Received:
17 February 2015

Revised:
19 May 2015

Accepted:
27 May 2015

doi: 10.1259/bjr.20150145

Cite this article as:

Kamper L, Haage P, Brandt AS, Piroth W, Abanador-Kamper N, Roth S, et al. Diffusion-weighted MRI in the follow-up of chronic periaortitis. *Br J Radiol* 2015; **88**: 20150145.

FULL PAPER

Diffusion-weighted MRI in the follow-up of chronic periaortitis

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Objective: To evaluate the usefulness of diffusion-weighted MRI (DWI) for the assessment of the intraindividual follow-up in patients with chronic periaortitis (CP) under medication.

Methods: MRI data of 21 consecutive patients with newly diagnosed untreated disease were retrospectively examined before and after medical therapy, with a median follow-up of 16 weeks. DWI parameters [b800 signal, apparent diffusion coefficient (ADC) values] of the CP and psoas muscle were analysed together with the extent and contrast enhancement. Pre- and post-treatment laboratory inflammation markers were acquired parallel to each MR examination.

Results: Statistically significant lower b800 signal intensities ($p \leq 0.0001$) and higher ADC values ($p \leq 0.0001$)

were observed after medical treatment within the fibrous periaortic tissue. Extent and contrast enhancement of the CP showed also a statistically significant decrease ($p \leq 0.0001$) in the follow-up examinations, while the control parameters within the psoas muscle showed no differences.

Conclusion: DWI seems to be a useful method for the evaluation of response to treatment without contrast agents. The technique may be helpful in the assessment of disease activity to guide further therapeutic strategies.

Advances in knowledge: DWI detects significant differences in the intraindividual follow-up of CP under medical therapy.

Chronic periaortitis (CP) is a proliferating fibroinflammatory disease of the perivascular retroperitoneal space and aortic wall.^{1–4} Owing to adventitial inflammation, some recent theories consider CP as a large vessel vasculitis.⁵ Clinical manifestations of CP include idiopathic retroperitoneal fibrosis, inflammatory aortic aneurysm and perianeurysmal retroperitoneal fibrosis.^{2,6,7} The three manifestations with very similar histopathological characteristics are distinguished by the diameter of the abdominal aorta and concomitant ureteral affection.^{1,3,7}

Specific clinical symptoms are caused by extrinsic compression of the ureters or retroperitoneal veins, resulting in hydronephrosis, oliguria, lower extremity oedema and deep vein thrombosis.^{1,8}

Under medical treatment with steroids, CP has a good prognosis.⁷ Today tamoxifen is suggested as a safe and effective therapeutic alternative, and immunosuppressive drugs can be considered in patients with suboptimal responses to these drugs or multiple relapses.^{9–11}

CT and MRI are the modalities of first choice for diagnosis and follow-up of CP.^{1,7,12} The fibrotic para-aortic tissue shows significant contrast uptake in gadolinium-enhanced MRI.^{12–14} Dynamic contrast-enhanced MRI was suggested for the assessment of the disease activity.^{15,16} However, in cases with impaired renal function (e.g. by ureteral compression), gadolinium-independent imaging methods should be preferred owing to the potential development of a nephrogenic systemic fibrosis.¹⁷

Diffusion-weighted MRI (DWI) is a non-contrast MR modality that has been successfully applied for the assessment of retroperitoneal masses, inflammatory abdominal aortic aneurysms and for the differentiation between retroperitoneal fibrosis and malignant retroperitoneal neoplasms.^{18–21}

DWI indicates restricted diffusion of water, for example caused by a high cellularity in malignant disease or active inflammation. The apparent diffusion coefficient (ADC) is a quantitative parameter for the level of restricted

diffusion, which is calculated from the signals of different diffusion gradients (*b*-values).²²

In the context of untreated CP diffusion-weighted MRI may detect restricted inflammation as a sign of high cellularity caused by active inflammation.

There are no data for the evaluation of intraindividual follow-up and the response to treatment by DWI of CP so far. Therefore, the aim of the present study was to analyse differences in DWI signals during follow-up in patients with CP before and after treatment. In addition, we sought to elucidate the potential of DWI in the therapy monitoring of CP.

METHODS AND MATERIALS

All patients gave written consent to storage and examination of their personal and diseases-related data including clinical imaging studies. Patients' data were recorded in a MySQL database for a nationwide registry headquartered in our Department of Urology. The MRI examinations were analysed retrospectively by two radiologists.

Study population

MR examinations of 21 consecutive patients (15 males and 6 females; mean age, 53 years) with newly diagnosed and untreated CP were retrospectively analysed between June 2011 and January 2014. The patients presented with CP manifestation in the form of idiopathic retroperitoneal fibrosis. Diagnosis was confirmed by histology in 14 patients. In the remaining seven patients, CP was diagnosed by typical clinical symptoms and imaging findings and later supported by regressive extent under medical therapy.

The extent, contrast uptake and diffusion-weighted MR parameters of the CP were compared with a follow-up examination after an average period of 16 weeks under medication. Laboratory infection parameters [erythrocyte sedimentation rate (ESR); C-reactive protein (CRP)] were analysed parallel to each MR examination. This study was approved by the local ethics committee. Clinical MR examinations, data storage and analyses were performed after written informed consent of the patients.

Imaging parameters

Identical MR protocols were applied before and after medical treatment. The examinations were performed using a standard body array coil with a 1.5-T scanner (Siemens MAGNETOM® Avanto; Siemens Healthcare, Erlangen, Germany). TrueFISP sequences in axial, coronal and sagittal orientation were used to localize the extent of the CP. We conducted standard T_1 and T_2 turbo spin echo sequences in axial and coronal orientation. The T_1 weighted images were acquired before and after intravenous administration of weight-adapted gadolinium contrast (0.2 mmol kg^{-1} , ProHance®; Altana Pharma, Konstanz, Germany).

Axial T_1 weighted sequences with fat saturation before and 5 min after contrast injection were carried out for the evaluation of the contrast enhancement within the CP. To prevent the development of nephrogenic systemic fibrosis, renal function was

determined by serum creatinine and glomerular filtration rate (GFR). In two of the patients with calculated $\text{GFR} < 30 \text{ ml min}^{-1}$, no gadolinium-based contrast medium was applied. Only contrast-independent DWI sequences were analysed for these two patients.

Single-shot echoplanar DWI sequence using tri-directional gradients and *b*-values of 50, 400 and 800 s mm^{-2} with in-line reconstruction of ADC maps was applied to detect changes in the diffusion. No respiratory motion correction was applied, owing to the infrarenal retroperitoneal focus. The total acquisition time for a complete examination was approximately 20 min, including 3.28 min for the DWI sequences. Specific sequence parameters are given in Table 1.

Image analysis

DWI signal intensities of the CP as well as a relative index compared with the psoas muscle were evaluated before and after medical treatment. These results were compared with classical MR parameters (disease extent and contrast uptake) and laboratory inflammation markers. The extent of the CP was acquired by the longest paravascular diameter in the axial plane. Quantitative measurements were performed by ellipsoid regions of interest (ROIs) with identical position and size in the contrast-enhanced T_1 weighted images with fat suppression, the b800 diffusion-weighted images and ADC maps. The ROI positions within periaortic tissue and psoas muscle were chosen according to the largest possible extent on a single slice. We avoided outer margins and areas of artefact to reduce partial volume averaging. The relative contrast uptake and relative DWI index was calculated by dividing the respective signal intensities of CP and psoas muscle. In addition, fusion images from the T_1 weighted images with fat suppression and the b800 images were generated with a commercial software package (AW-Server 2.0-5.5; GE Healthcare, Milwaukee, WI) for a better visualization of the DWI data.

The examinations were analysed independently by two board-certified radiologists with 6 and 10 years' experience in MRI using our picture archiving system (Centricity PACS 3.1.1.4; GE Healthcare). Two readers were blinded for the medication (prednisone *vs* tamoxifen) but were aware of the diagnosis of CP.

Medical treatment

Medication was conducted according to the standardized treatment protocol of our urological department by either prednisone or tamoxifen depending on the contraindications of these agents and the patients' will.

Prednisone was applied every second day for 10 weeks with a dose of 1 mg kg^{-1} body weight; thereafter, 40 mg day^{-1} for 2 weeks, 20 mg day^{-1} for 2 weeks, 10 mg day^{-1} for 2 weeks and then 5 mg day^{-1} . Patients under tamoxifen medication received 40 mg day^{-1} . Medical therapy was applied for a total period of 1 year.

Statistical analyses

Imaging findings were compared before and after medical therapy and correlated to laboratory infection markers. Mean

Table 1. Parameters for the applied MR sequences

Parameter	T_1	T_2	T_1 -fs	Diffusion-weighted MRI
Repetition time (ms)	110	3000	170	5.300
Echo time (ms)	4.76	103	4.76	75
Slice orientation	Axial	Axial	Axial	Axial
Slice thickness (mm)	8.0	8.0	8.0	6.0
Flip angle (°)	70	70	70	90
Matrix	256	256	256	192
Acquisition time (min)	0:37	1:07	1:27	3:28

fs, fat saturation; T_1 , T_1 weighted imaging; T_2 , T_2 weighted imaging.

values, standard deviation and the range of the acquired signal intensities were used for descriptive analysis. Differences between the two radiologists with respect to the signal intensities of the analysed parameters were quantified by calculating limits of agreement of measurements with multiple observations per individual. Mixed linear regression was used to test for differences between the two radiologists and between baseline and follow-up data. Spearman's rank correlation coefficients were calculated for the correlation between the DWI parameters (b800, ADC) and pre- and post-treatment laboratory inflammation markers (ESR, CRP). Statistical analysis was performed using a commercial software tool (Stata/IC 13.1 for Windows; StataCorp, College Station, TX). p -values < 0.05 were considered significant for all tests.

RESULTS

The comparison before and after medication revealed statistically significant smaller CP extent ($p < 0.001$) and lower laboratory infection markers (CRP, $p = 0.004$; ESR, $p < 0.001$)

in the follow-up (Table 2). Before treatment, significantly higher b800 signal intensities ($p < 0.0001$) and a higher DWI index ($p < 0.0001$) were observed together with significantly lower ADC values ($p < 0.0001$) compared with the follow-up under therapy (Figure 1). In addition, significant differences for the contrast enhancement ($p < 0.001$) were found within the fibrous tissue before and after medical treatment (Table 2). The evaluation of the respective parameters within the psoas muscle serving as reference revealed no statistical differences for DWI parameters (Figure 1) and contrast uptake (Table 2).

The comparison between prednisone vs tamoxifen medication revealed corresponding results for both medications. All examined diffusion-weighted parameters and the contrast uptake showed no significant differences depending on the medication used. Statistics found slight differences between both groups of medication for only the CRP values ($p = 0.016$) before and after treatment.

Table 2. Mean values with standard deviation (minimum and maximum) for the 21 newly diagnosed patients with chronic periaortitis and the individual follow-up under medication for a mean period of 110 days (minimum, 75 days to maximum, 192 days). Data show significant differences for all parameters before and after treatment, except for the diffusion-weighted (b800) and contrast-enhanced (post-contrast) control measurements within the psoas muscle

Parameter	Pre-treatment	Follow-up	p -value ^a
CP extent (mm)	21 ± 10 (6–45)	12 ± 8 (2–36)	<0.0001
CP (b800) (mm ² s ⁻¹)	27.2 ± 7.1 (14–47)	17.4 ± 5.7 (11–36)	<0.0001
CP (apparent diffusion coefficient) (×10 ⁻³ mm ² s ⁻¹)	0.89 ± 0.23 (0.60–1.75)	1.27 ± 0.22 (0.93–2.18)	<0.0001
CP (post-contrast) ^b	280.6 ± 70.6 (158–451)	213.3 ± 66.9 (116–359)	<0.0001
Psoas (b800) (mm ² s ⁻¹)	11.6 ± 1.9 (8–15)	11.7 ± 1.9 (8–15)	0.393
Psoas (post-contrast) ^b	164.6 ± 40.6 (78–282)	146.7 ± 41.3 (55–229)	0.101
Diffusion-weighted MRI index	2.4 ± 0.6 (1.4–3.7)	1.5 ± 0.4 (1–2.2)	<0.0001
Post-contrast index ^b	1.72 ± 0.2 (1–2.2)	1.48 ± 0.3 (0.8–2.8)	<0.0001
ESR (mm per 1 h)	47.2 ± 31 (8–99)	15.1 ± 13.6 (4–61)	<0.0001
ESR (mm per 2 h)	68 ± 27.4 (21–105)	29.9 ± 18.6 (7–84)	<0.0001
C-reactive protein (mg dl ⁻¹)	2.4 ± 3.3 (0.2–13.2)	0.9 ± 1.4 (0.1–5.9)	0.004

CP, chronic periaortitis; ESR, erythrocyte sedimentation rate.

^a p -value of the difference between Readers R2 and R1 (mixed linear regression with random effects patient).

^bIn two patients, no gadolinium was applied owing to impaired renal function (glomerular filtration rate < 30).

The additional analysis of potential correlations between DWI parameters (b800, ADC) with the laboratory inflammation (CRP, ESR) markers revealed no significant correlation.

Exemplary images of the examined MR sequences are given in Figure 2. We observed no significant differences between the results of the two radiologists (Table 3).

DISCUSSION

To our knowledge, the presented data show the first analyses of diffusion-weighted MRI for the intraindividual follow-up in patients with CP. We observed statistically significant differences for the examined DWI parameters before and under medication.

DWI indicates restricted diffusion of water, for example caused by a high cellularity in malignant diseases or active inflammation.²² DWI has been applied for a wide range of oncological abdominal imaging and in distinguishing malignant sarcomas from benign tumours in patients with neurofibromatosis.^{22–24} It has been used for the detection of inflammation in patients with Crohn's disease with decreased ADC values in inflamed bowel segments.²⁵ These examinations suggest restricted diffusion owing to malignant or inflammatory hypercellularity as a trigger for the resulting DWI differences, which is congruent with two preceding studies that applied DWI for the differentiation between retroperitoneal fibrosis and malignant retroperitoneal neoplasms.^{20,21} Another recent study found significant higher DWI signals in b800 images of 15 patients with untreated, active retroperitoneal fibrosis compared with 29 previously treated patients.²⁶ These observations are in agreement with our findings of restricted diffusion in untreated CP and support the theory of inflammatory hypercellularity in early stages of the disease compared with inactive or chronic stages.

The entity of CP comprises three presentations with common clinical and histopathological findings:^{6,7} (i) the idiopathic retroperitoneal fibrosis describes fibroinflammatory para-aortic tissue involving retroperitoneal structures without aortic aneurysm; (ii) the inflammatory aortic aneurysm is defined by a significant thickened aortic wall owing to adventitial inflammation with limited retroperitoneal extent of the fibrosis; and (iii) the para-aneurysmatic fibrosis is described as combination of both.² The aetiology of CP is not yet fully clarified.^{1–6} Common hypotheses accuse antibody formation with inflammatory response triggered by vascular deposits (e.g. oxidized lipoproteins and ceroid).^{2,3,6} Other theories suggest a vasculitis of the aorta or of aortic vasa vasorum as an underlying cause of CP.⁵

Today, the assessment of the response to treatment is based on regressive disease extent in contrast-enhanced CT or MRI and regressive clinical symptoms.^{7,8,14}

According to the guidelines of the European Society of Urogenital Radiology (ESUR), gadolinium-based contrast agents should be omitted in patients with severely impaired renal function (estimated GFR, <30).¹⁷

Renal dysfunction owing to ureteral compression is a frequent symptom in patients with CP. In those cases, diffusion-weighted MRI may be a sufficient alternative because of its independence from intravenous contrast media. The presented diffusion-weighted images showed an excellent delineation of the CP and statistically significant different signal intensities in b800 images and ADC maps in the individual follow-up. Further advantages of gadolinium-independent imaging include the lower costs and lower invasiveness.

Positron emission tomography (PET) and PET-CT have been applied for the assessment of disease activity and response to

Figure 1. Box plots for the change of the diffusion-weighted MRI (DWI) parameters of the chronic periaortitis (CP) and psoas muscle for the 21 patients before (untreated) and under medication (follow-up). Significant changes were observed for the b800 signal intensities (a) and apparent diffusion coefficient (ADC) values (b) of the CP as well as the relative DWI index (d). No differences were observed for the b800 signal for control measurements within the psoas muscle (c).

treatment.¹² Jansen et al²⁷ evaluated the value of fluorine-18 fludeoxyglucose-PET in 26 patients with retroperitoneal fibrosis and showed its potential in evaluation of the disease activity. Moroni et al²⁸ observed a correct discrimination between active and inactive disease in 93.9% of 22 patients by PET-CT. In another PET-CT study, Guignard et al²⁹ found an accurate determination of inflammation level and better delineation of remaining areas of residual inflammation in seven patients with idiopathic retroperitoneal fibrosis. However, PET and PET-CT are both associated with radiation and often show a lower availability compared with diffusion-weighted MRI. The presented results suggest DWI as an effective alternative to assess the response to treatment without radiation. However, further research is necessary to clarify the correlation between standardized uptake PET values with DWI parameters and the potential of DWI to evaluate the disease activity.

Medical therapy of CP is classically based on steroids such as prednisone.¹¹ In recent studies, tamoxifen proved a safe and effective alternative, especially if steroids are contraindicated or refused by the patient.^{9,10} We included only four patients with tamoxifen therapy in our study. However, consistent with the literature, our findings showed comparable response with

treatment, changes of the diffusion-weighted MRI parameters and contrast uptake of the CP compared with prednisone.

An association between disease activity and ESR with normalization under therapy is described in the literature.^{5,30} The reduced CP extent and decreased ESR and CRP values in our study indicate a reduced disease activity under therapy. In addition, we observed a significant reduction of median DWI signals under treatment. However, ESR and CRP values before treatment alone are only poor predictors of the therapeutic response to steroid therapy in patients with retroperitoneal fibrosis.³⁰ This may be supported by our findings of absent correlation between DWI parameters and pre- and post-treatment inflammation markers.

Limitations

Histological diagnosis of CP is mandatory in patients with an atypical formation, signs of malignancy or progression of fibrosis under medical therapy.⁷ In our patients, diagnosis of CP was established by a combination of clinical symptoms and typical imaging findings. As a consequence, diagnosis was not confirmed by histology for all patients. However, in all of our patients, the diagnosis was later supported by regressive extent under medication.

Figure 2. Before treatment, the para-aortic fibrous tissue in a 39-year-old male patient with chronic periaortitis shows remarkable contrast enhancement in the T_1 weighted images with fat suppression (a). Impaired diffusion was depicted by a high b800 signal (b) with correspondingly low apparent diffusion coefficient (ADC) signal (c) and within the fusion images between the b800 and native T_1 weighted images (d). After 15 weeks of medication with prednisone, the fibrous tissue showed reduced extent and contrast uptake (e). The follow-up examination reveals a reduction of the b800 signal (f, h) with parallel increase of the ADC signal (g). fs, fat saturation.

Table 3. Mean values with standard deviation (minimum and maximum) for the signal intensities of the analysed parameters for both Readers (R1, R2)

Parameter	R1 (<i>n</i> = 42)	R2 (<i>n</i> = 42)	Limit of agreement (Bland–Altman)	<i>p</i> -value ^a
CP (b800)	22.7 ± 8.5 (12.0–47.0)	21.9 ± 7.7 (11.0–42.0)	−5.3 to 3.7	0.720
CP (apparent diffusion coefficient) (×10 ^{−3} mm ² s ^{−1})	1.08 ± 0.29 (0.6–1.98)	1.07 ± 0.31 (0.64–2.18)	−237 to 224	0.227
CP (post-contrast) ^b	246.3 ± 79.5 (116–451)	247.6 ± 74 (123–405)	−36.7 to 39.3	0.760
Psoas (b800)	11.8 ± 1.9 (8–15)	11.5 ± 1.8 (8–15)	−2.0 to 1.5	0.417
Psoas (post-contrast) ^b	154.4 ± 41.0 (55–251)	156.9 ± 42.8 (65–282)	−18.0 to 22.9	0.755
Diffusion-weighted MRI (b800) index	1.9 ± 0.7 (0.9–3.6)	1.9 ± 0.7 (0.9–3.8)	−0.46 to 0.42	0.764
Post-contrast index ^b	1.6 ± 0.4 (0.8–2.8)	1.6 ± 0.3 (0.8–2.1)	−0.43 to 0.37	0.417

CP, chronic periaortitis.

^a*p*-value of the difference between U2 and U1 (mixed linear regression with random effects patient).

^bIn two patients, no gadolinium was applied owing to impaired renal function (glomerular filtration rate <30).

An additional biopsy at the end of medical therapy would have been the real gold standard. However, owing to ethical issues, repetitive para-aortic biopsy cannot be justified in patients with reduced CP extent.

A further limitation is the inhomogeneous duration of medical treatment, ranging from 12 to 25 weeks.

In addition, the assessment of quantitative signal intensities by the ROI method can be limited in patients with inhomogeneous signal intensities and in patients with a very small extent of the fibrotic tissue or significant regress under therapy. In those cases, semi-quantitative, visual assessment of the b800 and ADC signal intensities may be an alternative.

CONCLUSION

In conclusion, statistically significant differences for the examined DWI parameters were observed before and under medication. The presented results advocate the further use of DWI for the follow-up of patients with CP. The particular advantage is

the independence from radiation compared with PET and from gadolinium compared with contrast-enhanced MRI.

Forthcoming examinations are necessary to analyse the temporal course and sensitivity of the DWI changes compared with the reduced contrast enhancement after medication.

In addition, future studies have to prove the potential of DWI for the evaluation of the disease activity, for example by comparison with PET data or—whenever possible—with histology.

ACKNOWLEDGMENTS

The storage and evaluation of patient data in the Else Kröner-Fresenius Registry as well as the storage of blood samples was funded by the Else Kröner-Fresenius Stiftung (Foundation). The authors thank Mrs Hiltrud Niggemann for substantial support with the statistical analyses.

FUNDING

Statistical analyses were founded by the HELIOS Kliniken GmbH, Germany (grant ID: 000631).

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