

Exploring the Association between Legg-Calvé-Perthes Disease and Attention Deficit Hyperactivity Disorder in Children

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ABSTRACT: **Background:** Legg-Calvé-Perthes disease (LCPD) is an idiopathic hip osteonecrosis prevalent in children < age 15 years. The etiology remains incompletely understood, partly because of multiple potential environmental risk factors and partly because of lack of genetic markers. It has been hypothesized that hyperactivity may induce mechanical stress and/or vascular damage at a fragile joint.

Objectives: To assess children with LCPD for markers of attention deficit hyperactivity disorder (ADHD) relative to their unaffected comparably aged siblings to exclude the contribution of hyperactive behavior versus environmental and/or genetic factors in LCPD.

Methods: All children followed in the Pediatric Orthopedic Clinic, and their comparably aged siblings, were recruited. ADHD was assessed using the TOVA computerized test and DSM-IV criteria. Quality of life and sleep disorders as ancillary tests were assessed using the Child Health Questionnaire (Parent Form 50), Pediatric Outcomes Data Collection Instrument, and Pediatric Daytime Sleepiness Scale.

Results: Sixteen children with LCPD (age 9.1 ± 3.3 , 75% males) were compared with their closest-aged siblings (age 9.3 ± 2.6 , 30% males). Mean TOVA scores of children with LCPD (-3.79 ± 2.6) and of their non-LCPD siblings (-3.6 ± 4.04) were lower relative to the general population (0 ± 1.8 , $P < 0.0001$). Both group means were in the ADHD range (≤ -1.8) implying that 73% of this LCPD cohort and 53% of their non-LCPD siblings performed in the ADHD range, relative to 3.6% incidence expected in the general population ($P < 0.0001$). Other test results were similar in both groups.

Conclusions: Our findings in a small cohort of children with LCPD and their comparably aged siblings do not support an association between LCPD and ADHD. ADHD markers were equally high in the LCPD children and siblings.

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KEY WORDS: attention deficit hyperactivity disorder (ADHD), Legg-Calvé-Perthes disease (LCPD), sibling study

Despite decades of experience with varying medical and surgical management approaches to Legg-Calvé-Perthes disease (LCPD), an idiopathic osteonecrosis of the hip in children, the etiology remains incompletely understood. Hence, identifying at-risk pediatric patients has been unsuccessful. The incidence of LCPD ranges from 0.4/100,000 to 29.0/100,000 (approximately 1 in 1200) among children under 15 years of age with peak presentation between the ages of 4 and 8 years. There is some heterogeneity based on racial groupings and socioeconomic status, and some abnormalities in growth parameters [1,2]. While LCPD is more frequent among boys, it is generally accepted that the prognosis is worse for girls, who often present with radiological evidence of a greater degree of damage [3].

There is little evidence implicating a purely genetic etiology, whereas rat models of mechanical stress at the hip joint successfully mimic the LCPD hip [4]. Other indices of a non-genetic nature of those at risk of developing LCPD include commonality of some conditions: many of these children are products of a breech delivery, many are constitutionally shorter than their siblings and parents, they are often third- or later-born, and generally many are from low-income families. These factors presumably render these specific children at greater risk of trauma [5].

The more classic hypotheses of the pathophysiology of LCPD, such as intermittent arterial occlusion and/or repeated trauma to vulnerable revascularizing bone [6], are being re-interpreted as also being reflective of mechanical stressors such as impeded or forestalled plasticity of the acetabulum by age 9 years [7] and retroversion of the acetabulum [8]. Interestingly, both of these theories consider possible initiation and/or exacerbation of bone damage by hyperactivity. Indeed in a recent study, a significant percentage (> 90%) of LCPD patients reported being active at a moderate or high level although half of them also reported moderate or severe bone pain [9].

The long-term consequences of this complex hip deformity are readily recognized in terms of impaired ambulation/functioning, chronic pain, and reduced quality of life even in adulthood and regardless of therapeutic correction in childhood [9]. Associations with other disorders that evince hyperactivity in

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children have become of interest as a means towards understanding the pathology of LCPD [10,11]. Consequently, attention deficit hyperactivity disorder (ADHD) has been scrutinized as a confounding variable in the etiology of LCPD in children [9,10,12,13]. Those previous studies contained small cohorts and did not include evaluation of ADHD in control groups.

Meta-regression analyses have estimated the worldwide prevalence of ADHD to be between 5.3% and 7.1% in children and adolescents with an increased incidence among boys [14]. The hypothetical basis of the association of LCPD (which might yet have some unidentified genetic predilection) with ADHD is that LCPD could be induced by early and physiologically abnormal stress of a fragile bone because of hyperactivity.

The purpose of the present study was to assess (Israeli) children with LCPD for objective markers of ADHD relative to their unaffected and comparably aged siblings, to exclude the relative contribution of behavioral rather than environmental features of LCPD.

PATIENTS AND METHODS

All 16 children aged 4–15 years currently being followed for LCPD in the Pediatric Orthopedic Clinic were recruited. Healthy siblings of these patients who were aged 4–15 years, none of whom have LCPD or ADHD, were recruited as controls. Institutional Helsinki Committee approval was received for this study.

The diagnosis of LCPD was based on the child’s complaints and history, complete physical examination, and repeated radiological evidence, characteristic of LCPD. ADHD was assessed using the TOVA computerized test [15], where a score of 0 ± 1.8 points represents the norm. An in-depth interview was conducted with the child to evaluate the degree of meeting the criteria of the DSM-IV for ADHD by one of us (J.B.). In addition, the following tests were administered:

- Complete neurological physical examination
- The Child Health Questionnaire (Parent Form 50, CHQ-PF50) in Hebrew that queries 14 domains of physical, psychosocial, and familial conditions
- The Pediatric Outcomes Data Collection Instrument (PODCI), a standard form to assess changes in pediatric patients with musculoskeletal signs after orthopedic event/intervention. It is based on four functional assessment scores, a global function score, and a happiness score with each having a possible range from 0 to 100 [16]
- The Pediatric Daytime Sleepiness Scale (PDSS), since daytime sleepiness is related to reduced educational achievement, possibly due to inattention [17].

STATISTICAL ANALYSIS

The chi-square, Fisher’s exact, Student’s *t*-test and McNemar tests were applied as appropriate. For non-parametric compari-

Table 1. Demographic features and outcomes in pediatric LCPD patients and their comparably aged siblings

	LCPD patients (n=16)	Siblings (n=13)	P value
Mean age ± SD	9.1 ± 3.3	9.3 ± 2.6	NS
Males	12 (75.0%)	4 (30.8%)	0.017
ADHD as per DSM-IV	3 (18.8%)	1 (7.7%)	NS
Mean TOVA score SD	-3.79 ± 2.67	3.6 ± 4.04	NS
Diagnosis of ADHD as per TOVA	12 (75%)	7 (53.8%)	NS
CHQ: mean physical score	78.8	86.2	0.027
CHQ: mean psychosocial score	80.7	87.6	NS
CHQ: mean family score	79	86.4	NS
Mean PDSS score	7.75	7.5	NS
Mean PODCI score	88.25	Not applicable	

ADHD = attention deficit hyperactivity disorder, CHQ = Child Health Questionnaire, PDSS = Pediatric Daytime Sleepiness Scale, PODCI = Pediatric Outcomes Data Collection Instrument, NS = not significant

sons, the Mann-Whitney-Wilcoxon U test or Kruskal-Wallis R test was used.

RESULTS

Among the siblings of the LCPD patients, 13 met the age criterion and were recruited as the control population; for 3 children with LCPD there were no siblings to match the age criteria. None of the LCPD children had a sibling of any age with LCPD.

Table 1 presents the demographic features and outcomes in the two groups. Mean TOVA scores of children with LCPD (-3.79 ± 2.6) and of their siblings (-3.6 ± 4.04) were lower relative to the general population (0 ± 1.8 , $P < 0.0001$). Of the children with LCPD, 73% had TOVA scores in the ADHD range (≤ -1.8 SD), as did 53% of their non-LCPD siblings compared with the expected percentage (3.6%) in the general population ($P < 0.0001$). Mean Quality of Life scores in the physical domain of the CHQ were lower in children with LCPD (78.8 ± 11.3) compared with the mean score of the siblings (86 ± 8.3 , $P = 0.027$). There were no differences in sleep disturbance based on the Pediatric Daytime Sleepiness Scale between groups. The mean scores of the Pediatric Outcomes Data Collection Instrument (PODCI, evaluated in the LCPD group only) were in the upper quintile, representing near normal status.

DISCUSSION

This study attempted to evaluate the incidence of ADHD among patients with LCPD. Earlier studies have postulated it to be higher than in the general population [9,10,12,18]. It was assumed that the comparably aged healthy siblings of children with LCPD would be representative of the general

population but would have similar socioeconomic and genetic confounders. This type of case-control design had not been applied in the earlier studies. Of initial concern in the current study was that there was a significant difference between the cohorts with regard to gender because of the preponderance (as expected) of boys among the LCPD but not among the comparably aged siblings. In a sense this might have been the main limitation of the study, because ADHD also has a predilection among boys. Indeed, both groups had significantly lower sustained attention scores based on the TOVA examination compared to the general population, although with more girls among the siblings one might have expected fewer markers of ADHD among the siblings [19]. Nonetheless, the TOVA test results are controlled for both gender and age, and as such the gender inequality between groups might have a lesser impact.

Conversely, had we queried whether LCPD might be a risk factor for lower sustained attention (for example, because of pain-induced sleep deprivation), we would not have found a significant difference in both PDSS and TOVA scores between the two groups to support this hypothesis.

As expected, we found slightly lower Quality of Life scores in the physical domain of the CHQ in the children with LCPD, but scores in other domains were similar to those of their siblings. A potential explanation for comparable Quality of Life scores between groups is that the parent is the one who completes the questionnaire for both of the children and may thus inadvertently bias the results. However, the comparable TOVA scores, based on testing that is individual to each child and unrelated to a parental assessment, represents an unexpected finding of comparable performance indicative of ADHD among both groups of children, none of whom had been suspected of being ADHD. The imputation of a genetic factor in ADHD was previously reported as an endophenotype of ADHD/inattention [20] and is independent of gender.

In summary, this study aimed to implicate a predisposition to hyperactivity as an underlying stressor for hip osteonecrosis in LCPD patients. We uncovered a high percentage of children suspected of having ADHD among both the LCPD children and their non-LCPD siblings based on TOVA scores. This study attempted to isolate hyperactive behavior patterns as an etiological factor in LCPD by employing a comparably aged sibling cohort to decrease the environmental and genetic confounders. Thus, the hypothesis that a predilection to ADHD predisposes to LCPD is not supported by our findings.

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**“Don't walk in front of me... I may not follow
Don't walk behind me... I may not lead
Walk beside me... just be my friend”**

Albert Camus (1913-1960), French philosopher, author, and journalist