Abstract:

Background: In Wilson disease (WD), mutations in the gene encoding the ATP7B copper transport protein cause 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 with 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 the PortoSystemic Encephalopathy (PSE) and the Continuous Reaction Time (CRT) tests. Half of the patients were female, and their median age was 35.5 years (IQR 24.5). Their 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 their condition was stable as judged by urinary copper excretion, liver enzymes, and clinical assessment. The hepatic patients did not show signs of liver failure.

Results: In total, 16 (57%) patients performed worse than normal in the PSE and/or the CRT tests. The two tests were correlated (rho=0.60, p=0.0007), 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 patients.
stable WD patients independent of phenotype. Thus, our data questions the existence of a purely hepatic phenotype.
To editor-in-chief Gregory Konat,
Thank you for the opportunity to submit a revised version of our manuscript.

We would also like to thank both reviewers for their thoughtful and constructive criticism, which has helped us improve the manuscript. We revised the manuscript according to the editor’s and reviewers’ suggestions while trying to maintain the compact format of the article.

Reviewer 2:

1. “What is the justification of using tests primarily used for the diagnosis of MHE? There are plenty of tests used to detect cognitive impairment.”

- We agree that we have not motivated our choice of cognitive test in the manuscript. This is now addressed as requested (page 4 line 15). Our choice was to a large extent was based on a wish to be able to work with routine tests with which we are locally familiar and know strengths, weaknesses, and pitfalls from practical use. We realize that cognition tests cover a broad spectrum of possibilities and that is possible to construct complex testing batteries aiming at detailed cognitive mapping. Our goal, however, in this context was initially to study if the Wilson patients show dyscognition by the tests we use in daily clinical practice.
As this work was done within the Department of Hepatology, we wanted tests that could be performed safely by the hepatologic staff taking care of our Wilson patients. The PSE and CRT tests are both widely used in hepatology, the CRT particularly in Denmark where a large experience base is developed. Already these tests in fact revealed the disturbances in cognition we describe, and we acknowledge that the step forward would include more tests to get an idea of the cognition domains most involved.

2. “Cognitive impairment is defined when PHES results are compared to German healthy controls, however no Danish controls have been established. In addition, CRT results below 1.9 are defined as abnormal when in fact this cut-off was used to discriminate patients with hepatic encephalopathy from organic brain damage.”.

- German PHES norms are so far used in Denmark because the two populations are taken to be highly comparable as to such factors that influence the PHES. Still, a Danish PHES norm is recently under
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establishment, based on, now 200 control persons - and the results are comparable with the German controls.

- The reviewer is correct, the CRTindex (Which is a reaction time percentile ratio) threshold of 1.9 showed the best discrimination between HE and organic brain disease and better than any of the reaction time percentiles. We have later validated and confirmed this finding in a prospective fashion. However, your comment inspired us to take a second look at the 90, median, and 10 percentiles of reaction times of the Wilson patients. Here we found that 7 Wilson patients had a 90 percentile above the normal 250 msec (median 231 msec (67 IQR) vs. 186 msec (43 IQR), p = 0.003) between those with and without cognitive dysfunction. Neither the 10 nor the median percentile differed and none of the percentiles correlated to MELD, Child-Pugh, Presentation, or PHES score. The difference in 90 percentile seems to confirm that the Wilson patients tended to be slightly slower, but this difference did not convey information or discrimination beyond that obtained by the established CRTindex.

We now present some more data regarding CRT percentiles in table 1.

3. “How is neurological phenotype defined if manifest neurological decline was excluded?”

- The neurological phenotype is defined by the classical initial disease presentation symptoms. None of the patients in this study showed manifest clinical disease progression, whether neurological, hepatic, or other. So, a neurological patient in this study is a patient who clinically presented with neurologic manifestations of Wilson Disease, but who is now under stable treatment and followed once-a-year in the outpatient clinic. This is now clarified in the manuscript (page 3 line 22)

4. “Fig 1 does not distinguish PSE and CRT results in relation to phenotype but that both tests provide similar outcomes. Analysis with each test and phenotype would be required.”

- We agree, the correlation between CRT and PSE within phenotypes are not presented in figure 1. Thank you for noticing. The manuscript is modified accordingly (page 5 line 19 – deletion)

5. “The sub-domains or subtests are not properly analyzed, most likely due to insufficient number of patients.”
We fully agree that the low number of patients is a limitation of the study, as is often the case with very rare diseases. This limitation also implies that detailed domain-wise or response subset analyses cannot be conducted with a meaningful purpose. That is one reason why we chose to give a short overview of the lowest scores, also in respect of the wordcount limitation. Anyway, we now include a little more of such data in table 1 and have updated the results section to reflect this.

6. “"Tests to detect more severe cognitive impairment" needs to be explained.”

We agree that we have been unclear and have removed this from the manuscript.

Reviewer #3:

Major comments:
1. “Have all those patients had a brain MRI? Ophthalmologic evaluation?. It would be interesting to have this information, especially for those with hepatic presentation. Patients in this study have been diagnosed at a relatively later age, 17.5 years, where we could expect to have some form of neurologic involvement, hence the importance of a thorough neurologic evaluation before ruling out this manifestation.”

   Unfortunately, brain MRI is not available in several of the subjects, but we certainly agree they would have been relevant to have here. Ophthalmologic evaluation was available for 24 of 28. Seven patients had KF rings, 2 of them classified with the hepatic phenotype. Of the 7 patients with KF rings, 5 had cognitive impairment and two (1 neurologic, 1 mixed) did not. Data now included in table 1.

2. “Since most patients had a pathological CRT, maybe you should add more details about the exam and its limitations.”

   We would much appreciate to accommodate you, but the word limitation makes it unfeasible. However, we feel that most of what you ask for is likely found in Lauridsen MM et al, Metab Brain Dis 2013,28,231, now given as a reference(Lauridsen et al. 2013).
3. “Maybe you should weigh your conclusion of questioning the existence of a purely hepatic phenotype considering the rather adult population included. In the same line, perhaps you should include in the discussion the article from Favre et al 2016 addressing the cognitive abilities of WD children with hepatic phenotypes.”

- Yes, your comment calls for some consideration. Overall, our Wilson subjects were 17.5 years old at diagnosis. However, the cognitively impaired group was diagnosed at a younger age (13.5 years vs. 18.5 years p = 0.09). We would expect this to be the other way around if the measured cognitive dysfunction was a trait mostly of the neurological phenotype, which generally presents at a higher age (Merle et al. 2007).

The paper by Favre et al seems to be in line with our findings as it showed that pediatric Wilson patients with both the neurologic and the hepatic presentation had subtly affected cognition. We could not show that the neurological patients performed worse than the hepatic patients by the tests we used - or the hepatic patients better – while Favre found the neurological patients to perform worse (Favre et al. 2017). It thus seems plausible that while the two phenotypes are distinct, there is an overlap in cognitive defects so that a purely hepatic phenotype with no neurological involvement is unlikely. We now include a reference to Favre et al, 2017 on page 6 line 14.

4. “You state that minimal HE is unlikely to be causative of the measured cognitive impairment since neither MELD nor CP-scores were related to cognition. Have you compared those scores (CP, Meld, fibroscan) of the hepatic patients separately (not including the neurological/mixed phenotypes) between the impaired/unimpaired group? I think it would be essential to assure that it is not the severity of the liver disease causing this difference”

- Your suggestion is highly appreciated, and the manuscript now includes this issue (Page 7 line 4) in the discussion. We made the comparisons you indicate but could not find space for showing them in the manuscript and only give the conclusion following below.

We saw that the PSE correlated weakly but if anything, inversely to the Child-Pugh score in only hepatic phenotype (spearman’s rho = .6. p = 0.02). The CRTindex did not correlate to Child-Pugh, nor did either PSE or CRT correlate to fibroscan or MELD.

Of the 14 subjects with hepatic phenotype, 12 had a Child-Pugh score = 5. Only 2 subjects had elevated Child Pugh (6 and 7), and both were not cognitively impaired. Even with these small
numbers, these observations did not indicate that the severity of the liver disease in itself gave rise to
the cognitive differences - confirming that the dyscognition cannot be ascribed ‘simply’ to minimal
HE.

5. “Do you have any explanation about the 6/14 patients with neurological or mixed phenotypes that had
normal results for these cognitive tests? Maybe you should include a UWDRS score for the neurological
(and mixed) patients to better characterize them”

- The finding that 6/14 with neurologic or mixed phenotypes performed well here is likely because
these patients were stable and well treated over long time. Furthermore, as you suggest and as also
discussed above, it is a possibility that a more comprehensive test battery might have found defects
in more domains. Thus, UWDRS scores would be desirable but we simply do not have them.
Inclusion of at least part II of the UWDRS would have been very useful and in retrospect we should
have done it. This limitation has now been highlighted in the manuscript (Page 7 line 15)

6. “Knowing that the Danish team is performing exchangeable copper, I dare to ask if you have the ExcCu
values of these patients? If so, it would be interesting to add them, considering the relationship between high
ExcCu and neurological involvement (Poujois et al. 2017).”

- Unfortunately, we do not have the ExcCu data available as we only started measuring ExcCu after
onset of this study. This would certainly be of value for further investigation of cognition in our
patients. Still, Guillaud et al. 2018 showed that ExcCu normalized in many stable treated Wilson
patients, and from these data we would not expect to see many high ExcCu values (Guillaud et al.
2018).

7. “You could add a recommendation about the necessity of a thorough neurological evaluation: clinical,
neuropsychological, and ophthalmologic assessment + brain MRI at diagnosis, even in the absence of
apparent neurological involvement.”

- This is a very good point and is added (Page 7 line 15).
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Minor comments:
1. “In the abstract, the mixed phenotype should be corrected as you noted 4 4 instead of 4 .”
   - Thank you for noticing. This is corrected.
2. “Table 1 and figure 1: I think it would be preferable to use « mixed » instead of others when referring to the presentation/phenotype.”
   - Table 1 and figure 1 are updated with the use of the term “Mixed”.
3. “The term PHES is used before the meaning is given.”
   - The term PHES has been removed in order to avoid confusion from the use of both PSE and PHES.

The authors declare no conflict of interests.

Yours Sincerely
Frederik Teicher Kirk

References:
Cognitive impairment in stable Wilson Disease across phenotype.

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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 with 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 the PortoSystemic Encephalopathy (PSE) and the Continuous Reaction Time (CRT) tests. Half of the patients were female, and their median age was 35.5 years (IQR 24.5). Their 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 their condition was stable as judged by urinary copper excretion, liver enzymes, and clinical assessment. The hepatic patients did not show signs of liver failure.

**Results:** In total, 16 (57%) patients performed worse than normal in the PSE and/or the CRT tests. The two tests were correlated (rho=0.60, p=0.0007), 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.

**Keywords:** *Wilson Disease, neurological phenotype, hepatic phenotype, portosystemic encephalopathy test, continuous reaction test, cognitive function*
Manuscript

Background

In Wilson Disease (WD) copper accumulates in body tissues particularly the liver and brain [1].

The disease typically presents with either hepatic or neuropsychiatric symptoms and in some with a combination. The hepatic and neurological symptoms most often improve with treatment, but patients still hold an increased risk of psychiatric and somatic comorbidity including depression, anxiety, cardiac myopathy and decreased liver function [1-5].

Cognitive impairment in WD patients with neuropsychiatric presentation is well described [6-9] and probably related to the cerebral lesions detected by MRI [6, 10, 11]. However, recent studies suggest subtle cerebral structural changes even in hepatic WD patients [12]. Few papers assessing cognition in hepatic WD are available [8, 9, 13]. While most standard cognitive tests were normal in the hepatic WD patients, more sensitive tests of the sustained attention were also affected in hepatic patients according to one study [13]. In order to evaluate cognition across phenotype we studied a stable WD cohort and employed two psychometric tests developed to detect subtle cognitive disturbances with relation to sustained attention: The portosystemic encephalopathy (PSE) and the continuous reaction time (CRT) tests [14, 15].

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 were recently published [5]. The patients’ phenotype was defined by the incident patient’s dominating debut symptoms.
Stability was defined as stable urinary copper and liver enzymes over a 1-year period, and absence of clinically manifest neurological or hepatic decay. Patients were excluded if liver transplanted or unable to collect urine. No participant 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 most established for identification of minimal hepatic encephalopathy [15, 16]. 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 median in a healthy German age-adjusted population [16]. A Danish norm is under establishment but does not differ significantly from the German one [Lauridsen MM, Personal Communication]. The CRT is also validated as a diagnostic tool for minimal HE. It consists of 100 serial and randomly delivered auditory stimuli and gives a measure of sustained attention, vigilance, and inhibitory control [14, 17]. The key test outcome is the reaction time stability quantified by the CRTindex, the ratio reaction time 50 percentile/(90-10 percentile). An index below 1.9 is abnormal [18]. The CRTindex is not affected by age, gender, or educational level[19]. The PSE and CRT tests were chosen as they are commonly used in the field of hepatology, used widely in local practice with especially CRT having a large Danish experience base. These choices also allowed us to determine dyscognition in Wilson patients by the test we use in daily clinical practice. Fibroscan and blood test results were secured within 1 month of the test day (Table 1).

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 twenty-eight patients 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, PSE subtest scores and CRT percentiles comparing those with and without cognitive impairment.

Five (18% - 2 hepatic and 3 neurological phenotype) patients presented with a pathological PSE score (score median -6, IQR -2). These patients scored lowest in the digit symbol and line tracing A subtests (attention, visuo-spatial construction, working speed, accuracy, and visual orientation).

Fifteen (54% - 8 hepatic, 6 neurological and 1 mixed phenotype) patients presented with a pathological CRTindex (median 1.64, IQR 0.40). The PSE and CRT test results were positively related (rho=0.60, p=0.0007).

In total, sixteen (57%) patients performed worse than normal in cognitive function by either one or both the PSE and CRT tests, and four performed worse than normal in both tests. In these, patient characteristics were similar to those with normal PSE and CRT tests (table 1). Thus, there was no correlation between PSE or CRTindex and phenotype, Model for End-stage Liver Disease (MELD)-, CP-score, treatment, or 24-h urine copper excretion.
Discussion

We showed that more than 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. This suggests that these patients suffered from impaired motor reaction speed, sustained attention ability and inhibitory control [14, 17]. In the PSE test, patients performed worse in the digit symbol and line tracing A subtests suggesting impaired attention, as well as working speed, accuracy, visual orientation and visuo-spatial construction [16].

Our findings are in line with the known impact of neurological WD on cognition [6-8]. In the few available reports on cognition in WD patients without neurological symptoms, cognition was found normal [8, 9, 13] except for tests of sustained attention [13]. Both the PSE and CRT tests are widely used to detect subclinical cognitive dysfunction in cirrhosis patients with so-called minimal hepatic encephalopathy and because they are very sensitive to purpose and familiar to our staff, we chose them for initial cognitive screening of Wilson patients. A general trait seems to be loss of sustained attention and our results are thus in agreement with those of Iwanski, 2015 [13] and Favre, 2017 [20] where tests of sustained attention were also impaired in both phenotypes.

Taken together, our data suggest that mild cognitive disturbances are common in both phenotypes. The problem may be related to copper-dependent structural changes in the liver, even in stable patients and after long periods of treatment [6, 21], although we found that neither urinary copper or treatment modality correlated with the PSE or CRT measurements. Free copper was not measurable at the study time but is presumably under control in stable patients. Recent advanced MRI reports suggest subtle changes in brain domains even in hepatic WD patients, compatible with weakened attention, as we found in both phenotypes [12]. Further studies are awaited.

Alternatively, Wilsonian liver disease might in itself be associated with the attention deficit, as the same is seen in other liver diseases, e.g., non-alcoholic fatty liver disease and -steatohepatitis.
hepatitis C, and alcoholic cirrhosis [22-26]. The liver is also involved in most neurologic WD patients, and if cirrhosis emerges this may contribute towards cognitive impairment [1]. However, our patients presented with normal or only mildly affected liver function tests (Table 1) and neither their MELD nor CP-scores were related to the cognition test results, also not when only analyzing results from WD patients with hepatic presentation. 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 may be present regardless of phenotype. While current treatment often is highly effective in controlling the major neurological and hepatic manifestations of WD, it may still be inadequate to treat the cognitive manifestations as well. This is not a trivial matter because such mild dyscognition is closely related to impaired quality-of-life, not recorded here but widely documented in other liver patients. Our study and the discussion above suggest that WD patients without apparent neurological involvement should also be offered thorough neurological examination including brain MRI and neuropsychiatric examinations.

Our small study population (n = 28) remains a limitation of this study, somewhat counterbalanced by the well-characterized cohort of stable Danish patients and the high rate of disease population participation. Studies in larger populations as well as introduction of neurological tests of cognition are clearly motivated needed. These studies should also explore if and how these subtle cognitive disturbances affect the daily living of the patients.

In conclusion, our cohort of stable well treated WD patients performed worse than normal in cognitive function tests regardless of neurological or hepatic phenotype despite long-term successful therapy.

### Abbreviations

1. **WD** – Wilson Disease
2. **PSE** - Portosystemic Encephalopathy test
3. **CRT** - Continuous Reaction Time
4. **MELD** – Model for End-stage Liver Disease

| Table 1 Patient characteristics, biochemistry and cognitive test results |
|------------------|------------------|------------------|------------------|------------------|
|                  | 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/Mixed) | (14/10/4) | (8/7/1) | (6/3/3) | 0.68 |
| Kaiser-Fleischer Ring present | 7 | 5 | 2 | 0.71 |
| KF ring by presentation (Hepatic/Neurological/Mixed) | (3/3/1) | (3/2/0) | (0/1/1) | 0.51 |
| 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 1.73m2) | 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            |
| 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:   |                   |                  |                  |                 |


<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median (IQR)</th>
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<tr>
<td>24-u-copper (μmol/24h)</td>
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<tr>
<td>Child-Pugh score</td>
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<td>Fibroscan (kPa)</td>
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<td>1 Digit symbol test</td>
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<tr>
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</tr>
<tr>
<td>3 Line tracing B</td>
<td>0 (1)</td>
</tr>
<tr>
<td>4 Serial dotting</td>
<td>0 (1)</td>
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<tr>
<td>5.2 Line tracing – error score</td>
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<td>CRT percentiles (ms)</td>
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</tr>
<tr>
<td>90th percentile</td>
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</tr>
</tbody>
</table>

Parameters are presented as median (IQR). MELD, Model of End-stage Liver Disease. PSE, Portosystemic Encephalopathy. CRT, Continuous Reaction Time.
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

Funding
This study was supported with a grant from “The memorial foundation of manufacturer Vilhelm Pedersen and wife – and the Aarhus Wilson consortium”. Design of the study and collection, analysis and interpretation of data as well as writing of the manuscript was independently performed by the research group. 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.

Acknowledgements
Not applicable.

Authors’ information
Not applicable.
References

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**Fig. 1** Scatterplot of CRTindex and PSE score by phenotype

Designed using STATA IC 16.1.