



Duration of Legg-Calvé-Perthes Disease Stages in Children Under Four Years of Age at Disease Onset

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Introduction

Although it has been more than a century since its original description by Henning Waldenström and Arthur T. Legg, the etiology and natural history of Legg-Calve-Perthes disease (LCPD) remain controversial.¹ This rare condition of idiopathic osteonecrosis of the femoral head in children has a variable incidence of 0.2 to 29 per hundred thousand children less than fifteen years of age, depending on the geographic location and ethnicity of the children.^{2,3} Additionally, the disease is most commonly diagnosed in males between the ages of four years and fourteen years.²

As initially recognized by Waldenström, the affected femoral head in LCPD progresses through four distinct radiographic stages over the course of the disease.⁴ These four stages are the initial (I) stage, fragmentation (II) stage, reossification (III) stage, and residual (IV) stage. Joseph *et al* later modified Waldenström's classification system by further sub-categorizing the first three stages as either early (A) or late (B) in order to determine when radiographic changes occur in the femoral epiphysis during evolution of the disease.⁵ In terms of classification, the lateral pillar grading system, described by Herring *et al*, stratifies the femoral head into four distinct groups (A, B, B/C, and C) based on the height of the lateral third of the epiphysis during "early" fragmentation.⁶ Several publications have correlated increasing severity of Herring grade with poorer functional and radiographic outcomes.⁶⁻⁸

Several studies have evaluated long-term outcomes in LCPD patients under six years old. However, to our knowledge, there is a paucity of data on the disease progression and natural history of LCPD in patients diagnosed at a very young age. Thus, the purpose of this study was to describe the presentation and duration of modified Waldenström stages in patients with LCPD diagnosed prior to four years of age. We hypothesized that the length of modified Waldenström stages would be shorter in young patients compared to typical-aged children with LCPD, which might explain, in part, the favorable outcomes seen in younger patients with the disease.

Methods

After obtaining approval from our institutional review board, the medical records

and radiographs of all patients diagnosed with LCPD between 2007 and 2017 at a single pediatric tertiary care institution were reviewed. We included only those patients who were diagnosed with LCPD prior to their fourth birthday, and who had adequate radiographs obtained at initial diagnosis and during the active stages of the disease. Patients were excluded if they were diagnosed with a skeletal dysplasia, Meyer's dysplasia, had other diagnoses known to cause osteonecrosis (e.g. septic arthritis, sickle cell disease etc.), did not have at least 3 radiographs during the disease course, or were treated surgically as this would affect the natural history of the disease. When a patient had bilateral involvement, only the hip(s) that were diagnosed with LCPD prior to the patient's fourth birthday were included.

The time intervals between radiographs showing features of subsequent stages were calculated in order to determine the length of each stage. Mean and standard deviations, medians, and ranges were used to describe continuous variables. Non-normally distributed data were analyzed using non-parametric Mann-Whitney U test. The relationships between age at diagnosis, weight, BMI, presence or absence of symptoms at the time of diagnosis, Herring grades, and stage lengths were analyzed using Pearson Chi-square test or Fisher exact probability test with IBM SPSS statistics 15.0 software (Chicago, IL). Significance was set at two-sided alpha level of $p < 0.05$. In order to relate our findings to those in typical-aged patients, we compared our results with those reported by Joseph *et al*.⁵

Results

Twenty-seven patients (32 hips) were included in the study. The age at presentation ranged from 1.8 years to 4.0 years with a mean age of 3.1 years (SD = 0.6 years). Twenty-three patients (85%) were male; mean BMI was 16.7 kg/m² (range 14.4 to 24.0) at the time of diagnosis. Five patients had bilateral disease with onset under four years of age in both hips. Twenty-two patients presented with a limp and 25 patients presented with pain in the affected hip joint. The overall mean and median interval between sequential radiographs were 138 days (SD = 53.9 days) and 126 days (range, 29-272 days), respectively. The average follow-up interval during early stages (IA-IIA) and late

stages (IIB-III A) were similar (Table 1). Patients had an average of 5.6 radiographs (range 3-13) during the disease course, and all hips were treated conservatively without surgery as per our inclusion criteria.

Overall, sixteen hips (50%) were graded as Herring B, and 16 (50%) as grade C in the fragmentation stage. All 4 females (5 hips) were graded as Herring C while 9 males (11 hips) were Herring grade C. The remaining 14 males (16 hips) were graded as Herring B (Table 2). All hips remained in the same Herring grade throughout the duration of active disease. With the exception of one hip which presented during modified Waldenström stage IA, all hips presented at stage IB or later. At most recent follow-up, fifteen hips were in Waldenström stage IV; 6 in stage IIB; 5 in stage IIIA; 5 hips in stage IIB; and 1 in IIA. Mean age at last follow-up was 5.0 years (SD = 1.6 years).

Based on the time intervals between radiographs showing features of subsequent stages, the median duration of early stage disease (modified Waldenström IA-IIA) was 513 days, and of late stage disease (IIB-III B) was 833 days (Table 3). In our series, age, weight, BMI, and presenting symptoms at the time of diagnosis showed no association with duration of disease stages (all p values > 0.05).

Discussion

To our knowledge, this series is the first to specifically describe the course of LCPD in very young patients. Most literature describing LCPD in younger patients consists of

smaller, retrospective studies with patients ranging from 18 months to 12 years.^{5,8-10} The scarcity of data is even more pronounced in children with disease onset under the age of four years as none of the recent studies have been performed exclusively in this very young patient population with LCPD.

In their landmark series of 164 LCPD hips with disease onset under six years of age, Rosenfeld *et al* noted that the patients with disease onset prior to age four had a greater than 84% probability of a favorable disease course.¹⁰ They also observed that the combination of age at onset and lateral pillar involvement correlated more strongly with a favorable outcome compared to age at onset alone. In spite of the authors' conclusions that younger patients with LCPD tended to have improved outcomes, the authors did not separately report the number of patients in their series younger than four years of age, nor did they comment on the duration of disease stages in any of these younger patients. Similarly, other investigators have confirmed this apparent positive influence of younger age at onset on disease outcome.^{8,11,12} However, none of these studies in very young children report on the duration of Waldenström stages, which may be a factor that influences outcome. In an important study evaluating the natural history of LCPD in children up to 12 years of age, Joseph *et al* reported the length of modified Waldenström stages.⁵ The mean age in their series was 9.08 ± 2.91 years for males and 8.48 ± 3.56 years for females. Although the authors did not stratify their findings according to age at onset, it is the

Table 1. Mean and median follow-up intervals during early and late stages of LCPD.

	Follow-up Intervals (days)		
	Early stages (IA-IIA)	Late stages (IIB-IV)	<i>P</i> value
Median (range)	119 (29-252)	133 (36-272)	0.155
Mean \pm SD	126 \pm 51.7	143 \pm 59.3	

Table 2. Modified Waldenström stages and Herring grades of the hips.

Herring grades assigned during early fragmentation	Modified Waldenström stages at the time of presentation			
	IA*	IB*	IIA	IIB
B	1 (3.1%)	7 (21.9%)	6 (18.8%)	2 (6.3%)
C	0 (0.0%)	5 (15.6%)	6 (18.8%)	5 (15.6%)
Total no. of hips	1 (3.1%)	12 (37.5%)	12 (37.5%)	7 (21.9%)

* For hips presenting in Stage IA and IB, the Herring grades were assigned when they progressed to the fragmentation stage.

Table 3. Duration of Waldenström stages in children with LCPD presenting before age 4 years.

Stage (no. of hips)	Median duration (days)	Mean duration, in days (95% CI)
IA (1)	240	240 (n/a)
IB (12)	130	141 (108-173)
IIA (14)	199	162 (140-243)
IIB (17)	283	240 (140-339)
IIIA (15)	273	257 (194-320)
IIIB (11)	384	420 (312-528)

only other study in the literature that we are aware of which quantifies the duration of Waldenström stages.

Our study found that the modified Waldenström stages were longer in our LCPD patients with disease onset prior to four years of age compared to the cohort of older patients previously reported by Joseph *et al* (Figure 1).⁵ In their patient population, the combined median duration of the initial four stages of the disease (IA to IIB) was approximately 3.5 to 4 months, whereas the median durations of stage IIIA and IIIB were twice and three times as long as the initial four stages, respectively. In our patient sample, the median durations of stage IB, IIA, IIB, IIIA and IIIB were longer by 35 days, 80 days, 57 days, 58 days and 49 days, respectively, than those reported by Joseph *et al*.⁵ We also found that the combined duration of stages IIIA and IIIB was almost twice as long as the duration of stages IB-IIB. Since only one patient in our series initially presented during stage IA, the duration of stage IA was not included in the comparison.

Our findings suggest that factors other than stage duration may be responsible for the favorable outcomes seen in very young patients. From an anatomical perspective, younger children have a relatively greater proportion of cartilage in their hips, which may serve to resist mechanical deformation of the femoral head; however, biomechanical studies are warranted to establish a definitive relationship between the disease outcome and cartilage content of the affected hips. Another potential explanation for the more favorable disease course in younger patients is the longer period for potential remodeling prior to skeletal maturity.¹³

As a retrospective investigation of a sub-population of patients with an already rare disorder, our study has several inherent limitations. The duration of each stage was determined by measuring the time interval between radiographs showing

features of one stage and radiographs demonstrating features of the next stage. In reality, the stage may have progressed at any point between images. Thus, the accuracy of the stage duration depended on the time interval between subsequent radiographs. To partially address this issue, we included only patients with a minimum of 3 radiographs showing sequential progression through disease stages. In addition, the median follow-up interval during early stages was not significantly different compared to during late stages (119 days and 133 days, respectively; $p = 0.155$). However, the difference between median combined duration of early stages and that of late stages was found to be statistically significant (513 days and 833 days, respectively; $p = 0.011$). These findings suggest that our reported stage durations are not merely a function of the time intervals between successive radiographs. However, we certainly acknowledge that our calculated durations of LCPD stages are still an estimated value at best. That being said, our methodology for computing duration of stages is comparable to the one used by Joseph *et al*, and represents a good faith attempt to measure a continuous variable (i.e. stage length) using periodic data.⁵ Secondly, it is important to acknowledge that Joseph *et al* conducted their study on children from the Indian subcontinent where the incidence of LCPD is much lower and the age at onset is greater compared to North American population.^{3,5,14} While their study is the only previous work in the literature that reports on the duration of Waldenström stages, our direct comparison may not be generalizable to typical aged patients in North America.

Despite its limitations, this study is the first to characterize the duration of LCPD stages in very young patients. Our findings, in contrary to our original hypothesis, suggest that the duration of LCPD stages may actually be longer in these younger patients as compared to typical-aged LCPD patients.

This may imply that factors other than a shorter duration of disease stages could be responsible for the improved outcomes seen in these children.

References

1. Waldenström H. The classic. The first stages of coxa plana by Henning Waldenström. 1938. *Clinical orthopaedics and related research*. 1984(191):4-7.
2. Perry DC, Machin DM, Pope D, *et al*. Racial and geographic factors in the incidence of Legg-Calve-Perthes' disease: a systematic review. *Am J Epidemiol*. 2012;175(3):159-166.
3. Loder RT, Skopelja EN. The epidemiology and demographics of legg-calve perthes' disease. *ISRN Orthop*. 2011;2011:504393.
4. Waldenström H. The definite form of the coxa plana. *Acta Radiologica*. 1922;1:384-394.
5. Joseph B, Varghese G, Mulpuri K, *et al*. Natural evolution of Perthes disease: a study of 610 children under 12 years of age at disease onset. *Journal of pediatric orthopaedics*. 2003;23(5):590-600.
6. Herring JA, Kim HT, Browne R. Legg-Calve-Perthes disease. Part I: Classification of radiographs

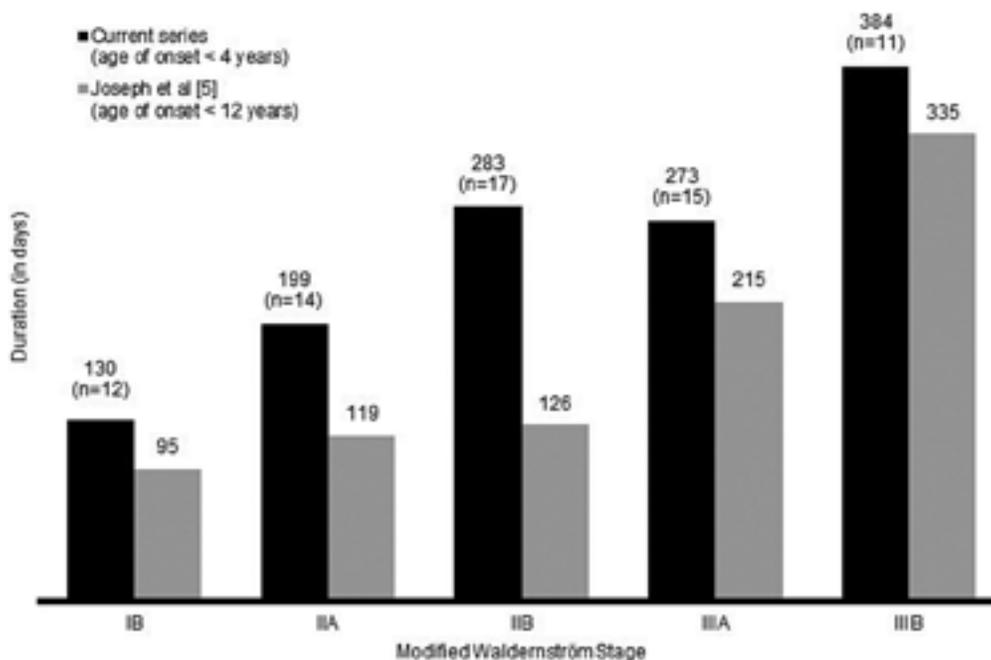


Figure 1. The median duration of modified Waldenström stages of LCPD in children younger than four years of age at the onset compared to older children.

with use of the modified lateral pillar and Stulberg classifications. *J Bone Joint Surg Am.* 2004;86-A(10):2103-2120.

7. **Wiig O, Terjesen T, Svenningsen S.** Prognostic factors and outcome of treatment in Perthes' disease: a prospective study of 368 patients with five-year follow up. *J Bone Joint Surg Br.* 2008;90(10):1364-1371.

8. **Schoenecker PL, Stone JW, Capelli AM.** Legg-Perthes disease in children under 6 years old. *Orthop Rev.* 1993;22(2):201-208.

9. **Fabry K, Fabry G, Moens P.** Legg-Calve-Perthes disease in patients under 5 years of age does not always result in a good outcome. Personal experience and meta analysis of the literature. *J Pediatr Orthop B.* 2003;12(3):222-227.

10. **Rosenfeld SB, Herring JA, Chao JC.** Legg-calve-perthes disease: a review of cases with onset before six years of age. *J Bone Joint Surg Am.* 2007;89(12):2712-2722.

11. **Kelly FB, Jr, Canale ST, Jones RR.** Legg-Calve-Perthes disease. Long-term evaluation of non-containment treatment. *J Bone Joint Surg Am.* 1980;62(3):400-407.

12. **Grasemann H, Nicolai RD, Patsalis T, et al.** The treatment of Legg-Calve-Perthes disease. To contain or not to contain. *Arch Orthop Trauma Surg.* 1997;116(1-2):50-54.

13. **Lindstrom JR, Ponseti IV, Wenger DR.** Acetabular development after reduction in congenital dislocation of the hip. *J Bone Joint Surg Am.* 1979;61(1):112-118.

14. **Joseph B, Chacko V, Rao BS, et al.** The epidemiology of Perthes' disease in south India. *Int J Epidemiol.* 1988;17(3):603-607.