



Wilson's disease: a cognitive neuropsychological perspective

Abstract

Background: Wilson's disease manifests as neuro-psychological or psychiatric symptoms along with neurological and liver disease. The present study aimed to probe into the declarative and non-declarative memory profile of Wilson's disease patients from a neurocognitive perspective. **Methods:** The study involved a sample of 12 Wilson's disease patients and 12 matched non-patient individuals who were assessed on Global Assessment Scale for Wilson's disease, the Edinburgh handedness inventory, memory scales from PGI Battery of Brain Dysfunction, Rey Auditory Verbal Learning Test, and mirror tracing task. **Results:** The overall result indicated that the Wilson's disease patient group differed with their non-patient counterparts with respect to immediate memory, recall, recognition, semantic memory, and procedural learning. **Conclusion:** The neural substrates related to the neuro-psychological symptoms of Wilson's disease patients are found to be a neural network involving basal ganglia, fronto-striatal circuits, and cerebellar region.

Keywords: Psychiatry. Liver Disease. Memory. Neural Substrates.

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INTRODUCTION

HM, a 24-year old woman, hailing from a middle socioeconomic Gujrati family, came to the Department of Neurology in Neuro-medicine, Bangur Institute of Neurosciences (BIN), Kolkata with the presenting complaints of motor rigidity, seizure attacks, and behavioural problems like stubbornness and lack of self-care. She used to study in a reputed English medium school and was an above average student along with excellence in the field of drawing and classical dance. When she was studying in class VIII, her teachers complained to her mother about her deteriorating handwriting. It was thought that she has been neglectful towards her studies. Gradually her fingers started bending, body became curved, speech got slurred, and her intellectual functioning also deteriorated. Medical tests confirmed the diagnosis of Wilson's disease. For the last eight years, the woman was under constant medical care. She recovered from most of the motor difficulties; however, frequent seizure attacks, lack of control over speed of speech, poor attention span, and slowness in learning were persisting. Her intellectual capacity was not same as before, though she had

resumed her studies and would be appearing for Xth grade examination from an Open Board. She was also suffering from mild depression and quality of life had been poor.

Wilson's disease or progressive hepato-lenticular degeneration is a rare autosomal-recessive genetic disorder of copper accumulation that manifests itself with neurological and psychiatric symptoms.[1] Onset of Wilson's disease symptoms is usually insidious in nature,[2] being associated with mild cognitive deterioration, clumsiness, and behavioural alteration. Specific neurological symptoms might follow, often in the form of Parkinsonism with or without a typical hand tremor, slurred speech, masked facial expressions, or dystonia.[1,3] Seizures and headache are also common in Wilson's disease.[1] Its adverse impact on cognitive functions of focused and sustained attention, verbal working memory, set-shifting ability, mental speed with visuo-spatial processing, constructional ability, and some aspects of memory are well-documented.[4,5] Though long term memory (LTM) is intact in Wilson's disease,[6] Portala *et al.*,[7] using a comprehensive neuropsychological battery, found immediate and short term memory (STM) impairment

in symptomatic Wilson's disease patients, particularly in females. Wilson's disease showed both lower capacity to learn and recall words across all stages of the Rey Auditory-Verbal Learning Tests (RAVLT);[6,8] but, results are conflicting in non-verbal memory tests.[4,9]

Wilson's disease being identified as reversible subcortical dementia,[10] procedural memory might be hypothesised to be more affected than declarative memory[11] owing to the involvement of neural substrates like basal ganglia and cerebellum. Referring back to the above case vignette, the index patient had similar presentation who could regain the lost ability to acquire and retain information that had resulted into resuming her academics; whereas, her procedural skill, like dancing which was early to deteriorate than the others, needed more time to be reversed. In this background, the present study aims to probe into the nature of impairment, if any, in the learning and memorisation of both the declarative and non-declarative skills. Unlike previous researches, present study used a matched control group to assess and compare the neuropsychological profiles of patients with Wilson's disease.

METHODS

Study design

The study was a hospital-based cross-sectional comparative study. Consecutive sampling method was followed for the study group.

Sample

Nineteen patients diagnosed with Wilson's disease (15 male and four female) were selected for the study following ethical processes for research. Mean age of the subjects was 20.59 ± 5.77 years with minimum five years of education. Mean age of onset of the disease was 11.94 ± 3.07 years. The diagnosis was made by experienced neurologists in a special clinic of Neurology Department in Movement Disorders Clinic of BIN, Kolkata after reviewing all the detail medical reports and by using Global Assessment Scale for Wilson's Disease.[12] Since seven of them had problem in understanding the test instructions due to high dysfunction and neurological complications, they could not be considered for detailed neuropsychological assessment and were excluded from the final sample. Twelve nonpaid volunteers with no neurological and psychiatric history served as the control subjects after one to one matching with the 12 finally selected study subjects in terms of age, education, and gender. Handedness was also matched using the Edinburgh inventory.[13] The overall assessment as mentioned below took 1.5 hours for each of the participants. All the assessments were done in one structured room with minimum distraction. Informed consent was taken from the participants before they were included in the current study.

Measures

PGI Battery of Brain Dysfunction (PGI-BDD)

This battery consists of tests of memory, perceptual-motor skill, visuo-motor skill, verbal and performance intelligence to assess gross brain dysfunction.[14] For this study, only few subtests of memory scale were administered,

namely mental balance, delayed recall, verbal retention for similar pairs, and verbal retention for dissimilar pairs. The subtests are standardised on Indian population.

Rey Auditory Verbal Learning Test (RAVLT)

RAVLT is widely used for the assessment of episodic memory with adequate internal consistency and good construct validity.[15] This test is designed as a list-learning paradigm to see the rate of learning across trials of meaningful verbal words with immediate recall in each of the five trials and 30 minutes delayed recall at the end. It also assesses level of interference in learning and recognition memory.

Mirror tracing task

The star mirror tracing task is a visual and motor test that involves learning a new motor skill.[16] The task requires that participants move a pencil to trace the diagram of a star while looking at their hand only as a reflection in a mirror. Drawing requires both visual and proprioceptive feedback to control muscle movement. The test is assessed based on how long it takes the participant to complete it and also how many times participant deviates from a line (error score). Keeping in mind the problem of motor speed in the Wilson's disease patients, only the pre and post measure error difference score was considered as procedural memory score.

RESULTS

Data were scored following the scoring criteria for each of the tests. All statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, 2001). A p-value of 0.05 was considered to determine the level of significance. Mann-Whitney U test was carried out to find out the difference between the patient and normal control on various neuropsychological functions (Table 1). Wilcoxon signed-rank test was used to find out the difference between pre-post measures on procedural learning (not in the table).

The results in Table 1 show that the Wilson's disease patients group performed significantly worse compared to the normal control in the domains of mental balance ($p=0.001$), immediate memory (digit forwards and digit backward) ($p<0.001$), retention of similar ($p=0.017$) and dissimilar pair ($p=0.003$), recognition ($p=0.025$), procedural learning ($p=0.003$), and procedural memory ($p=0.004$). However, both the groups did not show any significant difference in retroactive interference and delayed recall considering p-value of 0.05.

The pre-post analysis using Wilcoxon signed-rank test on procedural tasks identified that both the groups were significantly ($p=0.012$ for the Wilson's disease group and $p=0.013$ for control group) facilitated from the earlier learning of procedural skills, with considerably less error in their final recall trial than the baseline.

As sample size is 12 in each group, to obviate the possibility of error due to small sample size with the p-value, Cohen's guideline[17] to flag statistical significance was followed and only large or marked correlation strength ($r \geq 0.50$) were considered (Table 2). Mental balance was found to have significant positive correlation with digit

Table 1: Comparison of patients of Wilson's disease and normal control subjects on selected variables

Learning and memory variables	Group	M±SD	U-test value	p-value
Mental balance	Wilson	3.08±2.07	16.50	0.001
	Control	5.58±0.67		
Digit forward	Wilson	4.75±0.62	1.00	0.000
	Control	7.33±0.78		
Digit backward	Wilson	2.75±1.06	5.00	0.000
	Control	5.33±1.30		
Retention of similar pair	Wilson	3.92±0.90	34.50	0.017
	Control	4.75±0.45		
Retention of dissimilar pair	Wilson	2.92±0.67	24.00	0.003
	Control	4.17±0.94		
Retroactive interference	Wilson	19.83±12.83	53.50	0.282
	Control	13.17±9.37		
Recognition	Wilson	12.70±1.83	19.50	0.025
	Control	14.50±0.97		
Delayed recall	Wilson	4.58±3.96	61.00	0.523
	Control	5.92±5.12		
Procedural learning	Wilson	73.30±31.21	12.00	0.003
	Control	40.40±12.92		
Procedural memory	Wilson	66.67±16.73	22.50	0.004
	Control	84.64±11.29		

Table 2: Correlational matrix of variables on Wilson's disease patients sample

Variables	DF	DB	RSP	RDP	ROL	RGN	RI	DR	PL	PM
MB	0.456	0.792	0.609	0.747	0.685	0.125	-0.273	0.351	-0.226	-0.028
DF		0.594	0.516	0.306	0.362	0.144	-0.131	0.597	-0.824	-0.283
DB			0.648	0.534	0.618	0.170	-0.245	0.255	-0.384	0.295
RSP				0.634	0.934	0.497	-0.761	0.568	-0.234	0.078
RDP					0.724	0.269	-0.409	0.688	0.053	-0.275
ROL						0.626	-0.657	0.549	-0.079	0.116
RGN							-0.171	0.377	-0.124	0.031
RI								-0.410	-0.097	0.046
DR									-0.177	-0.607
PL										0.201

MB=Mental balance; DF=Digit forward; DB=Digit backward; RSP=Retention of similar pair; RDP=Retention of dissimilar pairs; ROL=Rate of learning; RGN=Recognition; RI=Retroactive interference; DR=Delayed recall; PL= Procedural learning; PM= Procedural memory

backward, retention of both similar and dissimilar pairs, and with rate of learning. Digit forward was observed to be positively correlated with digit backward, retention of similar pair, and delayed recall, and negatively correlated with procedural learning; whereas, digit backward correlated positively with retention of similar pair, dissimilar pair, and rate of learning. Retention of similar pair as well as dissimilar pair correlated positively with rate of learning and delayed recall, but retention of similar pair showed significant negative correlation with retroactive interference. Rate of learning correlated positively with recognition of words, but negatively with retroactive interference. Procedural memory was found to be significantly correlated negatively with delayed recall.

DISCUSSION

Digit forward is a task that selects auditory/verbal information to tap the selectivity aspect of attention and is closely related to the efficiency of attention, i.e. freedom from distractibility.[18] Digit forward involves the phonological short term store and is relatively passive compared to digit backward task. It requires minimal rehearsal process owing to its minimum involvement of working memory.[19] Poor performance of the Wilson's disease patients on digit forward task suggests that they not only have impairment in attention-monitoring on task that utilises working memory, but also have deficit in more basic processes of selectivity and focusing aspects of attention which are primarily the

functions of orbito-frontal cortex[20,21] and vulnerable to left hemispheric or diffuse damage of the brain.[18]

Different sub-domains of mental balance task of PGI-BBD including serial subtraction, reverse calling, and backward counting, characterised by variable loading of working memory detected deficit in attention-monitoring in the Wilson's disease patients. The task of digit backward requires conscious detection of events and monitoring attentional control over voluntary behaviour and thought process[22] which has been found to be impaired in Wilson's disease. Its impairment in Wilson's disease is expected owing to its greater task demand than digit forward. However, digit backward is more affected in lesions in anterior medial nuclei than in the posterior medial nuclei. The working memory deficit is also reflected in their impairment in forming association between paired stimuli of both similar and dissimilar pairs (Table 1). In general, in similar pair task, stimuli are more readily unitised than the dissimilar task due to preexisting semantic associations. Recall success of these pairs should be based on the familiarity of the words and their associative strengths. The impairment in associative learning with similar pairs suggests that the Wilson's disease patients had poor capacity for effective utilisation of semantic association between two pairs. Referring the positron emission tomography (PET)-based research findings,[23-25] it may be assumed that cued recall success which is evident from the activation of the frontal areas, is generally assumed to be facilitated by familiarity. Association deficit in Wilson's disease is evident from hypoactivity in frontal circuit that could not facilitate them to utilise posterior parietal mnemonic function[26] related to retrieval process. Also, in the present study, the learning material was juxtaposed pairs and not the fused one. Juxtaposed pairs (for example, day-night) yield a source in the right inferior and middle frontal gyri, thereby as expected showed impairment in Wilson's disease that has its pathognomy in midbrain region.[27] A diminished response of bilateral inferior frontal gyrus (IFG) and a small area within the left hippocampus during encoding of verbal paired associates have been observed in patients with schizophrenia also.[28] Patients with diminished brain response within the left IFG Brodmann Area (BA) 45 and right IFG BA 47 clusters were found to be less able to remember word pairs.[29] In a study, whole brain analysis suggested perhaps underactivation of ventrolateral prefrontal cortex which explains verbal learning deficits.[28] Difficulty in feedback and/or error utilisation is an important symptom in frontal lesion or in fronto-temporal dementia.[30] The finding of inability to utilise the familiarity of the stimuli in similar pair or to take the benefit of associative strength is another index that the Wilson's disease patients perhaps fail to utilise the pre-existing information relevant for performing task in hand, owing to their frontal pathology. It gives a clue that frontal pathology refrains a person from gaining insight from any experience. Thus, it can be assumed that the Wilson's disease patients have deficit in forming a semantic gestalt, and partially corroborates with the clinical note of their deficit in experiential integration. Since formation of association is the integrated function of parahippocampal and dorsal prefrontal cortices,[28,31] its link to the underlying neural substrates in Wilson's disease hints upon its neuropsychological significance in this disorder.

Dissimilar pairs used in this study, where the recall success requires spontaneous formation of association, the associative task became more difficult for the Wilson's disease patients, as

expected (Table 1). Their difficulty in searching and utilising cues might have prevented them from retrieving information from the memory system. Present study indicates the presence of the poor associative learning in Wilson's disease is so strong that it could serve as a prominent neuropsychological feature of Wilson's disease. Research indicates that basal ganglia and limbic cortex which are the pathognomonic site of Wilson's disease are the epicenters for associative learning.[32-35] Contribution of neural substrates along with poor attention and concentration, rate of learning and association formation might have resulted in poor learning ability in the patients with Wilson's disease.

It has been found that the associative memory and item memory involve distinct processes and they underlie different neural structures.[36] In our study, the Wilson's disease patients revealed impairment in word (Table 1) as well as in associative recall. Deficit in recall may be because of the fact that recall requires extensive retrieval strategies and planning. Enhanced bilateral cerebral blood flow in prefrontal cortex has been noted in both supra- and sub-span tasks.[37] Be it associative task or the word recall, perhaps the frontal deficit in Wilson's disease had detrimental effect on both the tasks, limiting their task-relevant executive function which is essential for forming strategies and planning.

Processing speed deficit recorded in Wilson's disease on digit span task and its positive correlation with rate of learning (Table 2) as evident on RAVLT indicate their poor working memory capacity and slow information processing. Again, rate of learning is directly associated with both similar and dissimilar association formation (Table 2) that suggest possibly their slowed down processing speed interfered with rate of learning and in turn with forming association between two stimuli, when the paired stimuli were presented at a normal rate of word per second. Their processing speed deficit may interfere with their formation of LTP, leaving a weak imprint during encoding which may cause under-learning of stimuli. Long term learning requires creating a LTP in the neural network of the organism. Slowed information processing disrupts the formation of LTP of tasks of high-cognitive load with many simultaneous mental operations[38] like the digit backward task. Moreover, extensive evidence now indicates the role of basal ganglia, in particular the dorsal striatum, in learning and memory.[33]

There exists a significant difference between the Wilson's disease patient group and non-patient control group with respect to their procedural learning and procedural memory capacity where the Wilson's disease patient group performed poor as compared to their non-patient counterparts. The given task of procedural memory required visuo-perceptual-motor ability along with ability to learn procedural skills. Although findings suggest difficulty in motor coordination in the Wilson's disease patients,[39] there is lack of researches exploring the visuo-perceptual-motor ability of the Wilson's disease patients. However, the difficulty in procedural learning is generally attributed to the difficulty in functioning of cerebellum. Damage to this area may prevent the proper relearning of motor skills and automating the unconscious process used when learning a procedural skill.[40] In case of Wilson's disease, exogenous substances like copper accumulates in the nervous system and liver having a depressant effect on central nervous system

function, especially on cerebellum, that can cause ataxia as well as other neurological and organ impairments[41] and thus, may have inhibiting effect on procedural learning capacity.

Conclusion

Overall findings of the study indicate that the impairment in the cognitive functions of Wilson's disease cannot be localised to any restricted region of the brain; but, predominantly involve fronto-parietal and fronto-striatal circuits. Increased sample size along with inclusion of comparable groups with other movement disorders and psychiatric patients, who share same neural circuits, would help to develop better insight in relating the cognitive dysfunction with its underlying neural network.

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