Reversible lesions in the brain parenchyma in Wilson’s disease confirmed by magnetic resonance imaging: earlier administration of chelating therapy can reduce the damage to the brain

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Abstract
The aim of this study was to evaluate the resolution of brain lesions in patients with Wilson’s disease during the long-term chelating therapy using magnetic resonance imaging and a possible significance of the time latency between the initial symptoms of the disease and the introduction of this therapy. Initial magnetic resonance examination was performed in 37 patients with proven neurological form of Wilson’s disease with cerebellar, parkinsonian and dystonic presentation. Magnetic resonance reexamination was done 5.7 ± 1.3 years later in 14 patients. Patients were divided into: group A, where chelating therapy was initiated < 24 months from the first symptoms and group B, where the therapy started ≥ 24 months after the initial symptoms. Symmetry of the lesions was seen in 100% of patients. There was a significant difference between groups A and B regarding complete resolution of brain stem and putaminal lesions (P = 0.005 and P = 0.024, respectively). If the correct diagnosis and adequate treatment are not established less than 24 months after onset of the symptoms, irreversible lesions in the brain parenchyma could be expected. Signal abnormalities on magnetic resonance imaging might therefore, at least in the early stages, represent reversible myelinolysis or cytotoxic edema associated with copper toxicity.

Key Words: nerve regeneration; Wilson’s disease; diagnostic imaging; chelating therapy; magnetic resonance imaging; delayed diagnosis; metabolic disorders; copper toxicity; hepatic encephalopathy; pontine myelinolysis; cirrhosis; neural regeneration

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Introduction
Wilson’s disease (WD) is a rare and treatable autosomal recessive disease with deficient biliary excretion of copper (Wilson, 1912). The initial symptoms of patients with WD are usually due to either cerebral involvement or liver failure (Ala et al., 2007; Hancu et al., 2011).

If treatment begins on time, especially in the asymptomatic phase of the disease, the occurrence of clinical signs can be prevented, and patients present with normal life expectancy (Walsha, 1993). Complete or partial remission of already developed neurological signs during chelating therapy can be expected in 20% and 60% of patients, respectively (Stremmel et al., 1989; Walche et al., 1993). Potential regression of increased signal intensity (SI) on T2-weighted images in the basal ganglia, brain stem or thalamus may document the effect of chelating therapy in patients with WD on magnetic resonance imaging (MRI).

In this study, we evaluated the resolution of brain lesions on MRI during the long-term chelating therapy, associated with the time latency in establishing the correct diagnosis of WD. To the best of our knowledge, no prior studies evaluating the presence of irreversible changes in the brain parenchyma, associated with late diagnosis of WD and treatment delay, are available in the literature.

Subjects and Methods
Patients
Thirty-seven patients with WD, 24 males and 13 females, underwent initial brain 1.5-T MRI (Table 1). The disease occurs at a wide age range of 12–41 years, with a mean of 28 years. The diagnosis of WD was established by the previously described criteria (Walsha, 1988). The reconfirmation of WD diagnosis was performed using Leipzig scoring system (Ferenci et al., 2003). Correlation with initial clinical presentation was performed.

Table 1
<table>
<thead>
<tr>
<th>Group</th>
<th>Therapy Duration (months)</th>
<th>Symmetry</th>
<th>Complete Resolution</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>&lt; 24</td>
<td>Yes</td>
<td>Yes</td>
<td>0.005</td>
</tr>
<tr>
<td>B</td>
<td>≥ 24</td>
<td>Yes</td>
<td>No</td>
<td>0.024</td>
</tr>
</tbody>
</table>

Note: Table 1: Comparison of group A (early therapy) and group B (late therapy) regarding complete resolution of brain lesions.
Magnetic resonance imaging
The following pulse sequences were used: (a) sagittal flash2D (FL2D) T1-weighted (T1W) matrix = 192 × 256, field of view = 240 × 240 mm², repetition time (TR) = 266 ms, echo time (TE) = 6 ms, parallel imaging reduction factor (SENSE factor) = 2, slice thickness of 5 mm and slice gap = 0.5 mm; (b) axial turbo spin echo (TSE) – double echo (T2W) matrix = 192 × 256, field of view = 230 × 230 mm², TR = 3,300 ms, TE = 93 ms, parallel imaging reduction factor (SENSE factor) = 1, slice thickness of 6 mm and slice gap = 0.6 mm.

MR reexamination
Follow-up MRI study was performed in 14 patients, 5.71 ± 1.29 years after initial scanning (median 5.71). They underwent follow-up after the introduction of D-penicillamine treatment at the Department for Movement Disorders of our institution between 1996 and 2005 (Tables 2, 3). The time latency between the appearance of the first symptoms and signs and the initiation of the chelation therapy was recorded for each patient. In the course of the follow-up, all the patients were continuously on optimized D-penicillamine treatment. This study was approved by the Ethical Committee of our institution. All the patients signed informed consent for their participation in the study.

Patients were divided into two groups: Group A (five patients who initiated chelating therapy < 24 months [range: 6–18 months] from the first symptoms of WD), and group B (nine patients whose therapy started ≥ 24 months [range 24–60 months] after the initial symptoms of the disease).

Data analysis
Signal abnormalities on the follow-up brain MRI study were defined as: (a) complete resolution; (b) partial resolution; (c) stable status/progression. Although the low SI in the globus pallidus, substantia nigra and nucleus ruber related to paramagnetic deposition is usually prominent, these abnormalities were not considered in this study because such SI may be present in the process of normal aging.

The determination of neuroanatomical localization, symmetry, volume of the lesions and the presence of atrophy were rated by two experienced radiologists (Duško Kozić and Robert Semnic, University of Novi Sad Faculty of Medicine, Novi Sad, Serbia) who were blinded to clinical data. Intra and inter-rater reliability for rating and monitoring brain abnormalities between two readers were determined using two-way mixed effect model (absolute agreement) intra-class correlation coefficients (ICC) from available scans. The ICC was considered as poor when it was below 0.4, fair to good between 0.4 and 0.75, and excellent for values above 0.75.

The data are presented as the mean ± SD or as percentages. Differences in categorical variables were assessed by Fisher exact test. The significance level for the analysis was set at P < 0.05.

Results

Image analysis in initial MR study
The lesions were 100% symmetric in the putamina, caudate nuclei, midbrain and pontine tegmentum. Putamen was affected in 78% of patients, but in 100% of those with dystonic clinical presentation (Table 1). Correlation between putaminal affection and dystonic presentation in comparison to cerebellar manifestation of the disease was statistically significant (P = 0.035). The ICC was excellent.

Image analysis in follow-up MR study
Follow-up MR examination (demographic and clinical characteristics of patients presented in Table 2) revealed complete or partial resolution of the MRI lesions after D-penicillamine treatment in a substantial number of patients with WD in the putamen, caudate nuclei, thalamus, and brainstem (Figure 1). These changes were particularly prominent in mesencephalon and pons and to a lesser degree in basal ganglia. In all three patients with complete resolution, the putaminal lesions were described only on the PDW sequence on initial scanning and they all belong to the group A (patients with introduction of D-penicillamine less than 24 months of the disease onset). In two patients from the group B (patients with delayed onset of such therapy), end-stage neurodegenerative changes were observed in the putaminal periphery (Figure 1A, D). Also, in two patients, focal deposition of paramagnetic substance in putamina and caudate nuclei was found.

Statistical analysis
Although statistical analysis was limited by the small number of patients in different subgroups (Table 3), Fisher’s exact test revealed significant difference in distribution of patients with complete or partial resolution, as well as those without change of putaminal lesions, between groups A and B (P = 0.024). There was a significant difference between groups A and B regarding complete resolution of brain stem lesions (P = 0.005).

Discussion
Numerous studies regarding the clinical course of WD disease are available in literature. Compared to previous studies, our results provide new contribution regarding the relationship between complete regression of brain lesions and delay in establishment of correct diagnosis.

Sinha et al. (2007) performed serial follow-up MR scans in 50 patients with WD and revealed an improvement in MRI parameters in 35 patients, with no significant changes in 10, worsening in 4 and a mixture of resolving and evolving changes in 1. However, no correlation between treatment delay and imaging confirmation of lesions regression had been performed in that study. Eighteen patients with neurological WD underwent pretreatment and posttreatment brain MRI scans in the study of da Costa Mdo et al. (2009) in order to evaluate the range of abnormalities and the evolution of lesions in WD during different periods, up to 11 years after the beginning of treatment. Neuroimaging pattern of evolution was more favorable for the group of patients that received exclusively D-penicillamin, compared to zinc. Supratentorial white matter is usually spared in WD in the majority of MRI studies. But, in one of more recent studies, involvement of corpus callosum had been reported (Trocello et al., 2011).

Regardless of the type of clinical presentation, most patients with WD will have at least subclinical degree of liver disease. However, the exact factors that induce relatively sharp differentiation of clinical presentation remain un-
Table 1 Frequency of brain lesions detected with magnetic resonance imaging examination in 37 patients with Wilson’s disease

<table>
<thead>
<tr>
<th>Lesion location</th>
<th>Subgroups according to clinical presentation of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total number of patients ( (n = 37) )</td>
</tr>
<tr>
<td><strong>Basal ganglia</strong></td>
<td></td>
</tr>
<tr>
<td>Putamen</td>
<td>29 (78%)</td>
</tr>
<tr>
<td>Nucleus caudatus</td>
<td>14 (38%)</td>
</tr>
<tr>
<td>Globus pallidus</td>
<td>21 (58%)</td>
</tr>
<tr>
<td>Thalamus</td>
<td>11 (30%)</td>
</tr>
<tr>
<td>Claustrum</td>
<td>2 (5%)</td>
</tr>
<tr>
<td><strong>Brain stem</strong></td>
<td></td>
</tr>
<tr>
<td>Mesencephalon (midbrain)</td>
<td>23 (62%)</td>
</tr>
<tr>
<td>Pons</td>
<td>20 (54%)</td>
</tr>
<tr>
<td>Base</td>
<td>18 (49%)</td>
</tr>
<tr>
<td>Tegmentum</td>
<td>16 (41%)</td>
</tr>
</tbody>
</table>

Bold values denote statistical significance.

Table 3 Number of patients with observed changes on magnetic resonance imaging (MRI) in specific brain regions between initial and follow-up MR studies

<table>
<thead>
<tr>
<th>Group A ( (n = 5) )</th>
<th>Group B ( (n = 9) )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion location</td>
<td>Total number with lesion</td>
<td>Complete resolution</td>
</tr>
<tr>
<td>Putamen</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Thalamus</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Brain stem (all involved area)</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Midbrain</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Pons (basis)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Pons (periaqueductal gray matter)</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Bold values denote statistical significance. Group A: There were five patients who initiated chelating therapy < 24 months from the first symptoms of Wilson’s disease (5–18 months); group B: there were nine patients whose therapy started ≥ 24 months after the initial symptoms of the disease.

Known (Brewer and Yuzbasiyan-Gurkan, 1992). It is known that severity of clinical course and therapeutic outcome in patients with neurologic form of WD depend significantly on early diagnosis (Prashanth et al. 2004; Brewer, 1995). In the study of Hu et al. (2001), only 30% of 1,011 patients with hepatolenticular degeneration were correctly diagnosed within 3 months after onset and the positive effect of treatment was significantly better in the group of patients with early diagnosis. In the study of Prashanth et al. (2004), the errors in establishing the diagnosis of WD were found in 62.5% of patients, with a mean (SD) delay of 2 years (0.08 – 30 years). The mean delay in the study of Walshe and Yealland (1993) was 12.8 months, while in the study of Miranda et al. (1995), it was 14 months. Pellecchia et al. (2003) searched 30 patients with WD between years 1970 and 2000 and found that the mean delay to diagnosis was 5.9 ± 5.7 years. These results suggest that WD was significantly less frequently included in differential diagnosis three decades ago, probably due to less reliable determination of copper and ceruloplasmin levels, limited availability of neuroimaging studies and decreased sensitivity for architectural liver changes on ultrasound examination. Aisen et al. (1985) reported no significant interval change of follow-up MRIs in five patients, probably because their patients had been on D-penicillamine therapy for several years and the follow-up period (4–8 months) was too short for changes to occur. According to Yuzbasiyan-Gurkan et al. (1992), neurological patients started to show clinical improvement 5–6 months after initiation of anticopper therapy and continued to improve over the succeeding 18 months.

Our study found complete or partial resolution of MRI lesions in a substantial number of patients with WD during 5.7 ± 1.3 years of D-penicillamine treatment (Table 3). These data are concordant with the studies describing that neuroimaging abnormalities, both on CT and MRI, may improve on D-penicillamine, trientine hydrochloride - trien (Williams and Walshe, 1981; Nazer et al., 1993; Thuomas et al., 1993; Roh et al., 1994; King et al., 1996; Takahashi et al., 1996) or zinc treatment, as a monotherapy or in combination with D-penicillamine (Prayer et al. 1990; Heckmann et al. 1994; Huang and Chu, 1996; Pellecchia et al. 2003). Improvement was also observed in patients after liver transplantation (Stracciar et al. 2000). Besides its effects on the brain tissue, D-penicillamine treatment during 3-year follow-up also improved laparoscopic and histological findings of the liver in one patient with WD (Sakaida et al., 2005). Complete regres-
Table 2 Demographic and clinical characteristics of patients with Wilson’s disease

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Data as presented</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>14</td>
</tr>
<tr>
<td>Female/male ratio</td>
<td>5/9</td>
</tr>
<tr>
<td>Age at the onset of Wilson’s disease</td>
<td>27.7±8.6 (11–42)</td>
</tr>
<tr>
<td>Duration of the disease</td>
<td>11.6±6.8 (6–32)</td>
</tr>
<tr>
<td>Duration of D-penicillamine treatment</td>
<td>9.4±6.3 (3–29)</td>
</tr>
<tr>
<td>Latency from the first symptoms/signs to the initiation of the treatment</td>
<td>28.3±16.2 (6–60)</td>
</tr>
<tr>
<td>Daily dose of D-penicillamine</td>
<td>1,027±285 (500–1,500)</td>
</tr>
</tbody>
</table>

*Data presented as the mean ± SD, with ranges in parenthesis.

sion of liver nodules in a patient with WD after D-penicillamine treatment has been shown (Kozic et al., 2006).

Published MRI studies in WD, including our own, have shown a number of symmetric abnormalities, including: (a) high SI on T2W images of the basal ganglia, brainstem, cerebellum, peduncles, and supratentorial white matter (Starosta-Rubinstein et al., 1987; King et al., 1996; van Wassenaer-van Hall et al., 1996; Svetel et al., 2001); (b) low SI on T2W images of the globus pallidus, substantianigra, red nucleus and corpus striatum (van Wassenaer-van Hall et al., 1996; Braffman, 2000); (c) high SI on T1W images of the globus pallidus in patients with portosystemic shunt (van Wassenaer-van Hall et al., 1996; Saatci et al., 1997); and (d) putaminal PDW signal elevation with neither T1W nor long echo T2W abnormalities (Kozic et al., 2003).

The high SI on T2W images of the basal ganglia may represent edema, gliosis, necrosis and cystic degeneration, while high SI of the white matter is most compatible with degeneration and spongy or cystic disintegration (Sener, 1993; van Wassenaer-van Hall et al. 1996). Gliosis, cystic degeneration or disintegration and necrosis represent histologically irreversible end-stage abnormalities of WD (Harper et al., 1992; Kim et al., 2006). In our study, however, not only brain stem lesions, but also putaminal and thalamic lesions, showed frequently total or marked resolution during the long course of chelating therapy, even in patients with longer delay to correct diagnosis. Signal abnormalities on MRI might therefore, at least in the early stages, represent reversible myelinolysis or cytotoxic edema associated with copper toxicity.

The reversibility of MRI changes in this study was particularly impressive in brainstem structures, while the putaminal lesions were more resistant to D-penicillamine, especially in patients with later introduction of the treatment (Table 3, Figure 1). Complete or almost complete resolution of the high SI lesions in the brainstem occurred even in patients with delayed initiation of such therapy (group B). In the follow-up study of 16 patients with neurologically symptomatic WD, Roh et al. (1994) found that high SI lesions in the thalami or the brainstem either disappeared or regressed more extensively and more rapidly than those in the basal ganglia. In our study, partial reversion of T2W/PDW putaminal lesions was detected even in patients from the group B. Sener (2003a, 2004, 1993) found restricted diffusion signal in basal ganglia in the initial stage of WD, followed by inverted restricted diffusion sign in the later course of the disease.

Figure 1 Effect of 24-month-long treatment delay on irreversible changes in the brain parenchyma in a 37-year-old woman with neurologic form of Wilson’s disease.

Initial (A–C) and follow-up MR (4.5 years later) images of the brain (D–F) in the patient. 24-month-long treatment delay resulted in marked resolution of the thalamic and brain stem lesions (long arrows) but the presence of irreversible, end-stage degenerative changes in the putamina (short arrows).

Such pattern of the symmetric T2W/PDW signal elevation is indistinguishable from pontine and extrapontine myelinolysis in different toxic and metabolic disorders (Sener, 2003b, 2004; Kizkin et al., 2004).

Recently, Kozic et al. (2012) found that significant hepato-splenomegaly, macronodular liver cirrhosis and peritoneal effusion were evident in 44% of patients with neurologic form of WD in whom the correct diagnosis was established after 2 or more years, while normal finding on MRI was evident in the group of patients where treatment was initiated in the early course of the disease.

Although our study included rather small number of patients with this rare disease, data suggested that reversibility might depend on a time lag between symptoms and signs onset and the initiation of D-penicillamine therapy. The significance of complete disappearance of high SI lesions in the putamen, mesencephalon and pons was higher among patients who started the treatment less than 24 months from the disease onset.

The main limitation of the study is the fact that only 14/37 patients were available for follow-up brain MR examination. However, the benefit of early diagnosis was statistically proven.

In conclusion, we confirmed that in patients with WD, some of the brain MRI lesions may be reversible during the long term D-penicillamine therapy. Moreover, our data suggest that likelihood of such resolution may be higher if such treatment starts earlier in the course of the disease. In order to prevent development of irreversible lesions of the brain parenchyma resistant on decoppering treatment, it is highly recommended to consider WD in differential diagnosis in any unexplained liver disease and/or progressive cerebellar, parkinsonian and dystonic symptoms, especially in younger patients. If the correct diagnosis and adequate treatment are not established within 18 months from the onset of symptoms, permanent clinical impairment associated with irreversible lesions within the brain parenchyma could be expected.
Author contributions: Kozić DB designed the study and analyzed experimental data. Petrović I and Svetel M performed the study and participated in data acquisition. Pekmezović T was responsible for data acquisition and data analysis. Ragaji A drafted the manuscript. Koštić VS edited the manuscript. All authors approved the final version of this article.

Conflicts of interest: None declared.

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