Legg-Calvé-Perthes disease and the risk of injuries requiring hospitalization

A register study involving 2579 patients

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Background and purpose **Previous studies have suggested that Legg-Calvé-Perthes disease (LCPD) is associated with repetitive trauma, coagulation problems and anatomical abnormalities of the blood supply to the femoral head. The hypothesis that repetitive trauma can affect the blood supply of the femoral head, leading to LCPD, is supported by an animal model. For evidence of an increased risk of repetitive trauma, we investigated whether patients with LCPD have a higher risk for severe injuries requiring hospitalization.**

Patients and methods **We identified 2579 patients with LCPD in Sweden during the period 1964–2005. 13,748 individuals without LCPD were randomly selected from the Swedish general population, matched by year of birth, sex and region (control group). Cox proportional hazard regression estimated the risks.**

Results **Compared to the control group, patients with LCPD had a modestly raised hazard ratio (HR) of 1.2 (95% CI 1.1–1.3) for injury requiring hospitalization. The risks were slightly higher for soft tissue injuries (HR = 1.3, 95% CI:1.1–1.4) than for fractures (HR = 1.1, 95% CI: 1.0–1.3) and more pronounced among females. Compared to the control group, the higher risk for injury only applied to the lower extremities (HR = 1.2, 95% CI: 1.0–1.4) in patients with LCPD.**

Interpretation **Patients with LCPD are vulnerable to injuries which could be interpreted as a marker of hyperactive behavior. It could also implicate that anatomical changes in the bone formation or blood supply of the femoral head – increasing its sensibility for trauma – contribute to the etiology of LCPD.**

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 of diagnosis between 5 and 8 years of age. Boys are affected four times more often than girls. The disease is bilateral in 8–24% of patients (Guille et al. 1998).

The etiology and pathophysiology of LCPD are still not completely understood. However, association between this disease and passive smoking, small stature, skeletal retardation, and low birth weight has been reported (Wynne-Davies and Gormley 1978, Hall et al. 1988, Rao et al. 1995, Eckerwall et al. 1996, Garcia Mata et al. 2000, Lappin et al. 2003). Disturbed circulation in the femoral head has been hypothesized, such as stasis in blood vessels because of increased intraarticular and intraosseous pressure or thromboembolic events as a result of coagulation abnormalities (Green and Griffin 1982, Liu and Ho 1991). It has also been suggested that anatomical changes in the blood supply with a reduced number or capacity of blood vessels may cause LCPD (Catterall 1971, Axer and Schiller 1972, de Camargo et al. 1984, Alpaslan et al. 2007). In earlier studies, repetitive trauma was suggested to affect the blood supply of the femoral head, leading to LCPD (Wynne-Davies and Gormley 1978, Douglas and Rang 1981). This phenomenon has been simulated and proven in an animal model in which mechanical stress was applied to the hip joints of ordinary growing Wistar Kyoto rats by forcing them to stand (Mihara and Hirano 1998, Suehiro et al. 2000, 2005). As children with hyperactive behavior are known to experience more injuries, (Uslu and Uslu 2008, Maxson et al. 2009, Merrill et al. 2009, Ertan et al. 2012) it has been suggested that hyperactivity disorders or attention deficit hyperactivity disorder (ADHD) might be more common among patients with LCPD (Loder et al. 1993).

In this population-based cohort study using Swedish register data we investigated if patients with LCPD have higher risk of injury compared with the general population.

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Table 1. Characteristics of the study subject

	Subjects with LCPD	Subjects without LCPD
Total	2,579	13,750
Male (%)	1,936 (75.1)	10,408 (75.7)
Female	643 (24.9)	3,340 (24.3)

Patients and methods

Patients

Swedish register data were used to identify a cohort of patients with a diagnosis of LCPD. This cohort was compared with a general population-based cohort without LCPD to assess the risk for injuries. The Swedish Patient Register includes data on individual hospital admissions and 2579 patients with LCPD (ICD-7 code 732.04; ICD-8 code 722.11; ICD-9 code 732B; and ICD-10 codes M91.1, M91.2) admitted to hospital between 1964 and 2005 (Socialstyrelsen 1996, WHO 2009) were identified. Using The National Registration Number, personal identifier assigned to every resident of Swedish from birth or immigration, we used the Total Population Register to identify each individual's date of birth, sex, region of residence at diagnosis, date of death and emigration. Census data provided a 6-category socioeconomic index based on occupation of parents (manual workers, non-manual workers, professionals, self employed, farmers and others). Patients with LCPD were individually matched with up to 5 individuals of a population-based cohort without LCPD. The matching criteria were date of birth, sex and region of residence and being alive at time the patient was diagnosed with LCPD (Table 1).

These two groups were compared in order to assess the risk of injury (ICD-10: S00–S99, T00-T14 and corresponding codes for previous revisions of ICD-7–9) during the study period from 1964 until death, emigration, or December 31, 2005 (Socialstyrelsen 2009). As we were interested in the location of injury, 3 groups of diagnoses identified injuries in the head and trunk (ICD-10: S00–S39, T08, T09) injuries in the upper extremities (ICD-10: S40–S69, T10, T11), and injuries in the lower extremities (ICD-10: S70–S99, T12, T13). Only severe injuries requiring hospital admission due to pain, need of surgery or other coexistent complications were identified in this study since minor injuries are treated in an outpatient setting.

Ethics

This study was approved by the ethics research committee at the Karolinska Institutet, Stockholm, Sweden, reg. number 2005/1004-31/2, date of issue October 7, 2005.

Statistics

With Cox proportional hazard regression, we estimated the risk of injuries in patients with LCPD and in those without the disease. Follow-up was from 1964, when the inpatient register was established, or from birth or immigration if this occurred subsequently. Follow-up continued until diagnosis of the injury, death, emigration, or December 31, 2005. The underlying time scale for all models was attained age. A person could have more than one study endpoint (different disease outcomes). We performed crude and adjusted analyses and adjustment was made for parental socioeconomic index.

Stratified analysis was performed by sex. Separate analyses examined soft tissue injuries and fractures. Furthermore site-specific injuries were analyzed: injuries in the upper extremity, injuries in the head and trunk, and injuries in the lower extremity.

To use the matching criteria all models were internally stratified by risk-set.

The assumption of proportional hazards was verified by hazard function plots and log-log plots of all covariates. No signs of insufficient proportionality were detected. For all covariates, all log-log plots ran strictly parallel. All statistical analyses were performed using the IBM SPSS Statistic software, version 20).

Results

Injuries

The risk of injury requiring hospital admission was higher in patients with a history of LCPD than in sex and age matched individuals without LCPD (HR = 1.2, 95% CI: 1.1–1.3) (Table 2). Analysis with stratification by sex showed that the increased risk was more pronounced among females with LCPD than in females without any history of LCPD (HR = 1.6, 95% CI: 1.3–1.9). In males with LCPD the risk of injury was slightly higher than in males without the disease (HR = 1.2, 95% CI: 1.0–1.3). The association with LCPD was only significant for injuries in the lower extremities (HR = 1.2, CI: 1.0–1.4). Adjustment for socioeconomic index did not change the results substantially.

Soft tissue injuries and fractures

Separate analysis for soft tissue injuries and fractures revealed that patients with a history of LCPD had a 26 % higher risk for soft tissue injuries (HR = 1.3, CI: 1.1–1.4) and a 14 % higher risk of fractures (HR = 1.1, CI: 1–1.3) requiring hospital admission than the individuals without LCPD. In stratified analysis the risks for both soft tissue injuries (HR = 1.7, CI: 1.4–2.2) and fractures (HR = 1.5, CI: 1.1–1.9) were of higher magnitude in females with a diagnosis of LCPD than in females without a history of LCPD. Adjustment for socioeconomic index did not change the results substantially.

Table 2. Association between Legg–Calvé–Perthes disease (LCPD) and injury requiring hospital admission

	Number of events (%)		Hazard Ratio (95% Confidence Interval)	
	Subjects with LCPD	Subjects without LCPD	Unadjusted	Adjusted for socioeconomic index
Injury [a]	588 (22.8)	2,703 (19.7)	1.2 (1.1–1.4)	1.2 (1.1–1.3)
Male	436 (22.5)	2,159 (20.7)	1.2 (1.0–1.3)	1.1 (1.0–1.3)
Female	152 (23.6)	544 (16.3)	1.6 (1.3–1.9)	1.6 (1.3–1.9)
Soft tissue Injury	404 (15.7)	1,777 (12.9)	1.3 (1.1–1.4)	1.3 (1.1–1.4)
Male	308 (15.9)	1,474 (14.2)	1.2 (1.0–1.3)	1.2 (1.0–1.3)
Female	96 (14.9)	303 (9.1)	1.7 (1.4–2.2)	1.7 (1.4–2.2)
Fracture	280 (19.9)	1,356 (9.9)	1.2 (1.0–1.3)	1.1 (1.0–1.3)
Male	202 (10.4)	1,054 (10.1)	1.1 (0.9–1.3)	1.1 (0.9–1.2)
Female	78 (12.1)	302 (9.0)	1.5 (1.1–1.9)	1.5 (1.1–1.9)
Site of injury				
Upper limb	133 (5.2)	770 (5.6)	0,9 (0.8–1.1)	0.9 (0.8–1.1)
Male	93 (4.8)	619 (5.9)	0.8 (0.7–1.0)	0.8 (0.6–1.0)
Female	40 (6.2)	151 (4.5)	1.4 (1.0–2.0)	1.4 (1.0–2.0)
Trunk or skull	226 (8.8)	1,070 (7.8)	1.2 (1.0–1.3)	1.1 (1.0–1.3)
Male	174 (9.0)	885 (8.5)	1.1 (0.9–1.3)	1.1 (0.9–1.3)
Female	52 (8.1)	185 (8.5)	1.4 (1.0–2.0)	1.4 (1.0–2.0)
Lower limb	212 (8.8)	959 (7.0)	1.2 (1.1–1.4)	1.2 (1.0–1.4)
Male	150 (7.7)	747 (7.2)	1.1 (0.9–1.3)	1.1 (0.9–1.3)
Female	62 (9.6)	212 (6.3)	1.5 (1.2–2.1)	1.5 (1.2–2.1)

[a] Soft tissue injury or fracture, whatever occurred first.

Discussion

This population-based study revealed that LCPD was associated with a higher risk of injuries. It is possible that trauma may be causally implicated in LCPD etiology.

Parents and orthopedic surgeons often mention that children with LCPD seem to be more active than average and seem to have a high pain threshold, which is difficult to quantify (Sharma et al. 2005). It is possible that patients with LCPD are vulnerable to injury simply because they expose themselves to increased risk, perhaps as a result of behavioral deviations such as hyperactivity. 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 (Attention Deficit Hyperactivity Disorder). The prevalence of ADHD in general population varies between 2 % to 19 % (Faraone et al. 2003).

Another speculation about the higher risk of injuries in patients with LCPD could be decreased muscle strength, derangement of joint mobility or coordination problems or bone mineral loss due to immobility caused by LCPD and treatment for it. A similar pathomechanism for bone mineral loss is described after lower extremity trauma (Karlsson et al. 1993a,b, van der Poest Clement et al. 1999). However, we observed a higher risk of injuries both before and after LCPD diagnosis, even after excluding events that happened during 1 year before and 5 years after the LCPD diagnosis (data not shown). Decreased muscle strength, derangement of joint mobility or coordination problems bone mineral loss due to immobility associated with acute LCPD and its treatment might not be the sole reason for the elevated injury risk.

A possible explanation for the higher risk of fracture in patients with LCPD could be that these patients may have weaker bone tissue due to hormonal, or circulation pathologies. Burwell et al. 1978 found in a cross-sectional anthropometric study of 232 children with LCPD smaller feet and disproportionate growth in the extremities compared with a control group. These findings could indicate a retardation or inhibition of growth. However, we know of no investigations of bone quality among patients with LCPD.

We observed that the relative risks of injury were higher among females with LCPD. In general, both, injuries and LCPD are more common among males (Landin 1997, Hedstrom et al. 2010). However, females with LCPD have a worse prognosis than males (Catterall 1971, Dickens and Menelaus 1978, Mukherjee and Fabry 1990). Thus, it is possible that females with LCPD suffer from more severe disease and may be more susceptible to related complications.

The adjustment for socioeconomic index did not change the results of this study remarkably. A possible explanation could be that Sweden has one of the lowest level of income inequality and poverty in the OECD (OECD 2011). However it has been suggested that LCPD is more common in deprived areas and is associated with low socioeconomic status (Hall et al. 1983, Kealey et al. 2000, Pillai et al. 2005) but the findings are inconsistent (Sharma et al. 2005). Similar findings are described in the epidemiology of injury showing associations with deprivation and low socioeconomic status (Menon et al. 2008).

To our knowledge this is the first epidemiological study with a population based design investigating the risk for injuries in patients with a history of LCPD. Strengths of our study include the large sample size, cohort design and relatively long follow-up. Unfortunately, we did not have outpatient data and we only investigated severe injuries requiring hospital admission due to pain, surgery or other coexistent complications. Minor soft tissue injuries, injuries of the upper extremity and the trunk and simple injuries of the lower extremity - which normally are handled in ambulatory or day-surgery settings - could not be investigated here. Since other diseases, such as hormonal or vascular diseases, are generally diagnosed and treated in outpatient settings, we were not able to investigate some diagnoses that could help to explain the findings.

Another potential limitation is that the coverage of the Swedish Patient Register was not complete until 1987, and the data for the events that happened before LCPD diagnosis may have been incomplete. However, misclassification is non-differential and could not result in spurious associations. Another caveat is that we were not able to verify the diagnostic accuracy of LCPD among the patients. However, the positive predictive value of coded diagnoses in the Patient Register is estimated to be accurate for 85–95% 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 for younger patients compared with older patients (Socialstyrelsen 2009). Despite the acceptable levels of diagnostic accuracy for LCPD and injuries, some error may have been present that could have influenced the accuracy of our estimates. As in most register-based studies, we lack some potentially important information. For example, both incident and prevalent cases of LCPD were included in the exposed cohort. Thus, we did not have exact age of diagnosis. Information on the side (right/left) of LCPD and injuries is not available from the register, so it was not possible to investigate if LCPD–affected joints and injuries tended to occur on the same side of the body.

In conclusion, patients with a history of LCPD had a higher risk of severe injury than individuals without LCPD and were more pronounced in female patients. The higher risk of injuries in patients with LCPD was confined to the lower extremities. Higher risk for injury in patients with LCPD may signal a tendency to more hyperactive behavior among these patients. It is also possible that anatomical abnormalities in bone formation and blood supply of the femoral head—increasing its sensibility for trauma—contribute to the etiology of LCPD.

YDH: data analysis, statistics, writing and revision of the manuscript. ON: Revision of the manuscript SB: writing and revision of the manuscript SM: revision of the manuscript. AE: revision of the manuscript

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