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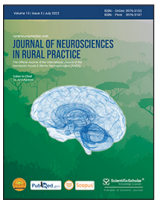

Brief Report

Bedside cognitive assessments in Wilson's disease: Comparing cases and matched controls

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ABSTRACT

Objectives: Wilson's disease (WD) is an autosomal recessively inherited disorder with a reported prevalence of 33–68/100,000 in Asian countries not including India. There is a paucity of research in India on prevalence, pattern, and profile of neuropsychological deficits among these patients. The objectives of the study were to profile neuropsychological differences between patients with WD and age- and education-matched healthy controls.

Material and Methods: A hospital-based, cross-sectional, and comparative study using strategic combination of neuropsychological tests. Persons with neurological WD receiving IP care over a 3-month period were compared with matched controls. The inclusion criteria were diagnoses of Chu Stage 1 and Chu Stage 2 neurological WD, age 15–45 years, illness of minimum 6 months, and diagnosis confirmed by low serum ceruloplasmin. Exclusion criteria were evidence or clinical suspicion of intellectual disability and past or current psychiatric illness.

Results: Median age of patients – 17.5, median age of controls – 18. R software was used to analyze the results. For all cases and controls, time taken to administer the set of tests was always <30 min. Non-parametric tests were chosen considering the data distribution. Statistically significant differences with $P < 0.05$ are noted in domains of processing speed, frontal executive function, focused attention, verbal, and visual memory in descending order.

Conclusion: A strategic compilation of easily performed bedside neuropsychological tests demonstrated differences between the two groups. This combination can be rapidly administered in the clinical setting and hence improve change tracking. This may aid in early identification and hence, earlier initiation of therapy with a possibility of improved clinical outcomes.

Keywords: Wilson's disease, Neurocognitive functioning, Neuropsychological testing, Dementia, Mild cognitive impairment

INTRODUCTION

Hepatolenticular degeneration, also known as Wilson's disease (WD), was described by Kinnear Wilson in 1912. It is an autosomal recessively inherited disorder of copper metabolism. It is caused by a mutation in the ATP7B gene on chromosome 13 and results in hepatic and neurological manifestations with onset at different ages. Estimates of worldwide prevalence of 0.5/100,000 population.[1] Indian studies, however, have been only hospital-based limiting generalizability.[2]

Neurological presentation may include rigidity, tremors, and ataxia.[1] Up to 1/3rd may present with mental health issues which may include personality changes, depression, paranoia, and schizophrenia.[3] Neuropsychological deficits in WD have also been reported. These deficits are linked to specific brain regions. Most commonly basal ganglia – putamen, head of caudate, and subthalamic nucleus – are involved. Less commonly the thalamus, cerebellum, frontal cortex, and pons are also involved.[4] The cognitive deficits in WD today are conceptualized as a progressive subcortical dementia implicating the dorsolateral prefrontal-subcortical circuit.[5,6] Neuropsychological tests may aid in detection of subclinical deficits. Earlier diagnosis and chelation therapy is known to slow down the progression of WD.[7] The mean time to diagnosis from onset of symptoms ranges from 0.5 years in hepatic WD, 1.5 years in neurological WD, and nearly 2.5 years for psychiatric symptoms.[8] At present, neuropsychological testing is not utilized for early identification of neuropsychiatric WD.

In Western literature, neuropsychological deficits in WD include attention, verbal memory, and executive functioning.

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Neurocognitive deficits indicate neurological symptoms. They may also be influenced by treatment with penicillamine and zinc.[5] Studies assessing neuropsychological deficits have made use of standardized batteries such as Wechsler's Adult Intelligence Scale and Wechsler's Memory Scale.[9] There is only one Indian study that has evaluated the neuropsychological deficits in WD. This study reported deficits in mental and motor speed, sustained and focused attention, visuo-constructive and set shifting ability, verbal learning, memory and fluency, working memory, and visual memory tested with the NIMHANS neuropsychological battery.[10] Assessment batteries have the advantage of having standardized norms that allow inferential comparisons. No study has examined strategic combination of fewer individual tests in the interest of clinical utility.

We report here a study that compared persons with neurological WD with age- and education-matched healthy controls on a combination of four easily administered bedside neuropsychological tests.

MATERIALS AND METHODS

This hospital-based study was done on inpatients with neurological WD (cases) admitted to a general medical or neurological ward of a government run tertiary care hospital in South India. Healthy family members accompanying patients admitted to other wards were selected as age- and education-matched controls. To all inpatients with neurological WD admitted over 3-month period, the following inclusion criteria were applied. (1) Patients diagnosed with WD based on clinical findings and low serum ceruloplasmin.[3] (2) Minimum time since diagnosis – 6 months. (3) Age 15–45 years. (4) Capable of providing written informed consent. Subjects who had a history of psychiatric illness, other comorbid chronic medical illness, intellectual disability, or acute behavioral problems were excluded from the study. A semi-structured questionnaire was used to collect sociodemographic and clinical information. Staging of the disease was done using Chu staging of WD.[11] Cases and controls were administered four tests – Digit span, Trail A and B, auditory verbal learning test (AVLT), and digit symbol substitution test (DSST) [Table 1].[12] Tests were selected on the basis of rapidity and ease of administration: Duration, simplicity, and no requirement of additional apparatus. This study received approval from the hospital ethics committee. Confidentiality of participants and data security was ensured. To ensure privacy, data were anonymized before analysis.

Statistical analysis

R software was used to analyze the results.[13] Data were tested for normality using the Kolmogorov–Smirnov test as the sample size was small. The data were found to have a non-normal distribution, and hence, non-parametric tests were performed for comparison between the two groups and association between illness, treatment variables, and neuropsychological performance.

Table 1: Neurocognitive tests used in the study.

Neuropsychological domain	Test	Anatomical correlates
Attention span	Digit forward and backward test	Right DLPFC, bilateral IPL, ACC, and medial occipital cortex
Divided attention	Trail A and B tests	Left DLPFC and medial PFC
Verbal memory	AVLT	IPL, middle frontal gyrus, temporal pole, medial temporal lobe, hippocampus
Processing speed	DSST	Poorly localized

DLPFC: Dorsolateral prefrontal cortex, IPL: Inferior parietal lobule, ACC: Anterior cingulate cortex, AVLT: Auditory verbal learning test, DSST: Digit symbol substitution test

RESULTS

Sociodemographic details

The median (range) age of the cases and controls was 17.5 (15–28) and 18 (15–28), respectively. About 90% ($n = 9$) of the cases were male and 40% ($n = 4$) of the controls were male.

Clinical/Illness details

The mean duration of illness was 1.85 (2.99) years. Two subjects had a positive family history of WD. Two subjects had a Chu staging of 1 and eight subjects with Stage 2. Four subjects were on penicillamine alone and six subjects were on penicillamine and zinc.

Performance on neuropsychological tests

For all cases and controls, time taken to administer the set of tests was always <30 min. Cases performed significantly worse than controls in digit span (backward), Trail A and B tests, AVLT, trials 3–5 and on immediate and delayed recall, and the digit symbol substitution tests. The two groups were not statistically different with regard to performance on digit span (forward), Trials 1 and 2 of AVLT. [Table 2] depicts the above findings.

Association between neuropsychological performance and illness parameters

We intended to analyze if there was any association between neuropsychological performance and the parameters of illness such as duration of illness, staging, and treatment. We

Table 2: Performance on neuropsychological tests.

TEST	Patients Median (range) *n*=10	Controls Median (range) *n*=10	Mann–Whitney U	*P*
Digit forward	6.5 (6–7.25)	7.5 (7–9)	26.5	0.066
Digit backward	3.5 (2.75–4)	6.5 (6–7)	8.5	**0.001**
Trail A	115 (83.75–158.75)	45 (30–62.5)	8	**0.002**
Trail B	277.5 (215.75–357.5)	92.5 (72.5–127.5)	11.5	**0.003**
AVLT_T1	7 (6.75–9)	7 (6.75–7.25)	41.5	0.534
AVLT_T2	9 (7–10.25)	10 (6.75–11.25)	41.5	0.562
AVLT_T3	9.5 (8.25–11.25)	12.5 (10.75–13)	21.5	**0.02**
AVLT_T4	10 (8.75–12.25)	13 (11.75–13.25)	24	**0.04**
AVLT_T5	12 (9.25–13.5)	14.5 (13–15)	23.5	**0.044**
AVLT_IR	10 (7–12)	13.5 (12–15)	16	**0.003**
AVLT_DR	8.5 (7–12.25)	14 (13–15)	11	**<0.001**
DSST	20 (17.5–38)	61.5 (52–64.5)	11	**<0.002**

AVLT: Auditory verbal learning test, AVLT_T: Trial, AVLT_IR/DR: Immediate recall/delayed recall, DSST: Digit symbol substitution test, Values in bold indicate statistical significance

performed a Spearman's correlation coefficient test for the same. The Chu staging of illness had a negative correlation with the performance on DSST. There was no statistically significant correlation between the duration of illness and neuropsychological performance. [Table 3] shows the correlation matrix.

DISCUSSION

Our study is the first from India comparing the neurocognitive functions in WD to healthy controls. Hegde *et al*. had examined the neuropsychological functioning on the NIMHANS battery for 12 cases correlating it with structural neuroimaging.[10] Sociodemographic profile of our sample is similar to the sample of the former study. Visuospatial deficits are rare in WD but deficits on Benton's visuospatial test and spatial neglect dysgraphia have been reported.[5,14] Executive dysfunction is reported as the most common deficit in neurological WD.[15] This study found that subjects with WD performed poorly as compared to healthy controls in digit span (backward), Trail A and B tests, auditory verbal recall test, and digit symbol substitution test alongside dysfunction in sustained attention, focused attention, processing speed, learning, and memory – similar to the previous reports.[5,9,10,15,16]

Previously, neurologically symptomatic and asymptomatic WD performed similarly on verbal memory tasks;[15] however, this study reports deficits in delayed verbal recall. With regard to the auditory verbal learning test, we found that differences between the two groups was statistically significant only in Trials 3–5. This implies an impairment in verbal learning, possibly contributing to poorer performance on immediate and delayed recall. Statically significant correlations were noted between disease staging and digit symbol substitution test. However, since the DSST was a motor task and higher stages imply more motor symptoms, this finding should be interpreted with caution. Similar to the previous reports, no significant association was noted between duration or severity of illness and performance on other neuropsychological tests.

In India, most clinical presentations involve neurological symptoms of 282 patients sampled, 69% had neurological symptoms while 14% had hepatic symptoms.[17] In another descriptive study of 350 patients by the same authors, 15 patients had psychiatric symptoms as presenting features (bipolar affective disorder – 9, schizophrenia – 5, and cognitive decline – 1).[18] This difference could be attributed to the distinct genetic mutations in the Indian subcontinent.[19] Similar findings were also obtained by Hegde *et al.*[10] In contrast to the above study, our study had an age- and education-matched control group. However, unlike the previous study, we have not evaluated the patients with neuroimaging; therefore, the correlation between structural abnormality and cognitive performance could not be ascertained. The implications of neurocognitive assessment in WD are manifold. Neurocognitive manifestations of WD may present clinically as decline in scholastic performance, mild cognitive impairment, or dementia. An hospital-based study has reported that 4.2% of the population studied (five out of 119) had dementia. The study also reported that mild cognitive impairment was commonly observed although a formal assessment was not done.[20] Performance on neurocognitive domains, especially verbal memory, processing speed, and executive functions are significantly worse in neurologic WD as compared to non-neurologic forms.[21,22] Studies also report that early diagnosis and treatment aids in better prognosis. In an observational study on patients with non-neurological as well as neurological WD, early institution of treatment in non-neurological WD helped stalling the progress of non-neurological to the neurological form.[7] In a retrospective study of an Austrian WD clinic cohort, with an average follow-up duration of 14.8 ± 11.4 years, it is reported that early diagnosis and treatment

Table 3: Spearman's correlation coefficient – illness parameters versus neuropsychological performance.

	Chu staging	Duration of illness
Chu staging		
Correlation coefficient	1	−0.133
Sig. (two tailed)	.	0.714
Duration of illness		
Correlation coefficient	−0.133	1
Sig. (two tailed)	0.714	.
Age		
Correlation coefficient	0.181	0.747*
Sig. (two tailed)	0.617	0.013
Digit span forward		
Correlation coefficient	−0.136	−0.3
Sig. (two tailed)	0.707	0.4
Digit span backward		
Correlation coefficient	−0.364	0.245
Sig. (two tailed)	0.301	0.495
Trail A		
Correlation coefficient	0.087	−0.037
Sig. (two tailed)	0.811	0.919
Trail B		
Correlation coefficient	0.218	0.012
Sig. (two tailed)	0.545	0.973
AVLT T1		
Correlation coefficient	**−0.676***	0.086
Sig. (two tailed)	0.032	0.813
AVLT_T2		
Correlation coefficient	**−0.712***	0.025
Sig. (two tailed)	0.021	0.945
AVLT_T3		
Correlation coefficient	−0.534	0.158
Sig. (two tailed)	0.112	0.663
AVLT_T4		
Correlation coefficient	−0.575	0.15
Sig. (two tailed)	0.082	0.678
AVLT_T5		
Correlation coefficient	−0.399	0.425
Sig. (two tailed)	0.253	0.221
AVLT immediate recall		
Correlation coefficient	−0.527	0.492
Sig. (two tailed)	0.117	0.148
AVLT delayed recall		
Correlation coefficient	−0.571	0.48
Sig. (two tailed)	0.085	0.161
Digit symbol substitution test		
Correlation coefficient	**−0.707***	0.125
Sig. (two tailed)	0.022	0.73

AVLT: Auditory verbal learning test, AVLT_T: Trial, Values marked *indicate statistical significance

resulted in a better prognosis.[23] The above studies indicate that early identification and intervention improve the quality of life (QOL) for patients. The Global Assessment Scale for WD which was developed considering the multisystem involvement of WD has included cognition as a domain in both the global disability tier and the neurological assessment tier.[24] This implies that neurocognitive dysfunction is a significant contributor to the QOL. It can be inferred that rapid and regular evaluation and subsequent intervention for cognitive dysfunction is indispensable and is conducive to improved QOL. A bedside neurocognitive assessment that is sensitive for WD may aid in early detection of the progress of non-neurological WD to neurological WD. The cognitive tests used in this study are paper and pen tests that are not time consuming taking no longer than 30 min. These tests would be appropriate for periodic change tracking.

The strengths of this study are that it was done on a homogeneous population (neurological WD) and the performance was compared with age- and education-matched healthy controls. We had excluded subjects with psychiatric symptoms or family history of psychiatric illness; therefore, the confounding effect of the above factors is absent in our study.

The limitations of the study are that it was done on a small sample. Comparison with standardized scores could not be done as we did not perform a battery of tests. However, the comparison with a control group has overcome this limitation. The sex of the cases and controls not being matched is another limitation that precludes generalizability of the findings. Both longitudinal and cross-sectional studies with larger sample sizes are required to replicate these findings and improve early identification.

CONCLUSION

WD, especially when presenting with neurological symptoms, may also have associated neurocognitive dysfunction, especially in frontal executive functions. Considering that the manifestation occurs in childhood or early adolescence, the crucial period for the development of one's scholastic skills, a rapid, bedside, or clinic-based assessment of neurocognitive functions, may be warranted in patients with neurological WD and subsequent cognitive remediation alongside early interventions may lead to improved clinical outcomes and QOL. More studies are required to analyze the effect of medications on neurocognitive function and whether the neuropsychological profile differs between hepatic WD and neurological WD in India.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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