4322 normal babies. The findings for the affected girls were not significantly different from the control girls.

Birth weight. The mean (and standard deviation) of the birth weight of the ninety affected boys was 3.283 ± 0.582 kilograms, and that of the eighty control boys for whom information was available was 3.409 ± 0.575 kilograms. The difference was not statistically significant.

In Figure 4, the birth weights for the two groups of boys are plotted as centile positions using the charts of Tanner and Thomson (1970) to correct for birth order and maturity. This gives an assessment of size for maturity. The skewness to the left in the affected boys is due to the low birth weight for maturity of most of the boys with multiple congenital abnormalities.

Fig. 2

The percentage of boys with and without Perthes' disease related to the numbers of minor anomalies which were observed. Note that the boys with Perthes' disease had more minor anomalies and especially more multiple anomalies than did the control boys (see Table V).

Fig. 3

The percentage of boys with and without Perthes' disease related to the number of minor anomalies which were considered to have been recognisable at birth. Comparison with Figure 1 suggests that the boys with Perthes' disease may have a single major congenital defect (see text).

Fig. 4

Histogram showing the number of boys with and without congenital abnormalities plotted against birth weight centiles corrected for birth order and maturity. Note the skewness to the left for the boys with Perthes' disease, the vertical columns being higher between 0 and the 50th centile due mainly to an excess of boys with multiple congenital abnormalities.

Socio-economic factors. Social class. Social class was judged by the father's occupation (Office of Population Censuses and Surveys 1970) and no significant difference was found between the distribution of the social classes in the affected and the control boys nor between the affected boys and the children in the 1970 British Births Survey (1975). However, the control boys had a lower social class distribution than did the children of the British Births Survey (1975) ($\chi^2=11.77$, $0.02 < P < 0.05$).

Parental age at birth. The mean maternal age (and standard deviation) for the ninety affected boys was 26.77 ± 5.52 years, and for eighty-one control boys was 27.08 ± 5.76 years. The mean paternal age for eighty-nine affected boys was 30.32 ± 7.68 years, and for eighty-two control boys was 29.35 ± 6.76 years. In neither case was the difference statistically significant.

Size of the family. The mean number (and standard deviation) of children in the families of the affected boys was 2.90 ± 1.38 and of the control boys was 3.38 ± 1.76 , the difference being statistically significant ($t=1.988$, $0.02 < P < 0.05$).

Geographical distribution of the children. Plotting the distribution of the children's home addresses on a map showed that about one third of the control boys lived in the declining inner city areas, whereas the boys with Perthes' disease were mainly scattered in the peripheral housing estates.

DISCUSSION

The high incidence of multiple major defects in the Perthes' children could be due to the specialised nature of our clinic and its close proximity to the main paediatric centre for the region. Three boys and one girl with multiple malformation syndromes, and also the boy with haemophilia, were referred from the Birmingham Children's Hospital. This explanation, however, cannot account for the high incidence of multiple minor anomalies in the children without major defect. These children had been referred with a problem concerning the hip and were otherwise apparently normal.

Many epidemiological studies of congenital abnormalities have been carried out in recent years (McKeown and Record 1960; Green 1964; Smithells 1968; Saxén and Rapola 1969; Hakosalo 1973; Kelly *et al.* 1976). It has been established that some congenital abnormalities show a social class gradient, being more frequent in the children of unskilled workers. There is also a slight increase in incidence with maternal age and parity (Butler, Alberman and Schutt 1969; Kelly *et al.* 1976). The socio-economic factors recorded in our study (social class, parental age, family size and geographical distribution), when considered together, showed that the socio-economic status of the boys with Perthes' disease was higher than that of the controls, and that the controls constituted a slightly deprived group, not fully representative of the general child population.

There was therefore no evidence to suggest that socio-economic factors had contributed to the different incidence of congenital abnormalities. Indeed, if these factors had been important, one would have expected a higher incidence in the controls. It must be added that Wynne-Davies and Gormley (1978) found that a high proportion of the children with Perthes' disease in Glasgow and Edinburgh came from low-income families. It is possible that this finding may reflect the difference in socio-economic structure between Glasgow and Birmingham.

Environmental influences during pregnancy, such as drugs, infections, smoking, alcohol and obstetrical complications, could have been factors in determining the congenital abnormalities we have described (Richards 1969; Saxén 1973; Wilson 1973; Robinson 1977). We did not consider it feasible to collect detailed information about ingestion of drugs so long after pregnancy. Klemetti and Saxén (1967) reported a great discrepancy between replies to the same questionnaire on drug consumption, during the second trimester and after delivery. We found a similar inconsistency at two different visits in replies about infections during the first trimester. Routine history-taking did not suggest any correlation between the children with multiple abnormalities and any of these environmental factors operating during early pregnancy.

Previous research has shown that major congenital abnormalities and particularly multiple malformation syndromes are often associated with a low birth weight (Yerushalmy *et al.* 1965; Polani 1974). It must therefore be asked whether low birth weight was associated with the congenital abnormalities in our children. Although there was no significant difference for birth weight between the affected and the control boys, the mean birth weight of the affected boys (3.283 kilograms) was very close to the national mean (3.287 kilograms) of the 1970 British Births Survey (1975). The latter, however, is for combined sexes, and includes stillbirths, abortions after the twenty-fourth week of pregnancy, and those babies who later died in infancy. One would therefore have expected our birth weight figure for surviving children to be higher than that of the British Births Survey mean. The mean birth weight of our affected

boys was less than that of the control boys by 0.126 kilogram; Molloy and MacMahon (1967) found the mean birth weight of seventy affected children to be significantly lower (by 0.322 kilogram) than that of a control group of children. Because only a proportion of the boys with Perthes' disease in our study had multiple congenital abnormalities, and the birth weight of each group was compared as a whole, it is possible that a low birth weight in children with congenital abnormalities was obscured in our statistical comparison. Evidence in favour of this view is our finding of the suggestion of an association between low birth weight for maturity and the presence of multiple major and minor abnormalities in the boys with Perthes' disease (Fig. 4). Wynne-Davies and Gormley (1978) reported that although the mean birth weight of their patients was not significantly different from normal, there was an excess of children of low birth weight and also of those of high birth weight. Their findings for birth weight were not analysed in relation to congenital abnormalities.

What then could be the significance of the association between the congenital abnormalities and the development of Perthes' disease in childhood? Some have sought a directly causative role suggesting anomalous blood vessels supplying the femoral capital epiphysis (McNutt 1962; Catterall *et al.* 1971; Lauritzen 1975; Chung 1976). We propose that there may be a more fundamental association, namely that the factor, or factors, that caused the congenital abnormalities could also have been responsible for the later development of Perthes' disease.

It is possible that the minor congenital anomalies mark the time in early embryonic life when the factor(s) had their effect. Smith (1976) has stressed the importance of recognising multiple minor anomalies as indicators of some more serious defect of morphogenesis. The remarkable similarity of the incidence of minor anomalies in the children with Perthes' disease to that in babies with a single major congenital defect invites the speculation that there is a major congenital defect in these children which in some way makes the hip susceptible to Perthes' disease at a later date. We suspect that the postulated defect affects the growing bones of these children (Burwell *et al.* 1978).

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