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Original Article

# Wilson's disease in children: Analysis of 41 cases

## *Çocuklarda Wilson hastalığı: 41 olgunun analizi*

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## ABSTRACT

**Aim:** This study aimed to present clinical and laboratory features of 41 children with Wilson's disease.

**Material and Methods:** The medical records of all of the patients who had got a diagnosis of Wilson's disease between 2001 June and 2005 March in Ankara Dr. Sami Ulus Training& Research Hospital, Turkey. Demographic, clinical and biochemical information was obtained from the patients' records. Findings were retrospectively analyzed by the SPSS Windows 16.0 (SPSS Inc. IL, USA) statistical software.

**Results:** A total of 41 patients had got the diagnosis of Wilson's disease: 24 boys and 17 girls, between in the range of 3-14 years old. The mean age of patients was 9.05±2.84 years. Kayser-Fleischer rings were observed in 24 patients. Urinary copper excretion in 24-hours urine was high in 39 of 40 patients. Serum ceruloplasmin levels were found low in 35 of 40 patients. Thirteen of patients were diagnosed after the family screening. Pathologic brain MR findings were detected in 4 of 8 patients without neurological system complaints or physical examination findings.

**Conclusion:** Especially in societies that consanguineous marriages are so common, Wilson's disease should be considered in differential diagnosis of chronic liver diseases, prolonged hypertransaminasemia, and degenerative brain disorders of unknown origin. In our study, it has been shown that Wilson's disease diagnosis and follow-up preserved the value of classical diagnostic methods and it has been shown that neuroimaging may be useful for early detection of neurological involvement even if neurological findings do not occur.

**Keywords:** wilson's disease; children; chronic liver diseases; copper metabolism; neurological involvement;

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## ÖZ

**Amaç:** Bu çalışmada Wilson hastalığı olan 41 çocuğun klinik ve laboratuvar özelliklerinin sunulması amaçlanmıştır.

**Gereç ve Yöntemler:** Ankara Dr. Sami Ulus Eğitim ve Araştırma Hastanesi'nde 2001 Haziran - 2005 Mart tarihleri arasında Wilson hastalığı tanısı konulan tüm hastaların tıbbi kayıtları geriye dönük olarak incelendi. Hastaların kayıtlarından demografik, klinik ve biyokimyasal bilgiler alındı. Bulgular SPSS Windows 16.0 (SPSS Inc. IL, USA) istatistik yazılımı ile analiz edildi.

**Bulgular:** Toplam 41 hasta Wilson hastalığı tanısı almıştı: 3-14 yaş aralığında 24 erkek ve 17 kız idi. Hastaların yaş ortalaması 9.05 ± 2.84 yıldı. 24 hastada Kayser-Fleischer halkaları gözlendi. 24 saatlik idrarda idrar bakır atılımı 40 hastanın 39'unda yüksekti. Serum seruloplazmin düzeyleri 40 hastanın 35'inde düşük bulundu. Hastaların on üçü aile taramasından sonra tanı aldı. Nörolojik sistem şikayeti veya fizik muayene bulguları olmayan 8 hastanın 4'ünde patolojik beyin MR bulguları saptandı.

**Sonuç:** Özellikle akraba evliliklerinin çok yaygın olduğu toplumlarda, kronik karaciğer hastalıklarının ayırıcı tanısında, uzamış hipertransamineminin ve nedeni bilinmeyen dejeneratif beyin bozukluklarının ayırıcı tanısında Wilson hastalığı da düşünülmelidir.

Bizim çalışmamızda Wilson hastalığı tanısı ve izleminin klasik tanı yöntemlerinin değerini koruduğu ve nörolojik bulgular ortaya çıkmasa bile nörolojik tutulumun erken saptanmasında nörogörüntülemenin yararlı olabileceği gösterilmiştir.


**Anahtar kelimeler:** Wilson hastalığı; çocuklar; kronik karaciğer hastalıkları; bakır metabolizması; nörolojik tutulum

## Introduction

Wilson's disease (WD) is a disorder of copper metabolism, resulting from the autosomal recessive occurrence of the ATP7B mutation in the short arm of chromosome 13. It is a rare congenital disorder of metabolism, with a frequency of 1/30,000 in live births[1,2]. Decreased biliary copper excretion and reduced combining of copper into ceruloplasmin, leading to excessive copper accumulation in many organs, predominantly to the liver, brain, and cornea. The clinical manifestations of WD are widely variable due to more than 500 disease-causing mutations[3]. It often presents with hepatic manifestations in early childhood, neurological manifestations add after the age of 20 years[4]. Due to lack of such descriptive tests, the diagnosis should be established on the combination of clinical features, laboratory findings, and the results of mutation analysis. In adults, the presence of typical clinical and laboratory findings, such as Kayser-Fleischer (K-F) rings and low serum ceruloplasmin levels can make easily to establish the diagnosis. However, in children typical clinical features are rarely seen before the age of 5 years and making the diagnosis of the disease more difficult than in adults[5,6]. In this study, clinical and laboratory features of 41 children with Wilson's disease were presented.

## Material and Methods

This study was conducted in Ankara Dr. Sami Ulus Training & Research Hospital, a tertiary care institution in Turkey. The medical records of all of the patients who had got a diagnosis of WD between 2001 June and 2005 March in the pediatric gastroenterology division were reviewed. Demographic, clinical and biochemical information was obtained from the patients' records. The diagnosis of WD has been established in the presence of the specific clinical features of the disease and abnormal copper metabolism tests. Slit lamp examination for the presence of K-F rings, measurement of serum ceruloplasmin levels, and determination of 24-hour urinary copper excretion before and after penicillamine administration were performed in the evaluation of the all patients. Serum ceruloplasmin level was measured by a nephelometric assay. Standard methods were used for liver function tests and other routine laboratory parameters. A percutaneous liver biopsy was performed in most patients after coagulation abnormalities had been corrected. The liver copper content was determined in selected cases. After the diagnosis was confirmed, siblings and first-degree relatives were screened for WD. The genetic analysis was not performed in patients and their families due to the lack of it in our center in the period which the study was conducted. Statistical analysis was performed by the SPSS Windows 16.0 (SPSS Inc. IL, USA) statistical software; the Fisher exact test was used for comparison of categorical variables and the Student t-test for continuous variables. $P<0.05$ was considered statistically significant.

This study was approved by the institutional review board of the related institution. Local ethics committee approved the study and informed consent was obtained from participant(s)

## Results

### *Epidemiology*

A total of 41 patients had got the diagnosis of WD: 24 (58.5%) boys and 17 (41.5%) girls, between in the range of 3-14 years

old. The mean age of patients during the first examination was 9.05±2.84 years. The majority of our patients were between the ages of 7-10 years. Mean age (±SD) at diagnosis was 9.05±2.84 years (range 3 years-14 years). 28 patients (68.2%) were 10 years old age or older. In 32 (78%) of the patients, there was consanguinity between the parents. In the history of patients, six families (14.7 %) had WD and 23 families (56.1%) had chronic liver diseases. Thirteen patients (31.7%) were diagnosed in family screening, and 4 of these pateints (30.7%) were diagnosed in presymptomatic period (Table 1).

**Table 1.** Baseline demographic characteristics and history of WD patients

| | | |
|---|---|---|
| Age (M±SD) | | 9.05±2.84 |
| Gender | Female (n) | 17 (41.5%) |
| | Male (n) | 24 (58.5%) |
| Diagnosis with family screening (n) | | 13 (31.7%) |
| Asymptomatic (n) | | 4 (9.7%) |
| Family history of WD (n) | | 6 (14.7) |
| Family history of undiagnosed chronic liver disease (n) | | 23 (56.1%) |
| Consanguity between parents (n) | | 32 (78%) |

### *Clinical Characteristics*

Thirty-seven (90.2%) patients were symptomatic. The presentations of the patients are shown in Table 2 Four patients (9.8%), with a positive family screening, were asymptomatic. Hepatomegaly was the most common clinical finding in 58.5% of patients, followed by splenomegaly in 43.9%. K-F rings were present in 24 of 41 patients (58.5%). Other most common clinical findings are shown in Table 2. In laboratory studies, the most common finding was high transaminase levels. 30 patients presented with WD hepatic involvement; 19 (63.3% ) patients with least two-fold elevated AST levels, compared to ALT level, 3 of them had ALT levels was at least twice as high compared to AST levels, 8 of them hadn't significant difference between AST and ALT levels Urinary copper excretion in 24-hours urine was high in 39 of 40 patients (97.5%). 21 of 40 patients had anemia (51.2%) and 4 of them (2.4%) was coombs negative hemolytic anemia.

Serum ceruloplasmin levels were found low in 35 (87.5%) of 40 patients. One patient had no a registry of the serum ceruloplasmin level. Most of the patients (n= 30, 73.2%) were presented as the hepatic form of WD. The major laboratory parameters of the patients are shown in Table 2.

**Table2.** Presenting symptoms, signs and particular laboratory findings of patients

| Presenting symptoms & signs | Frequency n (%) |
|---|---|
| Abdominal distantion | 19(46.3) |
| Abdominal pain | 18(43.9) |
| Jaundice | 15(36.6) |
| Headache | 8(19.5) |
| Recurrent Epistaxis | 7(17) |
| Gastrointestinal bleeding | 4(9.8) |
| Speech disturbance | 2(4.9) |
| Artralgia | 3(7.3) |
| ***Signs*** | |
| Hepatomegaly | 24(58.5) |
| Splenomegaly | 18(43.9) |
| Ascites | 14(34.1) |
| Edema | 11(26.8) |
| Particular laboratory findings | |
| Increased 24-hour urinary copper excretion* | 39(97.5) |
| Low serum ceruloplasmin level* | 35(87.5) |
| Elevated AST | 31(75.6) |
| Elevated ALT | 28(68.3) |
| Prolonged protrombin time | 27(65.9) |
| Prolonged partial thromboplastin time | 25(61.0) |
| Hypouricemia | 25(61.0) |
| Hypoalbuminemia | 24(58.5) |
| Anemia | 21(51.2) |
| Hypergammaglobulinemia | 18(43.9) |
| Hyperbilirubinemia | 17(41.5) |
| Hyopphosphatemia | 15(36.6) |

*24-hour urinary copper excretion and serum ceruloplasmin levels were measured in 40 patients.
10 patients (25%) had high levels of urinary copper after D-penicillamine challenge test.

Two of 5 patients below 5 years old were asymptomatic and remains were presented as the hepatic form of WD. 21 of 23 patients who were in 6-10 years old were presented as hepatic form, 1 of them was presented as the neurologic form, and 1 was asymptomatic.

Six of 13 patients older than 10 years were diagnosed as the hepatic form of WD, 5 of them were combined form, 1 of them was neurologic form, and 1 of them was asymptomatic. The youngest patient who had neurological symptoms was 9 years old. Clinical features according to age are shown in Table 3.

**Table 3.** Clinical features according to age of patients

| Age (years) | Hepatic form n (%) | Neurologic form n (%) | Combined form n (%) | Asymptomatic form n (%) | n (%) Total |
|---|---|---|---|---|---|
| 5≤ | 3 (7.4%) | - | - | 2 (4.9%) | 5 (12.2%) |
| 6-10 | 21 (51.2%) | 1 (2.45%) | - | 1 (2.45%) | 23 (56.1%) |
| ≥11 | 6 (14.6%) | 1 (2.45%) | 5 (12.2%) | 1 (2.45%) | 13 (31.7%) |
| n (%) Total | 30 (73.2%) | 2 (4.9%) | 5 (12.2%) | 4 (9.8%) | 41 (100%) |

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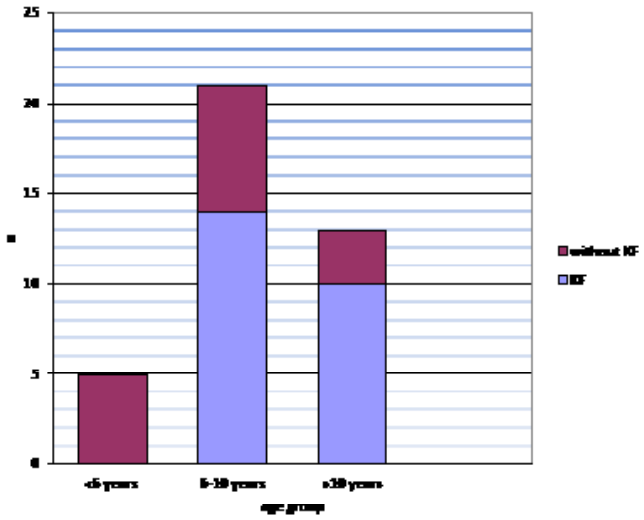
K-F rings existed in all 7 (100%) of patients with the neurological and combined form, 17/30 of (56.6%) those with the hepatic form. The youngest patient who had K-F rings on eye examination was 7 years old. The frequency of appearance of the K-F rings according to the clinical forms and distribution age of the patients are shown in Table 4 and Figure 1 respectively.

**Table 4.** Kayser-Fleischer rings frequency according to the clinical forms

| Clinical form | Patients number | Patients with KF number (%) |
|---|---|---|
| Neurologic | 2 | 2(100) |
| Combined | 5 | 5 (100) |
| Hepatic | 30 | 17 (56.6) |
| Asymptomatic | 4 | 0 (0) |

**Figure 1.** K-F rings according to age group of the patients.




Thirteen of patients (31.7%) were diagnosed after the family screening. Four of them (30.7%) were asymptomatic, three of them had K-F rings on eye examination.

24-hour urinary copper excretion was measured in 40 patients. 29 patients (72.5%) had high levels of urinary copper excretion, in first evaluation. 10 patients (25%) had high levels of urinary copper after D-penicillamine challenge test and one patient (2.5%) was normal. Respectively, urinary copper excretions were as; in seven patients above 1000 mg/24h, in 16 patients between 501-1000 mg/24h, in 11 patients between 201-500 mg/24h and in 5 patients between 100-200 mg/24h. A patient whose 24-hour urinary copper excretion couldn't be measured was transferred to another institution for emergency liver transplantation.

The liver copper content was measured in 18 patients. While 14 patients' copper contents were above 250 µg/g dry weight (77.8%), 4 patients' were between 120-250 µgr/gr.

Abdominal ultrasonography (USG) was performed in 39 patients. 34 of them (87.2%) had at least one pathological finding. The most common sonographic findings were hepatomegaly and splenomegaly (Table 5). Portal venous Doppler USG was performed in 19 patients. Six of them (31.5%) had portal hypertension.

**Table 5.** Abdominal ultrasound findings

| Ultrasound findings | Patient number | Frequency (%) |
|---|---|---|
| Hepatomegaly | 28 | 71.8 |
| Splenomegaly | 25 | 64.1 |
| Ascites | 17 | 43.6 |
| Increased renal parenchymal echogenicity | 15 | 38.5 |
| Gallstone | 2 | 5.1 |
| Cholecystitis | 2 | 5.1 |

Brain magnetic resonance imaging (MRI) was performed in 14 patients. Eight patients hadn't neurological symptom or any physical examination finding and these patients above 11 years old. Pathologic brain MRI findings were detected in 4 (50%) of 8 patients without neurological system complaints or physical examination findings. Six patients who performed brain MRI had headache, dysarthria, dystonia and confusion.

All patients with neurological symptoms had pathological brain MRI findings. The pathological MRI findings were cerebral atrophy and paramagnetic matter deposition in the basal ganglia.

Percutaneous liver biopsy was performed in 21 patients, of whom 14 patients with the hepatic form, 4 patients with were asymptomatic, 2 patients with combined form, and 1 patient with the neurological symptoms existed. In patients with the hepatic form, a liver biopsy performed and liver cirrhosis was found in 7 patients (50%), in 6 patients (42.8%) chronic active hepatitis, and in 1 patient (7.2%) had only inflammatory cell infiltration. In two patients with combined form of WD, also had liver cirrhosis. In one patient, who had been affected only neurologically, had chronic active hepatitis on biopsy evaluation. Three of 4 patients who are asymptomatic had only inflammatory cell infiltration and hepatocellular degeneration, only 1 of them had chronic active hepatitis. Of the 10 patients who underwent upper gastrointestinal endoscopy, 3 normal, 2 gastritis, and 5 esophageal varices.

Extrahepatic manifestations apart from neurological disease of patients are shown in Table 6.

**Table 6.** Extrahepatic involvements apart from neurological disease of patients

| | n (%) |
|---|---|
| Hematuria | 6(14.6) |
| Proteinuria | 5(12.1) |
| Coombs-negative hemolytic anemia | 4(1) |
| Joint pain | 3( 0.7) |
| Cholecystitis | 2(0.5) |
| Gallbladder stones | 2(0.5) |
| Membranoproliferative glomerulonephritis | 1(0.2 ) |

***Treatment and Outcome***

Penicillamine and zinc were administered as the initial treatment. One patient received trientine as the initial treatment, because his sibling had a history of nephropathy caused by penicillamine treatment. Penicillamine was discontinued because of an allergic rash in one patient and of penicillamine-induced dermopathy in the first week of treatment in another.

Four patients had never got chelation treatment in their history. One presented with fulminant hepatic failure and transported for emergency transplantation. Other 3 patients who have not taken chelation treatment were asymptomatic patients who were diagnosed by sibling screening and they only received zinc for treatment. Other than 4 patients who never had treatment and 3 patients who had trientine treatment, all remaining patients (n=34) received penicillamine and/or zinc treatment.

Two of 37 patients who had started to chelation treatment, discontinuied treatment right after the treatment started. Eight of them got worse clinically and transported to another center for liver transplantation. There were no side effects in patients who had trientine treatment. In patients who received penicillamine; 1 patient had neutropenia, 1 patient had nephropathy, 1 patient had dermopathy, 1 patient had an allergic rash, and 1 patient had hypocomplementemia.

## Discussion

Early diagnosis and treatment of WD are very important in those with the chronic liver disease. Patients who are diagnosed earlier not only can survive healthy if the treatment is started early, but also treatment can prevent serious organ damage and even after cirrhosis is present, treatment can lead to improvement of the disease [1, 4, 6]. Therefore, it is necessary to understand the disease fully, screening should be done in suspected cases, and relatives of diagnosed patients should be screened for the disease.

Early diagnosis requires suspicion, in patients who are with unexplained liver, neurological, psychiatric disorders, acute hemolysis or Fanconi syndrome. In our study, proportions of patients who are younger than 5 years old are determined relatively high (17%). It's thought that the reason for it is patients who are diagnosed by sibling screening. In 78% of our patients, there was consanguinity between parents. Of patients' 31.7% were diagnosed after the family screening. All these findings show the importance of sibling screening.

In WD, average diagnosis age changes due to clinical form of the disease. The hepatic form is more common in pediatric age group [2, 3, 5, 7]. In our study, average diagnosis age is determined as 9.05±2.84 years. This finding is consistent with the fact that majority of our patients have the hepatic form of the disease. In pediatric age group, first complaints are mostly related to hepatic involvement and the most common ones are abdominal distention, abdominal pain, and jaundice [2, 4, 5, 8, 9]. Congruently, our study showed first application complaints were abdominal distention, abdominal pain, and jaundice, by order frequency.

Wilson patients can apply to physician's office with neuropsychiatric complaints like speech disturbances, a decline in school success, dystonia, tremor and behavioral disturbances; although it's seen relatively less in childhood [5, 10, 11]. In our patients with neurological involvement, most common complaints were speech disturbances and dystonia.

In our study group, all four patients who are followed up with fulminant hepatic failure had jaundice and loss of consciousness, they had low serum ceruloplasmin levels, high 24-hour urinary copper excretion levels, higher AST levels than ALT levels and despite significant hyperbilirubinemia, serum ALP levels were normal [5, 12, 13].

Involvement of neurological system is mostly in ganglion basale but there can also be copper accumulation in pons, thalamus, mesencephalon, and cerebellum. In WD, the damage is limited to motor system and the sensory system is almost always preserved. Neurological findings include tremors ataxia, dysarthria, stiffness, oropharyngeal dysfunction such as dysphonia. Dysarthria and tremor are the most common neurological manifestations of WD and they will appear in the early stages [5, 7, 14, 15]. In this study, among limited number of neurologically affected patients (n=7, 17%), common findings were dysarthria, dystonia and behaviour disturbances.

In WD, besides hepatic and neurological findings, rarely, atypical findings related to other organ involvements can be the first physical findings. Other organ involvement signs are more often in patients older than 10 years old and 25% of patients can be affected in two or more different organ systems [1, 2, 8]. Glomerulonephritis, hemolytic anemia, osteoarthritis, arrhythmia, endocrine disorders and hyperpigmentation can be detected due to multisystemic involvement [5, 6, 8, 14]. There is no patient who is presented with other organ system symptoms, without liver and/or neurological involvement in our study group. Extrahepatic involvements apart from neurological disease of patients are shown in Table 6.

Similar to previous clinical studies [4, 9, 14, 16-18] in the pediatric age group, the majority of patients were hepatic form in our study. Nevertheless, in our study, neurological form of the disease has seen less than reported in the literature. It is thought that the reason of this, is most of our patients (68%) are younger than 10 years old. It is very well known that neurological form is less common in patients younger than 10 years old [4, 5, 19, 20].

Kayser-Fleischer ring occurs with copper accumulation in Descemet's membrane and it is characterized by green-brown color. Its presence is not pathognomonic because it can also be detected in chronic active hepatitis, primer biliary cirrhosis and intrahepatic cholestatic cirrhosis[1, 2, 14]. In the hepatic form of WD, it is detected in 50% of the patients and it's detected in almost every patient with neurological involvement [6, 8, 10]. In our study, similarly with literature [14, 16, 17] 56% of patients with hepatic involvement had K-F rings and it's detected in every patient with neurological involvement. K-F rings are more commonly detected with older age and it's unusual for patients younger than 6 years old. In our study group, the youngest patient who had K-F rings was 7 years old.

At the asymptomatic stage of the disease, the only sign of WD can be elevated liver enzymes. Therefore, in the differential diagnosis of asymptomatic transaminasemia, WD should be considered even if there aren't any classical findings of the disease [10, 21]. Serum aminotransferase levels characteristically mildly/moderately high. Generally, elevation in AST levels is more significant than the elevation in ALT levels but this finding is not sufficiently invariable to be diagnostic [5, 21-23]. Similarly in our study, the most common biochemical indicator of liver involvement is transaminase elevation. In the majority of patients (63%) AST levels were as twice as high compared to ALT levels.

In WD diagnosis, serum ceruloplasmin level is one of the first workups to be chosen. Co-occurrence of K-F rings existence and low serum ceruloplasmin levels is considered sufficient to establish the diagnosis of WD [4, 6, 8, 19]. Furthermore, solo serum ceruloplasmin levels can be detected as low in other diseases that affect liver functions besides WD, like malabsorption, malnutrition, severe liver failure, protein-losing enteropathy, in cases of hypoproteinemia like nephrotic syndrome, severe liver deficiency, Menkes disease, and hereditary aceruloplasminemia. Ceruloplasmin levels can also be high in active inflammatory and malignant conditions as acute phase reactant [5, 8, 18, 19]. Therefore, serum ceruloplasmin level shouldn't be used as only definitive diagnostic criteria and it should be supported by other diagnostic evaluation tests.

Two of 5 patients who had normal ceruloplasmin levels were siblings and they were diagnosed with sibling screening that is done because of another sibling who has WD. Three patients had parental consanguinity. In WD, even if serum ceruloplasmin levels are normal, especially if there is significant family history, patients should be investigated with other diagnostic methods. Approximately one-third of our patients had been diagnosed with family screening.

In WD, high levels of 24-hour urinary copper excretion are almost always present and its diagnostic value is significantly high. It can be incorrectly negative in presymptomatic stage of disease; however it can be incorrectly positive in patients who receive copper chelation treatment, primary biliary cirrhosis, chronic active hepatitis, autoimmune hepatitis, fulminant hepatitis, cholestatic cirrhosis, and nephrotic syndrome. Therefore, high urinary copper excretion level is not specific for WD. Previous studies have shown that urinary copper excretion may be less than 100 µg at the presentation in 16% to 23 % of patients [6]. In our study, all patients except one had high levels of 24-hour urinary copper excretion. 10 of them (25%) had basal 24-hour urinary copper excretion lower than 100 µg and penicillamine challenge resulted in an increase of copper excretion. The diagnostic performance of urinary copper excretion can be improved after penicillamine challenge and this technique is considered useful. The patient who had normal 24-hour urinary copper excretion was a presymptomatic patient who is diagnosed with sibling screening.

Measurement of quantitative copper amounts in liver tissue is considered as the best biochemical test for diagnosis [5, 8]. Normal liver copper concentration is below 50 µg/g dry liver weight. In patients and presymptomatic cases whose age older than 3 years old it's above 200-250 µg/g dry weight. In carriers, it can be measured as high as 150-200 µg/g but it does not exceed 250µg/g [5].

In present study, liver tissue could be measured copper dry weight of 18 patients. In 14 of theese higher than 250 µg/g, in four 120-250 µg/g dry weight was detected. All of the patients who have the dry liver copper weight lower than 250 µg/g had high levels of 24-hour urinary copper excretion, three of them had low serum ceruloplasmine levels, three of them had K-F rings, three of them had a family history of WD and all of them had parental consanguinity confirming the diagnosis.

Main histopathological liver findings in WD are steatosis, acute hepatitis, chronic active hepatitis, cirrhosis and fulminant hepatic necrosis. It is not helpful in in all cases, because histopathological findings of liver have a broad spectrum from hepatosteatosis to cirrhosis. The most common liver histopathological findings were cirrhosis (50%) and chronic active hepatitis (42.8%) followingly in our study.

In WD early diagnosis and treatment is lifesaving. Therefore, siblings of patients who are older than 3 years old should be screened [5, 8]. One third of our patients in our study group are diagnosed by sibling screening.

WD has a potential of causing progressive liver damage. Therefore, patients should be monitored for possible portal hypertension, with portal venous Doppler USG. Patients who have portal hypertension should be examined with upper gastrointestinal

system endoscopy for esophageal varices. Possible complications can be prevented by these evaluations [24]. In our study group, one-third of patients who were performed portal venous Doppler USG were diagnosed with portal hypertension. Half of the patients who were performed upper gastrointestinal system endoscopy were diagnosed with esophageal varices.

Main cranial imagining findings in WD are; dilatation of ventricles, cortical atrophy, atrophies of brainstem, pathological changes in ganglion basale and atrophy of posterior fossa. Abnormal imagine findings can be identified in patients with asymptomatic patients and only hepatic involvement. Correlation of these findings with clinical signs is not clear and their diagnostic value is poor [2, 7, 8, 25]. In our study, patients who were performed brain MRI, all patients with neurological involvement and 50% of patients without neurological involvement have pathological findings such as cerebral atrophy and symmetric paramagnetic matter accumulation in ganglion basale.

The goal of treatment in WD is dropping the amount of stored copper in tissues and prevention of reaccumulation. Low copper diet and zinc, chelation with ''D-penicillamine" or trientine is the classical recommended treatment [14, 26]. In asymptomatic patients who diagnosed early, zinc administration alone is sufficient [5, 14]. Although there are more side effects of chelation treatment, 'D-penicillamine" still is the first choice for standart treatment, because it is very well known and used for many years, so it is an easily accessible agent. Trientine is the alternative medicine for pregnant patients or patients who experienced serious side effects with "D-penicillamine" use [8, 27]. In present study, patients primarily received standard treatment. One of patients who received "D-penicillamine" treatment initially, experienced an allergic reaction and another one has dermopathy. Hence their medicine changed with trientine. Another patient has begun trientine treatment at first, cause of his sibling had a nephropathy history after "D-penicillamine" treatment. Although "D-penicillamine is the first choice in treatment, the hypersensitivity story of the patient should be considered.

Our study had several limitations. First, study design was retrospectively. Sample number was low and study reflects single centre results. The genetic analysis was not performed in patients and their families due to the lack of it in our center in the period which the study was conducted. Data collection from conventional archive files was difficult for reaching reliable information. There might be missing data about laboratory and radiologic investigatements.

## Conclusion

Especially in societies that consanguineous marriages are so common, WD should be considered in differential diagnosis of chronic liver diseases, prolonged hypertransaminasemia, and degenerative brain disorders of unknown origin. This report presents the clinical manifestations and laboratory findings of WD in children and underlines the importance of early diagnosis in positive clinical progress.

In our study, it has been shown that WD diagnosis and follow-up preserved the value of classical diagnostic methods and it has been shown that neuroimaging may be useful for early detection of neurological involvement even if neurological findings do not occur. This issue should be evaluated with larger patient series in multicentre prospective studies.

## Declaration of conflict of interest

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