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Correlation of the Brain Magnetic Resonance Imaging Findings with Biochemical Assays of the Pediatric Wilson Disease Patients : A Cohort Study

Pediatrik Wilson Hastalarının Biyokimyasal Testleri ile Beyin Manyetik Rezonans Görüntüleme Bulgularının Korelasyonu: Bir Kohort Çalışması

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ABSTRACT Objective: Wilson disease is a very rare disease of copper metabolism. The objective of this study is to describe the magnetic resonance imaging (MRI) findings and to correlate the laboratory values and brain MRI findings in Wilson disease. **Material and Methods:** A total of 55 patients with Wilson disease and 55 normal controls underwent conventional MRI and susceptibility weighted imaging (SWI). MRI findings and laboratory findings of the patients were analyzed retrospectively. The patients were examined in 3 groups according to T1-T2 signal intensity features and in 2 groups according to the dark paramagnetic signal in SWI. **Results:** A total of 25 (45.4%) patients had abnormal signal intensities either on T1 or T2 sequences. The globus pallidus and the putamen were the most commonly involved localizations on T1 and T2 sequences, respectively. Eighteen patients (32.7%) had dark paramagnetic signals in the basal ganglia in SWI. Ceruloplasmin levels were low in the 90% of the patients (n=50) and 24-hour urine copper levels were found high in the 94.5% of the patients (n=52). The mean ceruloplasmin level was lower and the mean urine copper level was higher in the group with high signal intensity on T2-weighted image and in the group with darc paramagnetic signal in SWI than others. **Conclusion:** Although biochemical tests are used in the diagnosis of Wilson disease, additional findings are needed to confirm the diagnosis. Brain MRI findings can be helpful in the diagnosis.

Keywords: Wilson disease (hepatolenticular degeneration); magnetic resonance imaging; ceruloplasmin

ÖZET Amaç: Wilson hastalığı çok nadir görülen bir bakır metabolizması hastalığıdır. Bu çalışmanın amacı, Wilson hastalığında manyetik rezonans görüntüleme (MRG) bulgularını tanımlamak ve laboratuvar değerleri ile beyin MRG bulgularını ilişkilendirmektir. **Gereç ve Yöntemler:** Çalışmamızda toplam 55 Wilson hastası ve 55 kontrol hastasının konvansiyonel MRG ve "susceptibility weighted imaging (SWI)" incelemeleri değerlendirildi. Hastaların MRG bulguları ve laboratuvar bulguları geriye dönük olarak incelendi. Hastalar T1-T2 ağırlıklı sekanslardaki sinyal özelliklerine göre 3 gruba ve SWI sekansındaki paramanyetik sinyal özelliğine göre 2 gruba ayrılarak incelendi. **Bulgular:** Toplam 25 (%45,4) hastada T1 veya T2 sekanslarında yüksek sinyal mevcuttu. Globus pallidus ve putamen, sırasıyla T1 ve T2 sekanslarda en sık tutulan bölgeydi. On sekiz hastada (%32,7) SWI görüntülerde bazal ganglionlarda paramanyetik sinyal izlendi. Hastaların %90'ında (n=50) serum seruloplazmin düzeyleri düşük iken, %94,5'inde (n=52) ise 24 saatlik idrar bakır düzeyleri yüksek bulundu. Serum seruloplazmin seviyelerinin ortalaması T2 ağırlıklı görüntülerde yüksek, sinyal intensitesi olan hastalarda ve SWI görüntülerde paramanyetik sinyal olan hastalarda daha düşük bulunurken; 24 saatlik idrar bakır seviyelerinin ortalaması T2 ağırlıklı görüntülerde yüksek, sinyal intensitesi olan hastalarda ve SWI görüntülerde paramanyetik sinyal olan hastalarda daha yüksek olarak bulundu. **Sonuç:** Wilson hastalığının tanısında biyokimyasal testler kullanılsa da erken dönemde tanıyı doğrulamak için ek bulgulara ihtiyaç vardır. Beyin MRG bulguları tanıda yardımcı olabilir.

Anahtar Kelimeler: Wilson hastalığı (hepatolentiküler dejenerasyon); manyetik rezonans görüntüleme; seruloplazmin

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Wilson disease (WD) is a very rare autosomal recessive disease of copper metabolism. Its prevalence is estimated to be 1 in 30-100,000.[1] The mutation of the ATP7B gene, which is involved in the transport of copper, is the reason of this disease. The copper, which can not be transported, first accumulates in the liver and in the brain in the later stages of the disease.[2]

In the diagnosis of the disease, the presence of the Kayser-Fleischer (KF) ring, decreased serum ceruloplasmin level in the blood and increased 24-hour urinary copper level in the urine are used.[3] Early diagnosis is very important for the prognosis of WD. The pathologies in the brain magnetic resonance imaging (MRI) may also be useful in the early diagnosis of the patients who especially first present with neurological symptoms. More than 90% of neurological-Wilson patients and ~ 40-70% of hepatic WD have pathology in brain MRI.[4] Also, susceptibility weighted imaging (SWI) has significant advantages over conventional MRI sequences in WD.[5]

Although there are studies on both conventional MRI sequences and SWI sequences about brain involvement of WD in the literature, there are very few studies involving only the pediatric age group patients. We aimed to describe the MRI findings in pediatric patients and to correlate the laboratory values and brain MRI findings in pediatric WD patients.

MATERIAL AND METHODS

The study was complied with the guidelines of the Health Insurance Portability and Accountability Act. Local institutional ethics committee approval was obtained (from: İnönü University Scientific Research and Publication Ethics Committee, date: 10.11.2020, no: 2020/1215).

An informed consent was taken from the parents of the patients and the study protocol was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

A total of 55 patients 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. MRI and laboratory findings of the patients were analyzed retrospectively. In Leipzig at 2001, a scoring system developed at the Eighth International Meeting on WD's. The diagnosis of WD was based on this scoring system in which a score >4 was considered reasonable for making a diagnosis of WD.[6] A data on genetic mutational analysis could not be provided. Detailed follow-up data were collected in relation to each patient. Clinically, the patients were defined as asymptomatic WD, acute-fulminant WD, chronic liver disease and neurological WD.

MR IMAGING

The 1.5 T Magnetom Avanto (Siemens, Erlangen, Germany) MR was used for MR images. All MR images were evaluated in terms of T1-T2 signal intensity by a pediatric radiologist with 4 years of experience. The patients were examined in 3 groups according to T1-T2 signal intensity features. In Group 1, MR images were normal. In Group 2, high signal intensity in the basal ganglia on T1-weighted image was observed. In Group 3, high signal intensity was observed on T2-weighted image. The high signal intensities on T2-weighted images were in the basal ganglia, white matter, midbrain, thalamus and hippocampus.

The following parameters were used for SWI: TR: 49 ms, TE: 40 ms, SNR: 1, number of slices= 80, slice thickness= 1.8 mm, flip angle: 15°. Since we did not use any special software, SWI images were visually evaluated by the same radiologist. The paramagnetic signal in SWI sequences was examined from SWI images, not from magnitude or filtered phase images. The patients were examined in 2 groups according to dark paramagnetic signal in SWI. In the SWI+ group, there was dark paramagnetic signal on SWI sequence. In the SWI- group, there was not dark paramagnetic signal on SWI sequence. A healthy control group of the same sex and age selected, free from any medical conditions. If the signal on the SWI-MRI in the patient group was dark compared to the control group, SWI was considered as pathological.

All MR images were obtained at the time of the diagnosis, before the initiation of the treatment.

STATISTICAL ANALYSIS

Statistical Package for the Social Sciences for Windows (SPSS Inc., Chicago) 21 software package was

used for statistical analysis. Study variables were presented as number (n) - percentage (%), mean±standard deviation. The normal distribution of variables was tested using the Kolmogorov-Smirnov test. Normally distributed parameters were evaluated by one-way analysis of variance (ANOVA) or Student's t-test; Kruskal-Wallis or Mann-Whitney U test was used for numerical variables that did not show normal distribution. Student's t-test, Mann-Whitney U test or chi-square tests were used to evaluate statistical significance.

RESULTS

In our study, there were 55 patients, 56% (n=31) of these were male and 44% (n=24) were female (n=24). The mean age of the patients was 11.8 years. There was a significant difference in the mean age between the 3 groups according to T1-T2 signal intensity features and between the SWI+ and SWI- groups ($p<0.01$) (Table 1). There was no significant difference between the groups in terms of gender ($p=0.8759$).

A total of 25 (45.4%) patients had abnormal signal intensities either on T1 or T2 sequences. Ten of these 25 patients (40%) had high signal intensities on T1 sequences in the basal ganglia and 15 patients (60%) had high signal intensities on T2 sequences (Figure 1, Figure 2). Eighteen patients (32.7%) had markedly dark paramagnetic signals in the globus pallidus, putamen or caudate nucleus in SWI (Figure 3). The demographic data of the patients according to the high signal intensity features on T1, T2 sequences were given in Table 1. The demographic data of the patients according to the dark paramagnetic signal intensity on the SWI sequences were given in Table 2.

The globus pallidus was the most commonly involved localization in the study. There were high signals in 10 (62.5%) patients on T1 sequences and high signals in 6 (37.5%) patients on T2 sequences in the globus pallidus. Putamen was the 2nd most common localization, and 70% (n=7) of putamen involvement were seen on T2 sequences and 30% (n=3) on T1 sequences. The involvements of the white matter, hippocampus, midbrain and thalamus were rare and all of which were seen on T2 sequences in 2, 1, 3, and 2 patients, respectively.

TABLE 1: Evaluation of the demographic data of the patients according to the high signal intensity features on T1, T2 sequences.

		Group 1 (n=30)	Group 2 (n=10)	Group 3 (n=15)
Mean age		10.21	11.18	14.16
Gender	Female (n=24)	14	5	5
	Male (n=31)	16	5	10
Presentation	Asymptomatic transaminase elevation (n=20)	17	2	1
	Acute fulminant WD (n=14)	9	2	3
	Chronic hepatitis (n=14)	4	6	4
	Neurological WD (n=7)	0	0	7
Kayser-Fleischer ring (n=20)		6	1	13
Involvement in				
MRI	Globus pallidus (n=16)	0	10	6
	Putamen (n=10)	0	3	7
	Caudate nucleus (n=7)	0	2	5
	White matter (n=2)	0	0	2
	Hippocampus (n=1)	0	0	1
	Midbrain (n=3)	0	0	3
	Thalamus (n=2)	0	0	2

WD: Wilson disease; MRI: Magnetic resonance imaging.
Group 1: Magnetic resonance images were normal.
Group 2: High signal intensity in the basal ganglia on T1-weighted image.
Group 3: High signal intensity on T2-weighted image.

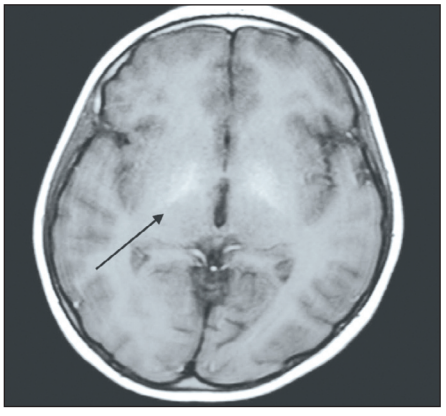

FIGURE 1: T1-weighted axial magnetic resonance images show bilateral increased signal intensity in the globus pallidus (arrows).

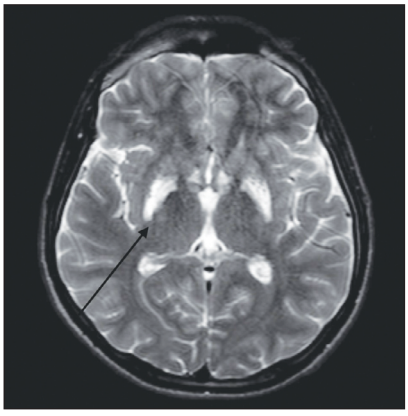

FIGURE 2: T2-weighted axial magnetic resonance image shows bilateral high signal intensity in the putamen (arrows).

There was a significant difference between 3 groups according to the clinical presentation of the patients ($p<0.05$). Brain involvement was significantly less common in patients with asymptomatic transaminase elevation ($p<0.001$). Pathologies on T1-T2 and SWI sequences were significantly more common in patients presenting with chronic hepatitis and neurological WD ($p<0.01$).

Twenty (36.3%) of the all patients had KF rings. Its detection was significantly higher in SWI+ group and in the group with high signal intensity on T2-weighted image compared to others ($p<0.001$).

Ceruloplasmin levels were low in 90% of the patients (n=50) and 24-hour urine copper levels were found high in 94.5% of the patients (n=52). The average of ceruloplasmin level and 24-hour urine copper level were given in Table 3. The serum

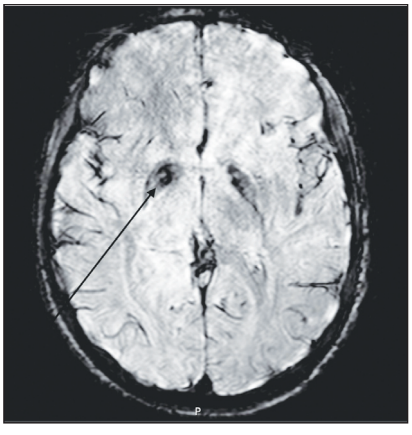

FIGURE 3: Susceptibility weighted imaging shows markedly dark paramagnetic signals in the globus pallidus in 11 years old boy with WD (arrows).

ceruloplasmin levels and 24-hour urine copper levels were not statistically significant between the groups according to T1-T2 signal intensity features and be-

TABLE 2: Evaluation of the demographic data of the patients according to the pathology on SWI sequence.

		SWI-	SWI+
Mean age		9.8	13.8
Gender	Female (n=24)	14	10
	Male (n=31)	15	16
Presentation	Asymptomatic transaminase elevation (n=20)	15	5
	Acute fulminant WD (n=14)	10	4
	Chronic hepatitis (n=14)	4	10
	Neurological WD (n=7)	0	7
Kayser-Fleisher ring (n=20)		5	15
Transplantation (n=14)		6	8

WD: Wilson disease; SWI: Susceptibility weighted imaging.
SWI-: There was not dark paramagnetic signal on SWI sequence.
SWI+: There was dark paramagnetic signal on SWI sequence.

TABLE 3: Evaluation of the mean of the ceruloplasmin level and the mean of the 24 hour urine copper level between the groups.

	Group 1 (n=30)	Group 2 (n=10)	Group 3 (n=15)
Ceruloplasmine level (mg/L)	116.2±77	108.4±86	77.2±54
24-hour urine copper level (µg/24 h)	556.4±772.8	603.25±1068.09	1046.8±1118.3

Group 1: Magnetic resonance images were normal.
Group 2: High signal intensity in the basal ganglia on T1-weighted image.
Group 3: High signal intensity on T2-weighted image.

tween SWI+ and SWI- group (p>0.01). But the mean ceruloplasmin level was lower and the mean urine copper level was higher in the group with high signal intensity on T2-weighted image and in the SWI+ group.

DISCUSSION

Pathological changes in the central nervous system seen in WD is associated with the increase of copper in the tissue. Although toxic copper is present everywhere, pathological findings seen on MRI is primarily limited to the basal ganglia, thalamus, and brainstem.[7]

The average age of the patients was 11.8 years, the youngest patient was 4 years old and 56% of the patients were male in our study. WD is known to be more common in men than women.[7] Although the disease had most frequently reported to be seen at the age of 10-30 in the literature, the youngest patient reported was 3 years old.[7] We observed a significant difference between the groups in terms of the average age. The average age was higher in the group with high signal intensity on T2-weighted image and in the SWI+ group. For copper to be stored in the brain, the liver had to be saturated with copper.[2] This may explain the difference of the average age in this study.

Of all patients, 36% and of neurological WD patients, 100% had KF rings in our study. This rate has been reported as 38-77% and 85-90% in previous studies.[8] We found that the probability of having a pathology in brain MRI in patients with KF ring was found 7.84 times higher than in other patients. This also shows that brain MRI can be helpful in the diagnosis of the pediatric WD patients with KF rings like adults.

The most common pathology of WD is symmetrical increased intensities on T2 sequence in the basal ganglia in brain MRI.[9] The study having the largest number of patients in which WD's brain MRI findings were discussed in the literature was the study of Yu et al., consisting of patients aged 5-42 years.[10] In this study, similar to many other studies, putamen was reported as the most commonly affected area in the brain. In contrast to these studies, globus pallidus was the most affected area in our study. In another study including 50 pediatric patients, the most common pathology in the brain was high signal intensities in the bilateral globus pallidus on T1 sequence, followed by bilateral putamen signal intensities on T2 sequence.[10] In addition to the basal ganglia, white matter involvement has also been reported in WD.[7,11,12] The white matter intensity was seen only in 2 patients in our study. Although there are studies on corpus callosum involvement in WD in recent years, no corpus callosum involvement was found in our study.[13] All these findings were related to the fact that the ages of patients were lower than 18 in this study. White matter and corpus callosum involvement been reported in recent studies were in adults.[7,13]

In addition to transporting copper, ceruloplasmin is important in iron transporting across the cell. Also the deficiency of ceruloplasmin can cause iron accumulation in the brain in addition to copper in WD.[14] Ceruloplasmin levels lower than 120 mg/L and 24-hour urine-copper levels higher than 40 µg are important for the diagnosis in WD.[15] Decreased ceruloplasmin levels were 91% in our study, similar to the ratio of 90-100% reported in the literature for WD patients.[16] Increased 24-hour urine-copper levels were 94.5% in our study while normal urine copper levels were reported to be 16-23% in the literature.[17,18] Although the levels of serum ceruloplasmin levels and urine copper levels were not statistically significant among the groups, no pathology was observed in MRI in any patients with normal serum ceruloplasmin or urine copper levels. Also the

mean ceruloplasmin levels of the patients with pathologic MRI were lower than in patients with normal MRI. These results suggest that if MRI findings are evaluated together with biochemical tests, the diagnosis of the WD can be easier.

SWI uses the magnetic sensitivity differences of various tissues and it has been used a lot in recent years.[14] It shows paramagnetic signals better than other MRI sequences.[14] Mineral deposits in the brain can be seen as hypointensity on SWI sequences.[19] There are studies that quantitatively evaluate the mineral accumulation in the basal ganglia with the SWI method and they have shown that there is a negative correlation between SWI signal change and mineral accumulation.[20,5] Copper and copper (I) compounds are diamagnetic, but copper (II) compounds are paramagnetic. In the study reported by Zhou et al. with 30 WD patients and 20 control groups, the values of corrected phase (CP) were measured from SW images.[21] They found that the CP values of basal ganglia of WD were lower than control groups.[22] Similarly, in other study involving adult patients, the mean CP values were found low in WD patients.[22] In recent years, measurements have been made in the basal ganglia and the brain stem in WD patients with the quantitative susceptibility mapping (QSM) method. There are only a few studies for pediatric patients with QSM method about WD.[23,24] In the study of Selim et al., it was found that all measurements in the basal ganglion and brain system were different in patients with neurological WD from the control group.[23] Also, they claimed that the QSM method can reveal susceptibility differences even if there is no signal changes on T1-T2 weighted images.[23] Saracoglu et al. observed increased susceptibility values in non-neurological WD, although there were not pathological intensities in their conventional MR images.[24] Paramagnetic dark signal was observed in 18 patients (32.7%) on the SWI sequence in our study. All patients with neurological WD had paramagnetic dark signals on SWI sequence. In addition, 7 patients (12.7%) had paramagnetic dark signals in SWI, although there was no signal change on their T1-T2 weighted images. In these patients, pathology may be detected in SWI before neurological symptoms develop. These results showed that qualitative evaluations in SWI can also be beneficial, although not as quantitative parameters.

There were few limitations in our study. This study was retrospective and the evaluation on SWI was not quantitative. Additionally, a small number of patients were examined, particularly in the neurologic WD group.

CONCLUSION

Although biochemical tests are used in the diagnosis of WD, additional findings are needed to confirm the early diagnosis. Considering the age of the onset of the disease, sometimes radiologists may be among the first to see the patient while the diagnosis has not been made yet. Therefore, the MRI findings of this disease should be well defined in childhood as in adults. Also SWI sequences have significant advantages over conventional MRI sequences in WD.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Şükrü Güngör, Ahmet Sığırcı, Güleç Mert Doğan;* ***Design:*** *Gökalp Okut, Aslınur Cengiz;* ***Control/Supervision:*** *Şükrü Güngör, Ahmet Sığırcı, Sezai Yılmaz;* ***Data Collection and/or Processing:*** *Güleç Mert Doğan, Şükrü Güngör, Aslınur Cengiz, Gökalp Okut;* ***Analysis and/or Interpretation:*** *Sait Murat Doğan, Fatma İlknur Varol, Güleç Mert Doğan;* ***Literature Review:*** *Güleç Mert Doğan, Fatma İlknur Varol, Şükrü Güngör, Gökalp Okut, Aslınur Cengiz;* ***Writing the Article:*** *Güleç Mert Doğan, Şükrü Güngör;* ***Critical Review:*** *Ahmet Sığırcı, Sezai Yılmaz, Sait Murat Doğan.*

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