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The impact of MRI findings in the liver in the diagnosis of pediatric Wilson's disease

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Ethics Committee Approval
The study was approved by the local Ethics Committee of the University of Health Sciences, Inonu University (approval number: 2021/1648, data:09.02.2021).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Wilson's Disease (WD) is one of the genetic diseases that can be successfully managed with early diagnosis and treatment. There is no single test used in its diagnosis; therefore, the diagnosis is made by laboratory and clinical findings, as well as genetic analysis results. This study aimed to describe the magnetic resonance imaging (MRI) findings in the livers of pediatric patients with WD and evaluate the relationship between serum ceruloplasmin, 24-hour urinary copper values, and MRI findings.
Methods: A total of 35 patients with WD younger than 18 years of age were included in this cohort study. Qualitative and quantitative parameters were evaluated in MRI. The qualitative parameters included parenchymal nodule, contour irregularity, honeycomb pattern, ascites, and increased periportal thickness. The quantitative parameters were splenomegaly and the ratio of the caudate lobe to the right lobe (CL/RL). All patients were classified according to the absence or presence of qualitative and quantitative parameters on MRI. The serum ceruloplasmin levels and 24-hour urinary copper values were evaluated according to the scoring system developed at the Eighth International Meeting on Wilson disease in Leipzig, in 2001. All qualitative and quantitative MRI findings were compared among patients with high and low serum ceruloplasmin levels and 24-hour urinary copper values.
Results: Ascites and splenomegaly were the most common findings, seen in 17 (48.6%) and 19 (52.7%) patients, respectively. Twenty-eight (80%) patients had normal caudate-lobe to the right-lobe (CL/RL) ratio in MRI. The serum ceruloplasmin levels in patients with parenchymal nodules, irregular liver contours, ascites in the abdomen, increased periportal thickness and splenomegaly were significantly lower than those without these findings ($P<0.05$). The 24-hour urinary copper values in patients with ascites and increased periportal thickness were significantly higher than in those without ($P<0.05$).
Conclusion: In case of nonspecific liver MRI findings such as parenchymal nodules, irregular liver contours, ascites in the abdomen, increased periportal thickness, and a normal caudate to right-lobe (CL/RL) ratio in a pediatric patient with decreased serum ceruloplasmin and increased 24-hour urinary copper values, WD should be considered among the causes of chronic liver disease.

Keywords: Wilson disease, Magnetic resonance imaging, Liver, Ceruloplasmin

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Introduction

Wilson disease (WD) is an autosomal recessive disease that occurs due to a defect in copper metabolism, and its prevalence is 1:30.000. In this disease, copper accumulates in various tissues including the liver and the brain due to impaired excretion of copper through bile [1, 2]. WD is one of the genetic diseases that can be successfully managed with early diagnosis and standard treatment. Early diagnosis is of great importance for the prognosis of this disease [3]. There is no single test used in the diagnosis of WD; therefore, the diagnosis is made by laboratory tests and clinical findings, as well as genetic analysis results. According to the scoring system which was developed at the Eighth International Wilson's Disease Meeting held in Leipzig in 2001, 4 points and above was considered sufficient for diagnosis [4]. Abnormal 24-hour urinary copper and serum ceruloplasmin values are also used in this scoring system alongside a few other clinical and laboratory data.

Imaging findings for the liver in WD generally reflect liver damage related to fat infiltration, acute hepatitis, chronic active hepatitis, and cirrhosis [5-8]. Nodular infiltrations and contour abnormalities in the liver were reported in the literature [5-9]. Although studies on liver imaging in WD are on ultrasound (US) and Computed Tomography (CT), only a few are on MRI [6, 7, 10].

We aimed to describe the liver MRI findings in pediatric WD patients, evaluate the relationship between 24-hour urinary copper levels, serum ceruloplasmin values and the MRI findings, and show the contribution of MR imaging to the diagnosis.

Materials and methods

The study complied with the guidelines of the Health Insurance Portability and Accountability Act. Informed consent was obtained from the parents of the patients. This study was approved by the İnönü Üniversity Ethics Committee on 09/02/2021 with the decision number 2021/1648.

A total of 35 patients (20 male, 15 female) younger than 18 years of age who were followed up in the pediatric gastroenterology clinic with the diagnosis of WD between 2006 and 2020 were included in our study. The scoring system, which was developed in Leipzig in 2001, at the Eighth International Meeting on WD was used for the diagnosis of WD. WD was considered if the score was 4 and above [4].

The serum ceruloplasmin levels were evaluated in 3 groups.

Group 1: A normal serum ceruloplasmin value (>0.2 g/dl).
Group 2: A ceruloplasmin value of 0.1 g/dl - 0.2 g/dl.
Group 3: A ceruloplasmin value of <0.1 g/dl.

The urinary copper values were evaluated in 3 groups:
Group 1: A normal urinary copper value (<100 µg).
Group 2: A urinary copper value of 100µg-200µg.
Group 3: A urinary copper value of >200µg.

MR images

The 1.5T (Siemens, Magnetom-Avanto) device was used for MRI. The studies included the following MR sequences: An axial T2-weighted fast spin-echo sequence, an axial T1-weighted fast spin-echo sequence, a coronal fat-suppressed true fast imaging TRUFI (True Fast Imaging with steady-state-free precession) sequence, unenhanced in-and out-of-phase fat-suppressed TSE sequence, and fat-suppressed gradient-echo sequences after intravenous administration of a gadolinium chelate.

A pediatric radiologist reviewed the MRI examinations over the picture archiving and communication system (PACS).

The qualitative parameters examined in MRI were the presence of parenchymal nodules, contour irregularity, a honeycomb pattern, ascites, and increased periportal thickness. The quantitative parameters were splenomegaly and the ratio of the caudate lobe to the right lobe (CL/RL). Per the description of Awaya et al. [11], the right portal vein was used as a landmark in the separation of the caudate and the right lobe for the calculation of CL/RL. A CL/RL value of >0.90 indicated caudate lobe enlargement [11]. The length of the spleen was measured in the coronal plane and values above the upper limit of normal for a particular age group were considered splenomegaly [12].

Statistical analysis

All qualitative and quantitative MRI findings were compared between three groups each, based on the serum ceruloplasmin and 24-hour urinary copper values. SPSS 22 program was used to analyze the data and *P*-values were calculated using the Chi-square test.

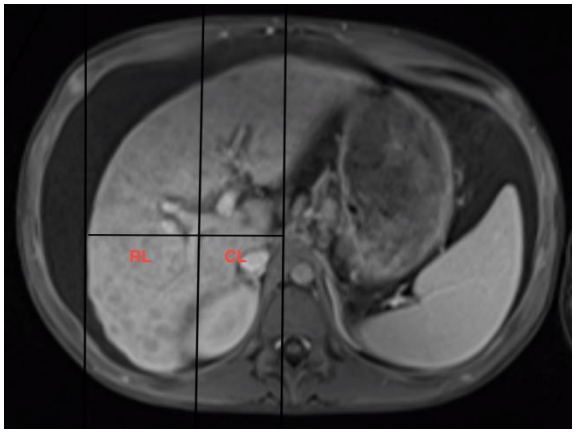
Results

There were 35 patients in our study, twenty (57.1%) males and 15 (42.9%) females. The mean age of the patients was 11.28 years. There was no significant difference between the genders according to the serum ceruloplasmin levels and 24-hour urinary copper values.

The mean serum ceruloplasmin levels and 24-hour urinary copper values were 0.12 g/dl and 378.35µg, respectively. Serum ceruloplasmin level was >0.2 g/dl in 5 (14.2%) patients and 24-hour urinary copper value was <100 µg in 10 (28.5%) patients.

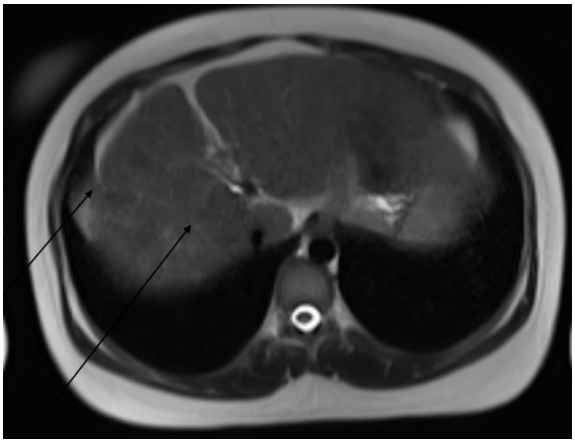
Twenty-eight (80%) patients had normal CL/RL (Figure 1). Splenomegaly was observed in 19 (52.7%) patients, contour irregularity (Figure 2), in 17 (48.6%), ascites (Figure 3), in 17(48.6%), increased periportal thickness (Figure 4) in 12 (35.2%), parenchymal nodules, in 10 (28.6%) and the honeycomb pattern (Figure 3) were seen in 4 (11.4%).

Figure 1: T1-weighted fat-suppressed transverse image



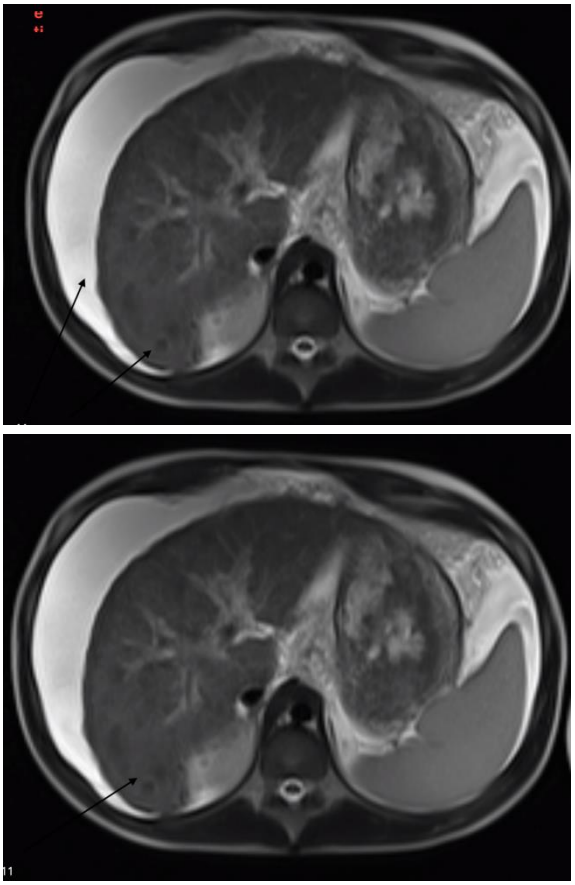
A 14-year-old male with liver cirrhosis and ascites. The MR image obtained in the transverse plane after intravenous administration of a gadolinium chelate shows the calculation method of caudate lobe-to-right lobe ratio (CL/RL). CL indicates the width of the caudate lobe (38 mm). RL is the width of the right lobe (51 mm). In this patient, CL/RL = 0.74.

Figure 2: T2 weighted- transverse image



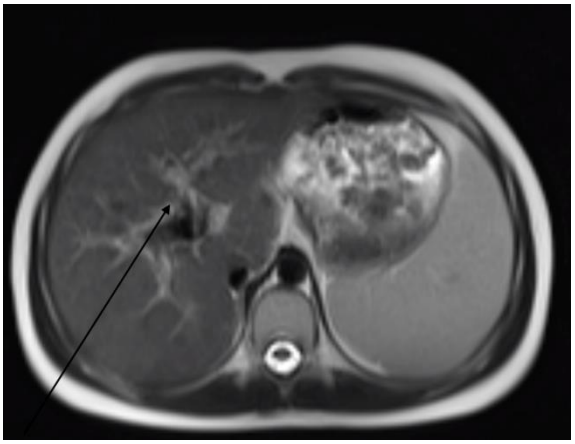
An 8-year-old male with liver cirrhosis had contour irregularity of liver surface and multiple hypointense nodules (shown with arrows).

Figure 3: T2-weighted transverse image, A: Ascites and multiple hypointense nodules (shown with arrows), B: Hyperintense septa (shown with arrows)



A 16-year-old female had ascites in the abdomen and a honeycomb pattern with multiple hypointense nodules surrounded by hyperintense septa.

Figure 4: T2-weighted transverse image



A 7-year-old female had periportal thickening in the liver because of fibrosis (shown with an arrow).

MRI findings of the groups according to the serum ceruloplasmin and urinary copper values are shown in Tables 1 and 2.

Table 1: MRI findings of the patients in the grouping made according to the serum ceruloplasmin values

	Group 1	Group 2	Group 3	Total patients
Parenchymal nodule	0	4(40%)	6(60%)	10(28.6%)
Contour irregularity	0	8(47%)	9(53%)	17(48.6%)
Honeycomb pattern	0	2(50%)	2(50%)	4(11.4%)
Ascites	0	8(47%)	9(53%)	17(48.6%)
Increased periportal thickness	0	4(33.3%)	8(66.6%)	12(35.2%)
Splenomegaly	1(5.2%)	8(42.1%)	10(57.9%)	19(54.3%)

Group 1: Urinary copper value was normal (<100 µg), Group 2: Urinary copper value was 100µg - 200µg, Group 3: Urinary copper value was >200µg

Table 2: MRI findings of the patients in the grouping made according to the 24-hour urinary copper values

	Group 1	Group 2	Group 3	Total patients
Parenchymal nodule	0	2(20%)	8(80%)	10(28.6%)
Contour irregularity	0	6(35.3%)	11(64.7%)	17(48.6%)
Honeycomb pattern	0	1(25%)	3(75%)	4(11.4%)
Ascites	0	7(41.1%)	10(58.9%)	17(48.6%)
Increased periportal thickness	1(%)	2(16.6%)	9(83.4%)	12(35.2%)
Splenomegaly	3(%)	8(50%)	8(50%)	19(54.3%)

Group 1: Urinary copper value was normal (<100 µg), Group 2: Urinary copper value was 100µg - 200µg, Group 3: Urinary copper value was >200µg

Ceruloplasmin levels in patients with parenchymal nodules (P=0.038), irregular liver contours (P=0.005), ascites in the abdomen (P=0.027), splenomegaly (P=0.025) and increased periportal thickness (P=0.02) were significantly lower than in those without. No significant difference was found in terms of the presence of the honeycomb pattern and hypertrophy of the caudate lobe between the patient groups according to serum ceruloplasmin values (P>0.05).

The 24-hour urine copper values in those with ascites in the abdomen (P=0.021) and with an increased periportal thickness (P=0.04) were significantly higher than in those without.

Discussion

There are few studies in the literature about liver MRI findings in WD in childhood. The mean age was 11.28 years in our study, which was the lowest mean age in the literature among the studies on WD. In a study discussing the US, CT, and MRI findings of WD, the mean age was 16 years [5]. The mean age was 14 years in the study of Cheon et al. [6]. The number of male patients was higher in our study, which is compatible with the literature [13].

Copper accumulation in the liver occurs in the periportal regions and hepatic sinusoids in the early stages of the WD [14]. Subsequently, periportal inflammation, necrosis, fibrous inflammatory cell infiltration, and irreversible cirrhosis occur [15]. The differences in the liver imaging findings of WD are associated with the stage of the disease [7]. Many nonspecific imaging findings of liver cirrhosis were described in WD. The honeycomb pattern and normal CL/RL ratio were shown as specific findings [5,6]. Akhan et al. first reported that the caudate lobe is not hypertrophied in WD, unlike other causes of cirrhosis [5]. In our study, consistent with the literature, the CL/RL ratio was normal in 80% (28) of the patients. Liver MRI with the imaging findings of liver cirrhosis but a normal CL/RL ratio should suggest WD, especially in pediatric patients.

Honeycomb pattern was defined as the appearance of hypointense nodules surrounded by hyperintense septa in T2-weighted sequences [8]. The reason for this pattern is still not fully understood and it was reported even in a 2-year-old

asymptomatic patient [16]. The honeycomb pattern was observed in 42% of the patients in the study of Akhan et al. and it was reported as a specific finding in WD [5]. However, it can be seen in other chronic liver diseases such as viral hepatitis [10]. In our study, the honeycomb pattern was observed in only 6 (17.1%) patients. Compared with the literature, our study had the lowest number of patients with the honeycomb pattern. This may be because our study included pediatric patients only.

The irregular contour developing due to parenchymal necrosis and regeneration in the liver was observed in 48.6% of our patients. This rate was 50% in the study of Akhan et al. [5], 62% in the study of Cheon et al. [6], and 36% in the study of Vargas et al. [10]. Irregular contour has high sensitivity in indicating chronic liver disease [17]; however, it is not specific for WD. Ascites is seen in liver cirrhosis, especially in the advanced stages of the disease. While ascites was seen in 48.6% of patients in our study, it was found in only 7% of the patients in the study of Cheon et al. and 8.6% of the patients in the study of Vargas et al. The high rate of ascites in this study can be explained with the high number of end-stage liver disease patients referred for transplantation to our hospital, which is one of the leading liver transplantation centers in the world.

Increased periportal thickness is one of the early-stage imaging findings of liver cirrhosis [5]. Akhan et al. observed this finding in 67.9% of their patients in ultrasound, but they found that this rate was much lower in MRI. In our study, 35.2% of the patients had increased periportal thickness, which was higher than the other studies in the literature on ascites. Parenchymal nodules in WD, which are seen in the liver MRI, develop due to copper accumulation and the nodules are generally hypointense on T2-weighted images [5]. This finding was reported between 40-50% in the literature [5,6]. Parenchymal nodules were quite low compared to the literature in our study. Ko et al. claimed that this finding can be observed in the early period in WD [18]. This may be the reason why our results were lower than those in the literature.

Serum ceruloplasmin values are generally <200 mg/L in WD, except for an exceedingly small proportion [19]. In the largest study in the literature about the role of biochemical measurements in the diagnosis of WD, serum ceruloplasmin values were low in all 715 WD patients and ceruloplasmin value was found to have high sensitivity in diagnosis [20]. The 24-hour urinary copper value is another biochemical measurement used in WD and it is significant for diagnosis if it exceeds 100 µg [19]. However, its sensitivity is lower compared to the serum ceruloplasmin value. Although these biochemical tests are especially important in the diagnosis, the definitive diagnosis of the disease cannot be based on them alone. MRI evaluation showed that patients with parenchymal nodules, irregular liver contours, ascites in the abdomen, splenomegaly and increased periportal thickness had lower serum ceruloplasmin values than patients without. These findings are nonspecific for WD, but they correlate with serum ceruloplasmin values. Ascites and increased periportal thickness correlate with 24-hour urinary copper values.

Our study had some limitations. First, it was a retrospective study. The MRI variables were not evaluated in terms of interobserver reliability. Also, the patients were a heterogeneous group in terms of the treatment they received during MRI examination, which may affect the MR images.

Conclusion

Although serum ceruloplasmin and 24-hour urine copper values are included in diagnostic scoring, supportive findings are needed for early diagnosis. In case of nonspecific liver MRI findings such as parenchymal nodules, irregular liver contours, ascites in the abdomen and increased periportal thickness, a normal CL/RL in the liver MRI with decreased serum ceruloplasmin and increased 24-hour urinary copper values in children, WD should be considered among the causes of chronic liver disease.

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