Cognitive Impairment In Stable Wilson Disease Across Phenotype.

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Short Report

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Abstract

Background: In Wilson disease (WD), mutations in the gene encoding the ATP7B copper transport protein causes accumulation of copper especially in liver and brain. WD typically presents with hepatic and/or neuropsychiatric symptoms. Impaired cognition is a well-described feature in patients neurological WD, while the reports on cognition in hepatic WD patients are fewer and less conclusive. We examined cognition in a cohort of WD patients with both phenotypes.

Methods: In this cross-sectional pilot study, we investigated cognition in 28 stable Danish WD patients by portosystemic encephalopathy (PSE) and continuous reaction time (CRT) tests. Half of the patients were female and median age was 35.5 years (IQR 24.5). The phenotype was hepatic in 14 (50%), neurologic in 10 (36%) and mixed in 4 (14%). The duration of treatment was >2 year in all patients, and the condition stable as judged by urinary copper excretion, liver enzymes, and clinical assessment.

Results: In total, 16 (57%) patients performed worse than normal in the PSE and/or CRT tests. The two tests correlated ($\rho=0.60$, $p=0.0007$) with each other, but neither correlated with phenotype, MELD-, Child-Pugh score, 24h-U-Cu, or treatment type.

Conclusion: Measurable cognitive impairment was present in more than half of the stable WD patients independent of phenotype. Thus, our data questions the existence of a purely hepatic phenotype.

Background

In Wilson Disease (WD) copper accumulates in body tissues particularly the liver and brain (European Association for the Study of the 2012). The disease typically presents with either hepatic or neuropsychiatric symptoms or a combination. Hepatic and neurological symptoms most often improve with treatment, but patients still hold an increased risk of psychiatric and somatic comorbidity including depression, anxiety, and cardiac myopathy (European Association for the Study of the 2012; Schaefer et al. 2016; Litwin et al. 2018; Grandis et al. 2017).

Cognitive impairment in WD patients with neuropsychiatric presentation is well described (Frota et al. 2013; Hegde et al. 2010; Seniów et al. 2002; Wenisch et al. 2013) and possibly related to the cerebral lesions that can be detected by MRI (Dezortova et al. 2020; Frota et al. 2013; Yu et al. 2019). However, recent studies suggested subtle cerebral structural changes even in hepatic WD patients (Tinaz et al. 2020). Few papers assessing cognition in hepatic WD are available (Wenisch et al. 2013; Seniów et al. 2002; Iwański et al. 2015). While most standard cognitive tests were normal in the hepatic WD patients, more sensitive tests of the sustained attention were also affected hepatic patients in one study (Iwański et al. 2015). In order to evaluate cognition across phenotype we studied a stable WD cohort and employed two tests developed to detect subtle cognitive disturbances with relation to sustained attention: The portosystemic encephalopathy (PSE) and the continuous reaction time (CRT) (Elsass 1986; Nabi and Bajaj 2014).

Methods

In this cross-sectional pilot study, all stable Danish WD patients at the Danish Wilson Center, Aarhus University Hospital over the age of 18 with at least 2 years of treatment duration were examined over a time span of 9 months. Baseline characteristics and inflammatory data was recently published (Björklund et al. 2018).

Stability was defined as stable urinary copper and liver enzymes over a 1-year period, and absence of clinically manifest neurological or hepatic decompensation. Patients were excluded if liver transplanted or unable to collect urine. None of the participants had known concomitant non-Wilsonian neurological disease.

After informed consent was obtained, the patients were evaluated by the PSE and CRT tests. The PSE test is a validated and widely used pen and paper test battery for identification of minimal hepatic encephalopathy (HE) (Nabi and Bajaj 2014; Weissenborn et al. 2001). Complex cognitive functions such as attention, accuracy, working speed, and visual orientation are assessed through five subtests. A score of ≤ -5 is abnormal, and lower than 2 SD below the mean in a healthy German age-adjusted population (Weissenborn et al. 2001). The CRT is also validated as a diagnostic tool for minimal HE. It evaluates reaction time stability (CRT index) to 100 serial auditory stimuli and gives a measure of sustained attention, vigilance, and inhibitory control (Elsass 1986). An index below 1.9 is abnormal (Elsass et al. 1985). CRT index is not affected by age, gender, or educational level (Lauridsen et al. 2012). Fibroscan and blood test results were secured within 1 month of the test day (Table 1).

Table 1
Patient characteristics.

	All WD patients N = 28	Impaired cognition N = 16	Unimpaired cognition N = 12	p-value
Gender (M/F)	(14/14)	(10/6)	(4/8)	0.25
Age (years)	35.5 (24.5)	35.5 (18)	35 (35.5)	0.95
Time since diagnosis (years)	18 (15)	18 (18)	18 (22)	0.42
Age at diagnosis (years)	17.5 (11)	13.5 (13)	18.5 (8)	0.09
Treatment:				0.051
D-penicillamine	10	6	4	
Trientine dihydrochloride	5	2	3	
Zinc	6	3	3	
Zinc + D-penicillamine or trientine dihydrochloride	7	5	2	
Presentation (Hepatic/Neurological/Other)	(14/10/4)	(8/7/1)	(6/3/3)	0.68
Blood samples:				
Amylase (U/L)	43 (31)	40 (20)	50 (34.5)	0.36
Lactate Dehydrogenase (U/L)	161 (38)	158 (37)	176.5 (37.5)	0.11
Alanine aminotransaminase (U/L)	38 (48.5)	40 (51.5)	38 (41.5)	0.76
Bilirubin (μmol/L)	10 (6)	9 (5)	10 (14.5)	0.79
Alkaline Phosphatase (U/L)	97 (50)	97 (64)	97 (39.5)	0.90
PP	0.83 (.21)	0.78 (.18)	0.89 (.15)	0.16
Potassium (mmol/L)	4 (.3)	4 (.5)	4 (.2)	0.40
Sodium (mmol/L)	140 (2.5)	140 (3)	141 (2.5)	0.88
Albumin (g/L)	38 (5)	38 (4.5)	39 (7.5)	0.72
Creatinine (μmol/L)	69 (23)	69 (24)	64 (18.5)	0.54
eGFR (mL/min 1.73m ²)	91 (2)	91 (9)	91 (0)	0.42
B-leukocytes (10 ⁹ /L)	5.9 (1.3)	6.3 (1.92)	5.5 (1.7)	0.08

Parameters are presented as median (IQR). MELD, Model of End-stage Liver Disease. NS = Not Significant

	All WD patients N = 28	Impaired cognition N = 16	Unimpaired cognition N = 12	p- value
Hemoglobin (mmol/L)	8.9 (1)	9 (.8)	8.7 (1.1)	0.22
Platelets (10 ⁹ /l)	203 (90.5)	198 (105.5)	207 (67.5)	0.61
Iron (μmol/L)	16 (9.5)	17.5 (9.5)	14.5 (9)	0.74
Transferrin (μmol/L)	34 (5.5)	34 (4)	35 (8.5)	0.44
Transferrin-saturation	0.26 (.13)	0.27 (.14)	0.24 (.1)	0.34
Haptoglobin (g/L)	0.94 (.71)	1.03 (.75)	0.9 (.57)	0.44
p-zinc (μmol/L)	17 (11)	17.5 (13.5)	16.5 (11.5)	0.72
Urine samples:				
24h-u-zinc (μmol/24h)	38.4 (52.3)	37.1 (54.3)	46.5 (52.3)	0.75
24-u-copper (μmol/24h)	4.9 (6)	5.4 (4.5)	2.34 (8.3)	0.54
Other:				
MELD score	7.8 (1.8)	8.3 (1.7)	7.5 (2.4)	0.54
Child-Pugh score	5 (0)	5 (0)	5 (.5)	0.66
Fibroscan (kPa)	7.8 (3.4)	7.2 (5.5)	6.8 (4)	0.06
Parameters are presented as median (IQR). MELD, Model of End-stage Liver Disease. NS = Not Significant				

The study was approved by The Central Denmark Region Committees on Health Research Ethics (50611), and the Danish Data Protection Agency (1-16-02-614-15), registered at clinicaltrials.gov (NCT02702765), and conducted in accordance with The Helsinki declaration.

Statistical analysis:

Histograms and Q-Q plots were used to check normality. Results are presented as median and IQR. Wilcoxon Mann-Whitney test was used to compare groups and Spearman's correlation was used for analysis of correlations within the dataset. A p-value < 0.05 was considered statistically significant. We used STATA version 16.1 (StataCorp LP, College Station, TX) for data analysis.

Results

Of 38 screened patients, 9 could not be included (4 < 18 years of age; 1 newly diagnosed; 1 too ill; 3 without hospital contact during the study period), 1 refused and 28 were included in the study.

Figure 1 displays the results of PSE and CRT related to the WD disease phenotype. Table 1 presents patient characteristics comparing those with and without cognitive impairment.

Five (18% – 2 hepatic and 3 neurological phenotype) patients presented with pathological PHES (score median – 6, IQR – 2). These patients scored lowest in subtest 1 and 2 (attention, visuo-spatial construction, working speed, accuracy, and visual orientation).

Fifteen (54% – 8 hepatic, 6 neurological and 1 other phenotype) patients presented with a pathological CRT index (median 1.64, IQR 0.40). The PSE score (PHES) and CRT test results were positively related ($\rho = 0.60$, $p = 0.0007$) (Fig. 1).

In total, 16 (57%) patients performed worse than normal in cognitive function by PSE and/or CRT. In these, patient characteristics were similar to those with normal PSE and CRT (Table 1). Thus, there was no correlation between PHES or CRT index and phenotype, MELD-, CP-score, treatment, or 24-h urine copper excretion.

Discussion

We showed that approximately half of our stable WD cohort performed below normal in cognitive function tests regardless of liver or brain disease involvement. More patients sub-performed in the CRT test than in the PSE test. The CRT test measures motor reaction speed, sustained attention and inhibitory control (Elsass 1986; Lauridsen et al. 2013). In the PSE test, patients performed worse in subtest 1 and 2, the Number Connection Tests A and B which also measures attention, as well as working speed, accuracy, visual orientation and visuo-spatial construction (Weissenborn et al. 2001).

Our findings support the known impact of neurological WD on cognition (Hegde et al. 2010; Frota et al. 2013; Seniów et al. 2002). In available reports on cognition in WD patients without neurological symptoms, cognition was found to normal (Seniów et al. 2002; Wenisch et al. 2013; Iwański et al. 2015) except for tests of sustained attention (Iwański et al. 2015). These studies mostly used test batteries designed to detect more severe cognitive impairment (Frota et al. 2013; Hegde et al. 2010; Seniów et al. 2002; Wenisch et al. 2013; Medalia, Isaacs-Glaberman, and Scheinberg 1988; Iwański et al. 2015). Both the PSE and CRT are widely used to detect subclinical cognitive dysfunction in HE patients and may be more sensitive to these subtle changes to cognition in hepatic WD. The test results depend on sustained attention and our results are in agreement with those of Iwanski, 2015 (Iwański et al. 2015) where tests of sustained attention were also impaired in both phenotypes.

Taken together, these data suggest that while severe cognitive dysfunction is exclusive to the neurological phenotype of WD, mild cognitive disturbances involving sustained attention is common in both phenotypes. The pathophysiological mechanism behind this result is not examined in this study. Since structural changes in the brain and elevated hepatic copper is present even in stable patients after long periods of treatment, residual cerebral copper overload was considered (Scheinberg et al. 1987; Frota et al. 2013). Cerebral copper cannot be measured but neither urinary copper or treatment modality

correlated with PSE or CRT measurements in our cohort and free intracellular copper is presumably under control in stable patients. Recent advanced MRI reports suggested subtle changes in brain structure even in hepatic WD patients, involving areas with relation to sustained attention which was affected in both phenotypes in our study (Tinaz et al. 2020). Further studies should explore these possibilities.

Alternatively, it was considered whether liver disease itself could be associated with impaired sustained attention, as similar cognitive dysfunctions have been documented in other hepatic diseases, e.g., non-alcoholic fatty liver disease and -steatohepatitis, hepatitis C and alcoholic cirrhosis as well as chronic disease in general (Colognesi, Gabbia, and De Martin 2020; Kjærgaard et al. 2021; Perry, Hilsabeck, and Hassanein 2008; San Martín-Valenzuela et al. 2020; Yohannes et al. 2017). Hepatic disease is also present in most neurologic WD patients, potentially contributing to their cognitive impairments (European Association for the Study of the 2012). However, in our stable treated patients presented with normal or only mildly affected liver function tests (Table 1) and neither MELD nor CP-scores were related to cognition. Minimal HE is thus unlikely to be causative of the measured cognitive impairment.

Our findings thus indicate that the occurrence of subclinical cognitive dysfunction in stable WD is much more common than previously thought and present regardless of phenotype. While current treatment often is highly effective in treating the major neurological and hepatic manifestations of WD, it may be inadequate to treat the cognitive manifestations as well.

The relatively small study population (n = 28) is a limitation of this study but counterbalanced by the well-characterized cohort of stable Danish WD patients and the high rate of participation. Studies in larger populations are clearly needed.

In conclusion, our cohort of stable well treated WD patients performed worse than normal in cognitive function tests regardless of phenotype. These changes persisted after long-term therapy in clinically stable WD patients.

Abbreviations

WD – Wilson Disease

PSE - Portosystemic Encephalopathy test

PHES – Portosystemic Hepatic Encephalopathy Score

CRT - Continuous Reaction Time

HE – Hepatic Encephalopathy

Declarations

Ethics approval and consent to participate

The study was approved by The Central Denmark Region Committees on Health Research Ethics (50611) and approved by the Danish Data Protection Agency (1-16-02-614-15). The study was conducted in accordance with the Helsinki II declaration.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used in the current study are available from the corresponding author on reasonable request.

Competing interests

H.G.: research grants from Intercept, Abbvie, NOVO Nordisk Foundation, Arla, ADS ALPHIA Development Services AG, and “Savværksejer Jeppe Juhl og hustru Ovita Juhls mindelegat”. Advisory board at Ipsen. Speaker Norgine.

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Research grants were obtained and accounted for in the Competing interest’s section.

Authors’ contributions

FK wrote the manuscript, analyzed the data and acquired parts of the data.

DM, TL, MML, TS assisted in writing the manuscript. TL acquired data and assisted in data analysis. DM and TS also assisted in data analysis. HV, PO and HG helped form the project and gave inputs to the manuscript.

All authors read and approved the final manuscript.

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Authors’ information

Not applicable.

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Figures

Figure 1

Created using StataIC v. 16.1 Scatterplot of CRT index and PHES by phenotype