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ABDOMINAL IMAGING

ORIGINAL ARTICLE

Diffusion-weighted MRI of the kidneys in patients with familial Mediterranean fever: initial experience

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PURPOSE

To evaluate the feasibility of diffusion-weighted magnetic resonance imaging (DW-MRI) in the assessment of renal function in patients with familial Mediterranean fever (FMF).

MATERIALS AND METHODS

Thirty healthy volunteers who had no history of renal disease, hypertension or vascular disease and 60 patients with FMF were included in the study. Transverse diffusion-weighted multisection echo-planar MRI was performed with the following diffusion gradient b values: 0, 111, 222, 333, 444, 556, 667, 778, 889 and 1000 s/mm^2. The apparent diffusion coefficient (ADC) values, urine protein and serum creatinine levels, and glomerular filtration rates of the healthy volunteers, patients with renal involvement, and patients without were compared by using ANOVA test. ADCs of the kidneys were calculated separately for low (ADC_{low}; b = 0, 111, 222, 333 s/mm^2), average (ADC_{avg}; of all b values), and high (ADC_{high}; b = 778, 889, 1000 s/mm^2) b values to enable the differentiation of the relative influence of perfusion fraction and true diffusion. ADC_{high} reflects almost only diffusion, whereas ADC_{low} is composed of both diffusion and perfusion.

RESULTS

There was statistically significant difference between ADC_{low} values of the FMF patients with renal involvement and the control group ($P < 0.05$). Negative correlation was found between the duration of disease and ADC_{low} values of the kidneys (r = -0.223, $P = 0.087$).

CONCLUSION

DW-MRI of the kidneys might allow early detection of the renal changes in patients with FMF. This might prevent the progression of disease by giving proper medical treatment. Further studies with larger numbers of FMF patients and more experience on MRI technique are required to help define more conclusively the precise role of DW imaging in detection of renal changes.

Key words: • *diffusion magnetic resonance imaging* • *kidney* • *familial Mediterranean fever*

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Familial Mediterranean fever (FMF) is a genetic disorder frequently diagnosed among the Arabs, Turks, Armeniens, and Jews. It is an autosomally recessive inherited disorder characterized by recurrent episodes of fever and inflammation in the form of sterile polyserositis as pleuritis, peritonitis, synovitis, and pericarditis (1). The most serious complication of FMF is the development of amyloidosis, leading to nephrotic syndrome and end-stage renal disease (2).

Diffusion-weighted magnetic resonance imaging (DW-MRI) is used to show molecular diffusion, which is the Brownian motion of the spins in biological tissues. The apparent diffusion coefficient (ADC), as a quantitative parameter calculated from DW-MR images, combines the effects of capillary perfusion and water diffusion in the extracellular extravascular space (3). For this reason, DW-MRI can be used to differentiate normal and abnormal tissue structures and might help characterize different abnormalities. DW-MRI, first put into use extensively for brain lesions, has also been used in extracranial organs. Recently, DW-MRI has been used to perform functional evaluation of the kidneys. Thoeny et al. have reported DW-MRI of the kidneys in healthy volunteers and patients with various renal abnormalities (4).

The aim of this study was to prospectively evaluate the feasibility of DW-MRI in the assessment of renal function in patients with FMF and in healthy volunteers.

Materials and methods

Study population

Thirty healthy volunteers (12 men, 18 women; median age, 30 years; age range, 21–45 years) who had no history of renal disease, hypertension or vascular disease and 60 patients with FMF (22 men, 38 women; median age, 30 years; age range, 15–63 years) were included in the study. The patients were diagnosed as FMF according to the Tel Hashomer's criteria (5). The patients with FMF were also divided into two groups as the patients with renal involvement and the patients without renal involvement according to presence of urine protein. The histopathological examination for kidney involvement was not performed since nephrologists did not consider the clinical data as a specific indication for biopsy. The disease duration ranged from 10 to 360 months (median disease duration, 89.9 months). All volunteers were medical personnel. The age and sex of controls were matched with the study group.

Serum creatinine levels, glomerular filtration rates (GFR), and urine protein levels were obtained from all patients within one week of the MRI examination. GFR was calculated by Cockcroft-Gault formula.

Informed consent was obtained from all volunteers and patients.

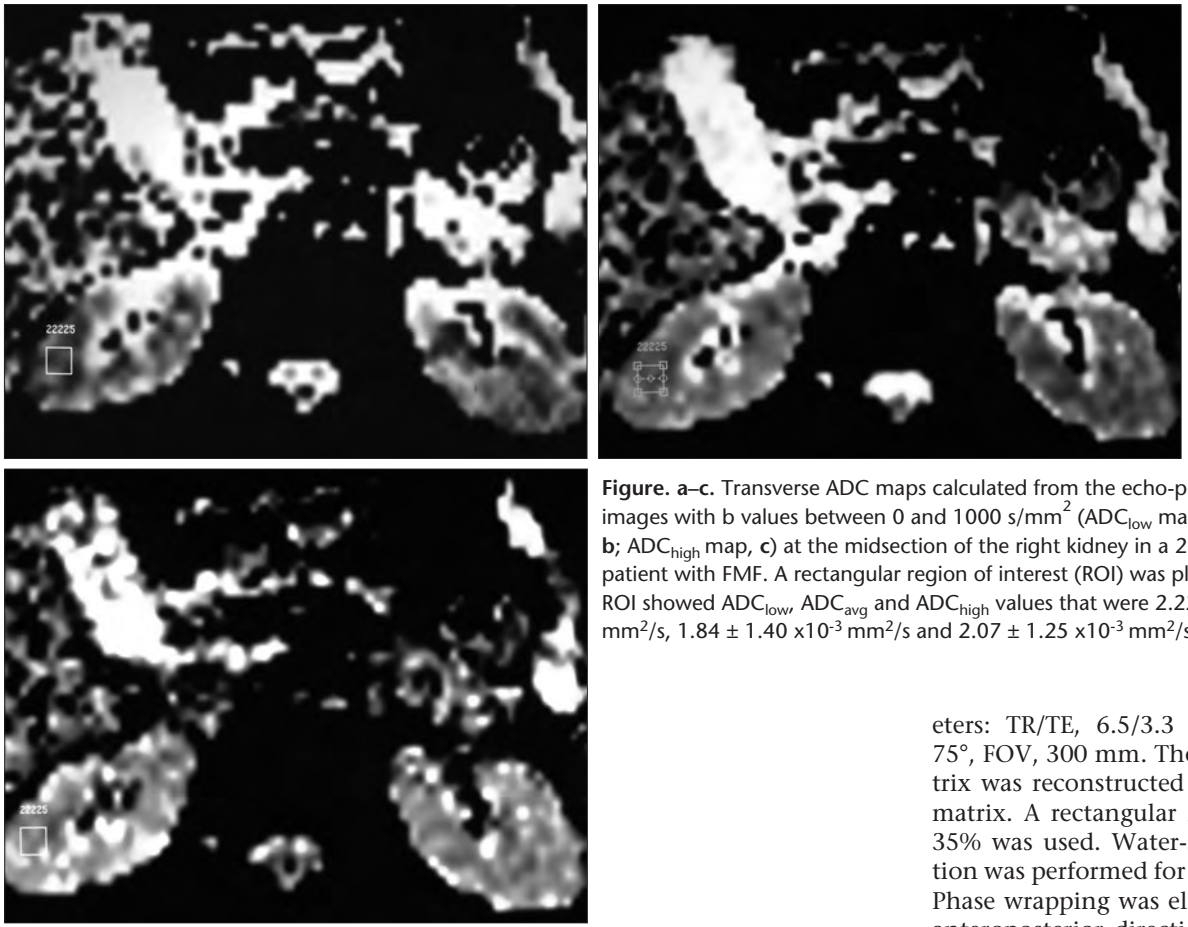

Figure. a–c. Transverse ADC maps calculated from the echo-planar DW-MR images with b values between 0 and 1000 s/mm^2 (ADC_{low} map, **a**; ADC_{avg} map, **b**; ADC_{high} map, **c**) at the midsection of the right kidney in a 21-year-old female patient with FMF. A rectangular region of interest (ROI) was placed in the cortex. ROI showed ADC_{low}, ADC_{avg} and ADC_{high} values that were 2.22 ± 1.24 x10^{-3} mm^2/s, 1.84 ± 1.40 x10^{-3} mm^2/s and 2.07 ± 1.25 x10^{-3} mm^2/s, respectively.

Magnetic resonance imaging

MRI was performed with a 1.5 T system (Philips Gyroscan Intera, Best, The Netherlands). Transverse DW multisection echo-planar MRI was performed with the following diffusion gradient b values: 0, 111, 222, 333, 444, 556, 667, 778, 889 and 1000 s/mm^2. These were applied in 3 orthogonal directions and were subsequently averaged to minimize the effects of diffusion anisotropy. The body coil was used. The following parameters were used for this sequence: parallel imaging reduction factor of 2; TR/TE, 3100/74 ms; section thickness, 5 mm; intersection gap, 1 mm; flip angle, 75°; NEX, 1; matrix size, 128 x 128; field of view (FOV), 380 x 380 mm; and rectangular field of view, 100%. Fat saturation was used to avoid chemical shift artifacts. Pre-saturation slabs were not used. The entire sequence consisted of 20 sections (acquisition time, 142 s). The examination was performed during normal respiration. ADC maps were calculated automatically with the MR system. Additionally, we evaluated the kidneys morphologically with T2-weighted MR images and excluded other pathologies such as cysts, focal scars, or mild hydronephrosis.

In transverse ADC maps, rectangular regions of interest were placed completely on the cortex of each kidney in 3 parts (upper pole, middle part, and lower pole). ADCs of the kidneys were calculated separately for low (ADC_{low}; b = 0, 111, 222, 333 s/mm^2), average (ADC_{avg}; of all b values), and high (ADC_{high}; b = 778, 889, 1000 s/mm^2) b values to enable the differentiation of the relative influence of perfusion fraction and true diffusion (Figure). Each ROI was about 105 mm^2. ADC_{high} reflects almost only diffusion, whereas ADC_{low} is composed of both diffusion and perfusion.

In addition, a multi-slab balanced turbo field-echo MR angiographic technique (without a contrast agent) was used to exclude renal artery stenosis. Again the body coil was used. A balanced fast field echo sequence was applied in the coronal plane to identify the origin of the main renal arteries. A balanced turbo field echo sequence was applied with the following parameters: TR/TE, 6.5/3.3 ms; flip angle, 75°, FOV, 300 mm. The 240 x 240 matrix was reconstructed to a 512 x 512 matrix. A rectangular field of view of 35% was used. Water-selective excitation was performed for fat suppression. Phase wrapping was eliminated in the anteroposterior direction. Before each balanced turbo field-echo shot, three saturation pulses were applied to provide venous signal suppression. The hilum of each kidney was covered by two saturation slabs. A third saturation slab was positioned parallel and caudal to the three-dimensional imaging at a distance of 10 mm to suppress the signal from the inferior vena cava. Breath holding was not performed. Duration of the sequence was 67 s in each patient.

One radiologist, who was blinded to the serum creatinine and urine protein levels, and GFR of each patient, calculated the ADC value for each kidney and evaluated renal MR angiography.

Statistical analysis

Statistical analyses were performed with Statistical Package for Social Sciences (SPSS Inc., Chicago, USA). The sex of each three groups were compared with chi-square test. ADC values were evaluated in 180 kidneys as both kidneys were examined in each patient. ADC values, urine protein and serum creatinine levels, GFR and age were compared by using ANOVA test between healthy volunteers, patients

with renal involvement, and patients without. In addition to this, the duration of disease was compared between patients with and without renal involvement by independent sample t test. Probability values of less than 0.05 were considered significant.

Results

Table shows the mean values of different variables in patients with and without renal involvement, and the control group. There was no statistically significant difference in sex, age and GFR levels between the three groups. None of the patients with FMF had renal artery stenosis.

There was a statistically significant difference in terms of urine protein levels between the patients with renal involvement and the control group. The serum creatinine level was normal in the patients with FMF and in the control group. There was no statistically significant difference in terms of serum creatinine levels between the patients with renal involvement and the patients without. There was no statistically significant difference in terms of the duration of disease between the patients with renal involvement and the patients without. There was a statistically significant difference between ADC_{low} values of the three groups. But this difference was due to the ADC_{low} values of the patients with FMF which were significantly different from those of the control group. Positive correlation was detected between the duration of disease and serum creatinine and urine protein levels, whereas negative correlation was found between the duration of disease and GFRs. Although there was no statistically significant relation between the duration of disease and ADC values of the kidneys, negative correlation was detected between the duration of disease and ADC_{low} values of the kidneys ($r = -0.223$, $P = 0.087$).

Discussion

The major cause of renal involvement in FMF is the occurence of amyloidosis. Amyloid proteins may infiltrate the adrenals, gastrointestinal tract, liver, spleen, thyroid, lung, and heart. The most common cause of death from FMF is renal failure (6–8). The amyloid protein in FMF is of the AA type (9). The first clinical sign of renal amyloidosis is usually persistent proteinuria, due to the deposition of amyloid fibrils in the kidneys (10). Preclinical, proteinuric, nephrotic and uremic stages are four types of nephrotic amyloidosis. Unfortunately, the onset and duration of the preclinical stage can not be known. The progression of disease to the terminal renal failure takes about 2–13 years (10). Amyloidosis can appear in two modes in FMF. In type 1, patients develop this complication following years of attacks of the disease, usually because they do not receive colchicine or they are non-compliant. In type II, the first presentation of FMF is either proteinuria or nephrotic syndrome due to renal amyloidosis (11). Regular colchicine treatment may prevent amyloidosis and decrease kidney damage in patients with proteinuria (12). In addition to amyloidosis, the patients with FMF may have other glomerular disease such as vasculitis, crescentic rapidly progressive glomerulonephritis, mesangial IgA nephropathy, IgM nephropathy and diffuse proliferative glomerulonephritis. Among them IgA nephropathy is the most common primary glomerulopathy (11, 13). Kidney biopsy is most informative in the diagnosis of amyloidosis in FMF; however, life-threatening bleeding can occur during biopsy. The abdominal fat pad aspirate is the easiest way of obtaining tissue, but it is a disappointing procedure in amyloidosis of FMF (14). In pathological examination of kidneys, renal amyloidosis involves the glomeruli as well as the interstitium. In the glomeruli, glomerular basement membrane (GBM) and mesangial area are the preferred targets for amyloid fibril deposition. In the interstitium, tubular basement membrane (TBM), interstitial space and the vessel walls of arteries and arterioles are usually affected (15).

In the literature, there are some articles about DW-MRI of the kidneys (4, 16). Thoeny et al. have reported DW-MRI of the kidneys in healthy volunteers and patients with various renal abnormalities (4). They demonstrated that all ADC values of the kidneys in the patients with pyelonephritis were substantially lower compared with the opposite site. This corresponded to zones of inflammation involving the papilla and cortex. In addition to this, they showed that the patients with renal failure had significantly lower ADC of the cortex and medulla than did volunteers (4). Fukuda et al. showed that the patients with high serum creatinine levels had also lower ADC values

Table. Mean values and ranges of different variables in FMF patients with renal involvement, FMF patients without renal involvement, and the control group

	FMF patients with renal involvement	FMF patients without renal involvement	Control group	*P* value
Age (years)	30.88 ± 10.36	29.72 ± 11.57	30.53 ± 7.31	0.897
ADC_{low} ($x10^{-3}mm^2/s$)	2.36 ± 2.94	2.37 ± 2.04	2.48 ± 2.52	0.025
ADC_{avg} ($x10^{-3}mm^2/s$)	2.02 ± 1.67	2.03 ± 1.74	2.08 ± 1.65	0.146
ADC_{high} ($x10^{-3}mm^2/s$)	2.16 ± 1.29	2.17 ± 1.61	2.16 ± 1.32	0.963
GFR (mL/min)	112.70 ± 33.71	120.78 ± 32.59	121.68 ± 14.45	0.425
Proteinuria (mg/24 hours)	172.00 ± 72.01	42.45 ± 18.90	25.94 ± 13.77	0.000
Creatinine (mg/dL)	0.88 ± 0.21	0.77 ± 0.13	0.80 ± 0.81	0.130

FMF, familial Mediterranean fever; ADC, apparent diffusion coefficient; GFR, glomerular filtration rate.

in comparison to those with normal levels (16).

The aim of our study was to assess the renal involvement in patients with FMF using DW-MRI. In addition to this, we considered the effect of FMF on the ADC values to identify the early stage of disease (proteinuria stage or preclinical stage). According to our results, ADC_{low} values of the FMF patients with renal involvement were significantly lower than the ADC_{low} values of the control group ($P < 0.05$). This implies that DW-MRI might provide early detection of renal damage in patients with FMF before laboratory findings are positive. In the study of Thoeny et al., the group of patients with renal failure were divided into two subgroups according to the serum creatinine levels (an arbitrary threshold of 2.5 mg/dL was used) to compare diffusion differences at different serum creatinine levels (4). They found that the group of patients with serum creatinine levels lower than this threshold had lower ADC values (except for the ADC_{high} in the medulla) than those in volunteers. However, the second group whose serum creatinine levels were higher than 2.5 mg/dL showed significant differences from the volunteers for all ADC values, except for ADC_{high} in the medulla. In our study, serum creatinine levels of all patients were lower than 2.5 mg/dL and the levels of proteinuria were also similar to the control group. Still, the results of DW-MRI were statistically significant. This may show the value of DW-MRI in the detection of early changes in FMF patients with renal involvement. Negative correlation between the duration of disease and ADC_{low} of kidneys found in our study shows that if the duration of disease increases, the probability of renal involvement may also increase in FMF patients.

Several limitations of our study have to be outlined. Firstly, our patients had early stage of the disease according to renal function parameters. This might have been the reason of statistically insignificant differences in serum creatinine levels and GFRs among patients with FMF and controls. Secondly, the only confirmation of renal involvement was proteinuria in our study group and there was no subclassification of types of renal involvement. Thirdly, the measurements were restricted only to the renal cortex. Therefore, we do not have any data about the medulla where amyloid proteins could be deposited.

In conclusion, DW-MRI of the kidneys may allow early detection of changes in patients with FMF which is thought to be due to various glomerular diseases, especially amyloidosis. ADC values may be an important parameter in the early diagnosis, thereby helping to prevent the progression of disease by the timely administration of proper medical treatment. The present study is our initial experience about DW-MRI of the kidneys in FMF patients and further studies with larger series of FMF patients are warranted to assess the efficacy of DW-MRI for the detection of renal parencyhmal involvement.

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