Legg-Calvé-Perthes disease and the risk of ADHD, depression, and mortality

A registry study involving 4,057 individuals

Yasmin D Hailer and Olle Nilsson

Department of Orthopedics, Uppsala University Hospital, Uppsala, Sweden.
Correspondence: yasmin.hailer@surgsci.uu.se
Submitted 13-11-23. Accepted 14-02-28

Background and purpose — Hyperactive behavior pattern (such as attention deficit hyperactivity disorder (ADHD)) is proposed to be present in individuals with Legg-Calvé-Perthes disease (LCPD). We investigated whether individuals with LCPD have a higher risk of ADHD, depression, and mortality.

Subjects and methods — We identified 4,057 individuals with LCPD in Sweden during the period 1964–2011. 40,570 individuals without LCPD were randomly selected from the Swedish general population and matched by year of birth, sex, and region (control group). We used Cox proportional hazard regression to estimate the relative risks.

Results — Compared to the control group, individuals with LCPD had a raised hazard ratio (HR) of 1.5 (95% CI: 1.2–1.9) for ADHD. The risks were higher for female individuals (HR = 2.1, CI: 1.3–3.5) than for male individuals (HR = 1.4, CI: 1.1–1.8). Individuals with LCPD had a modestly higher hazard ratio for depression (HR = 1.3, CI: 1.1–1.5) than the control group. Furthermore, individuals with LCPD had a slightly higher mortality risk than the control group (HR = 1.2, CI: 1.0–1.4)

Interpretation — Individuals with LCPD have a higher risk of ADHD. Hyperactivity could expose the femoral head to higher mechanical stress and contribute to the etiology of LCPD. The higher risk of depression may be due to the burden of LCPD itself or could reflect neurobehavioral aspects of ADHD changing into depression later in life. Individuals with LCPD have a higher mortality risk, with higher risk of suicide and cardiovascular diseases. ■

Legg-Calve-Perthes disease (LCPD) is an osteonecrosis of the femoral head epiphysis in children less than 15 years of age, with a peak age at diagnosis of between 5 and 8 years. The etiology of LCPD is still unclear, which makes it impossible to create prevention strategies or to identify individuals at risk. Circulation disturbances of the femoral head based on coagulation abnormalities (Green and Griffin 1982 together with Liu and Ho 1991, Glueck et al. 1994) or increased intraarticular and intraosseous pressure (Liu and Ho 1991) are discussed as underlying pathophysiology, but the findings are inconsistent. However, associations between LCPD and passive smoking, low birth weight, and skeletal retardation in childhood have been reported (Wynne-Davies 1980, Hall et al. 1988, Eckerwall et al. 1996, Garcia Mata et al. 2000, Lappin et al. 2003). In addition, individuals with LCPD appear to have a higher risk of cardiovascular diseases in adulthood (Hailer et al. 2010), which could reflect a vascular "fragility" in these individuals. Earlier studies have suggested repetitive (micro-) trauma as a catalyst for vascular failure leading to LCPD (Wynne-Davies and Gormley 1978, Douglas and Rang 1981). Perthes-like changes of the femoral head were induced in an animal model in which mechanical stress was applied to the hip joint in growing Wistar rats by forcing them to stand on their hind limbs during feeding time. (Mihara and Hirano 1998, Suehiro et al. 2005).

Individuals with LCPD are said to have a hyperactive behavior pattern. In a case-control study, Perry et al. (2013) revealed associations between LCPD and the domain "Inattention-Hyperactivity" of the Goodman 25-item Strength and Difficulties Questionnaire. Furthermore, individuals with LCPD have a higher risk of injuries requiring hospitalization than controls without the disease, which could derive from hyperactive and risk-taking behavior (Hailer et al. 2012).

The aim of this study was to determine whether individuals with a history of LCPD differ from the general population in terms of psychological characteristics such as hyperactive behavior pattern and depression. Since it is difficult to quantify hyperactivity in an epidemiological setting, we used the diagnosis of attention deficit hyperactivity disorder (ADHD)

as the only International Classification of Diseases (ICD-) coded diagnosis available.

It is believed that individuals with undiagnosed/untreated ADHD have a higher risk of suffering from depression (Das et al. 2012). Furthermore, we know of no publication on mortality risk in individuals with LCPD. Both hyperactivity and a possible risk-taking behavior pattern along with the higher risk of cardiovascular diseases in individuals with LCPD could alter the mortality risk in these individuals compared to the general population.

Our hypothesis was that individuals with LCPD (1) have a higher risk of ADHD, (2) have a higher risk of depression, and (3) have a higher mortality risk than individuals without LCPD. The overall aim of the study was to identify persons at risk and to find associations to other diseases, possibly leading to a better knowledge of LCPDs etiology.

Individuals and methods

We used the Swedish Patient Register to identify a cohort of individuals with a diagnosis of LCPD by ICD code. Since 1964, when the Swedish Patient Register started, the ICD code has been revised from version 7 to 10 and has resulted in new codes for LCPD (until 1968: ICD-7 code 732.04; until 1987: ICD-8 code 722.11; until 1997: ICD-9 code 732B; and since 1997: ICD-10 codes M91.1 and M91.2) (Socialstyrelsen 1996, WHO 2009). From 1964 until 2000, the Swedish Patient Register included data on individual hospital admissions. As of 2001, ambulatory consultations were also included and registered with ICD codes. Between 1964 until December 31, 2011, 4,194 individuals were identified with the diagnosis LCPD. 137 individuals were recorded as also having hip diseases other than LCPD (developmental dysplasia of the hip, slipped capital femoral epiphysis) and were excluded, leaving 4,057 individuals with LCPD for our study (3,056 men and 1,001 women). Using the Swedish national registration number, a personal identifier assigned to every resident of Sweden from birth or immigration, we used the Total Population Register to identify each individual's date of birth, sex, region of residence at diagnosis,s and date of death or emigration. Individuals with LCPD were individually matched with 10 individuals in a population-based cohort without LCPD. The matching criteria for these 10 individuals were date of birth, sex, region of residence, and being alive at the time when the LCPD patient was diagnosed.

These 2 groups were compared in order to assess the relative risk of ADHD (ICD-9: 314.0; ICD-10: F90.0) and depression (ICD-7: 790.29; ICD-8: 790.20; ICD-9: 308, 311; ICD-10: F32-38, F92.0) and mortality.

Ethics

This study was approved by the Ethics Research Committee in Uppsala, Sweden (registration number 2012/065, date of issue March 21, 2012).

Table 1. Associations between LCPD and ADHD, depression, and mortality

| | No. of events (%) | | Hazard ratio (95% CI) | |
	Subjects with LCPD	Subjects without LCPD	Crude	Adjusted for matching [a]
ADHD	102 (2.5)	675 (1.7)	1.5 (1.2–1.9)	1.5 (1.2–1.9)
Male	83 (2.7)	585 (1.9)	1.4 (1.1–1.8)	1.4 (1.1–1.8)
Female	19 (1.9)	90 (0.9)	2.1 (1.3–3.5)	2.1 (1.3–3.5)
Depression	151 (3.7)	1206 (3.0)	1.3 (1.1–1.5)	1.3 (1.1–1.5)
Male	89 (2.9)	784 (2.6)	1.2 (0.9–1.4)	1.2 (0.9–1.4)
Female	62 (6.2)	422 (4.2)	1.5 (1.1–2.0)	1.5 (1.1–1.9)
Mortality	179 (4.4)	1597 (3.9)	1.2 (1.0–1.4)	1.2 (1.0–1.4)
Male	123 (4.0)	1103 (3.6)	1.2 (1.0–1.4)	1.2 (1.0–1.4)
Female	56 (5.6)	494 (4.9)	1.3 (1.0–1.7)	1.3 (1.0–1.7)

[a] Matching variables: date of birth, sex, region of residence, and being alive at the time when the LCPD patient was diagnosed.

Statistics

To estimate the relative risk of ADHD, depression, and mortality in individuals with LCPD and in those without the disease, we used Cox proportional hazard regression. All analyses were performed crude and adjusted to the matching variables mentioned above. Follow-up was from 1964, when the Swedish Patient Register was established, or from birth or immigration if this occurred subsequently. Follow-up continued until the diagnosis of ADHD or depression, death, emigration or December 31, 2011, whichever occurred first. The underlying time scale for all models was age reached. A person could have more than one study endpoint due to different outcomes of the diseases of interest.

Stratified analyses were performed by sex and on data before 2001 (only inpatient data) and after 2001 (both inpatient and outpatient data). Hazard function plots and log-log plots of all covariates verified the assumption of proportional hazards. No signs of insufficient proportionality were detected. For all covariates, all log-log plots ran strictly parallel.

Results

Individuals with a history of LCPD had a 1.5-fold higher risk of ADHD than sex- and age-matched individuals without LCPD (Table 1). Stratified analysis revealed a 2.1-fold higher risk of ADHD in females with LCPD than in females without LCPD. Stratified analysis of data before 2001 (inpatient data alone) and after 2001 (inpatient and outpatient data) did not change the estimates (data not shown).

Individuals with LCPD had a 1.3-fold higher risk of depression than age- and sex-matched individuals without a history of LCPD. The risk rose to 1.5 times higher for females with LCPD than for females without LCPD when stratifying the analysis by sex.

Table 2. Causes of death

| | No. of events (%) | | Hazard ratio (95% CI) | |
	Subjects with LCPD	Subjects without LCPD	Crude	Adjusted for matching [a]
Suicide	7 (3.9)	24 (1.5)	3.0 (1.3–6.8)	2.9 (1.3–6.8)
Vascular	65 (36.3)	574 (35.9)	1.3 (1.0–1.6)	1.2 (0.9–1.6)
Oncological	31 (17.3)	313 (19.6)	1.1 (0.7–1.5)	1.1 (0.7–1.5)
Hemato-oncological	3 (1.7)	32 (2.0)	1.0 (0.3–3.2)	1.0 (0.3–3.5)
Injuries	11 (6.2)	129 (8.1)	0.9 (0.5–1.6)	0.8 (0.4–1.4)
Neurological, psychiatric or drug abuse	6 (3.5)	109 (6.8)	0.6 (0.3–1.4)	0.7 (0.3–1.5)
Other	56 (31.1)	416 (26.1)		
Total	179 (100)	1597 (100)		

[a] Matching variables: date of birth, sex, region of residence, and being alive at the time when the LCPD patient was diagnosed.

The mortality risk for individuals with LCPD was 1.2-fold higher than for individuals without LCPD. Exclusion of individuals with depression and ADHD did not change the slightly higher mortality risk for individuals with LCPD compared to individuals without LCPD. Individuals with LCPD had a 2.9-fold higher risk of committing suicide and a slightly higher risk (HR = 1.2) of dying of vascular diseases (Table 2).

Discussion

This population-based study of 4,057 individuals with LCPD and 40,570 controls without LCPD revealed that individuals with LCPD had a higher risk of ADHD, depression, and mortality than their sex- and age-matched controls, thereby confirming our hypothesis (1).

Hyperactive behavior pattern has been discussed as a possible promoter of LCPD (Wynne-Davies and Gormley 1978, Douglas and Rang 1981). Hyperactivity is difficult to quantify, and the only ICD-coded diagnosis that includes hyperactivity is ADHD. In 1993, Loder et al. (1993) found in a group of 24 children with LCPD that one-third had abnormally high scores in profiles associated with ADHD. In a case-control study of 619 individuals with LCPD between the ages of 0 and 14 years, Perry et al. (2013) found hyperactivity associated with LCPD but could not find a significantly higher risk of diagnosis of ADHD (Perry et al. 2012a). Although ADHD is commonly diagnosed between 5 and 8 years of age, a delay between age at onset and age at diagnosis is not unusual. Since our observation time was much longer (from 1964 until diagnosis of ADHD or emigration, death, or December 31, 2011, whichever occurred first), this may explain our results, which contrast with the findings of Perry et al. (2012a). We observed that the risk of ADHD was higher in females with LCPD. Both ADHD and LCPD are more common in boys (Catter-

all 1977, Rucklidge 2010). However, girls with LCPD have a worse prognosis than boys (Catterall 1971, Mukherjee and Fabry 1990). Thus, it is possible that girls with LCPD suffer more severely from the disease and may be more susceptible to related complications.

ADHD and LCPD share common risk factors through inheritance or exposure, such as deprivation (Lingineni et al. 2012, Perry et al. 2012b), higher injury risk (Maxson et al. 2009, Hailer et al. 2012), and maternal and passive smoking (Garcia Mata et al. 2000, Button et al. 2005). Especially in adults, neurobehavioral aspects of ADHD can change from hyperactivity to more inattentiveness or depression (Yang et al. 2013), which may explain the higher risk of depression in individuals with LCPD than in their controls, and which also supports our hypothesis (2). While the association of LCPD with "emotional symptoms" (Perry et al. 2013) has been described, to our knowledge ours is the first study to investigate associations between LCPD and depression as a formal diagnosis. The higher risk of depression could also be a result of the psychological burden of LCPD as a response to chronic pain, restriction in physical activity, and the relatively uncertain outcome of LCPD compared to other chronic diseases (Cassileth et al. 1984, Moussavi et al. 2007).

Individuals with LCPD had a slightly higher mortality risk than controls without LCPD, which supports our hypothesis (3). The higher mortality risk remained even when we excluded individuals with ADHD and depression. This rules out possible adverse effects of ADHD therapy—sudden death or cardiac infarction (Martinez-Raga et al. 2013). However, individuals with LCPD have a higher risk of committing suicide than controls. No individual with both LCPD and ADHD had committed suicide in this study, even though suicide is associated with ADHD (James et al. 2004, Impey and Heun 2012). Individuals with LCPD have a higher risk of cardiovascular disease (Hailer et al. 2010), which appears to be an underlying cause of the higher mortality risk in these individuals.

The strengths of the present study include the large sample size, the cohort design, and relatively long follow-up. The data in the Swedish Patient Register are collected prospectively and undergo no further selection, so they provide a nationwide perspective and a sample that is representative of the population. One limitation is that the coverage of the Swedish Patient Register was not complete until 1987. Data for events that happened before 1987 may have been incomplete. However, misclassification is non-differential and could not result in spurious associations. Another caveat is that we were unable to verify the diagnostic accuracy of LCPD among the individuals, or the diagnoses of ADHD or depression. However, the positive predictive value of coded diagnoses in the Swedish Patient Register is estimated to be accurate for 85–95% of cases, and generally higher for somatic diseases (Ludvigsson et al. 2011). Furthermore, the ICD-coding errors in the Swedish Patient Register are less common in the records of younger

individuals than in those of older individuals (Socialstyrelsen 2009). Another possible confounder might be that individuals with LCPD may be more easily diagnosed with other diseases due to them receiving more healthcare attention. To minimize this confounder, we analyzed the data by excluding the time frame of 2 years before and after the diagnosis of LCPD, and this did not change the estimates noticeably.

Until 2000, only inpatient data were collected in the Swedish Patient Register; it was not until 2001 that both inpatient and outpatient data were registered. Since both ADHD and depression are generally diagnosed in an outpatient setting, only severe cases requiring hospitalization might have been included before 2001. An ICD code for ADHD exists first in versions 9 and 10, although only younger individuals at follow-up may have been registered with this diagnosis. However, this would be true for both cases and controls, and may not noticeably influence the study outcome.

As in most registry studies, we lack some important information such as the exact age at diagnosis of LCPD, even though both incident and prevalent cases were included in the exposed cohort. Furthermore, we lacked data on the socioeconomic status of the individuals' parents. Both LCPD and ADHD are more common in families with a lower socioeconomic index (Perry and Hall 2011, Thapar et al. 2013). However, we have shown in earlier studies of individuals with a history of LCPD that the data were not influenced by socioeconomic status (Hailer et al. 2010, 2012). Furthermore, the cases and controls were matched for "region of residence", which should have minimized confounding through SEI. Information on smoking habits, physical activity, or heredity of diseases of interest was not available through the Swedish Patient Register, and could be a confounding factor in the estimation of mortality risk.

In summary, our findings contribute to a better knowledge of LCPD and its association with other diseases, which could lead to a better understanding of the etiology. Individuals who show a hyperactive behavior pattern at orthopedic consultation may have severe difficulties in coping with LCPD. It remains to be seen whether these individuals would benefit from a psychological consultation for ADHD screening in order to be offered adequate medication—or whether the hyperactive behavior pattern may be a result of the physical and psychological burden of having LCPD.

Button T M, Thapar A, McGuffin P. Relationship between antisocial behaviour, attention-deficit hyperactivity disorder and maternal prenatal smoking. Br J Psychiatry 2005; 187: 155-60.

Cassileth B R, Lusk E J, Strouse T B, Miller D S, Brown L L, Cross P A, et al. Psychosocial status in chronic illness. A comparative analysis of six diagnostic groups. N Engl J Med (Comparative Study Research Support, U.S. Gov't, P.H.S.) 1984; 311 (8): 506-11.

Catterall A. The natural history of Perthes' disease. J Bone Joint Surg (Br) 1971; 53 (1): 37-53.

Catterall A. Perthes's disease. Br Med J 1977; 1 (6069): 1145-9.

Das D, Cherbuin N, Butterworth P, Anstey K J, Easteal S. A population-based study of attention deficit/hyperactivity disorder symptoms and associated impairment in middle-aged adults. PLoS One 2012; 7 (2): e31500.

Douglas G, Rang M. The role of trauma in the pathogenesis of the osteochondroses. Clin Orthop 1981; (158): 28-32.

Eckerwall G, Wingstrand H, Hagglund G, Karlberg J. Growth in 110 children with Legg-Calve-Perthes' disease: a longitudinal infancy childhood puberty growth model study. J Pediatr Orthop B 1996; 5 (3): 181-4.

Garcia Mata S, Ardanaz Aicua E, Hidalgo Ovejero A, Martinez Grande M. Legg-Calve-Perthes disease and passive smoking. J Pediatr Orthop 2000; 20 (3): 326-30.

Glueck C J, Glueck H I, Greenfield D, Freiberg R, Kahn A, Hamer T, et al. Protein C and S deficiency, thrombophilia, and hypofibrinolysis: pathophysiologic causes of Legg-Perthes disease. Pediatr Res 1994; 35 (4 Pt 1): 383-8.

Green N E, Griffin P P. Intra-osseous venous pressure in Legg-Perthes disease. J Bone Joint Surg (Am) 1982; 64 (5): 666-71.

Hailer Y D, Montgomery S M, Ekbom A, Nilsson O S, Bahmanyar S. Legg-Calve-Perthes disease and risks for cardiovascular diseases and blood diseases. Pediatrics 2010 Jun; 125 (6): e1308-15. Erratum in: Pediatrics 2013;132 (1):186-7.

Hailer Y D, Montgomery S, Ekbom A, Nilsson O, Bahmanyar S. Legg-Calve-Perthes disease and the risk of injuries requiring hospitalization: a register study involving 2579 individuals. Acta Orthop 2012; 83 (6): 572-6.

Hall A J, Barker D J, Dangerfield P H, Osmond C, Taylor J F. Small feet and Perthes' disease. A survey in Liverpool. J Bone Joint Surg (Br) 1988; 70 (4): 611-3.

Impey M, Heun R. Completed suicide, ideation and attempt in attention deficit hyperactivity disorder. Acta Psychiatr Scand 2012; 125 (2): 93-102.

James A, Lai F H, Dahl C. Attention deficit hyperactivity disorder and suicide: a review of possible associations. Acta Psychiatr Scand 2004; 110 (6): 408-15.

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): 307-10.

Lingineni R K, Biswas S, Ahmad N, Jackson B E, Bae S, Singh K P. Factors associated with attention deficit/hyperactivity disorder among US children: results from a national survey. BMC Pediatr 2012; 12: 50.

Liu S L, Ho T C. The role of venous hypertension in the pathogenesis of Legg-Perthes disease. A clinical and experimental study. J Bone Joint Surg (Am) 1991; 73 (2): 194-200.

Loder R T, Schwartz E M, Hensinger R N. Behavioral characteristics of children with Legg-Calve-Perthes disease. J Pediatr Orthop 1993; 13 (5): 598-601.

Ludvigsson J F, Andersson E, Ekbom A, Feychting M, Kim J L, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health 2011; 11: 450.

Martinez-Raga J, Knecht C, Szerman N, Martinez M I. Risk of serious cardiovascular problems with medications for attention-deficit hyperactivity disorder. CNS Drugs 2013; 27 (1): 15-30.

Maxson R T, Lawson K A, Pop R, Yuma-Guerrero P, Johnson K M. Screening for attention-deficit/hyperactivity disorder in a select sample of injured and uninjured pediatric individuals. J Pediatr Surg 2009; 44 (4): 743-8.

Mihara K, Hirano T. Standing is a causative factor in osteonecrosis of the femoral head in growing rats. J Pediatr Orthop 1998; 18 (5): 665-9.

Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. Lancet 2007; 370 (9590): 851-8.

Mukherjee A, Fabry G. Evaluation of the prognostic indices in Legg-Calve-Perthes disease: statistical analysis of 116 hips. J Pediatr Orthop 1990; 10 (2): 153-8.

Perry D C, Hall A J. The epidemiology and etiology of Perthes disease. Orthop Clin North Am (Review). 2011; 42 (3): 279-83.

Perry D C, Bruce C E, Pope D, Dangerfield P, Platt M J, Hall A J. Comorbidities in Perthes' disease: a case control study using the General Practice Research database. J Bone Joint Surg (Br) 2012a; 94 (12): 1684-9.

Perry D C, Bruce C E, Pope D, Dangerfield P, Platt M J, Hall A J. Perthes' disease of the hip: socioeconomic inequalities and the urban environment. Arch Dis Child 2012b; 97 (12): 1053-7.

Perry D C, Pope D, Bruce C E, Dangerfield P, Hall A J, Platt M J. Hyperactivity and the psychological burden of perthes disease: a case-control study. J Pediatr Orthop 2013; 33 (6): 644-9.

Rucklidge J J. Gender differences in attention-deficit/hyperactivity disorder. Psychiatr Clin North Am 2010; 33 (2): 357-73.

Socialstyrelsen. Kvalitet och innehåll i patientregistret. In: Utskrivningar från slutenvården 1964–2007 och besök i specialiserad öppenvård (exklusive primärvårdsbesök) 1997–2007. Stockholm, Sweden: Patientregistret, Epidemiologiskt Centrum, Socialstyrelsen; 2009: 41.

Suehiro M, Hirano T, Shindo H. Osteonecrosis induced by standing in growing Wistar Kyoto rats. J Orthop Sci 2005; 10 (5): 501-7.

Thapar A, Cooper M, Eyre O, Langley K. What have we learnt about the causes of ADHD? J Child Psychol Psychiatry (Research Support, Non-U.S. Gov't Review). 2013; 54 (1): 3-16.

Wynne-Davies R. Some etiologic factors in Perthes' disease. Clin Orthop 1980; (150): 12-5.

Wynne-Davies R, Gormley J. The aetiology of Perthes' disease. Genetic, epidemiological and growth factors in 310 Edinburgh and Glasgow individuals. J Bone Joint Surg (Br) 1978; 60 (1): 6-14.

Yang H-N, Tai Y-M, Yang L-K, Gau S S-F. Prediction of childhood ADHD symptoms to quality of life in young adults: Adult ADHD and anxiety/depression as mediators. Res Dev Disabil 2013; 34 (10): 3168-81.