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ORIGINAL ARTICLE

Brain magnetic resonance imaging and severity of neurological disease in Wilson's disease — the neuroradiological correlations

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Abstract

Introduction Wilson's disease (WD) is a genetic disorder with pathological copper accumulation and associated clinical symptoms in various organs, particularly the liver and brain. Neurological disease is assessed with the clinical Unified Wilson's Disease Rating Scale (UWDRS). There is a lack of quantitative objective markers evaluating brain involvement. Recently, a semiquantitative brain magnetic resonance imaging (MRI) scale has been proposed, which combines acute toxicity and chronic damage measures into a total score. The relationship between MRI brain pathology and the MRI scale with disease form and neurological severity was studied in a large cohort.

Methods We retrospectively assessed 100 newly diagnosed treatment-naïve patients with WD with respect to brain MRI pathology and MRI scores (acute toxicity, chronic damage, and total) and analyzed the relationship with disease form and UWDRS part II (functional impairment) and part III (neurological deficits) scores.

Results Most patients had the neurological form of WD (55%) followed by hepatic (31%) and presymptomatic (14%). MRI examination revealed WD-typical abnormalities in 56% of patients, with higher pathology rates in neurological cases (83%) than in hepatic (29%) and presymptomatic (7%) cases. UWDRS part II and III scores correlated with the MRI acute toxicity score ($r=0.55$ and 0.55, respectively), chronic damage score ($r=0.39$ and 0.45), and total score (0.45 and 0.52) (all $P<0.01$).

Conclusions Brain MRI changes may be present even in patients without neurological symptoms, although not frequently. The semiquantitative MRI scale correlated with the UWDRS and appears to be a complementary tool for severity of brain injury assessment in WD patients.

Keywords Wilson's disease · Magnetic resonance imaging · Clinical scales · Neuroradiology

Introduction

Wilson's disease (WD) is a genetic disorder with pathological copper accumulation in various organs (mainly the liver and brain) and clinical symptoms resulting from damage to the affected tissues [1, 2]. WD is potentially treatable with anti-copper drugs, including chelators or zinc salts, as well as symptomatic therapy [1–9]. Most correctly treated patients respond well, with improvement of liver function tests and neurological deficits. However, some neurological symptoms persist or even deteriorate over time [10, 11]. The course of clinical deterioration is not predictable, and hence, it is very important to detect WD early and initiate the correct treatment [1, 10, 11]. In addition to the standard methods of copper metabolism assessment during diagnosis and treatment, there is a need to establish objective tools to further assess the severity of disease and help verify treatment efficacy (or failure) [4, 8].

The most common form of WD, which occurs with hepatic manifestations, is characterized using detailed liver examination (e.g., using imaging, liver function or secretory tests, liver biopsy, and other more advanced different laboratory results) [1, 2, 12–14]. Another common form of WD, the neurological form, is usually assessed with different tools [1, 5, 6, 13, 15], including the Unified Wilson's Disease Rating Scale (UWDRS) or the Global Assessment Scale for WD (GAS) [1, 15] and routine brain magnetic resonance

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imaging (MRI) [1–4, 15]. In a pilot study, Dusek et al. developed and validated a brain MRI severity scale, which was found to be a reliable instrument that allows semiquantitative assessment of neurological WD [16]. The aim of the current study was to verify if this MRI scale is complementary to clinical neurological WD assessment using the UWDRS in a large group of newly diagnosed WD patients to determine if the MRI scale could serve as an additional marker of brain involvement in WD.

Materials and methods

The study was approved by the Bioethical Committee of the Institute of Psychiatry and Neurology, Warsaw. This retrospective study included consecutive, newly diagnosed drug-naïve patients who were hospitalized between 1 June 2010 and 1 June 2017 in the Second Department of Neurology, Institute of Psychiatry and Neurology, Warsaw, Poland.

WD diagnosis was performed based on clinical signs and symptoms, serum and urine copper metabolism abnormalities, the presence of Kayser–Fleischer rings, and genetic examination according to international criteria [2]. Laboratory assessments of copper metabolism were performed in the same laboratory using methods described previously [3]. Patients were classified as having the hepatic or neurological form of WD, according to the presence of hepatic and/or neurologic signs and symptoms at presentation, or classified as presymptomatic cases, as described previously [2]. Symptomatic WD patients with no neurological symptoms were classified as hepatic.

All patients with neurological manifestation were assessed by a trained neurologist using UWDRS part I (consciousness), part II (activities of daily living), and part III (neurological deficits) [15]. Brain MRI was performed at the time of diagnosis using the Philips Achieva 1.5-T system (Philips, Healthcare, Eindhoven, the Netherlands) using a standard protocol as described previously [16]. The MRI protocol included the following routine images: T1 weighted (SE, $TR = 596$ ms, $TE = 15$ ms), T2 weighted (SE, $TR = 6783$ ms, $TE = 140$ ms), FLAIR ($TR = 11{,}000$ ms, $TE = 140$ ms), T2* weighted ($TR = 693$ ms, $TE = 23$ ms), and VEN_BOLD ($TR = 49.7$ ms, $TE = 34.7$ ms). All images covered the entire brain and were acquired in the axial plane. For atrophy assessment, T1-weighted images were also acquired perpendicular to the dorsal edge of the brain [16].

Blinded to the patients' clinical information, all images were further analyzed retrospectively by an experienced neuroradiologist (B R-O) according to overall pathology typical for WD (0, not present; 1, present) (as described previously [17]) and according to the semiquantitative MRI scale [16]. The semiquantitative scale includes three types of neuroradiological abnormalities: T2/FLAIR hyperintensities, T2/T2*/susceptibility-weighted imaging (SWI) hypointensities, and atrophy scored in T1 [16] (Fig. 1). The acute toxicity score is calculated as the sum of scores of T2/FLAIR hyperintensities in the caudate nucleus, thalamus, putamen, mesencephalon, pons, or other areas (scored from 0 [none] to 2 [severe] for each, with a total score range of 0–12 points). This score reflects potentially reversible acute brain MRI lesions, resulting from edema, demyelination, and gliosis.

The chronic damage score reflects the sum of T2/T2*/SWI hypointensities assessed in the putamen, globus pallidus, thalamus, caudate nucleus, and dentate nucleus (scored from 0 [none] to 1 [severe] for each, with a total score range of 0–5 points) [16]. The atrophy score is the sum of subscores assessed on T1 sequences describing atrophy of the cortical, central, midbrain, and cerebellar regions (scored from 0 [none] to 2 [severe] for each, with a total score range of 0–8 points). Together, the chronic damage score and the atrophy score represent irreversible total chronic damage, resulting from iron accumulation, necrosis, and degeneration.

The relationship between the semiquantitative MRI scale and the form of WD (hepatic, neurological, or presymptomatic) was investigated [17]. Correlations between the semiquantitative MRI scale and the severity of neurological disease scored by UWDRS (part II and III in patients with neurological WD) and also copper metabolism parameters (serum ceruloplasmin levels, serum copper levels, and urinary copper excretion) were performed in the total group of WD patients. The concentration of non-ceruloplasmin-bound copper (*NCC*) was calculated according to a standard formula: *NCC* (μg/dl) = total serum copper (μg/dl) − 3.15 × serum ceruloplasmin (mg/dl) [1].

Statistical analysis

Calculations were carried out using Statistica v.10 (StatSoft Inc. 2011, Tulsa, OK, USA). Data are presented as a number with percentage or mean with range and standard deviation. Comparisons were made using the two-tailed Fisher's exact test or the Mann–Whitney *U* test, as appropriate. Analysis of the correlations between the brain MRI semiquantitative scale (acute toxicity score, chronic damage score, and total MRI score) and the severity of neurological disease scored in UWDRS and also copper metabolism parameters was performed using Spearman's rank correlation coefficient. We considered $P < 0.05$ to indicate significance.

Results

Demographic data as well as the initial clinical form of WD, disease severity scored by UWDRS parts II and III, and copper metabolism parameters of the 100 analyzed patients

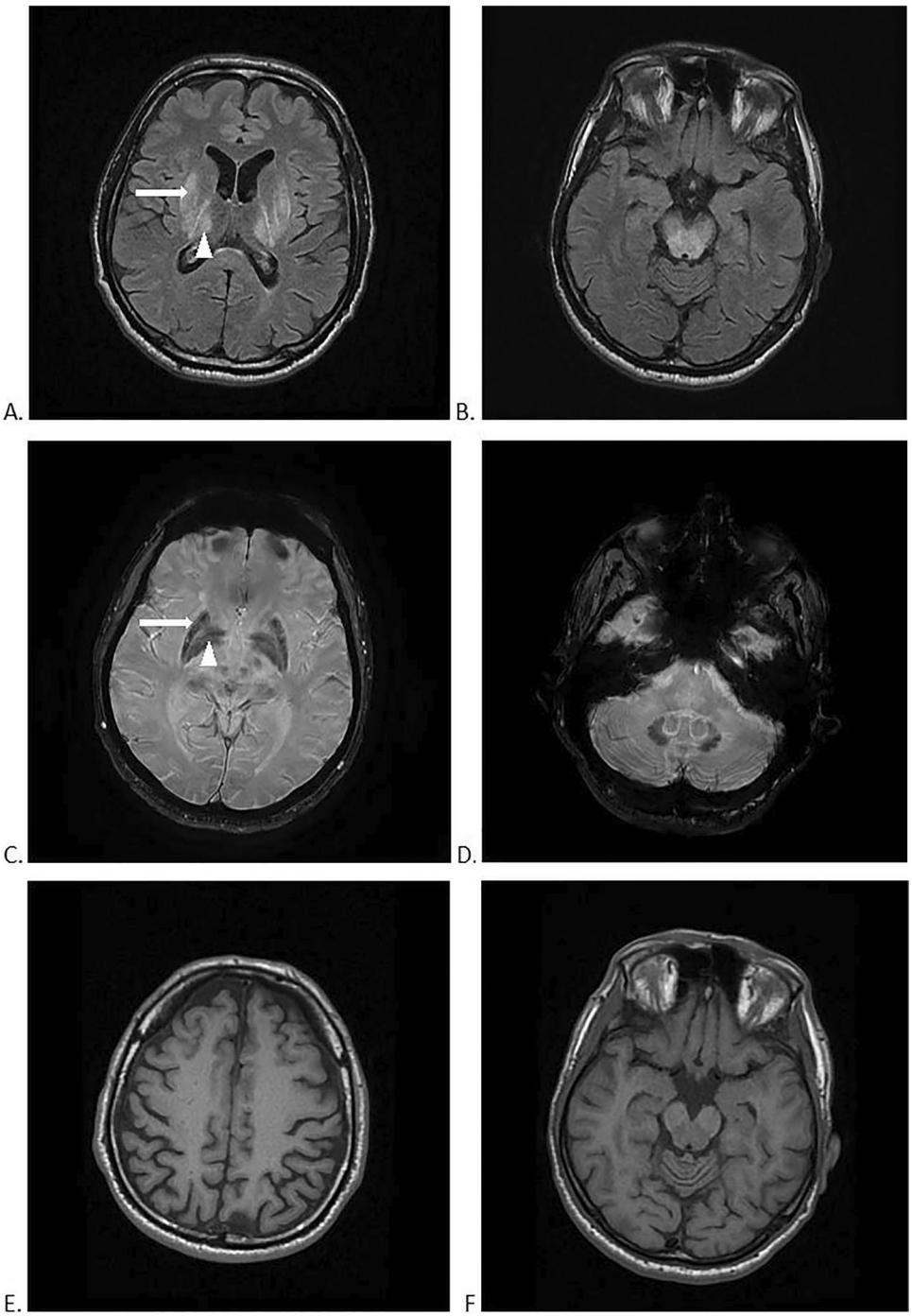

Fig. 1 Examples of 1.5-T magnetic resonance images showing typical acute and chronic changes in a patient with neurological Wilson's disease. **A**, **B** FLAIR hyperintensity scoring acute toxicity; **A** putamen (arrow) and thalamus (arrowhead) severe changes — score 2 for both; **B** mesencephalon severe changes — score 2; **C**, **D** SWI hypointensity scoring chronic damage; **C** putamen (arrow) and globus pallidus (arrowhead) severe changes — score 1 for both; **D** dentate nucleus; **E**, **F** T1 images for atrophy assessment; **A** midbrain atrophy — score 1; **B** cortical atrophy — score 1

are presented in Table 1. The mean age of WD onset was 27.9 years, with a mean age of diagnosis of 31.4 years. Most patients were symptomatic and had the neurological form of WD (55%).

Typical brain MRI abnormalities associated with WD were observed in 56% of WD patients at the time of diagnosis, occurring more frequently in patients with neurological symptoms followed by hepatic and presymptomatic cases (Table 2). For the semiquantitative MRI scale, patients with the neurological form of the disease had significantly higher mean total scores (5.4, range 0–14) compared with patients with the hepatic form (0.87, range 0–10, $P < 0.001$) or presymptomatic cases (0.78, range 0–10, $P < 0.001$) (Table 2). The significant difference between patients with the neurological form and the other forms was observed for both the acute toxicity score and the chronic damage score. There were no statistically significant differences in brain MRI scores between

Table 1 Demographic, clinical, and laboratory characteristics of analyzed patients with WD

Variable	Value
Number of patients (*n*)	*N* = 100
Gender, male, *n* (%)	53 (53)
Age at onset, mean ± *SD* (years) (*n* = 86)	27.9 ± 9.6
Age at diagnosis, mean ± *SD* (years) (*n* = 100)	31.4 ± 10.9
Clinical form of WD	
Neurological, *n* (%)	55 (55)
Hepatic, *n* (%)	31 (31)
Presymptomatic patients, *n* (%)	14 (14.8)
Severity of neurological disease scored in UWDRS	
UWDRS part II score in points, mean (range)	3.1 (0–38)
UWDRS part III score in points, mean (range)	13.1 (0–96)
Baseline copper metabolism	
Serum ceruloplasmin, mean ± *SD* (mg/dl) Normal range: 25–45 mg/dl	13.1 ± 6.8
Serum copper, mean ± *SD* (µg/dl) Normal range: 70–140 µg/dl	59.2 ± 21.8
Non-ceruloplasmin-bound copper, mean ± *SD* (µg/dl)	18.2 ± 15.0
Urinary copper excretion, mean ± *SD* (µg/24 h) Normal range: 0–50 µg/24 h	401.2 ± 936.9

SD standard deviation, *UWDRS* Unified Wilson's Disease Rating Scale, *WD* Wilson's disease

patients with the hepatic or the presymptomatic form of the disease.

In a subanalysis of 55 patients with the neurological form of the disease, all items of the semiquantitative MRI scale (acute toxicity, chronic damage, and total MRI score) moderately correlated with the severity of neurological disease scored by UWDRS part II and part III (Fig. 2A–F) ($P < 0.01$). For example, Spearman's correlations for the total score were $r = 0.45$ for UWDRS part II and $r = 0.42$ for UWDRS part II (both $P < 0.01$) (Fig. 2A–F).

Analyzing the relationship between the semiquantitative MRI scale and copper parameters in neurological WD patients, we found that both serum ceruloplasmin and serum copper levels correlated negatively with the brain MRI acute toxicity score ($r = -0.43$ for serum ceruloplasmin levels; $r = -0.32$ for serum copper levels; both $P < 0.05$). Serum *NCC* levels correlated positively with the brain MRI acute toxicity score (Fig. 3A–C).

When analyzing the relationship between semiquantitative MRI scale and copper parameters in the entire group of patients, we found that only serum ceruloplasmin and serum copper levels correlated negatively with brain MRI acute toxicity score ($r = -0.32$ for serum ceruloplasmin levels; $r = -0.24$ for serum copper levels; both $P < 0.05$).

There were no other significant correlations between copper parameters and the semiquantitative MRI scale scores in the entire group of WD patients as well as in those with the neurological form.

Discussion

Our study in a large cohort of newly diagnosed WD patients confirmed the frequent occurrence of brain MRI pathology observed in the pilot validation study of the semiquantitative MRI scale by Dusek et al. [16]. Regardless of the presence of neurological symptoms, we demonstrated that brain MRI changes may occur in any form of WD, even in presymptomatic cases, which is consistent with a previous report [17]. The findings indicate that the semiquantitative MRI scale could serve as a diagnostic tool [1], as well as a marker of brain involvement in WD [11].

In the available literature, there are many papers describing the brain MRI pathology in WD [17–30]; however, most were performed on small heterogenous groups of WD patients (treated, not treated, with various clinical presentations, varied times of WD treatment, etc.) [17–30]. Hence, a strength of our study is that it was performed in a homogenous group of drug-naïve, newly diagnosed WD patients, with brain MRI performed at the time of diagnosis, using the same MRI machine and examination protocol, evaluated and scored by the same neuroradiologist, to avoid the limitations of the mentioned studies.

Table 2 Frequency and severity of brain MRI changes in patients with WD according to clinical form and the brain semiquantitative MRI scale

Clinical form of WD	No. (%) of brain MRI changes typical for WD	Brain MRI semiquantitative scale (mean, range)		
		Acute toxicity score	Chronic damage score	Total score
All patients (*n* = 100)	56 (56)	1.6 (0–9)	1.6 (0–10)	3.3 (0–14)
Neurological (*n* = 55)	46 (83)	3.0 (0–9)[a,b]	2.72 (0–10)[a,b]	5.4 (0–14)[a,b]
Hepatic (*n* = 31)	9 (31)	0.03 (0–1)	0.19 (0–2)	0.87 (0–10)
Presymptomatic (*n* = 14)	1 (7)	0.0 (0)	0.28 (0–2)	0.78 (0–10)

MRI magnetic resonance imaging, *SD* standard deviation, *UWDRS* Unified Wilson's Disease Rating Scale, *WD* Wilson's disease

[a] $P < 0.01$ for the neurological vs. hepatic form

[b] $P < 0.01$ for the neurological vs. presymptomatic form

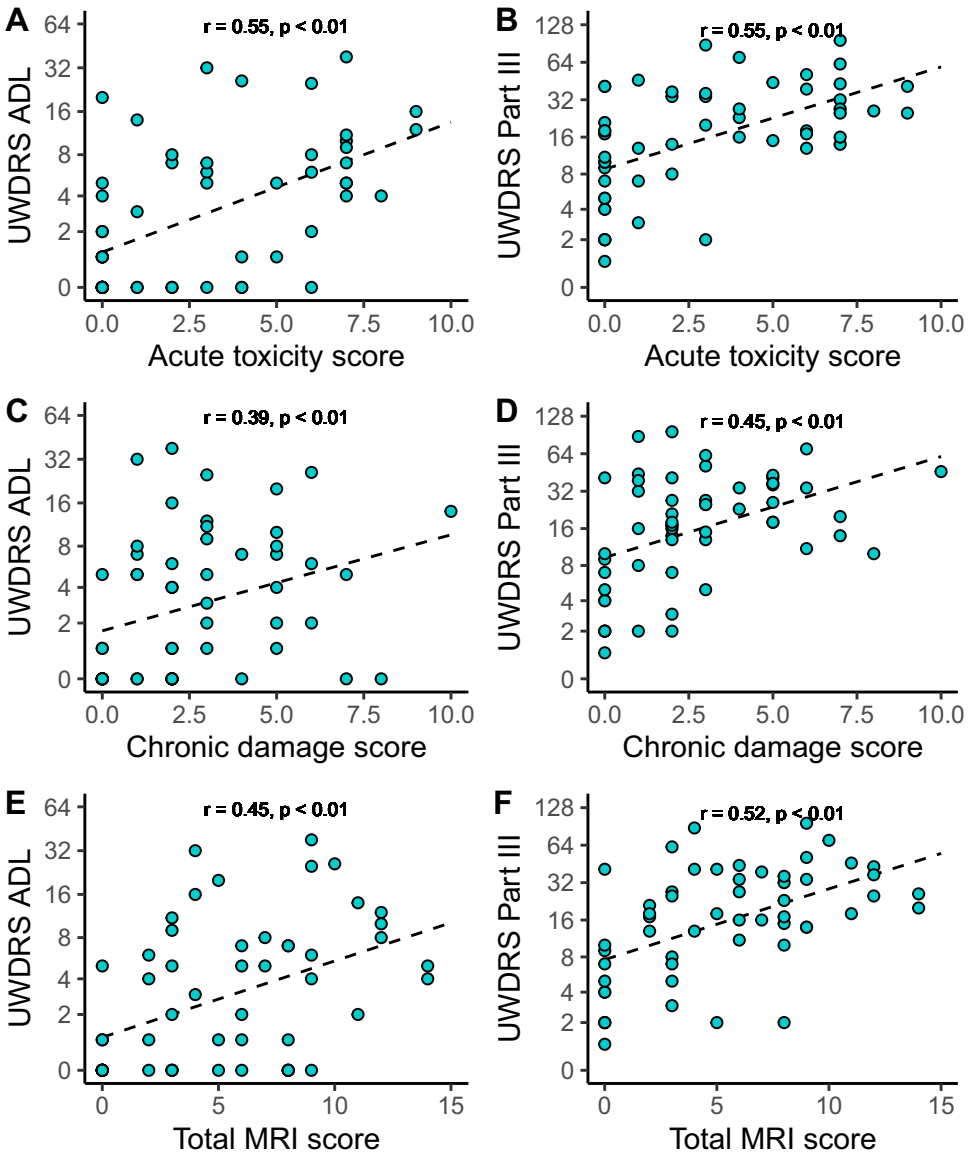

Fig. 2 Relationships between brain MRI semiquantitative scale (acute toxicity score, chronic damage score, and total brain MRI score) and severity of neurological disease scored with UWDRS and analyzed with Spearman's rank correlations. **A** Brain MRI acute toxicity score and UWDRS part II (impairment of activities of daily living); **B** brain MRI acute toxicity score and UWDRS part III (detailed neurological deficits); **C** brain MRI chronic damage score and UWDRS part II; **D** brain MRI chronic damage score and UWDRS part III; **E** brain MRI total score and UWDRS part II; **F** brain MRI total score and UWDRS part III. Each result circle is not equal to 1 patient (some overlap each other). ADL, activities of daily living; MRI, magnetic resonance imaging; UWDRS, Unified Wilson's Disease Rating Scale

Reviewing the literature for neuroradiological biomarkers of WD, we found proposals of neuroradiological scales, which were mostly based on so-called MRI load (calculation of brain MRI lesions independently of MRI sequences) [18, 20, 30]. However, taking into account the pathophysiology of WD [1, 2], the significance of different brain MRI sequences and the potential reversibility of changes (especially acute with brain edema), the proposition of an MRI scale that differentiates between acute (potentially reversible changes) and chronic (non-reversible atrophy, necrosis, etc.) brain lesions is justified.

Expanding on the findings of the validation study [16], we here document the accuracy of the semiquantitative MRI scale and its correlation with neurological UWDR scale in newly diagnosed WD patients with neurological symptoms. Firstly, patients with neurological disease, as expected, had higher scores of brain MRI injury compared with hepatic or presymptomatic patients. Further, positive correlations were observed between UWDRS part II and brain MRI acute toxicity score, chronic damage score, and total MRI score. The same positive correlations were observed between UWDRS part III (detailed neurological examination) and all items of the brain MRI scale. It should be mentioned that in the validation study by Dusek et al. [16], the authors did not present correlations between UWDRS part II and brain MRI scale [16]. Furthermore, positive correlations were not observed at baseline examination between UWDRS part III and the acute toxicity score. This discrepancy may be due to the small number of neurologic WD patients ($n=21$) in the validation study. The current study was performed on a larger group ($n=55$) of WD patients with neurological presentation and documented positive correlations between all items

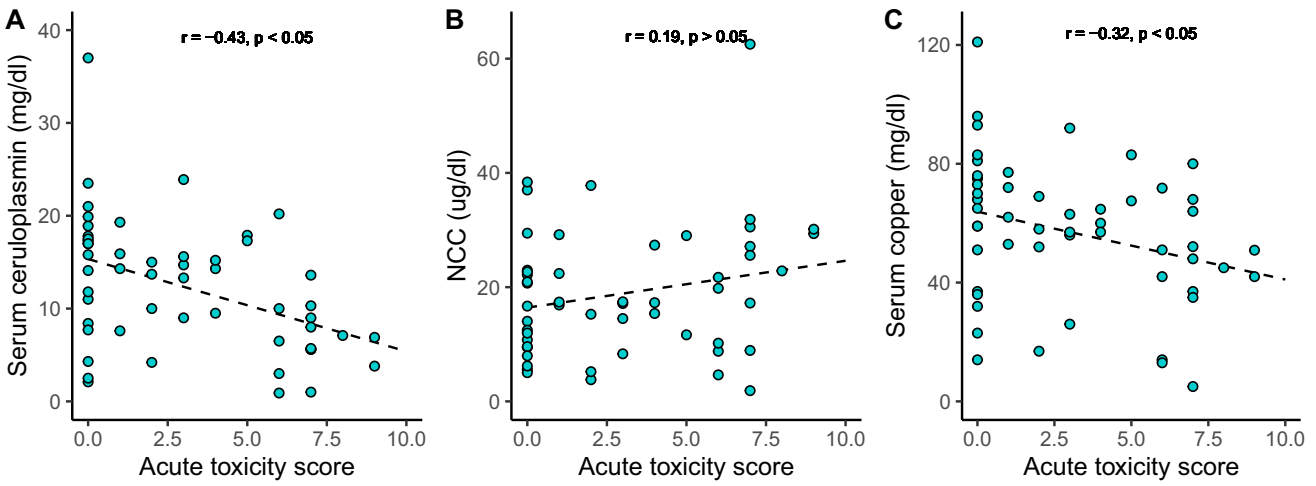

Fig. 3 Relationships between brain MRI semiquantitative scale acute toxicity score and copper metabolism (serum ceruloplasmin, non-ceruloplasmin-bound copper [*NCC*] and serum copper) analyzed with Spearman's rank correlations. **A** Brain MRI acute toxicity score and serum ceruloplasmin; **B** brain MRI acute toxicity score and serum *NCC*; **C** brain MRI acute toxicity score and serum copper. Each result circle is not equal to 1 patient. MRI, magnetic resonance imaging; *NCC*, non-ceruloplasmin-bound copper

of the brain MRI scale with both items of the UWDRS. As brain MRI is currently included in the European Association for the Study of the Liver (EASL) recommendations for diagnosing and evaluating neurologic patients suspected of WD (grade II-2, B, 1) [1], based on positive correlations between brain MRI scale and UWDRS, we postulate that both UWDRS and brain MRI scale should be included in the obligatory assessment of WD patients as complementary tools describing the severity of neurological involvement in WD.

Assessing correlations between brain MRI and UWDRS in our cohort, we found some discrepancies. Some patients had high scores in brain MRI and low in UWDRS; others had high scores in UWDRS and low brain MRI scores. This could be explained by the fact that even presymptomatic and hepatic WD patients (without neurological symptoms) may present with brain MRI pathology (21% and 42%, respectively) [17]. Additionally, some patients with higher UWDRS scored fewer points in brain MRI score, which could be explained by the fact that some neurological symptoms may more significantly affect the UWDRS score. Moreover, additional disorders not related to WD could affect the UWDRS score, which may result in discrepancies between UWDRS and brain MRI scores. However, the final summarized results found correlations between UWDRS and all brain MRI scores, which reduces the significance of those findings.

Analyzing the correlations between brain MRI scale and copper metabolism in neurological patients, we found negative correlations between serum ceruloplasmin levels, serum copper levels, and brain MRI acute toxicity score, as well as positive correlations between *NCC* and acute toxicity score (only in neurological patients), but no correlations with chronic damage or total MRI scores. Such observations are concordant with studies by Magalhaes et al. and Prayer et al. [18, 19], which documented that WD patients with lower serum ceruloplasmin and copper level present with more severe neurological symptoms. The authors explained this clinical effect as result of more severe mutations in the *ATP7B* gene (frameshift or non-sense mutations). Unfortunately, our group of neurological patients ($n = 55$) was too small to perform genotype–brain MRI scale correlations.

Our study has some limitations, including the retrospective nature of the study. However, WD is a rare disease and it is very difficult to collect prospective data from a large cohort of newly diagnosed treatment-naïve WD patients. The cohort studied here is one of the largest published so far where MRI and WD clinical scales (UWDRS as well as MRI scale) were evaluated. Our analysis was performed only at the time of diagnosis, and the prospective longitudinal observations of UWDRS as well as brain MRI could provide further data to determine the accuracy of the semiquantitative scale following WD treatment. Another limitation is that the Institute of Psychiatry and Neurology is the main Polish reference center for adults with WD. However, our department serves also as a neurological ward, which could potentially impact patient selection. In our study, we found most patients presented with neurological symptoms, which may not be representative of other centers. However, despite it being a neurological department, almost 40% of patients diagnosed with WD are referred to our department with liver injury symptoms by hepatologists. In our cohort, there is a lack of patients with acute liver failure or severe decompensated liver cirrhosis because these patients are directly

referred to hepatology departments or transplantation centers. However, they are also referred back to our center after disease stabilization (or transplantation). We thought that the studied cohort was well suited for our aim of establishing the relationship between neurological symptoms and the brain MRI scale.

It should be noted that brain imaging was performed on a 1.5-T MRI scanner in our study and the results cannot be generalized to other MRI scanners (3 T and higher). Hence, our data as well as the semiquantitative MRI scale should be verified on other MRI scanners (3 T and higher). In addition, as the semiquantitative scale was assessed by a blinded radiologist, we cannot exclude the subjectivity of assessment. However, in the pilot validation study of the brain MRI in WD [16], good intrarater and interrater assessments were achieved ($r > 0.93$ and $r > 0.74$; $P < 0.001$). In the near future, we hope we may be able to exclude the human factor (subjectivity) as the MRI scale could potentially be analyzed using artificial intelligence.

Conclusions

In addition to documenting the high rate and significance of brain MRI pathology in WD, we have demonstrated that the semiquantitative MRI scale is a complementary tool with UWDRS to assess the severity of neurological symptoms in WD. As some papers have documented the significance of specific brain MRI lesions (for example, the pons) as a predictor of neurological worsening in WD [11], further prospective studies evaluating changes and correlations between UWDRS and brain MRI scale during WD treatment (improvement/deterioration during disease) [31] would be useful to additionally confirm our observations in WD management.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval The study was approved by the Bioethical Committee of the Institute of Psychiatry and Neurology, Warsaw, Poland.

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