Master's Thesis of Medicine

Changes in Contrast Enhancement and Diffusion in Legg-Calvé-Perthes Hips and Optimal Timing of MRI Evaluation

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Abstract

Introduction:

Magnetic resonance (MR) imaging indices of contrast enhancement and diffusion measured at the proximal femur are known to be prognostic of later femoral head deformity in Legg-Calvé-Perthes (LCP) disease. However, the usefulness of an index as an indicator for the prognosis for such disease may be limited if the index changes rapidly within time. The purpose of this study was to evaluate longitudinal changes of contrast enhancement and diffusion in the proximal femur with disease progression, and to determine the disease stage in which MR imaging indices are best associated with a later femoral head deformity in children with LCP disease.

Materials and Methods:

In this prospective case series, 26 children (23 boys and 3 girls) with unilateral LCP disease who had contrast-enhanced and diffusion MR imaging carried out two times at different disease stages were reviewed. The amount of contrast enhancement was measured in five different areas (whole, central, lateral, medial epiphysis, and metaphysis) on contrast-enhanced MR images, and the apparent diffusion coefficient (ADC) value was measured only at the metaphysis. The contrast-enhancement ratio (CER) and ADC ratio (ADCR) were defined as ratios of increase or decrease relative to the contralateral normal side. We evaluated the changes in these MRI indices with the progression of the disease stages. We also investigated the MR index and disease stages most relevant to the Stulberg classification at the final follow-up.

Results:

The CER values of the whole ($p < 0.001$) and central ($p < 0.001$) epiphysis and metaphysis ($p = 0.018$) among the six indices showed a significant change between the first MRI and the second MRI. Final Stulberg classification and ADCR of the metaphysis value of 1b–2a ($p = 0.002$) and 2a–2b ($p = 0.008$) modified Elizabethtown stage were significantly related. When subgroup analysis was performed with ADCR of the metaphysis values of 1b, 2a, and 2b stages, the value of stage 2a was statistically associated significantly with the final outcome. ($p=0.020$)

Conclusions:

This study showed that the CER of the whole, central epiphysis, and metaphysis among MRI indices in the early stages of LCP disease changed significantly. Accordingly, this study conducted an investigation into which index was statistically related to the final Stulberg classification for each disease stage. As a result, the ADCR of the metaphysis at stage 2a was found to be the most likely.

Keyword: Legg–Calvé–Perthes, Contrast–enhanced ratio, Apparent diffusion coefficient, Epiphyseal perfusion, Femoral head deformity

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Chapter 1. Introduction

Legg-Calvé-Perthes (LCP) disease is ischemic necrosis of the epiphysis in the proximal femur due to unknown pathophysiology. Because LCP disease is one of the most common childhood hip disorders and can cause permanent femoral head deformity and debilitating osteoarthritis without appropriate treatment, it is important to predict the prognosis of this disease and to establish a therapeutic strategy.[14]

To date, the widely accepted prognosticators of LCP are limited to the age of onset, the Herring method of assessing the collapse of the lateral pillar, and the presence or absence of a "head-at-risk" sign.[3] Among these prognosticators, the method of measuring the height of the lateral pillar (which is known as the Herring method) is most commonly used clinically. However, since it can only be applied after fragmentation of the femoral head has progressed ("wait-to-clarify"), the method has a critical disadvantage in that it cannot be used to predict the prognosis in the early stage of LCP disease.[13]

To overcome the issues with conventional prognosticator, recent studies have reported some results with MRI. In 1997, Sebag et al.[18] found that early recognition of LCP disease is possible using dynamic gadolinium-enhanced subtraction (DGS) MRI or perfusion MRI. Subsequently, various authors have tried not only conventional MRI, but also perfusion imaging, contrast-enhanced imaging, and diffusion-weighted imaging to attempt early diagnosis and to predict the prognosis of LCP disease.[5,10-12,19] However, these early studies have some important limitations. First, if there is a purpose

in predicting a prognosis through the MR index, it is necessary to focus on the index before collapse occurs; however, existing studies have included assessment over the entire stage period and has obtained vague results. Second, the reliability of the data is low because the index values that could be changed for each stage were combined as the research was conducted. Third, previous studies have used surrogate indices based on outcomes, such as the deformity index (DI), Catterall classification, without using the Stulberg classification that measures the final femoral head deformity.

Thus, the aim of this study was to discover whether there is a change in the MRI index as the LCP stage progresses and to determine which stage and MRI index is the most relevant to the final femoral head deformity among the indices that change according to disease stage.

We hypothesized that MR imaging indices would not change as the disease stage progresses, and there will be no association between the final femoral head deformity and MR index for a particular stage.

Chapter 2. Materials and Methods

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (800-20130130) funded by the Ministry of Education, Science and Technology of the Republic of Korea. The study was designed as a prospective case series, from December 2010 through December 2014. We obtained IRB approval from our institution (SNUH IRB) and received written informed consents from parents of patients at the time of MR imaging.

Inclusion criteria

We conducted this study in patients with unilateral LCP disease. The diagnosis of LCP disease was made by plain radiograph. Patients who agreed to be included in this study had two contrast-enhanced and diffusion MRIs taken at different stages of the disease. Only patients with a follow-up period of at least two years were included in the study analysis. Patients who had reached the residual stage at the final follow-up were included.

Patient enrollment

Among the patients diagnosed with LCP disease, those who were eligible for this study were enrolled at our institute between February 1, 2010, and November 1, 2014. These patients were followed-up from April 17, 2015, to March 13, 2020. Follow-up plain radiographs were obtained every 3- to 6-months on the judgment of clinicians, until the latest follow-up visit or until the disease course reached the residual stage.

Twenty-six patients (23 boys, 3 girls) who had reached the residual stage at the final follow-up were included in the study. The average age at the last follow-up was 154.19 months (range from 82 to 225 months), and the average follow-up period from the first visit to the last visit was 68.54 months (range from 32 to 106 months). Of the 26 patients, 12 had undergone surgery; eight of 12 patients had undergone femoral varization osteotomy; three had undergone triple innominate osteotomy, and one had undergone articulated distraction surgery. The average age of patients at the first MRI was 88.19 months (range from 34 to 138 months), and the average age of patients at the second MRI was 98.27 months (range from 41 to 161 months). The MRI scan interval was 10.08 months (range from 2 to 40 months). When the first MRI was taken after diagnosis, there were seven patients in Elizabethtown stage 1a, 14 were in 1b, one was in 2a, three were in 2b, and one was in 3a. At the second MRI, one patient was in stage 1b, eight were in 2a, eight were in 2b, eight were in 3a, and one was in 4. Of the 26 patients at the time of the final follow-up, three patients were in Stulberg classification 1, ten were in classification 2, nine were in classification 3, and four were in classification 4 (Table 1).

Table 1. Characteristics of the study group.

Sex (M/F)	23/3
Age at final follow-up (month)	154.19 (82-225)
Follow-up periods (month)	68.54 (32-106)
Surgery (Y/N)	12/14
Age at first MRI scan (month)	88.19 (34-138)
Age at second MRI scan (month)	98.27 (41-161)
MRI scan interval (month)	10.08 (2-40)
Disease stage at first MRI scan (1a/1b/2a/2b/3a/3b/4)	7/14/1/3/1/0/0
Disease stage at second MRI scan (1a/1b/2a/2b/3a/3b/4)	0/1/8/8/8/0/1
Stulberg classification (1/2/3/4/5)	3/10/9/4/0

Month is described as mean and range.

Image acquisition

MR imaging was performed using a 1.5T system (MAGNETOM Avanto; Siemens Healthcare, Erlangen, Germany) with a 6-channel body-array coil combined with a 4-channel spine coil. We examined both hips with the following sequences: coronal and sagittal T1-weighted turbo spin-echo imaging with and without fat saturation; coronal T2-weighted turbo spin-echo imaging with fat saturation; and sagittal 3-dimensional multiecho data image combination (Siemens Healthcare), which has a heavily T2-weighted spoiled gradient-echo sequence with multiple echoes. Diffusion-weighted images were obtained using the single-shot echoplanar imaging technique with parallel imaging (generalized auto-calibrating partially parallel acquisition factor of 2) that included both hip joints in coronal planes. Diffusion gradients were applied in three orthogonal directions, and three b values (0, 250, and 500 sec/mm2) were used. Contrast material-enhanced MR images (coronal and sagittal T1-weighted images with fat saturation) were obtained two minutes after a manual injection of 0.1 mmol/kg of gadoterate meglumine (Dotarem; Guerbet, Aulnay, France).

Measurement of MRI indices

The degree of contrast enhancement and the apparent diffusion coefficient (ADC) values were measured via picture archiving and communication system (PACS). Three fully trained pediatric orthopedic surgeons measured the indices with patient information blindly and separately. The mean value of the separately measured indices was used for the analysis.

The degree of contrast enhancement was defined as a mean pixel

value measured on three to five coronal contrast-enhanced MR images. Regions of interest (ROIs) were the whole, lateral third, medial third, and central third areas of the secondary ossification center in the epiphysis and whole metaphysis. A circular ROI was placed on the lateral third, central third, and medial third of the secondary ossification center in the epiphysis. A freehand-drawn ROI was placed on the whole epiphysis and metaphysis, excluding the cortical bone. The ROI for the metaphysis was from slightly below the proximal femoral physis to a position just proximal to the lesser trochanter. The size and shape of the ROI were variable and depended on the size and shape of the secondary ossification center in the epiphysis and metaphysis in each child (Figure 1).

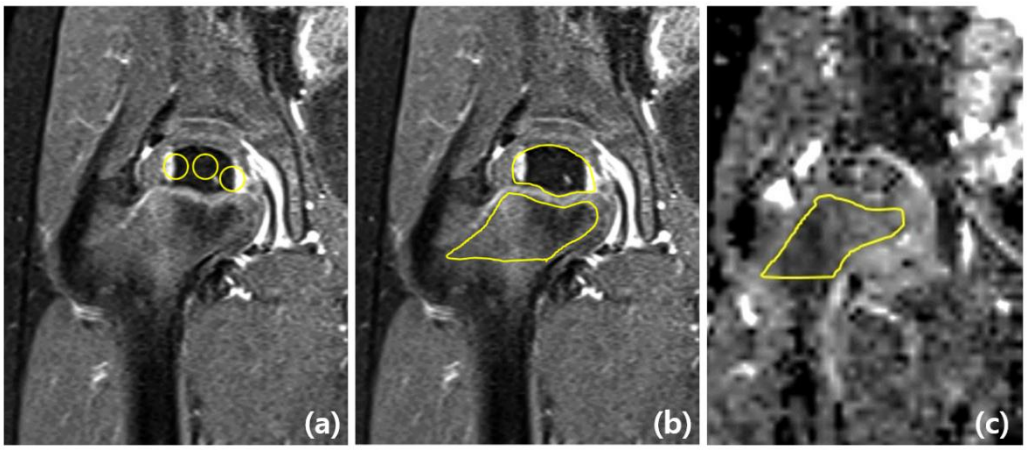

Figure. 1. Drawn region of interest (ROI) map

(a) Contrast-enhanced area of lateral, central, and medial epiphysis are drawn with a yellow circle line, (b) Contrast-enhanced area of whole epiphysis and metaphysis are drawn, (c) Area for apparent diffusion coefficient (ADC) of metaphysis is drawn.

We defined the contrast-enhancement ratio (CER) to quantify an increase or decrease in contrast enhancement relative to the contralateral normal side and to compensate for potential variability of the baseline normal contrast enhancement in each patient. CER was defined as [(contrast enhancement value in disease side – contrast enhancement value in normal side)/contrast enhancement value in normal side] x 100 (%). The mean ADC value was measured on three to five coronal images of the ADC map, and the mean value obtained was used for further analysis. The ROIs were the whole epiphysis and metaphysis, which excluded the cortical bone. We frequently referred to the diffusion-weighted images to select the ROI on the ADC map. The ADC difference ratio (ADR) was defined as [(ADC value in disease side – ADC value in normal side)/ADC value in normal side] x 100(%).[20]

Other radiological measurements

The modified Elizabethtown stage and Stulberg classification were determined by three fully trained pediatric orthopedic surgeons with the final agreement.

Surgery

Surgery was performed if it was deemed necessary and all 3 operators were pediatric orthopedic surgeons with a minimum 15 years of experience in our institute (I.H.C performed 5 operations, T.J.C performed 5 operations, and W.J.Y performed 2 operations). Depending on the hip condition of the patient, femoral varization osteotomy, triple innominate osteotomy, or articulated distraction were performed.

Analysis

The interobserver reliability of the CER and ADCR was analyzed by calculating the intraclass correlation coefficient by using all patient measurements.

The paired t-test method was used to determine the degree of change in the index value measured in two MRI scans. For nonparametric values, the Wilcoxon signed-rank test was used. In order to examine whether the measured values showing significant changes between the two MRI scans and between the disease stages, the time period when the MRI index value changed rapidly was determined using the modified Elizabethtown stage as a reference. We focused on the earliest point in time which rapid change ceased because the ultimate goal of this study was to find a relationship with the final Stulberg classification prognosis through the MRI index; an index in which collapse has already progressed has no role as an early prognosticator. The relationship between the MRI index and Stulberg classification measured at the earliest stage at which the rapid change period ended was determined by one-way ANOVA (Jonckheere-Terpstra test in case of nonparametric data). Indices that did not change significantly with stage progression of the disease were analyzed separately. One-way ANOVA (Jonckheere-Terpstra test in case of nonparametric data) was used to find the stage where the correlation between these indices and Stulberg classification was significant.

Chapter 3. Results

The interobserver reliability for the MR imaging indices ranged from 0.491 to 0.957 (Table 2).

Table 2. Interobserver reliability for the Contrast Enhancement and Diffusion Indices

Indices	Interobserver reliability
CER of whole epiphysis	0.688 (0.463, 0.821)
CER of lateral epiphysis	0.598 (0.282, 0.773)
CER of central epiphysis	0.615 (0.297, 0.838)
CER of medial epiphysis	0.491 (0.176, 0.731)
CER of metaphysis	0.862 (0.738, 0.937)
ADCR of metaphysis	0.957 (0.918, 0.979)

Data in parentheses are 95% confidence intervals.

CER = Contrast enhancement ratio, ADCR = Apparent diffusion coefficient ratio

The CER of the whole epiphysis, lateral epiphysis, central epiphysis, medial epiphysis and metaphysis, and ADC values of the metaphysis were measured in two MRI scans. The CERs of whole epiphysis ($p < 0.001$), central epiphysis ($p < 0.001$), and metaphysis ($p = 0.018$) showed significant differences (Table 3).

Table 3. Changes of indices between first and second MRI

	1st MRI value	2nd MRI value	P-value
CER of whole epiphysis	10.096	60.119	0.000#
CER of lateral epiphysis	46.985	73.427	0.080
CER of central epiphysis	-5.500	51.519	0.000#
CER of medial epiphysis	35.827	64.812	0.292*
CER of metaphysis	31.435	21.381	0.018#
ADCR of metaphysis	35.742	36.869	0.819

CER = Contrast-enhancement ratio; ADC = Apparent diffusion coefficient ratio

* = Wilcoxon signed-rank test; # = statistically significant

The change of each patient of CER of whole epiphysis, central epiphysis, and metaphysis, which showed significant changes between the first MRI and the second MRI, is expressed as a line graph as follows. (Fig. 2) The change of each patient of CER of lateral epiphysis, medial epiphysis, and ADCR of metaphysis, which showed no significant changes between the first MRI and the second MRI, is expressed as a line graph as follows. (Fig. 3)

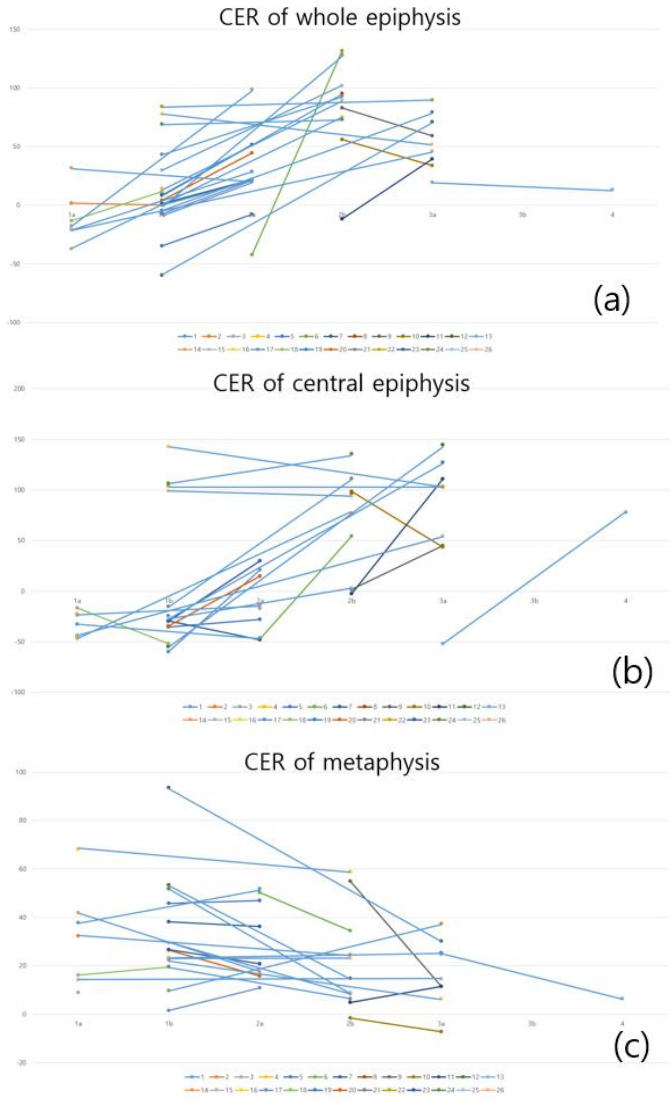

Figure 2. Line graphs of changes of indices which differ significantly in each patient between the first MRI and second MRI

(a) CER of whole epiphysis, (b) CER of central epiphysis, (c) CER of metaphysis

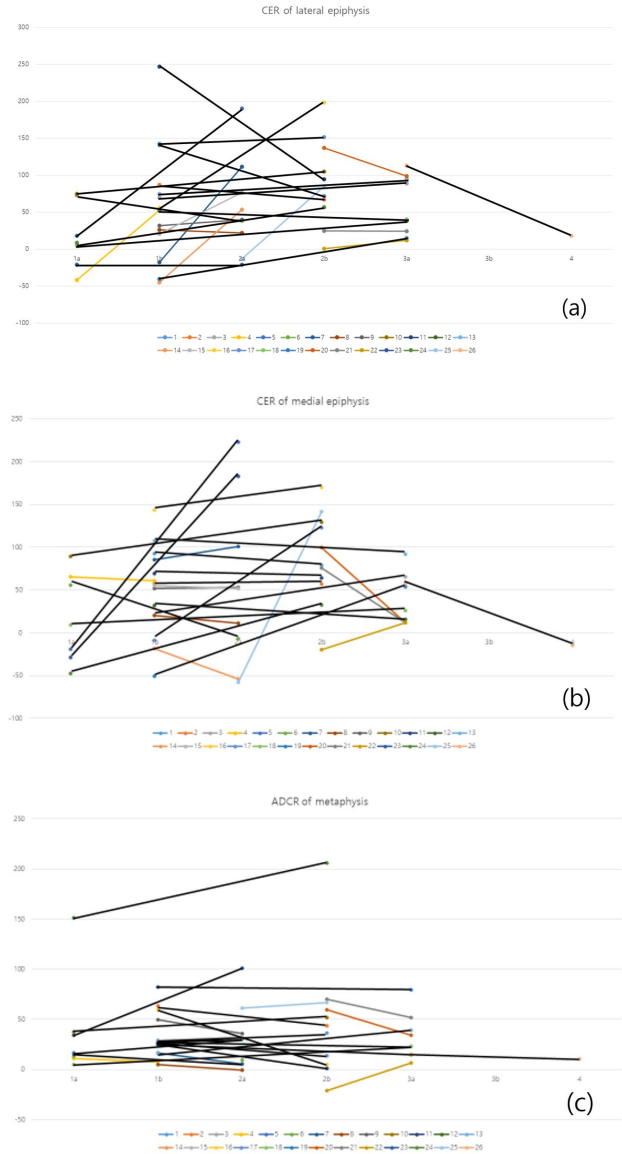

Figure 3. Line graphs of changes of indices which differ insignificantly in each patient between the first MRI and second MRI (a) CER of lateral epiphysis, (b) CER of medial epiphysis, (c) ADCR of metaphysis

The following is the change in epiphyseal contrast enhancement of a patient included in this study. At the first MRI, the patient's age was 106 months and the stage of LCP disease was 1a. The interval until the second MRI was 8 months, and the stage at the time of the second MRI was 2a. At this time, the difference in contrast enhancement seen in the same cut of the same sequence is included in figure 4.

Figure 4. Example of index changes within a patient

(a) Simple x-ray at the time of the first MRI (stage 1a), (b) Simple x-ray at the time of the second MRI (stage 2a), 8 month interval (c) contrast enhanced images of the first MRI, (d) contrast enhanced images of the second MRI. It can be seen even with the naked eye that the epiphyseal contrast has changed significantly.

To focus on finding an early prognosticator, which is the objective of this study, the extent of change was re-measured only for patients who had taken two MRIs in the early stage (modified Elizabethtown stage 1,2). The analysis included a total of 17 patients. The values of CER of whole, central, medial epiphysis and metaphysis showed significant changes between the two MRIs. (Table 4.)

Table 4. Changes of indices between first and second MRI in patient group who had MRI scan at early stage of LCP disease

	1st MRI value	2nd MRI value	P-value
CER of whole epiphysis	2.300	63.529	0.000*
CER of lateral epiphysis	46.194	87.024	0.059
CER of central epiphysis	−18.412	31.182	0.004*
CER of medial epiphysis	35.406	83.182	0.049*
CER of metaphysis	33.624	24.706	0.037*
ADCR of metaphysis	38.435	39.829	0.841

CER = Contrast-enhancement ratio; ADCR = Apparent diffusion coefficient ratio

* = statistically significant

Subgroup analysis was performed to determine which interval period between stages was significant in the CERs of the whole epiphysis, central epiphysis, and metaphysis, which showed significant differences between the values of first and second MRIs. Among the CERs of the whole epiphysis, the index of the patient group with the first MRI at stages 1a and 1b was significantly different compared to the second MRI index value, and the index of the patient group with the second MRI at stages 2a and 2b was significantly different compared to the first MRI index value. Thus, it can be concluded that the value of the CER of whole epiphysis varies greatly from stages 1a to 2a, given that the MRI index value of the patient group that took the first MRI at stage 2b was not significantly different. Among the CERs of the central epiphysis, the index of the patient group with the first MRI at stage 1b was significantly different compared to the second MRI index value, and the index of the patient group with the second MRI at stage 2b was significantly different compared to the first MRI index value. Thus, it can be concluded that the value of the CER of central epiphysis varies greatly from stages 1b to 2a, given that the MRI index value of the patient group that took the first MRI at stage 2b was not significantly different. Of the CERs of the metaphysis, the index of the patient group with the first MRI at stage 1b was significantly different compared to the second MRI index value, and the index of the patient group with the second MRI at stage 2b was significantly different compared to the first MRI index value. Thus, it can be concluded that the value of the CER of metaphysis varies greatly from stages 1b to 2a, given that the MRI index value of the patient group that took the first MRI at stage 2b was not significantly different (Table 5).

Table 5. Analysis for determining significant interval period between stages in CER of whole, central epiphysis, and CER of metaphysis

Stage	1st MRI (n)	2nd MRI (n)
	CER of whole epiphysis	
1a	−10.94 → 58.49 (0.028*, 7)	
1b	16.79 → 62.63 (0.001*, 14)	(1)
2a	(1)	−4.48 → 34.99 (0.017*, 8)
2b	41.37 → 44.00 (1.000, 3)	11.04 → 98.56 (0.012*, 8)
3	(1)	25.51 → 58.75 (0.208, 8)
4		(1)
	CER of central epiphysis	
1a	−32.96 → 14.31 (0.237, 7)	
1b	6.36 → 64.87 (0.010*, 14)	(1)
2a	(1)	−33.59 → −10.96 (0.208, 8)
2b	32.53 → 66.23 (0.593, 3)	−3.46 → 83.73 (0.017*, 8)
3	(1)	27.73 → 91.43 (0.123, 8)
4		(1)
	CER of metaphysis	
1a	31.37 → 29.63 (1.000, 7)	
1b	33.18 → 20.84 (0.007*, 14)	(1)
2a	(1)	28.40 → 27.59 (1.000, 8)
2b	19.43 → 5.27 (0.593, 3)	41.03 → 22.49 (0.012*, 8)
3	(1)	27.63 → 16.19 (0.484, 8)
4		(1)

Data in this table is the change of mean value.

The group with one patient was not subject to statistical analysis.

P−value, number of patients in parentheses

CER = Contrast enhancement ratio; n = Number of patients

* = statistically significant

We will show the actual procedure of doing this with CER of whole epiphysis. At the time of the first MRI, 7 patients were stage 1a. When the second MRI was taken, among these 7 patients, 1 patient reached stage 1b, 3 patients reached 2a, 2 patients reached 2b, and 1 patient reached 3a. However, regardless of the stage at the time of the second MRI, all of these patient groups were grouped into one group to evaluate whether the change was significant within each patient. The result was shown that the change was significant ($p = 0.028$). And 8 patients were stage 2a at the time of the second MRI. When these 8 patients were taken for the first MRI, 3 were stage 1a and 5 were stage 1b. However, regardless of the stage at the time of the first imaging, this patient group was grouped into one group to evaluate whether the change was significant and the change was shown as significant ($p=0.017$). (Table 6.)

Table 6. Example of analysis using CER of whole epiphysis to determine when the index changes significantly.

Analysis of changes in CER of whole epiphysis in a patient group with the first MRI taken on stage 1a					
	Stage at the first MRI	Stage at the second MRI	Index at the first MRI	Index at the second MRI	p-value
1	1a	1b	-13.4	11.6	0.028
2	1a	2a	-17.7	98.9	
3	1a	2a	31.6	20.9	
4	1a	2a	-20.9	28.8	
5	1a	2b	1.6	128.3	
6	1a	2b	-37.2	74.9	
7	1a	3a	-20.6	46	
Analysis of changes in CER of whole epiphysis in a patient group with the second MRI taken on stage 2a					
1	1a	2a	-17.7	98.9	0.017
2	1a	2a	31.6	20.9	
3	1a	2a	-20.9	28.8	
4	1b	2a	1.1	21.8	
5	1b	2a	-7.5	21.1	
6	1b	2a	4.1	44.6	
7	1b	2a	-34.8	-7.9	
8	1b	2a	8.3	51.7	

Statistical analysis was performed on the relationship between the value at the 2b stage and the final Stulberg classification which was determined after the initial change of the three variables (CER of whole, central epiphysis, and metaphysis). A total of 11 patients were enrolled: 3 patients with the first MRI and 8 patients with the second MRI at stage 2b. All three variables showed no statistical significance with the final Stulberg classification. (Table 7.)

Table 7. Correlation between indices at the stage 2b to the final Stulberg classification

	CER of whole epiphysis	CER of central epiphysis	CER of metaphysis
Stulberg correlation (P-value)	1.000	0.135	0.135

CER = Contrast-enhancement ratio

An analysis was performed to determine whether the change amount of the index itself, which has a significant change in the early stages of LCP disease, correlates with Stulberg classification. The amount of change in the index did not show a statistically significant relationship with the final prognosis. (p value; CER of whole epiphysis = 0.634, CER of central epiphysis = 0.349, CER of metaphysis = 0.671)

Then, the variables (CER of lateral epiphysis, CER of medial epiphysis, ADC of metaphysis), which did not change significantly during the course of the disease, were examined for statistical relevance to the final outcome at a specific point of time. First, for statistical power, 1a-1b, 1b-2a, and 2a-2b were grouped in the statistical analysis. No statistically significant correlation was found between the three variables and the final Stulberg classification in 22 subjects who had an MRI at stage 1a-1b (21 who had the first MRI, and 1 who had the second MRI). Analysis of the association between the three variables and the final Stulberg classification in 24 patients who had an MRI at stage 1b-2a (9 who had the first MRI and 15 who had the second MRI) showed a significant statistical correlation in the ADC of the metaphysis. Analysis of the association between the three variables and final Stulberg classification for 20 patients who had an MRI at stage 2a-2b (4 who had the first MRI and 16 who had the second MRI) showed a significant statistical association in the ADCR of the metaphysis (Table 8).

Table 8. Analysis for determining specific disease stages of MRI indices related to final Stulberg classification

	CER of lateral epiphysis	CER of medial epiphysis	ADC of metaphysis
1a-1b stage value to Stulberg (n=22)	0.304	0.073	0.444*
1b-2a stage value to Stulberg (n=24)	0.477	0.527	0.002#
2a-2b stage value to Stulberg (n=20)	0.654	0.980	0.008#

CER = Contrast-enhancement ratio; ADC = Apparent diffusion coefficient

* = Welch's one-way analysis of variance; # = statistically significant

Among stages 1b, 2a, 2b ADC of the metaphysis index, we further analyzed which best predicted the Stulberg classification prognosis. A total of 15 patients (14 in first MRI, 1 in second MRI) were included in the 1b stage analysis, a total of 9 patients (1 in first MRI, 8 in second MRI) were included in the 2a stage analysis, and a total of 11 patients (3 in first MRI, 8 in second MRI) were included in the 2b stage analysis. It was found that the value of 2a, which showed a p-value of 0.020, was statistically significant. (Table 9).

Table 9. Most correlated stage of ADCR of metaphysis predicting the final Stulberg classification

	1b (n=15)	2a (n=9)	2b (n=11)
ADCR of metaphysis to Stulberg (p-value)	0.177	0.020#	0.246

ADCR = Apparent diffusion coefficient ratio,

= statistically significant

Chapter 4. Discussion

The first main finding of this study is that the MRI index of LCP patients varies from stage to stage. In particular, the CERs of the whole, central epiphysis, and metaphysis changed significantly in the early stages of the disease. Among MRI indices of each part of the proximal femur, the index showing statistical significance with Stulberg classification was the ADCR of the metaphysis; the ADCR of metaphysis value at the modified Elizabethtown 2a stage was considered to have the highest correlation.

Historically, proposed prognosticators of the LCP disease have included the lateral pillar method and pinhole scintigraphy. The most commonly used method is the lateral pillar method, suggested by Herring et al., and classifies severity according to the degree of collapse of the lateral column of femoral epiphysis. If normal height is maintained, type A; collapsed lateral column is maintained at 50% or more of the original height, type B; and collapsed lateral column is classified as type C if it is less than 50% of the original height. This method classifies severity after the collapse has already occurred, and is inadequate as a prognosticator for predicting disease prognosis at the beginning stage of the disease. Another prognosticator is pinhole scintigraphy, a method for evaluating revascularization of lateral pillars. However, there are problems with this method. Pinhole scintigraphy requires the use of radiation, which has a risk of radiation exposure to patients; it also suffers from poor accuracy in delivering anatomical information and causes disturbance due to enhancement by reperfusion of metabolic inactive necrotic tissue. Thus, existing prognosticators have inherent disadvantages, and there have been numerous attempts to

find better early prognosticators that use MRI.

The study of LCP disease using the MRI index initially focused on epiphyseal perfusion because of the disease characteristic of avascular necrosis. Sebag et al.,[18] in 1997, first claimed that early recognition of LCP disease is possible using dynamic gadolinium-enhanced subtraction (DGS) MRI or perfusion MRI. In 2013, Kim et al. [11] announced that perfusion MRI showed greater interobserver reliability than conventional MRI, and demarcated the area of involvement more clearly. Subsequently, Du et al.[5] tried to predict the prognosis of LCP disease using the MRI perfusion index of the epiphysis. The study set as an outcome variable the DI of patients who were followed-up for two years and suggested that it was statistically related to the perfusion index. Also, in 2014, Harry et al.[12] measured the perfusion of the lateral third and whole epiphysis in patients at an early fragmentation stage and claimed that these values correlated with the degree of lateral pillar collapse, a prognostic factor of LCP. Furthermore, another study evaluated revascularization using perfusion MRI. In 2016, Kim et al.[10] conducted a study on patients who had taken perfusion MRI more than once and suggested that the percent perfusion on MRI taken later increased significantly. The percent perfusion can be interpreted as an indicator of revascularization, and the study argued that revascularization is in the order of lateral and medial, starting with posterior. This pattern is the same as scintigraphic track A, which Conway described.[4] However, there are major problems in evaluating LCP disease by MRI perfusion index. Since the information delivered by perfusion MRI is momentary, it can be said that reliability is low depending on the interval between the time when the MRI scan is taken and the time when the contrast

agent is injected. That is, if the exact timing for actually obtaining an MRI is not taken into consideration, the study based on perfusion can be said to be meaningless.[17]

Various studies have suggested that decreased contrast enhancement in the epiphysis is associated with prognosis of LCP disease. In 2000, Song et al. published a study of 85 cases of LCP hip using MRI with contrast. MRI with contrast, of the Catterall classification 3, 4 group included in this study, showed more false cysts and more metaphyseal enhancement changes. This study argues that the usefulness of contrast MRI is that it is possible to obtain findings that can estimate a bad prognosis from contrast MRI.[19] We focused our attention on the variability of decreased contrast enhancement seen in Jerry Du's study.[5] We believe that if the contrast enhancement index changes significantly by stage in a patient, the reliability of the prognostic value of previous studies with multiple stages at the time of MRI would be questionable. In this study, we observed changes in the CER of the lateral third, medial third, central and whole epiphysis, and CER of the metaphysis, and found that CER changes abruptly with change in stage. This result is in contrast to the results of previous studies, which indicated that decreased contrast in the epiphysis and bad prognosis was associated, regardless of disease stages.

Diffusion-weighted imaging (DWI) was first used in neuroradiology for assessing post-ischemic tissue changes after a stroke. DWI has the advantage of being relatively fast and no need for a contrast medium. In addition, the absolute values of diffusion vary greatly depending on the image cut, and scanning time, but the apparent diffusion coefficient ratio (ADCR) has the advantage of being more consistent.[2] Several previous studies have shown that increased

diffusion seen in MRI in LCP patients is associated with prognosis. In 2003, Jaramillo et al. induced iatrogenic ischemia in the proximal femur by maximum abduction of the hip joints of piglets, and observed the MRI diffusion index. Diffusion decreased in the acute phase within three hours, and oppositely increased in MRI taken at 6 hours later and 96 hours later.[7] In 2010, Merlini and colleagues reported MR images of patients with sclerotic and early fragmentation stages, showing that diffusion was higher in the epiphysis and metaphysis of an affected hip than of a normal hip.[15] The association of increased diffusion with prognosis was first mentioned in a study by Yoo et al. in 2011. In this study, patients with a metaphyseal ADC in the affected hip greater than 50% higher than the normal side had a 13-fold higher odds ratio that would lead to a poor prognosis. Patients with increased diffusion are also more likely to develop physeal irregularities.[21] However, this study has a critical disadvantage that the patient group was not divided into stages but analyzed altogether. In 2012, Boutault et al.[2] showed that an increase in ADC was significantly associated with the Catterall classification; accordingly, they suggested that an ADC increase had a prognostic value. However, this study also had a problem in the study design in that the outcome variable was set to the Catterall classification and not the Stulberg classification, which indicates the final outcome. The Catterall classification does not fully reflect the final hip articulation. In 2014, there was a study in which Baunin et al.[1] evaluated correlation with the Herring classification, by measuring the ADCs of femoral epiphysis and metaphysis in 31 patients of early-stage LCP disease. In this study, the increased ADC ratio of the metaphysis was statistically related to the Herring classification. In contrast, the ADC ratio of the epiphysis was not

related. The authors claimed that this increase in ADC ratio of the metaphysis is associated with transphyseal neovascularization, an indicator of poor prognosis. However, this study also had a limitation in the study design in that it used the Herring classification, which is not a final outcome variable. Subsequently, in 2016, Yoo et al.[20] reported that increased diffusion in the metaphysis and reduction of perfusion in the central epiphysis on the MRI before deformity were associated with prognosis. However, this study also had the limitation of evaluating only outcomes after a limited period of two years, not evaluating final femoral head deformity. We observed the change of MRI diffusion of the affected femoral head metaphysis during stage progression. In conclusion, MRI diffusion values did not change statistically through disease progression. Among them, the variable most closely related to the final prognosis was the ADC of the metaphysis at stage 2a. This result is in line with existing studies. In 2019, Gracia et al.[6] published a study on the correlation between metaphyseal ADCR and Stulberg classification in LCPD patients. The results of this study are very similar to those of this study. However, unlike Gracia's study that ADCRs in the sclerosis or fragmentation stage (modified Elizabethtown stages 1 and 2) were all correlated with the final outcome, this study resulted in a need to focus more on stage 2a. The results of this study are also significant in that prognosis can be predicted without using a contrast agent. In 2014, Sankar et al.[16] published the results of a study on the safety of perfusion MRI in 165 children and concluded that the use of contrast agents is relatively safe. However, the question of safety of contrast agent use has been raised continuously, and the implication for deposition of gadolinium-based contrast agent

(GBCA) into the brain is not known.[8,9] There are also concerns about GBCA anaphylaxis and nephrogenic systemic fibrosis.

There are several limitations to this study. First, the number of patients was small that statistical power was too weak. Secondly, 12 out of 26 patients (46.15%) had surgery during the study period: eight received containment surgery (femoral varization osteotomy), three received coverage surgery (triple innominate osteotomy), and one received articulated distraction surgery as a salvage procedure. Surgery as a variable was excluded when evaluating the results of this study due to the prospective study design; observing the natural course without any surgical intervention when the patient's hip condition is getting worse is not ethically possible. However, we believe it is better to design a study in which the enrolled patient number is of a size large enough to be evaluated by dividing the group with and without surgery. Third, drawing the ROI is could be subjective. In particular, the CER of lateral and medial epiphysis has less reliability due to the severe degree of change depending on the size of the ROI. However, it is fortunate that the ADC of the metaphysis focused on in this study is relatively reproducible. Fourth, treatment strategy has not changed as a result of this study, and further research is warranted as to when it is a good time to treat the patient. Fifth, the patients involved in this study had a random stage at the time of MRI imaging and the interval range between the two MRIs ranged from 2 to 40 months. Although all patients underwent serial MRIs, the power of statistical analysis decreased because they were not all taken on the same stage. If MRI was taken only in patients in the early stage (modified Elizabethtown stage 1, 2), the results would be more clear. Since this study is a prospective study, efforts were

made to limit the stage at the time of imaging, but there were problems of patient follow-up schedule and waiting for several months if an MRI order was placed. Despite the limitations mentioned above, we believe that the results of this study is meaningful because it is rare to analyze data obtained by serially-taken MRI.

Conclusions

This study showed that the CER of the whole, central epiphysis, and metaphysis among MRI indices in the early stages of LCP disease changed significantly. Accordingly, this study conducted an investigation into which index was statistically related to the final Stulberg classification for each disease stage. As a result, the ADCR of the metaphysis at stage 2a was found to be the most likely.

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국 문 초 록

배경:

근위 대퇴골에서 측정된 조영 증강 및 가중 확산 영상의 자기 공명 영상 지표는 소아 대퇴골두 무혈성 괴사 질병 (Legg-Calvé-Perthes disease)에서 최종 예후 예측 인자로 알려져 있다. 그러나 시간이 지남에 따라 자기 공명 영상 지표가 급격히 변하는 경우, 예후 예측 인자로서의 유용성이 제한 될 수 있다. 따라서 본 연구의 목적은 질병 진행과 함께 근위 대퇴골의 조영 증강 및 확산 영상의 시간에 따른 변화를 평가하고, 자기 공명 영상 지수 중 소아 대퇴골두 무혈성 괴사 환아에서 대퇴골두 기형과 가장 관련이 있는 지수와 질병 단계를 결정하는 것이다.

방법:

질환의 각기 다른 질병 단계에서 조영 증강 및 확산 자기 공명 영상 검사를 두 번 실시한 소아 대퇴골두 무혈성 괴사 26명의 환아 (23 명의 남환과 3 명의 여환)를 대상으로 연구하였다. 조영 증강 비율값은 5 곳의 다른 영역 (중앙, 측면, 중간 골단 및 전체 골단, 골간단)에서 측정되었고, 확산 계수 비율값은 골간단에서만 측정되었다. 우리는 질병 단계의 진행과 함께 이러한 자기 공명 영상 지수의 변화를 평가했고, 또한 최종 추적 조사에서 Stulberg의 분류와 가장 관련된 지수 및 질병 단계를 분석했다.

결과:

6 개의 지표 중 전체 골단 ($p < 0.001$), 중앙 골단 ($p < 0.001$) 및 골간단 ($p = 0.018$)의 조영 증강 비율값이 첫 번째 MRI와 두 번째 MRI 사이 유의하게 변화하였다. 최종 Stulberg의 분류와 1b-2a ($p = 0.002$) 및 2a-2b ($p = 0.008$) 단계의 골간단 확산 계수 비율값은 유의한 관련이 있었다. 1b, 2a 및 2b 단계의 골간단에서 측정된 확산계수 비율값으

로 부분 군 분석을 수행했을 때 Stulberg와는 유의한 관련 단계는 2a 단계로 나타났다. ($p = 0.020$).

결론:

이 연구는 소아 대퇴골두 무혈성 괴사 질환의 초기 단계에서 자기 공명 영상 지수 중 전체, 중앙 골단 및 골간단의 조영 증강 비율값이 크게 변화함을 보여 주었다. 이어서 각 질병 단계에서 최종 Stulberg의 분류와 통계적으로 관련이 있는 자기 공명 영상 지표를 통계적으로 분석하였고, 결과적으로, 단계 2a에서의 골간단 확산 계수 비율값이 예후를 예측할 가능성이 가장 높을 것으로 예상되었다.

주요어: 소아 대퇴골두 무혈성 괴사, 조영 증강 비율, 피상 확산 계수, 골단 관류, 대퇴골 두 기형

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