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Original paper

Diffusion tensor magnetic resonance imaging in the grading of liver fibrosis associated with congenital ductal plate malformations

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Abstract

Purpose: Liver biopsy is still the standard method for the diagnosis of ductal plate malformations (DPM). However, it is an invasive tool. Magnetic resonance imaging (MRI) has shown its accuracy in the diagnosis of this pathology. Herein, a study was conducted to elucidate the role of diffusion MRI parameters in predicting the degree of hepatic fibrosis.

Material and methods: This prospective study included 29 patients with DPM and 20 healthy controls. Both groups underwent diffusion tensor magnetic resonance imaging (DT-MRI), and its parameters were compared between patients and controls, and then they were correlated with the degree of liver fibrosis in the patient group.

Results: All patients with DPM, whatever its type, expressed a significantly lower hepatic apparent diffusion coefficient (ADC) compared to controls. However, fractional anisotropy (FA) showed no significant difference between them. The ADC value of 1.65×10^{-3} mm^2/s had sensitivity and specificity of 82.1% and 90%, respectively, in differentiating DPM patients from healthy controls. It was evident that patients with higher fibrosis grades had significantly lower hepatic ADC, indicating a negative correlation between ADC and the grade of hepatic fibrosis; rs = −0.901, $p < 0.001$.

Conclusions: DT-MRI showed good efficacy in the diagnosis of congenital DPM. Moreover, ADC could be applied to monitor the degree of liver fibrosis rather than the invasive liver biopsy. No significant correlation was noted between the FA and the grades of liver fibrosis.

Key words: diffusion tensor magnetic resonance imaging; ductal plate malformation; liver fibrosis; apparent diffusion coefficient.

Introduction

Ductal plate malformations (DPM) or fibropolycystic liver disease are broad terms used to describe a complex group of congenital disorders that result from aberrant remodelling or persistence of the ductal plate [1,2]. This disease spectrum entails multiple subtypes, including congenital hepatic fibrosis (CHF), Caroli disease, polycystic liver disease, biliary hamartoma, and choledochal cysts, in addition to biliary atresia [3]. The manifestations of this pathology are variable, but most of them are related to portal hypertension. The patient may present with oesophageal varices, splenomegaly, or spontaneous luminal gastrointestinal bleeding [4]. Some patients may present with cholangitis [5,6]. Associated renal anomalies have also been reported, including polycystic kidney disease (PCKD), nephronophthisis, and medullary sponge kidney [2]. It is worth mentioning that this pathology progresses into liver fibrosis and subsequent true cirrhosis, and this is responsible for the previously mentioned portal hypertensive manifestations [4,7].

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A Study design · **B** Data collection · **C** Statistical analysis · **D** Data interpretation · **E** Manuscript preparation · **F** Literature search · **G** Funds collection

Moreover, these patients are at increased risk of developing hepatocellular carcinoma [2,4]. Therefore, frequent evaluation of patients with DPM is important for early detection and grading of the degree of liver fibrosis. The definite diagnosis of DPM is established by liver biopsy [2], which is also helpful in the assessment of the degree of fibrosis [8]. Nonetheless, it is an invasive procedure that carries some risk of complications like bleeding [9].

Magnetic resonance imaging (MRI) plays a crucial role in the diagnosis and management of this disease spectrum because it helps the physician accurately detect and differentiate its subtypes [3,10]. It also provides multiplanar imaging with high-contrast resolution without radiation exposure, as in computed tomography with good efficacy in the diagnosis and monitoring of liver diseases [11-13]. Diffusion MRI is a variant of conventional MRI, which depends on water molecule movement inside tissues without the application of chemical tracers or contrast intake [14]. The diffusion of these molecules between tissues depends on multiple factors, including tissue type, architecture, integrity, as well as the presence of barriers [14,15]. The liver fibrosis process is an integral part of the natural history of DPM. It was previously mentioned that fibrosis is associated with an increase in the impermeable structures in the cell membrane and is often accompanied by oedema and an increase in the intracellular to extracellular volume ratio, leading to restriction of water molecule free movement [16]. Therefore, fibrosis will lead to a restricted diffusion, which in turn will cause a decline in the measured ADC values [17-19]. The current literature is poor, with studies evaluating the role of DT-MRI in the grading of liver fibrosis associated with DPM. Hence, the current research was conducted to report DT-MRI findings in patients with DPM and to elucidate the role of its parameters (ADC and FA in particular) in predicting the degree of hepatic parenchymal fibrosis.

Material and methods

Patient population

This prospective case-control study was conducted at the Radiology Department in collaboration with Mansoura University Children's Hospital, Egypt. This was done after obtaining approval from the local Scientific Committee in our medical school.

The study was designed for children whose ages ranged between 2 and 18 years, diagnosed with DPM, and confirmed by liver biopsy. Patients were recruited during the period between January 2020 and December 2021. We excluded children aged below 2 years or whose serum creatinine was elevated (> 1.2 mg/dl).

Twenty-eight paediatric patients met our inclusion criteria, and they were enrolled in our study after obtaining consent from their guardians after a simple explanation of the benefits and possible drawbacks of each intervention. The data of these patients were collected and compared with the data of 20 age- and gender-matched healthy paediatric subjects who presented to the children's hospital for seasonal vaccination.

Clinical assessment

All patients were subjected to full history taking, including the age at the time of diagnosis, disease presentation, and family history of similar conditions. After clinical examination and routine laboratory assessment (mainly coagulation profile), an ultrasound-guided liver biopsy was done for all patients, and the existing hepatic fibrosis was graded according to the 6-stage Modified Histological Activity Index (Ishak system) (Suppl Figure 1) [20].

Magnetic resonance imaging

All patients and controls were subjected to pelviabdominal MRI using a 1.5-tesla machine (Philips, Inginea). The T2 MRI-weighted images were obtained in axial and coronal axes with respiratory gating, using the following parameters: 80 ms echo time, 1250 ms repetition time, 400×400 matrix size, 6-mm slice thickness, $400 \times 350 \times 196$ mm field of view.

The DTI was performed using a single-shot fast spin-echo echo-planar sequence with respiratory gating, using the following parameters: 85 ms echo time, 6000 ms repetition time, 128×128 matrix size, 2.5-mm slice thickness, $224 \times 224 \times 196$ mm field of view, and 3 averages.

The apparent diffusion coefficient (ADC) of the liver was estimated using the b values of 50, 400, and 800 s/mm^2. The ADC values were calculated at each of the 4 right liver segments, and the mean of them was calculated to get the final ADC. We omitted the left lobe to avoid motion artifacts (caused by cardiac movements). The collected ADC values were compared between patients and controls, and then correlated with the degree of liver fibrosis in the patient group. Merged images between colour-mapped axial cuts of DTI and axial T2 WI were obtained, and example images are presented in Figure 1 and Figure 2.

Statistical analysis

Our data were transferred to SPSS software for analysis. The receiver operator characteristic (ROC) curve was used to determine the best cut-off point for both FA and ADC measurements. Spearman's correlation was used to test the correlations between the grades of liver fibrosis and our DTI parameters. All our results were deemed significant with a p-value of 0.05 or less.

Results

Patient characteristics

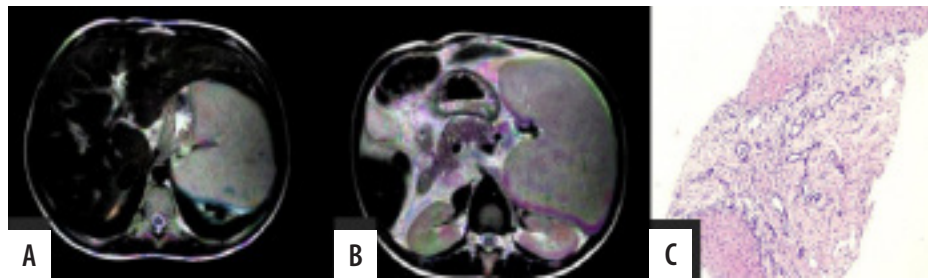CHF was the most commonly encountered pathology among our patients (75%). CHF was combined with

Figure 1. A, B) Merged axial T2 and diffusion tensor images showing cirrhotic liver and enlarged spleen in an 11-year-old male child. **C)** Liver biopsy revealed grade IV congenital hepatic fibrosis with fibrotic tissue, dilated ducts, and absent inflammatory changes
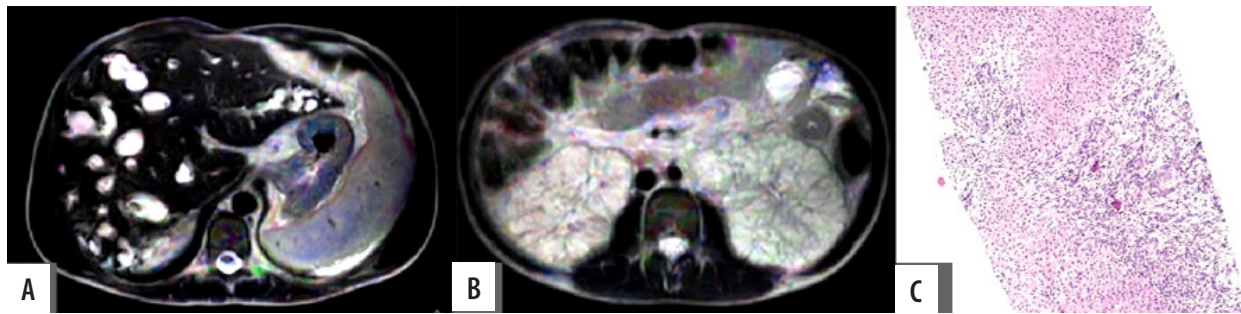

Figure 2. A, B) Merged axial T2 and diffusion tensor images showing cirrhotic liver with dilated radicals and multiple small liver and renal cysts. **C)** Liver biopsy revealed cholangitic congenital hepatic fibrosis with fibrotic tissue, dilated inflamed ducts, and surrounding connective tissue

PCKD in 3 patients (10.7%), while it was combined with solitary kidney in one patient (3.6%). Additionally, 3 patients (10.7%) had PCKD along with Caroli disease (Figure 1). The sociodemographics of our included sample with regards to age, sex, and family history of different pathologies are shown in Table 1.

Comparison between patients and controls regarding fractional anisotropy and apparent diffusion coefficient

All patients with DPM, whatever its type, expressed significantly lower hepatic ADC compared to controls ($p < 0.001$). The mean ADC values of the patients diagnosed with CHF, PCKD with Caroli disease, PCKD with CHF, and solitary kidney with CHF were 1.29×10^{-3}, 1.32×10^{-3}, 1.89×10^{-3}, and 1.02×10^{-3} mm²/s, respectively, while the same value was 1.915×10^{-3} mm²/s for controls. Liver FA

had mean values of 0.242, 0.297, 0.263, and 0.293 in the same patient groups, respectively, with no significant difference between our encountered pathologies and controls ($p = 0.873$) (Table 2).

Correlation between apparent diffusion coefficient and hepatic fibrosis grade

When the included DPM patients were classified based on the fibrosis grade, it was evident that patients with higher fibrosis grades had significantly lower hepatic ADC, indicating a negative correlation between ADC and the grade of hepatic fibrosis; $r_s = -0.901$, $p < 0.001$ (Table 3, Figure 3). On the other hand, no statistically significant differences or correlations were noted between the FA and hepatic fibrosis grades; p-value = 0.4 and 0.7, respectively.

Table 1. Sociodemographic characteristics of the included patients versus controls

Factor		CHF (75%)	PCKD + Caroli (10.7%)	PCKD + CHF (10.7%)	Solitary kidney + CHF (3.6%)	Controls	Test of significance
Age/years, mean ± SD		11.57 ± 3.79	10.33 ± 2.08	11.67 ± 5.03	7.0 0± 0.00	9.85 ± 4.63	$F = 0.675$ $p = 0.613$
Sex							
	Male	13 (61.9%)	1 (33.3%)	2 (66.7%)	0 (0%)	11 (55%)	$\Sigma^{2MC} = 2.34$
	Female	8 (38.1%)	2 (66.7%)	1 (33.3%)	1 (100%)	9 (45%)	$p = 0.673$
Family history							
	Negative	16 (76.2%)	2 (66.7%)	2 (66.7%)	1 (100%)	20 (100%)	$\Sigma^{2MC} = 6.72$
	Positive	5 (23.8%)	1 (33.3%)	1 (33.3%)	0 (0%)	0 (0%)	$p = 0.152$

CHF – congenital hepatic fibrosis, PCKD – polycystic kidney disease

Table 2. Apparent diffusion coefficient and fractional anisotropy values in ductal plate malformation patients versus controls

Factor	CHF	PCK + Caroli	PCK + CHF	Solitary kidney + CHF	Control	Test of significance
Liver ADC	1.29 ± 0.35	1.32 ± 0.23	1.89 ± 0.27	1.02 ± 0.0	1.915 ± 0.19	$F = 15.16$ $p < 0.001*$
Liver FA	0.242 ± 0.101	0.297 ± 0.238	0.263 ± 0.141	0.293 ± 0.0	0.206 ± 0.0	$F = 0.232$ $p = 0.873$

ADC – apparent diffusion coefficient, FA – fractional anisotropy

Table 3. Apparent diffusion coefficient in patients with different fibrosis grades

Factor	II	III	IV	V	VI	Test of significance
Liver ADC	2.18 ± 0.03	1.65 ± 0.09	1.35 ± 0.30	1.05 ± 0.029	0.977 ± 0.03	$F = 13.31$ $p < 0.001*$
Liver FA	0.200 ± 0.084	0.357 ± 0.171	0.248 ± 0.127	0.238 ± 0.046	0.240 ± 0.101	$F = 0.868$ $p = 0.499$

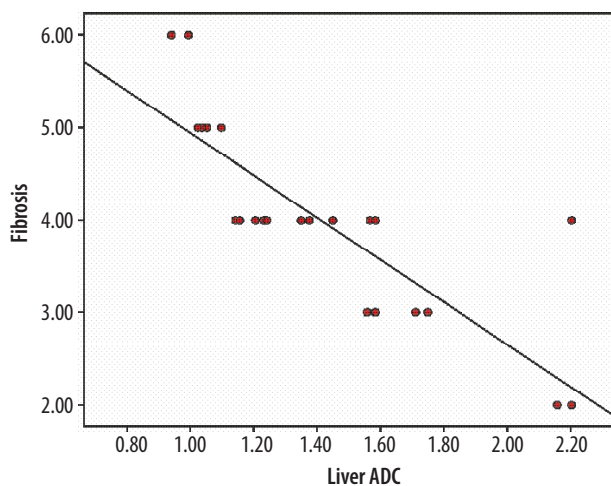ADC – apparent diffusion coefficient, FA – fractional anisotropy

Figure 3. Spearman correlation between the liver apparent diffusion coefficient values and grades of hepatic fibrosis
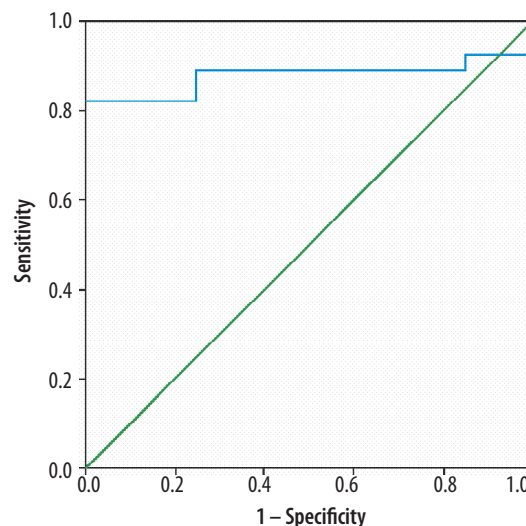

Figure 4. Receiver operating curve for liver apparent diffusion coefficient in differentiating ductal plate malformation patients from controls

The ADC value of 1.65 mm²/s × 10⁻³ had sensitivity and specificity of 82.1% and 90%, respectively, in differentiating DPM patients from the healthy controls, with an accuracy of 85.4% (Figure 4).

Discussion

This study showed and confirmed a significant decline in ADC values in DPM patients compared to controls ($p < 0.001$). In particular, the ADC cut-off value in our study of 1.65 mm²/s × 10⁻³ had sensitivity and specificity of 82.1% and 90%, respectively, in differentiating DPM patients from the healthy controls. Moreover, our study noted a significant negative correlation between the grades of liver fibrosis and ADC.

In a previous similar study, which correlated the ADC values with the degree of liver fibrosis in adult patients with chronic hepatitis, Hu *et al.* noted that the ADC val-

ues were significantly decreased as the liver fibrosis state progressed [16]. Bonekamp *et al.* also confirmed the previous findings [21]. In our opinion, this finding could be applied in clinical practice to mitigate the need for repeated liver biopsies, especially for monitoring the progress of liver fibrosis in patients with DPM. Serial DTI-MRI with its ADC should be recorded and compared over different time points, and the biopsy should be reserved as the last assessment method. However, that concept needs to be further studied in larger-scale investigations.

In contrast to the previous findings, other researchers denied any significant relationship between ADC and fibrosis grades [22,23]. The difference between the published reports could be explained by heterogeneous imaging parameters as well as different disease criteria and fibrosis grading systems.

Our findings showed no significant relation between FA and the grade of liver fibrosis. FA reflects the direc-

tion of water diffusion across tissue microstructure, and this depends mainly on tissue orientation [24-26]. Surprisingly, the literature contains studies reporting positive [27] and negative correlations [28,29] between FA and the degree of liver fibrosis. The previous heterogenicity related to FA findings could be attributed to the complex histopathological changes associated with fibrosis, such as inflammation, fatty infiltration, as well as extracellular collagen breakdown. The diffusion of water molecules is presumably constrained during the period when extracellular matrix proteins increase, resulting in a drop in the FA values. However, when cell necrosis occurs at the advanced stage, the FA increases.

Although our study handled a unique research point that was poorly mentioned in the literature, we included a small sample size, and all of them were gathered from a single educational centre. Also, some subtypes of DPM, rather than CHF, entailed very few patients. More studies, including more patients from different paediatric hepatology centres, should be conducted to cover the mentioned drawbacks.

Conclusions

According to our findings, DT-MRI showed its efficacy in the diagnosis of DPM and grading of associated liver fibrosis. Moreover, ADC could be applied to monitor the degree of liver fibrosis rather than the invasive liver biopsy. However, our findings showed no significant relation between FA and the grade of liver fibrosis. The application of this modality should be encouraged when evaluating such patients.

Disclosure

The authors report no conflict of interest.

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