Diffusion MRI of the neck of the femur in Legg-Calve-Perthes disease: A preliminary study

J.-R. Boutault, C. Baunin, E. Bérard, J. Vial, D. Labarre, C. Domenech, J. Sales de Gauzy, N. Sans

© 2012 Éditions françaises de radiologie. Published by Elsevier Masson SAS. All rights reserved.

Abstract

Purpose: To evaluate diffusion MR imaging of the neck of the femur in Legg-Calve-Perthes disease (LCPD).

Material and methods: This is a prospective study in 27 children followed for unilateral LCPD. Forty-six MRIs were carried out with bilateral quantification of the apparent diffusion coefficient (ADC) of the neck of the femur. The intra- and inter-observer variability of the ADC measurements was evaluated. The association between the ADC and age as well as the healthy or pathological status of the neck of the femur and the Catterall classification were looked for.

Results: Intra- and inter-observer reproducibility of the ADC measurements was excellent. A statistically significant negative correlation between the ADC of the healthy neck and age was found. There was a significant increase in the ADC of the pathological neck of the femur compared to the healthy neck. The ratio of the pathological neck ADC and the healthy neck ADC was significantly associated with the Catterall classification.

Conclusion: The quantification of the ADC of the neck of the femur is reproducible. This could be useful in the treatment of LCPD, where there is an early and significant increase in the ADC on the pathological side. This increase could have a prognostic value, as it is correlated with the Catterall classification.
Legg-Calvé-Perthes disease (LCPD) is a paediatric disease characterised by an idiopathic ischaemic necrosis of the head of the femur that can cause painful limping in children, most often between the ages of 3 and 10 years [1]. The course after the reconstruction period is very variable. Deformations of the head of the femur and femoroacetabular incongruence can persist and cause arthritis in the young adult [2]. The prognostic evaluation remains a challenge in order to select children that could benefit from an early preventive treatment [3–5].

The currently known prognostic factors include age of onset, the importance and the distribution of the necrosis evaluated by the radiographic classifications of Catterall and Herring [4–7] and the method of revascularization of the head of the femur initially described in scintigraphy by Conway and Tsao [8–10]. Lamer showed that the dynamic MRI after injection of gadolinium (DGS MRI) made it possible to study the revascularization and metaphysary abnormalities with great precision [11]. The rapid recanalization of the lateral epiphysary arteries is associated with a better prognosis than the slow transphysary neovascularization from the neck of the femur. Scintigraphic hyperactivity and the increase in metaphysary enhancement after injection of gadolinium are thus associated with a prognosis that is not as good [10–12]. The neck of the femur, though not directly affected by the ischaemia, could play a determining role in the method of revascularization and thus in the prognosis.

In addition to conventional radiographies, the MRI has become the reference method for confirming the diagnosis and evaluating the severity of the damage. It makes it possible to perform a bilateral, comparative, exhaustive and very precise study of both hips, i.e. not only the epiphysis, growth cartilage and joint congruence, but also the metaphysis [13–16].

Animal studies have shown the value of diffusion weighted MR imaging (DWI) of the head of the femur in the early diagnosis of ischaemia [17–19]. In man, a persistent increase in the apparent diffusion coefficient (ADC) in the head of the femur has been described in patients with ischaemic necrosis [20–23]. More particularly, two paediatric series studied the variations of epiphysary and also metaphysary ADC in LCPD [22,23]. These two series concern a small number of patients and confront the ADC values with the result of the other MRI sequences carried out at the same time.

Our objectives in this study are first and foremost to check the reproducibility of the ADC measurements in the neck of the femur during LCPD, and then to confront these results with prognostic factors other than the MRI in order to determine whether the ADC measurement in the neck of the femur could be an additional useful tool in the treatment of LCPD.

Material and methods

Patients

Prospective study carried out in 27 children followed for unilateral LCPD. The inclusion criteria were as follows: diagnosis of unilateral LCPD established by a paediatric orthopaedic surgeon from our institution using standard radiographic images. The pathological hips were classified using the Catterall classification (1, 2, 3 or 4) after analysis of all of the radiographs carried out during the follow-up, with the most severe ranking being retained. From November 2008 to November 2010, 46 MRIs were performed.

Imaging protocol

All of the examinations were carried out on the same 3 T unit (Achieva, Philips, Best, The Netherlands) using a body antenna with 16 elements positioned around the pelvis of the child, and adding a diffusion sequence to the morphological sequences that we usually use.

The morphological exploration included a coronal T1-W SE sequence: matrix 272 × 216; TR 605 ms/TE 10 ms and coronal T2-W SE: matrix 336 × 264; TR 2460 ms/TE 100 ms. The common geometric parameters of these two sequences were: FOV 270 × 270 mm; 4 mm cut thickness with a gap of 0 mm.

The DWI was a single shot EPI sequence with two b values: 0 and 1000 m²/s. The parameters were: FOV 360 × 292 mm; 5 mm cut thickness with a gap of 1 mm; matrix of 120 × 94; voxel size 3 × 3.06 × 5 mm; TR 3549 ms/TE 55 ms; SPAIR type fat signal saturation; EPI factor 51; excitation number = 3; SENSE parallel imaging with reduction factor 2. Acquisition duration of 1’59 s.

Analysis of the imaging

The images were transferred to a Philips ViewForum console for analysis and quantification of the ADC via an integrated software programme (Fig. 1).

The ADCs were measured by manually placing a circular or elliptical region of interest (ROI) in the neck of the femur on a single cut under the growth cartilage. The morphological sequences were used in order to position the largest possible ROIs and avoiding the partial volume effects with the growth cartilage and the joint liquid effusions. During each measurement, the mean ADC value in the ROI was retained.

Three series of measurements were thus obtained, each on a blind-basis with regard to the others: two series by a junior radiologist (J.R.B.) at several week intervals and one series by a senior radiologist (C.B.). The ADC value of the neck of the femur used for the study of associated factors was the mean of these three measurements. For each child, the ADC of the healthy side was used as a control compared to the ADC of the pathological side and the ADC ratio was the pathological neck of the femur ADC: healthy neck of the femur ADC ratio, calculated for each examination.

Statistical methods

The description of the study population was described in terms of number of patients and percentage for the qualitative variables and in terms of the mean and the standard deviation if the distribution was normal (in terms of 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 search for factors associated with the ADC was based on the calculation of a Spearman correlation coefficient for the age when MRI was used and a Wilcoxon test for unpaired series (for the healthy or pathological status of the neck of the femur).

The association between the ADC ration and the classification of the hip according to Catterall 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 of the 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 of significance was 0.05.

**Results**

The population concerned 27 children: 22 boys (81%) and five girls (19%), i.e. a sex-ratio of 4.4:1. The age of the onset of symptoms was 5.5 years ($\pm$ 1.69). Forty-six MRIs were carried out, a mean of 13 months after the beginning of symptoms ($\pm$ 12 months). The hips were classified Catterall 2 ($n=4$, 15%), 3 ($n=5$, 18%) or 4 ($n=18$, 67%). Fourteen children had several MRIs with a mean interval of 5.5 months ($\pm$ 1.5 months) between two MRIs.

The intra-observer reproducibility of the ADC measurements was deemed to be excellent with an ICC = 0.929 (95% CI: 0.876, 0.960) for the healthy necks of the femur and ICC = 0.973 (95% CI: 0.952, 0.985) for the pathological necks of the femur. The inter-observer reproducibility was also deemed excellent for the healthy necks of the femur with an ICC = 0.879, (95% CI: 0.791, 0.931) and for the pathological necks of the femur with an ICC = 0.950, (95% CI: 0.911, 0.972). The ADC value retained for the rest of the statistical analysis was the mean of the three measurements.

The age of the patients during the MRIs and the ADC of the necks of the femur are summarized in Table 1.

There was a statistically significant association ($P=0.0072$) between the ADC of the healthy neck of the femur and the age (Fig. 2). The greater the age, the more the ADC decreased (rho = $-0.3912$). The correlation was not significant ($P=0.2032$) between the ADC of the pathological neck of the femur and the age.

**Figure 1.** Seven-year-old child, 4 months after the onset of symptoms: a: T1 sequence: LCPD on the right side in the fragmentation stage; b: DWI: b0 cut passing through the necks of the femurs; c: DWI: b1000 cut for the same area; d: corresponding ADC cartography showing a hypersignal of the pathological side compared to the left side (ADC increase by 95%).
Table 1 Summary of the age (years) when the MRI was performed, the ADC values ($\times 10^{-3}$ mm$^2$/s) in the necks of the femur (mean of three series), and the ratio of the ADC values between the pathological side and the healthy side. The ratio corresponds to that of pathological neck of the femur ADC/healthy neck of the femur ADC, calculated for each MRI.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>ADC ($\times 10^{-3}$ mm$^2$/s) Healthy side</th>
<th>ADC ($\times 10^{-3}$ mm$^2$/s) Pathological side</th>
<th>Ratio (Pathological ADC/Healthy ADC)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n=46$</td>
<td>$n=46$</td>
<td>$n=46$</td>
</tr>
<tr>
<td>Median</td>
<td>5.8</td>
<td>0.41</td>
<td>0.73</td>
</tr>
<tr>
<td>Mean</td>
<td>6.2</td>
<td>0.41</td>
<td>0.75</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>1.7</td>
<td>0.08</td>
<td>0.23</td>
</tr>
<tr>
<td>Min</td>
<td>2.8</td>
<td>0.25</td>
<td>0.32</td>
</tr>
<tr>
<td>Max</td>
<td>10.5</td>
<td>0.59</td>
<td>1.36</td>
</tr>
</tbody>
</table>

The ADC was significantly higher ($P < 0.0001$) in the pathological neck of the femur than in the contralateral healthy neck of the femur: median (interquartile interval) $= 0.41$ (0.36--0.48) for the ADC of the healthy neck of the femur compared to 0.73 (0.57--0.94) for the pathological neck of the femur (Fig. 3).

The ADC ratio increased significantly with the Catterall classification ($P=0.0224$): mean ± standard deviation $= 1.161 \pm 0.234$ for Catterall two hips; $1.853 \pm 0.368$ for Catterall three hips; $1.978 \pm 0.629$ for Catterall four hips (Fig. 4).

All of the analyses that were performed again on the sample that only included the first MRI of each patient (i.e. $n=27$) showed no significant difference compared to the results of all of the MRIs. Our results thus appear robust. In addition, these results show that the values obtained are stable over time in children who had several MRIs.

Discussion

Our study is the third to evaluate the usefulness of the diffusion MRI in LCPD. Our ADC measurements in the neck of the femur during LCPD were reproducible with good intra- and inter-observer reproducibility. There is a statistically significant negative correlation between the ADC of the healthy neck of the femur and age. Our results show a significant increase in the ADC of the pathological neck of the femur compared to the healthy neck of the femur, which made it possible for us to calculate an ADC ratio between the pathological side and the healthy side. This ratio increased significantly following the Catterall classification. In children who had several MRIs, this ratio remained stable over time.

The DWI measures the mobility of protons in the living tissues at a microscopic level. Historically developed for...
the exploration of cerebral ischaemic accidents, its use has spread to many diseases. In paediatric bone imaging, it is studied in tumour characterisation, the evaluation of the anti-tumoural therapeutic response, infections, the study of cartilage and osteonecrosis [24–27]. Though several experimental works [17–19] have studied the consequences of ischaemia on bone diffusion, few studies have analysed the results of the diffusion in LCPD while comparing it to the other MRI sequences [22,23]. These two studies concern a smaller number of patients: 12 patients for Merlini [22] and 17 for Yoo [23].

It is difficult to compare the absolute ADC values between different series, as several factors come into play in their calculations. First of all, there are the technological factors, such as the type of antenna used, the sequence chosen, the method of application of the diffusion gradient and particularly the choice of the b values [28,29]. We used an EPI type diffusion sequence that has the advantage of being very fast, thus reducing the artefacts related to movement. In addition, no sedation was necessary during these examinations. On the other hand, these sequences have limited spatial resolution, a poor signal to noise ratio and are particularly sensitive to artefacts of magnetic susceptibility, which are increase by the use of a 3T field [25,26]. The upper extremity of the femur in children, due to the proximity of structures with very different magnetic properties, is particularly exposed to this type of artefact. We noticed that in the heads of the femurs at a stage of condensation or fragmentation, these artefacts could alter the quality of the images. With the coronal approach, where the magnetic field is more heterogeneous, the images obtained w ere of mediocre quality, which is why we chose the axial approach.

Other factors related to the studied tissue explain the changes in the absolute ADC values. In particular, we know that the ADC of healthy bone marrow decreases with age, probably due to the medullar conversion where the hematopoietic bone marrow is progressively replaced with fatty bone marrow [23,26,29,30]. Our study confirms and puts a number on these data in the age bracket concerned with LCPD.

For all of these reasons, it does not seem very useful to define the normal absolute values of the bone marrow ADC in children and the use of a ratio between the healthy side and the pathological side in the same patient appears preferable.

Our absolute values of mean ADCs in the pathological neck of the femur: 0.776 are very different from those of Merlini [22]: 1.042 and of Yoo [23]: 0.58, who use different techniques on 1.5 T MRIs from different constructors: coronal cuts, in EPI sequence with a b of 800 for Merlini [22], sagittal cuts in LSDI sequence with a b of 700 for Yoo [23]. On the other hand, the median ratios are close in all three studies: 1.89 in our study, 1.7 in Merlini’s study [22] and 1.63 in that of Yoo [23]. This shows the reproducibility of this method and opens perspectives for its generalization.

The increase in the ADC of the neck of the femur appears starting from the first month in our series, which is in agreement with the results obtained in animals [17–19]. The DWI could thus be useful starting from the beginning of the LCPD. This technique would need to be compared to bone scintigraphy or dynamic MRI following injection of gadolinium in the hips at an early infra-radiological stage in order to specify the diagnostic potential of the diffusion. On the other hand, the increase in ADC could possibly provide a prognostic argument starting from the first stages of the disease. In our study, the ADC ratio of the neck of the femur increases significantly with the Catterall classification, which is one of the radiological classifications that is traditionally accepted. In the same child, this radiological classification can change during the fragmentation phase, and in our series, the grade retained was the worst grade that was established before the date the MRI was performed on. This increase in ADC appears to be stable over time: the results concerning the first MRIs mirror those of the following MRIs in children who had several examinations. These results can be compared to those obtained in the earlier series [22,23], which showed the negative meaning of a high ADC of the neck of the femur, but only when compared with other MRI signs. In addition, they studied children at a radiological stage that was already advanced with only one MRI examination, and therefore with no notion of change over time. The studies would have to be carried out over a longer time period in order to measure the change of the ADC in the neck of the femur and to check the prognostic value of the DWI by comparing it with the final outcome of the LCPD.

With no histological correlation in our study, the precise causes of the change in the ADC of the neck of the femur over the course of the LCPD remain unknown. Many histological studies have looked into metaphysary cysts, but this abnormality was only found in four of our patients [31–34]. In a review published in 1982, Catterall [31] described accumulations of non-ossified cartilage derived from growth cartilage in the metaphysis, but also a case of avascular necrosis of the medial part of the metaphysis associated with vascular thrombosis in the adjacent periosteum. These abnormalities concerned the region in immediate contact with the growth cartilage, while in our study, the ROIs excluded the cartilaginous signal regions. Eckerwall, in a study of 22 biopsies of necks of the femur observed fatty necrosis, a fibrous reaction and vascular proliferation without bone necrosis [32]. Revascularisation effects starting from the neck of the femur are known for being signs of a worse prognosis than direct revascularisation from the epiphysary arteries. Therefore, it has been shown that this neovascularization from the neck of the femur, which results in metaphysary scintigraphic hyperactivity and an increase in metaphysary enhancement after injection of gadolinium is associated with a worse prognosis [10–12]. As DWI is a reflection of both the cellularity of a tissue and the pseudo-differentiation where perfusion plays a predominant role [30], its changes in the neck of the femur could be related in part to Hypervascularization-type vascular changes. The comparison between the DWI of the neck of the femur and the dynamic MRI shows parallel changes [22,23]. The changes in the ADC of the neck of the femur, since they are probably related to the method of revascularisation, appear to be a determining factor of the modalities of reconstruction that make up the prognosis of LCPD.

**Conclusion**

In conclusion, the quantification of the ADC of the neck of the femur in MLPC is a reproducible and comparable method by the use of ratios between the pathological side and the
healthy side. Non-invasive compared to scintigraphy and dynamic MRI, it could be an important tool for the treatment of LCPI. Studies with a longer monitoring period and a larger number of patients are necessary to confirm these encouraging results.

Disclosure of interest

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

References