A Twin Study of Perthes Disease

David Metcalfe, LLB, MSc, MRCS,[a,b,c] Stephanie Van Dijck, FRACS,[d] Nicolas Parsons, MSc, PhD,[c] Kaare Christensen, MD, PhD,[e] Daniel C. Perry, PhD, FRCS(Orth)[f]

abstract

BACKGROUND: Legg-Calvé-Perthes disease (LCPD) is an idiopathic avascular necrosis of the femoral head. Its etiology is poorly understood, although previous studies have implicated low birth weight and possible genetic determinants. The aim of this study was to identify potential birth weight and genetic associations with LCPD.

METHODS: We extracted all twin pairs from the Danish Twin Registry (DTR) in which at least 1 individual had LCPD. The DTR captures every twin pair born alive in Denmark, and those with LCPD were identified by using health record linkage. Probanwise concordance was calculated to describe the likelihood that any given individual had LCPD if their co-twin was also diagnosed.

RESULTS: There were 81 twin pairs: 10 monozygotic, 51 dizygotic, and 20 unclassified (unknown zygosity [UZ]). There was no association between birth weight and being the affected co-twin. Four pairs (2 dizygotic and 2 UZ) were concordant for LCPD, which is greater than would be expected assuming no familial aggregation. There were no concordant monozygotic twin pairs. The overall probandwise concordance was 0.09 (95% confidence interval [CI]: 0.01–0.18): 0.00 for the monozygotic, 0.08 (95% CI: 0.00–0.18) for the dizygotic, and 0.18 (95% CI: 0.00–0.40) for the UZ twin pairs.

CONCLUSIONS: This study found evidence of familial clustering in LCPD but did not show a genetic component. The absolute risk that a co-twin of an affected individual will develop LCPD is low, even in the case of monozygotic twin pairs.

[a]Center for Surgery and Public Health, Harvard Medical School, Boston, Massachusetts; [b]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom; [c]Warwick Medical School, University of Warwick, Coventry, United Kingdom; [d]Department of Orthopaedic Surgery, Middlemore Hospital, Auckland, New Zealand; [e]The Danish Twin Registry, University of Southern Denmark, Odense, Denmark; and [f]Institute of Translational Medicine, University of Liverpool, Liverpool, United Kingdom

Mr Metcalfe contributed to the study design, data analysis, and data interpretation and drafted the initial manuscript; Drs Van Dijck, Christensen, and Parsons contributed to the study design, data interpretation, and drafting of the manuscript; Mr Perry conceived the original idea, conducted the primary data analysis, contributed to the manuscript, and is the study guarantor; and all authors approved the final manuscript as submitted.

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Address correspondence to Daniel C. Perry, PhD, FRCS(Orth), Institute of Translational Medicine, University of Liverpool, Liverpool, L12 2AP, UK. E-mail: danperry@doctors.org.uk

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WHAT'S KNOWN ON THIS SUBJECT: Legg-Calvé-Perthes disease is an idiopathic avascular necrosis of the femoral head. Its cause(s) are unknown but previous studies have implicated low birth weight and a possible genetic etiology.

WHAT THIS STUDY ADDS: There is evidence of Legg-Calvé-Perthes disease clustering within families, but the absence of concordant monozygotic pairs in this study suggests that the cause(s) of Legg-Calvé-Perthes disease may occur in utero or in the early childhood environment.

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Legg-Calvé-Perthes disease (LCPD) is an idiopathic avascular necrosis of the femoral head, with severe cases resulting in collapse of the femoral head and osteoarthritis in young adult life. It currently has an annual incidence of 6 cases per 100 000 children,[1] which has been steadily in decline in recent years. The etiology of LCPD is poorly understood. A number of studies have shown a strong association with socioeconomic deprivation in childhood.[2–4] Other proposed associations include small stature,[5] dietary deficiencies,[6] passive smoking,[7,8] childhood hyperactivity,[9] white European ancestry, latitude distance from the equator,[10] and an inherited predisposition to abnormal clotting.[11,12]

In their early descriptions of LCPD, both Jacques Calvé[13] and Georg Perthes[14] described siblings with the disease. There have since been a number of familial cases reported,[15] which raises the possibility of a major heritable component. Only 2 studies have used twins to investigate the etiology of LCPD.[5,16] These were both small series drawn from LCPD registries and reported a total of 11 pairs in which 1 twin had the disease. Although these studies could not show a genetic basis for LCPD, it was noted that the twin with the lowest birth weight was universally affected in the smaller series of 5 twin pairs.[16]

Twin studies are useful for delineating the importance of environmental and genetic factors. They can be used to study variation in environment (across pairs) and genetic constitution, because "identical" (monozygotic) twins share almost 100% of genes and "nonidentical" (dizygotic) twins ~50%.[17] If monozygotic twins exhibit a greater concordance of LCPD than dizygotic twins, this suggests a genetic basis for the disease.

This study used a national cohort of LCPD twin pairs to explore the potential effects of heritability and birth weight on the development of LCPD. We hypothesized that there would be a measurable heritable component to the etiology of LCPD.

METHODS

A classic twin study was performed with the use of the Danish Twin Registry (DTR). The Danish Data Protection Agency confirmed that ethical approval was not required for analysis of data from which patient identifiers were removed.

Data Source

The DTR is the oldest national twin registry in the world with 85 000 twin pairs born in Denmark since 1870.[18] Although different data sources have been used over the decades to identify twin pairs, manual searching of parish registers suggests that 80% to 90% of eligible twins born after 1931 were captured. However, the DTR has more recently identified twins by using prospective administrative databases, ie, the Medical Birth Register and Danish Civil Registration System, and is thought to have included every twin pair born alive in Denmark since April 1, 1968.[18] Zygosity within the DTR is determined by self-reported degree of similarity, which has been shown to assign the correct zygosity in 96% of cases when confirmed with genetic testing.[19] Data within the DTR are collected by using linkage to administrative data sets such as the Danish National Patient Register (all admissions to hospital since 1977 and outpatient visits since 1996), large-scale postal questionnaires (administered in 1966, 1994, 2002, and 2003), and regular interview surveys.[20] Data were available until March 2014.

Participants and Variables

All individuals with an International Classification of Diseases diagnosis code of LCPD captured within the national patient register during childhood (<16 years old) were included. The International Classification of Diseases codes were International Classification of Diseases, Eighth Revision (ICD-8), 722.11 and International Classification of Diseases, 10th Revision (ICD-10), M91.1 and M91.2. We excluded those diagnostic codes for diseases that "mimic" LCPD to attenuate misclassification: multiple epiphyseal dysplasia (ICD-10 Q78.8), spondyloepiphyseal dysplasia (ICD-10 Q77.7), hypothyroidism diagnosed before 16 years old (ICD-8 244, ICD-10 E03.9), and hip dysplasia (ICD-8 755.6, ICD-10 Q65). We also excluded LCPD cases diagnosed before the age of 2, because these were likely to represent either atypical disease or misclassification. In total, 3 twin pairs were excluded; 1 had a diagnosis of multiple epiphyseal dysplasia and 2 received their LCPD diagnosis before the age of 2 years.

Data fields extracted were gender, zygosity, and concordance for LCPD. Linkage to the Medical Birth Register enabled birth weight (to the nearest 100 g) for each co-twin to be determined from the birth cohort from 1979 onward. The total number of person-years of exposure of 0 to 16 year olds within the twin cohort since data on inpatient admissions began to be routinely captured (January 1977) was 1 017 054 years.

Statistical Analysis

Proband-wise concordance describes the likelihood that the co-twin of an individual with LCPD would also have the disease. It is calculated by using $2X/(2X + Y)$ where X represents the number of concordant pairs (both co-twins affected) and Y the discordant pairs.[21]

χ^2 Tests were used for categorical variables and unpaired t tests for normally distributed continuous variables. Poisson confidence intervals (CIs) were used for estimates of disease incidence. All statistical analyses were performed

TABLE 1 Twin Pairs and Probandwise Concordance

	Number of Pairs	Concordant, *n*	Discordant, *n*	Probandwise Concordance	95% CI[a]
Monozygotic	10	0	10	0.00	—
Dizygotic	51	2	49	0.08	0.00–0.18
UZ	20	2	18	0.18	0.00–0.40
Overall	81	4	77	0.09	0.01–0.18

[a] ±2 SEs, where $SE^2 = (\rho^2) \times ([1 - \rho]^2) \times (1/n11 + 1/nd)$ or $\rho \times (1 - \rho) \times (2 - \rho)/(2 \times n11 + nd)$; expressions are equivalent.

TABLE 2 Discordant Twin Pairs With Recorded Birth Weight

Group	LCPD-Affected Twin			Mean (SD) Birth Weight, kg	
	Heaviest	Lightest	Same	Affected Twins	Unaffected Twins
Monozygous (*n* = 6)	4	2	0	2.8 (0.3)	2.6 (0.5)
Dizygous, same gender (*n* = 19)	6	9	4	2.6 (0.5)	2.6 (0.5)
Dizygous, opposite gender (*n* = 21)	12	6	3	2.4 (0.7)	2.4 (0.6)
UZ, same gender (*n* = 18)	6	11	1	2.1 (0.9)	2.3 (0.9)
Total (*n* = 64)	28	28	8	2.4 (0.7)	2.4 (0.7)

by using Stata 13.0 (StataCorp, College Station, TX), and $P < .05$ was adopted as the threshold for significance.

Outpatient diagnoses were not captured within the Danish National Register of Births until 1996 onward. The data were therefore subanalyzed by a diagnostic date recorded "pre-1996" and "post-1996" to identify any systematic differences between these groups, particularly because less complex cases may be managed on a solely outpatient basis.

RESULTS

There were 81 twin pairs identified within the DTR, the earliest of which was born in 1966. Seventy-four males and 11 females were affected, with a mean age at diagnosis of 6.3 years (95% CI: 5.6–7.0 years). The incidence of LCPD was 8.4 (95% CI: 6.7–10.3) cases per 100 000 child-years of exposure, equating to a cumulative incidence of 1.3 cases per 1000 children. Ten pairs were monozygotic, 51 dizygotic (25 opposite gender, 26 same gender), and 20 of unknown zygosity (UZ). There were only 4 concordant pairs: 2 each in the dizygotic same-gender group and UZ groups. On the basis of this incidence, and assuming no familial aggregation, no concordant pairs were expected. Table 1 shows that the overall probandwise concordance was 0.09 (95% CI: 0.01–0.18): 0.00 for the monozygotic, 0.08 (95% CI: 0.00–0.18) for the dizygotic, and 0.18 (95% CI: 0.00–0.40) for the UZ group.

Sixty-four discordant pairs (83.1%) had a birth weight recorded within the DTR. Birth weight was not different between those twins with LCPD and those without LCPD in any of the 4 groups (Table 2). Across the data set of 64 discordant pairs with recorded birth weight, those with LCPD weighed 2.4 kg (SD: 0.7 kg) and those without LDPD weighed 2.4 kg (SD: 0.7 kg) ($P = .999$, t test). The affected twin was heaviest in 28 (43.8%), lightest in 28 (43.8%), and of equal weight in 8 (12.5%) cases ($P = .632$, χ^2 test).

DISCUSSION

To our knowledge, this is the largest reported twin study to investigate the etiology of LCPD, but we did not find any evidence of a strong heritable component or an association with birth weight. Although there were several episodes of concordance across the data set of twins, none were found among the monozygotic pairs. Given that the cumulative incidence of LCPD across the whole twin registry was 1.3 cases per 1000 children, the observation that 4 co-twins were affected among 81 twin pairs suggests that LCPD does cluster within families. However, the absence of concordant monozygotic twin pairs suggests that such clustering is unlikely to have a strong genetic basis. Because twins are typically raised together, it is possible that the origins of LCPD occur in utero or in the early childhood environment.

A number of sibling cases have previously been described,[13–15] including reports of identical twins in whom both children developed LCPD.[22–25] However, these cases are likely to have been published because of the interesting observation of sibling concordance and so the literature is likely to reflect a selection bias. Studies that have reported high family concurrences often did not distinguish between LCPD and the many skeletal dysplasias that affect the hip joint, eg, multiple epiphyseal dysplasia.[5] Two earlier studies that drew twins from LCPD registries were unable

to support a genetic cause[5,16] but included only 11 twin pairs (3 monozygotic pairs). Our study in 81 twin pairs provides much stronger evidence of an environmental etiology for LCPD.

In 1 of the 2 previous studies, Lappin et al noted that the affected individual was the twin with the lowest birth weight in all 5 cases.[16] This finding is consistent with evidence that children with LCPD are of relatively small stature,[26,27] have disproportionately reduced arterial caliber,[28] and may exhibit delayed skeletal maturation.[29] However, there were no differences between the birth weights of affected and unaffected twins in our study. It is likely that the finding reported by Lappin et al arose by chance given the small number of patients in their series.

The strengths of this study are the relatively high number of twin pairs and the use of a comprehensive population-based twin registry. It was important to use a population data setbecause both monozygotic and concordant twins are often overrepresented in disease registries.[30,31] A further advantage of the DTR is that the diagnosis of LCPD was prospectively recorded as a part of routine clinical care due to linkage between the DTR and administrative data sets such as the Danish Patient Registry. Although internal validation of each LCPD diagnosis was not possible, the cumulative incidence was consistent with published literature, and the appropriate age/gender distribution of cases offers external validity to suggest that disease coding was appropriate.

The principal limitation of this study is the limited number of twin pairs available, particularly within the monozygotic group. In addition, zygosity was unavailable for 2 concordant twin pairs, which raises the theoretical possibility of there being 2 additional concordant monozygotic pairs. However, because the DTR is one of the largest twin registries in the world,[20] it is unlikely that a larger cohort of affected twin pairs could be identified without systematic registration of LCPD cases on an international scale.

CONCLUSIONS

We have reported the largest existing study of twin pairs affected by LCPD drawn from a comprehensive population registry. These data suggest that the absolute risk that a co-twin of an affected individual will develop LCPD is low, even in the case of monozygotic twin pairs. Although our study found evidence of familial clustering, it was unable to show a major genetic component.

ABBREVIATIONS

CI: confidence interval
DTR: Danish Twin Registry
ICD-8: International Classification of Diseases, Eighth Revision
ICD-10: International Classification of Diseases, 10th Revision
LCPD: Legg-Calvé-Perthes disease
UZ: unknown zygosity

REFERENCES

1. Perry DC, Bruce CE, Pope D, Dangerfield P, Platt MJ, Hall AJ. Legg-Calvé-Perthes disease in the UK: geographic and temporal trends in incidence reflecting differences in degree of deprivation in childhood. *Arthritis Rheum*. 2012;64(5):1673–1679
2. Hall AJ, Margetts BM, Barker DJ, et al. Low blood manganese levels in Liverpool children with Perthes' disease. *Paediatr Perinat Epidemiol*. 1989;3(2):131–135
3. Kealey WD, Moore AJ, Cook S, Cosgrove AP. Deprivation, urbanisation and Perthes' disease in Northern Ireland. *J Bone Joint Surg Br*. 2000;82(2):167–171
4. Margetts BM, Perry CA, Taylor JF, Dangerfield PH. The incidence and distribution of Legg-Calvé-Perthes' disease in Liverpool, 1982-95. *Arch Dis Child*. 2001;84(4):351–354
5. Wynne-Davies R, Gormley J. The aetiology of Perthes' disease: genetic, epidemiological and growth factors in 310 Edinburgh and Glasgow patients. *J Bone Joint Surg Br*. 1978;60(1):6–14
6. Hall AJ, Barker DJ, Dangerfield PH, Taylor JF. Perthes' disease of the hip in Liverpool. *Br Med J (Clin Res Ed)*. 1983;287(6407):1757–1759
7. García Mata S, Ardanaz Aicua E, Hidalgo Ovejero A, Martinez Grande M. Legg-Calvé-Perthes disease and passive smoking. *J Pediatr Orthop*. 2000;20(3):326–330
8. Gordon JE, Schoenecker PL, Osland JD, Dobbs MB, Szymanski DA, Luhmann SJ. Smoking and socio-economic status in the etiology and severity of Legg-Calvé-Perthes' disease. *J Pediatr Orthop B*. 2004;13(6):367–370
9. Perry DC, Pope D, Bruce CE, Dangerfield P, Hall AJ, Platt MJ. Hyperactivity and the psychological burden of Perthes disease: a case-control study. *J Pediatr Orthop*. 2013;33(6):644–649
10. Perry DC, Machin DM, Pope D, et al. Racial and geographic factors in the incidence of Legg-Calvé-Perthes' disease: a systematic review. *Am J Epidemiol*. 2012;175(3):159–166
11. Dilley A, Hooper WC, Austin H, et al. The beta fibrinogen gene G-455-A polymorphism is a risk factor for Legg-Perthes disease. *J Thromb Haemost*. 2003;1(11):2317–2321
12. Balasa VV, Gruppo RA, Glueck CJ, et al. Legg-Calve-Perthes disease and thrombophilia. *J Bone Joint Surg Am*. 2004;86-A(12):2642–2647

13. Calvé J. On a particular form of pseudo-coxalgia associated with a characteristic deformity of the upper end of the femur: 1910. *Clin Orthop Relat Res*. 2006;451:14–16

14. Perthes G. The classic: on juvenile arthritis deformans. 1910. *Clin Orthop Relat Res*. 2012;470(9):2349–2368

15. Burlington H. Legg-Perthes disease in siblings; a report of two cases with simultaneous onset. *Pa Med J*. 1958;61(7):887–888

16. Lappin K, Kealey D, Cosgrove A, Graham K. Does low birthweight predispose to Perthes' disease? Perthes' disease in twins. *J Pediatr Orthop B*. 2003;12(5):307–310

17. Engell V, Damborg F, Andersen M, Kyvik KO, Thomsen K. Club foot: a twin study. *J Bone Joint Surg Br*. 2006;88(3):374–376

18. Skytthe A, Kyvik K, Holm NV, Vaupel JW, Christensen K. The Danish Twin Registry: 127 birth cohorts of twins. *Twin Res*. 2002;5(5):352–357

19. Christiansen L, Frederiksen H, Schousboe K, et al. Age- and sex-differences in the validity of questionnaire-based zygosity in twins. *Twin Res*. 2003;6(4):275–278

20. Skytthe A, Kyvik KO, Holm NV, Christensen K. The Danish Twin Registry. *Scand J Public Health*. 2011;39(7 suppl):75–78

21. Lee MS, Lee SI, Yun S, Kang W. Concordance odds ratios and approximate rate ratios in longitudinal twin studies. *Eur J Epidemiol*. 2003;18(11):1047–1050

22. Giannestras N. Legg-Perthes disease in twins. *J Bone Joint Surg Am*. 1954;36-A(1):149–152

23. Dunn AW. Coxa plana in monozygotic male twins. *J Bone Joint Surg Am*. 1960;42-A(1):178–183

24. Inglis A. Genetic implications in coxa plana. *J Bone Joint Surg Am*. 1960;42-A(4):711–715

25. Fisher RL. An epidemiological study of Legg-Perthes disease. *J Bone Joint Surg Am*. 1972;54(4):769–778

26. Burwell RG, Dangerfield PH, Hall DJ, Vernon CL, Harrison MH. Perthes' disease: an anthropometric study revealing impaired and disproportionate growth. *J Bone Joint Surg Br*. 1978;60-B(4):461–477

27. Hall AJ, Barker DJ, Dangerfield PH, Osmond C, Taylor JF. Small feet and Perthes' disease: a survey in Liverpool. *J Bone Joint Surg Br*. 1988;70(4):611–613

28. Perry DC, Green DJ, Bruce CE, et al. Abnormalities of vascular structure and function in children with Perthes disease. *Pediatrics*. 2012;130(1). Available at: www.pediatrics.org/cgi/content/full/130/1/e126

29. Harrison MH, Turner MH, Jacobs P. Skeletal immaturity in Perthes' disease. *J Bone Joint Surg Br*. 1976;58(1):37–40

30. Harvald B, Hauge M. Hereditory factors elucidated by twin studies. In: Neel JV, Shaw MW, Schull WJ, eds. *Genetics and the Epidemiology of Chronic Diseases*. Washington, DC: Department of Health, Education and Welfare; 1965

31. Lykken DT, Tellegen A, DeRubeis R. Volunteer bias in twin research: the rule of two-thirds. *Soc Biol*. 1978;25(1):1–9

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