Prognosis value of early diffusion MRI in Legg Perthes Calvé disease

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ABSTRACT

Purpose: To evaluate diffusion MRI of the proximal femoral epiphysis and metaphysis as a prognosis factor in Legg Calvé Perthes (LCP) disease.

Methods: Thirty-one children (mean age 5.5 years, range 2.5–10.5) with unilateral LCP were included in a prospective, consecutive series. Radiographs were analysed and classified as per Herring criteria. Mean follow-up was 19 months (range 6–30). Forty-nine MRI scans were performed at either the condensation or fragmentation stage. Apparent Diffusion Coefficient (ADC) of both the femoral epiphysis and metaphysis were measured bilaterally and ADC ratio was calculated, then compared to the Herring group.

Results: Sixteen hips were rated Herring A or B, 3 Herring B-C and 12 Herring C. ADC was increased in affected hips compared to unaffected sides, both at the femoral epiphysis (P<0.001) and metaphysis (P<0.0001). ADC ratio of the femoral metaphysis was positively correlated to Herring classification: if superior to 1.63, it was associated with a bad prognosis (Herring B-C or C) (P=0.0017, sensitivity =89%, specificity =58%). Interobserver reliability of ADC measurement was excellent. The 1.63 threshold could be determined as early as the condensation stage.

Conclusions: Diffusion presents several advantages including being non radiating and non invasive. It does not need contrast medium administration and it can be performed without anaesthesia. The origin of the increased ADC remains unknown. Basically, it reflects molecular changes (true diffusion) but is also influenced by the vascular supply (pseudo-diffusion). ADC ratio could provide an early prognosis before Herring classification is applicable. Level of evidence: Level III. Prospective uncontrolled study.

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1. Introduction

Legg Perthes Calvé disease (LPC) refers to an avascular necrosis (AVN) of the proximal femoral epiphysis in children, most often between the age of 3 and 10 [1]. The articular outcome after the reconstruction stage is highly variable and deformity of the femoral head and femoroacetabular incongruity may occur and lead to premature hip osteoarthritis [2]. Determining articular prognosis from the condensation stage remains a challenge. The objective would be to select patients who would benefit from an early preventive treatment [3–5]. Prognosis factors currently include age of onset, volume and localization of the necrosis as per the radiological classifications of Catterall and Herring [4–7] and revascularization mode of the femoral epiphysis as initially described by Conway and Tsaoon bone scan [8–10], then by Lamer et al. on Dynamic Gadolinium-Enhanced MRI (DGS MRI) [11]. Early permeation of the lateral epiphyseal arteries is associated with a better outcome than slow transphyseal neovascularization from the femoral neck [9].

As an adjunct to plain radiographs, MRI is useful for both diagnosis and prognosis. It allows bilateral, comparative, precise and comprehensive analysis of the hips, including epiphysis, physis, metaphysis and also joint congruity [11–15]. Animal experimental studies have demonstrated the usefulness of Diffusion-Weighted Imaging (DWI) of the femoral head in early diagnosis of AVN [16–18]. A continuing increase of Apparent Diffusion Coefficient (ADC) of the femoral head has been reported in human AVN [19–22]. Three studies specifically investigated ADC in LPC [21–23]. They were short cases series comparing ADC values to other MRI sequences performed at the same time and also Catterall classification, though without clinical follow-up.

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The objectives of our study were first to correlate ADC values of the femoral head and neck with radiographic data and second to assess the former’s reproducibility.

2. Material & Methods

2.1. Patients

Thirty-one patients with unilateral LPC were included in a prospective series. Inclusion criteria comprised: diagnosis of unilateral LPC by an orthopaedic surgeon from our institution then follow-up at least until fragmentation stage. MRI scan was performed at first presentation and repeated when the patients reached the fragmentation phase. No patient received any treatment apart from non weight bearing regimen until fragmentation phase, according to the usual protocol at our institution. Affected hips were classified according to Herring (A, B, B-C, and C). Herring A’s and B’s were considered having a good prognosis, B-C’s and C’s were considered having a bad prognosis. Thirty-one patients were included between November 2008 and November 2011 (25 males and 6 females, sex ratio 4:1). The age of onset of symptoms was 5.5 years (2.5–10.5). Mean time between first symptoms and early fragmentation stage was 8.5 months (range 1–9). Patients were followed up an average 18.6 months (range 6–30) so as to observe the progression of the disease. Forty-nine MRI scans were performed either at the condensation (16) (Fig. 1), or the fragmentation (33) stage. Mean time from first symptoms was 6.5 months (1–22).

2.2. Imaging

All MRI scans were obtained from the same 3 Tesla unit (Achieva, Philips, Best, The Netherlands), using a 16 elements body antenna placed around the pelvis of the child, added with a diffusion sequence. DWI consisted of a single shot EPI with 2 values for b: 0 and 1000 mm²/s. Parameters were as follows: FOV 360 × 292 mm; slice thickness 5 mm with 1 mm gap; matrix120 × 94; size of voxel


Fig. 1. Ten-year-old boy: right LCP. A. Anteroposterior (left) and lateral (right) radiograph of the hip at initial presentation. Condensation phase. B. MRI T1 sequence, coronal view: condensation stage. Hyposignal of the femoral epiphysis with relative flattening. C. DWI imaging ADC cartography, axial view of the metaphysis. Asymmetry with relative hypersignal on the affected side. (ADC ratio = 1.9). D. Anteroposterior radiograph of the pelvis 7 months after the above mentioned imaging. Fragmentation stage. Herring type B.
2.3. Imaging analysis

Images were transferred to a Philips View Forum station for analysis and ADC quantification via an integrated software. ADC’s were measured manually by placing a circular or ellipsoidal Region of Interest (ROI) onto either the epiphysis or the metaphysis. Great care was taken not to include cartilage (physis and/or metaphyseal cysts). Slices were selected from morphological coronal sequences avoiding partial volume effect due to the growth plate and articular fluid. For each measurement, mean ADC in ROI was recorded in s/mm². Two consecutive series of measurements were obtained: by a junior radiologist (D.S.V) and a senior radiologist (C.B). The unaffected hip was used as a control and ADC ratio corresponded to the ratio affected side vs unaffected side. This ratio was calculated for each case for proximal femoral epiphysis and metaphysis.

2.4. Statistical analysis

The study population was described with number of patients and percentage for the qualitative variables and with the mean and the standard deviation if the distribution was normal (median and interquartile interval if necessary) for the quantitative variables.

Intraclass correlation coefficients (ICCs) along with their 95% confidence interval were calculated to evaluate the intra and inter-observer reproducibility of the ADC measurements. The distribution of “epiphysis ADC ratio” and metaphysis ADC ratio variables being normal, relation between these ratios and Herring classification was analyzed using a Kruskal Wallis test. As several measurements were performed on the same patient (and that these measurements therefore cannot be considered as independent), all analyses were carried out again using only the first MRI of each patient, in order to evaluate the robustness of the results. The STATA statistical software, release 11.0 (STATA Corporation, College station, TX, USA) was used to carry out the statistical analyses. The threshold for significance was 0.05.

3. Results

Sixteen hips were rated Herring A or B, 3 were rated B-C, and 12 C. At the latest follow-up, sensitivity and specificity of the Herring classification as a prognosis factor were 100% and 80%, respectively. Interobserver reproducibility of ADC measurements was deemed excellent both for affected epiphyses (ICC: 0.83) and affected metaphyses (ICC: 0.87). ADC was increased in all affected femoral epiphyses (1.49, range 1.41–1.56), as compared to controls (0.63, range 0.54–0.7) (P<0.001) (Fig. 2). ADC was also increased in all affected metaphyses (0.776, range 0.71–0.84), as compared to controls (0.42, range 0.39–0.44) (P<0.0001) (Fig. 3). There was no correlation between epiphysis ADC ratio and Herring classification (Fig. 4). However, metaphysis ADC ratio increased significantly with Herring types (Fig. 5). A metaphysis ADC ratio higher than 1.63 was correlated to Herring classification, with a sensitivity of 89% and a specificity of 58% (P<0.0017). The repetition of all analyses when including only the first MRI data (n = 31) did not show any significantly different results. Therefore, the results were deemed robust. This also demonstrated that ADC ratio values were significant at an early stage, and that they remained over time for patients with several MRI scans.

4. Discussion

We investigated diffusion MRI in order to answer 2 questions:

- is it of any interest for the prognosis of LPC?
bad prognosis in comparison to revascularization from epiphyseal arteries [9].

Yet, diffusion measures 2 phenomena at the femoral neck:

- actual diffusion, which represents cells alterations;
- pseudodiffusion, directly dependent upon the blood supply.

Therefore, ADC variations may be partly related to hypervascularization. Variations of the metaphyseal DWI are consistent with those of DGS MRI [21,22]. Metaphyseal ADC depends on the revascularization determining the reconstruction process and therefore the prognosis of LPC. It is difficult to compare ADC values from different series as several factors, either technical or tissue related, may vary. Technical variability includes: MRI machine and antenna, sequence, application method of diffusion gradient and b value [25,26,33,34]. Diffusion imaging is an appealing non radiating, non invasive technique which necessitates neither contrast medium administration nor sedation. It can be easily performed following any standard MRI scan. We have used EPI diffusion sequence which is very quick, thus reduces movement related noise and avoids the need for general anesthesia. However, these sequences have limited spatial resolution, low signal/noise ratio and they are prone to magnetic artifacts. Because it comprises structures of different magnetic properties, the proximal femur of the child is particularly exposed to those artifacts. We observed that artifacts may impair image quality at the condensation and fragmentation stages. The magnetic field is less homogeneous in the coronal plane and is responsible for low quality images. Therefore, the axial plane was selected.

Other tissue related factors influence ADC values, i.e. ADC of the bone marrow decreases with age, most likely in relation with fatty degeneration [22,23]. It is therefore preferable to rely on a ratio between affected and unaffected sides of the same individual. Our mean metaphyseal ADC on the affected side: 0.776 was much different from the one of Merlini et al.: 1.42 [21] and Yoo et al.: 0.58 [22], who used different techniques with 1.5T MRI machines. However, median ratios were close in the 3 studies: 1.8, 1.7 and 1.63, respectively. Calculation of the ratio lead to the threshold value of 1.63 above which it was considered of a bad prognosis. Yoo et al. have also presented results as a percentage and suggested a 50% increase of the ADC on the affected side is correlated with transphyseal neovascularization [22]. But is DWI yet only another prognosis factor amongst others, or does it provide early information? Indeed, Herring score is only possible at the fragmentation stage which started in our series a mean 8.5 months after the onset of the first symptoms. MRI scans were obtained an average 6.5 months after the first symptoms. The 16 MRI scans performed at the condensation stage, an average 4.5 months after the first symptoms, were analyzed separately. Metaphyseal ADC ratios were similar to those obtained at the fragmentation stage for the same patients. Animal studies had already demonstrated early alterations of the diffusion, without addressing their evolution [16–18]. Human studies displayed the results of a single DWI MRI scan, performed either at the condensation or the fragmentation stage, but did not provide their evolution with time [21,22]. Readiness with time of ADC values of the same patient was reported by Boutault et al., as well as their correlation with Catterall classification, though without long term follow-up [23]. The steadiness of metaphyseal ADC ratio through the condensation and the fragmentation stages validates the hypothesis according to which DWI MRI may provide non invasive and early prognosis for LPC, namely before Herring and Catterall classifications are applicable.

5. Conclusion

DWI MRI in association with standard MRI scan may be useful and relevant in the management of LPC. Diffusion increased in both femoral head and neck as early as the condensation stage. However, only an increased ADC of the femoral neck seemed to correlate with Herring classification. Calculation of the ratio between affected and unaffected side provided reliability to the technique. Larger, multicentric series are needed to validate further the threshold value.

Disclosure

The authors declare that they have no conflicts of interest concerning this article.

References