Eur Arch Psychiatry Clin Neurosci (2001) 251 : 262 – 268

ORIGINAL PAPER

Kamilla Portala · Sten Levander · Kerstin Westermark · Lisa Ekselius · Lars von Knorring

Pattern of neuropsychological deficits in patients with treated Wilson's disease

Received: 24 April 2001 / Accepted: 24 September 2001

Abstract The study aimed to describe the neuropsychological profiles in patients with treated Wilson's disease (WD). The series included 19 symptomatic and 2 asymptomatic patients with a mean age of 35.3 ± 9.2 years. They were tested with the Automated Psychological Test system (APT), a comprehensive computerised neuropsychological test battery. APT comprised eleven separate tests and assessed five essential types of neuropsychological functions: motor functions, basic neuropsychological functions, specific cognitive functions, memory, and executive functions. The results were compared to current norms of the test battery.

The symptomatic WD patients had significantly lower performance than the norms on all finger tapping tasks, the simple reaction time, the simultaneous capacity background task, the short-term memory test, the index of word decoding speed, the grammatical reasoning test, and the perceptual maze test. They were significantly higher on the index of impulsive errors, and used a significantly more global processing mode in the test of selective attention. The female symptomatic patients displayed more pronounced neuropsychological deficits than the males in the complex tasks.

WD patients displayed a specific profile of moderate neuropsychological impairment. The results are theoretically interesting and have practical implications for the management of WD patients, e. g. some patients confronted with the results have had increased compliance.

Key words Wilson's disease · hepatolenticular degeneration · neuropsychology · executive impairment · fronto-striatal dysfunction

Kamilla Portala, M.D. (✉) · L. Ekselius, M.D., Ph.D. ·
L. von Knorring, M.D., Ph.D.
Dept. of Neuroscience, Psychiatry
University Hospital
75185 Uppsala, Sweden
Tel.: +46-18-6 11 52 43
Fax: +46-18-51 58 10
E-Mail: Kamilla.Portala@UASpsyk.uu.se

S. Levander, M.D., Ph.D.
Department of Psychiatry
University of Lund
Malmö, Sweden

K. Westermark, M.D., Ph.D.
Department of Internal Medicine
University Hospital
Uppsala University
Uppsala, Sweden

EAPCN 342

Introduction

Wilson's disease (WD), hepatolenticular degeneration, is a treatable autosomal recessively inherited disorder of copper metabolism with a prevalence of about 20 to 30 per million [43]. The gene that causes Wilson's disease, chromosome 13 band q14.3 [3], is known to code for a copper-transporting P-type ATPase. A mutation in the WD gene (ATP7B) results in reduced excretion of copper into bile and leads to its accumulation in the liver, brain and other organs [9]. The clinical picture varies considerably, and includes different kinds of severe hepatic states (from acute hepatitis to fulminant liver failure), neurological (e. g. dystonia, ataxia and Parkinsonism) and psychiatric symptoms and disorders (e. g. anxiety, affective syndromes and personality disorders) [43].

The distribution of neuronal damage in the brain caused by copper deposition and/or encephalopathy due to hepatic dysfunction in WD is highly variable, and may include a certain degree of general brain atrophy [43]. Histopathological examination as well as computer tomography (CT) and magnetic resonance tomography (MRT) have repeatedly demonstrated the presence of structural abnormalities in the corpus striatum [47] but all brain areas may be affected [15]. Moreover, an abnormal metabolism of neurotransmitters, particularly dopamine, noradrenaline and serotonin, has also been reported [6, 15, 35, 43]. Neuroimaging findings in WD suggest a complex pathogenesis involving efferent [37, 50] and afferent [44] dopaminergic projections as well

as dopamine transporter abnormalities [17]. Furthermore, Hawkins et al. [13] demonstrated a reduction of glucose metabolism in all brain regions except the thalamus.

Impairments of a descending frontobulbar saccadic pathway (slow saccadic eye movements) [18], corticomotorneuronal pathways (EMG) [2, 3], somatosensory, auditory and visual pathways at the brainstem level (evoked potential) [4, 12] have been reported. These studies support the hypothesis that impairments of the frontal and parietal-subcortical circuits in WD may cause both cortical and subcortical symptoms [5].

The spectrum of clinical, pathological, neuroimaging and neurophysiological signs varies somewhat in WD studies depending on the sample of patients included. Elapsed time since onset, treatment history, and subtype (hepatic, neurological or asymptomatic) appears to be important.

In contrast to the literature, our clinical observations of a Swedish sample of patients with treated WD suggest some cognitive and behavioural dysfunction in most patients irrespective of whether the clinical form is hepatic or neurological. It is well known that patients with non-alcoholic cirrhosis [30, 46] and patients with basal ganglia pathology show significant cognitive impairments, mostly in motor and memory function [45]. There is a need to understand the nature of the cognitive deficits among treated WD patients, as individuals and as a group, to be able to optimise medical treatment and management in order to maximise social and occupational functioning.

The main aim of the current study was to explore the degree and the pattern of cognitive impairment among a series of Swedish treated WD patients using a comprehensive neuropsychological test battery.

Material and methods

Patients

This study forms part of an ongoing research project comprising 22 consecutive WD patients, 7 women and 15 men, recruited from north and central Sweden and admitted to the Dept. of Internal Medicine, Uppsala University Hospital between November 1996 and April 1998. The patients were studied in association with regular clinical appointments. The WD diagnosis was based on clinical symptoms, low levels of plasma ceruloplasmin, increased serum (free) and urinary copper concentrations, mostly on the occurrence of Kayser-Fleischer rings at slit-lamp examination, and increased liver copper concentrations on needle biopsy. Genetic charting was performed in all patients [49]. The psychopathology and MRT findings in a sub-sample of the included patients are described in a previous report [38, 47]. Of the 22 patients, one recently diagnosed man was excluded because he did not complete the testing. At the time of diagnosis 19 of the 21 patients were symptomatic and 2 were asymptomatic, i. e. pre-symptomatic (a 27-year-old male and a 30-year-old female, diagnosed by family screening at the age of 3 and 7 years, respectively).

At the time of the psychological testing, serum (free) and urinary copper levels were recorded. All patients were in a copper-depleted state. The neurological impairments ranged from negligible to moderate. All patients received pharmaceutical treatment for WD, except one patient who was liver transplanted. Twelve patients were on triethylene tetraamine dihydrochloride (Trientine) treatment, seven on D-penicillamine (D-P) and one on zinc acetate (Zn) treatment. Two of the 21 patients were treated with psychotropic drugs (citalopram, nefazodon and flupentixol).

The 19 symptomatic WD patients were subdivided into three subgroups according to their clinical status at the time of diagnosis: predominantly hepatic, n = 8; predominantly neurological, n = 7; and mixed, n = 4. The mixed group was too small for separate statistical analyses; therefore descriptive statistics for this group are presented only when relevant. Demographic and clinical characteristics of the 19 symptomatic patients are presented in Table 1.

The neuropsychological test battery

When studying neuropsychiatric disorders which involve subcortical dysfunction, and particularly basal ganglia diseases known to be associated with movement impairments, bradyphrenia and a specific dementia profile [39, 52], it is important to use a neuropsychological test battery that measures response speed accurately and with a high resolution (1 ms or better). A computerised and comprehensive neuropsychological test battery matches the specific needs in this context. The results of early reports [2–5, 12, 18] about motor impairments and the relatively good cognitive performances of WD patients were taken into consideration when we decided to use the Automated Psychological Test (APT) system [23] for this study. The APT set is one of the most often used computerised neuropsychological tests in Scandinavia [36]. The different tests of the APT set have been applied to evaluate cognitive and motor impairments in somatic [40] and psychiatric diseases [11, 22], biological psychology [10] as well as to study various CNS effects of drugs [25, 48]. The clinical version of APT used in the present study comprised eleven separate tests (presented below) and assessed five essential types of neuropsychological functions: motor functions, basic neuropsychological functions, specific cognitive functions, memory, and executive functions.

Motor and basic neuropsychological functions

Finger Tapping and Alternation (FTA) Test. The FTA test, a simple manual dexterity task to measure motor speed and co-ordination, includes 5 subtasks (each 12 seconds long): right index finger tapping (TR); left index finger tapping (TL); right index-middle finger alternation (AR); left index-middle finger alternation (AL); and right – left index finger alternation (ARL).

The *Reaction Time (RT) Test* comprised four subtests: simple auditory and simple visual RT, responding with the dominant index fingers (9 stimuli); two-choice (left-right) visual RT (17 stimuli); and two-choice visual RT with auditory signals for response inhibition (25 stimuli with 50 % inhibition rate).

The average RT for a simple task with only one response alternative is approximately 200 ms (shorter for auditory and longer for visual and tactile moods). The average RT for more complex stimuli increases logarithmically with the number of response alternatives. The RT data are analysed using a regression algorithm based on the plot

Table 1 Demographic and clinical characteristics of the 19 symptomatic patients with treated WD, who were in the copper-depleted state at the time of investigation

	Neurological N = 7	Hepatic N = 8	All N = 19
Age (range 22–56)	35.8 ± 9.8	32.6 ± 3.5	36.0 ± 9.3
Age at onset (range 9–25)	16.0 ± 6.0	17.5 ± 5.0	18.1 ± 5.4
Duration since diagnosis	19.5 ± 8.9	15.3 ± 4.5	20.3 ± 5.1
Education (years, range 8–16)			12.2 ± 2.0
Family history of WD (N = 17*)			29%
Family history of psychiatric disorders (N = 17*)			24%
Family history of neurological disease (N = 17*)			12%

* Two patients were adopted without knowledge about their biological parents

of actual RT:s vs the complexity of the task. Two main meta indices are extracted, RT200 and RT2000. RT200 is the speed relative norms, expressed in T-scores (Mean=50, SD=10) for a virtual RT task that takes a healthy average person, aged 17 to 50 years, exactly 200 ms to respond to; RT2000 is the virtual RT task that takes a healthy person, aged 17 to 50 years, exactly 2000 ms to respond to. Both RT200 and RT2000 are important aspects of cognitive capacity and their correlation in normal subjects is very high.

The *k-test* is a continuous performance task that assesses *Selective Attention* (SelAtt). The task is to decide if the letter k is present in a set of 10 characters presented in random positions on a screen, and respond 'yes' or 'no' as fast and accurately as possible to the continuous stream of stimuli.

The *Simultaneous Capacity* (SCap) test (dual task) is designed to assess a subject's capacity to handle more than one task simultaneously. One index reflects the performance in Background task (SCapBG) and another index the Foreground task (SCapFG). A marked difference in priorities signals an executive problem as well as inability to concentrate.

Memory and cognitive aptitudes tests

The *Digit Span* test: a series of digits are presented on the monitor, one by one, with process-controlled string length. The sequence should be reproduced forwards for 13 strings and then backwards for 11 strings. The test assesses the verbal short-term memory (STM).

The *Associative Learning* test is modelled on the Digit Symbol Substitution Test, a subtest of the Wechsler Adult Intelligence Scale, but uses letters instead of symbols. A translation table of 10 letters and digits is continuously present in the top of the screen. Letters are presented one by one in the centre of the screen. The subject should respond by entering the corresponding digit according to the letter-digit translation list. Subjects are instructed that they will do the test again without access to the translation table.

The *Long-Term Memory* (LTM) test comprises the same task as the Associative learning test, but without access to the translation table between letters and digits. The LTM test is administered 20 minutes after the Associative learning test. The performance index reflects the number of remembered letter-digit pairs.

The *Word Recognition* test is a lexicon decision task in which subjects decide whether a combination of letters presented on screen is a word or not. From the test, an index of vocabulary (Vocab) and an index of word decoding speed (VerbSp) are calculated.

In the *Grammatical Reasoning* test subjects are required to determine the true status of verbal statements describing geometrical figures and their relations. Performance is calculated as the average of speed and accuracy indices.

The *Perceptual Maze Test (PMT)* assesses visual search, visuospatial ability and general intelligence. The PMT was originally constructed as a test of frontal-lobe impairment, implying deficient planning skills [7, 8]. The cerebral activation pattern elicited during testing with the PMT (anterior cingulate cortex, prefrontal and posterior parietal cortex) was visualised in the PET study by Ghatan et al. [10]. The PMT task is to select a pathway through a triangular maze pattern (from the bottom to the top) that passes as many targets (filled circles) as possible as fast as possible by operating a set of four keys on the keyboard. Performance in the test (VisoSpat) is calculated by summing speed and accuracy indices with equal weight.

Executive functions

The *Austin Maze Test* is based on the equivalent test described by Lezak [26]. The task is to find a hidden pathway out of a maze. A performance index is computed based on the maximum number of steps that a subject can handle. The Executive Consistency Index (ExecCons) reflects the consistency with which a subject tries to find the pathway out by trial and error. There is a time limit in each node and for the total test. The Executive Speed Index (ExecSp) reflects the correlation between speed and overall performance.

Most of the APT tests can supply information about executive functions. Unspecified instructions are given that speed and accuracy are equally important. The actual balance between these two aspects is usually consistent across tests and can be calculated as the *Speed vs. Accuracy preference* (SpPref). In some of the APT tasks, errors are made because of sloppiness and excessive stimulus boundedness rather than because of pronounced preference for speed. The Impulse index reflects an *Impulsive vs. a Reflective cognitive style* (Impuls). Other meta indices reflecting executive functions are *Global vs. Sequential strategy* (Global) and *Strategy flexibility* in the k-test (KFlex) and in the perceptual maze test (MFlex).

APT performance can be summarised in three meta indices, expressed as IQ scores (M = 100, SD = 15). IQ1 represents basic motor and speed indices; IQ2 represents attention mechanisms and speed in more complex tasks. IQ3 is equivalent to a conventional IQ index and correlates approximately 0.75 with a WAIS IQ score.

Procedure

The Ethics Committee at the Medical Faculty of the Uppsala University approved the study design. The purpose and the structure of the study were explained to the patient by the investigators. The APT system was run on a standard IBM-PC under DOS [23]. The test session took between 2.5 and 3 hours, subdivided into three parts. The patients had the possibility to take a pause between the separate parts but none of them did. A test leader (the first author) was continuously present during the test sessions. Twenty-one patients with treated WD completed all the tests.

Statistical methods

To reduce the number of output variables of APT system, the raw ATP data were transformed into a standardised set of meta indices, and expressed as T-scores (M=50, SD±10). Norm data are based on data collected since the early 1980s and continuously updated. The number of healthy volunteers varies for the different tests, from approximately 250 up to several thousand [23]. No data from the general population are available.

Statistical analysis included parametric and non-parametric tests. Correlations between the APT and age, age of onset, and duration of disease were sought by mean partial correlations, controlled for confounding variables. The Mann Whitney U-test was used to compare statistical significance of differences between the predominantly neurological and the predominantly hepatic WD patients, and between sexes.

Results

Differences in the APT variables between the patients with treated WD and norm data

The 95% confidence intervals and means of the APT variables for the 19 symptomatic and two asymptomatic WD patients are illustrated in Fig. 1.

The 19 symptomatic WD patients had significantly lower performance than the norms on all finger tapping tasks (TR, TL, AR, AL, ARL), the simple reaction time (RT200), the simultaneous capacity background task (SCapBG), the short-term memory test (STM), the index of word decoding speed (VerbSp), the grammatical reasoning test (GrReas), and the perceptual maze test (VisoSp). They had significantly higher scores on the index of impulsive errors (Impulse), and used a significantly more global processing mode in the k test of selective attention. There was a conspicuous variability among the patients in simple RT (RT200). There was no significant correlation between simple and complex reaction time (RT2000). In the groups of healthy volunteers this corre-

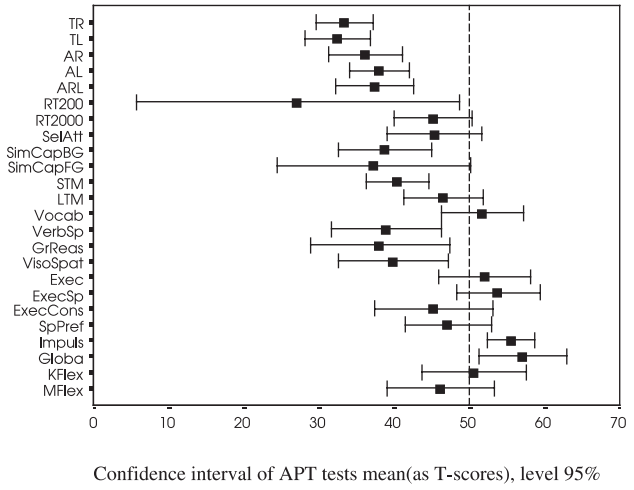

Fig. 1 The neuropsychological profile in the symptomatic WD patients (n=19) expressed as T-scores (Mean=50, SD±10). *TR* tapping with right index finger, *TL* tapping with left index finger, *AR* alternation between the right index and middle fingers, *AL* the same alternation with left fingers, *ARL* alternation between the right and left index fingers, *RT200* the simple reaction time, *RT2000* the complex reaction time, *SCapBG* simultaneous capacity in background task, *SCapFG* simultaneous capacity in foreground task. *STM* the short-term memory, *LTM* the long-term memory, *Vocab* the index of vocabulary, *VerbSp* the index of word decoding speed, *GrReas* the grammatical reasoning test, *VisoSpat* performance in the visuo-spatial test. *Exec* the executive index, *ExecSp* the executive speed index, *ExecCons* the executive consistency index. *SpPref* the speed preference index, *Impulse* the impulsive index, *Global* the global/sequential index, *KFlex* the index of strategy flexibility (global vs. sequential) in the k-test and *MFlex* in the Perceptual Maze test.

lation is approximately 0.70 (50 % shared variance). The two asymptomatic patients had similar but less pronounced impairments, especially as concerns RT200 and Global strategy.

Data for the APT IQ scores are shown in Table 2. They were moderately inter-correlated (r=0.42 to r=0.52). The variability of IQ1 was much higher than expected, whereas the variability of IQ2 and IQ3 was approximately 15. As can be seen from Table 2, WD patients have a normal conventionally assessed IQ. They are somewhat deteriorated for IQ2 (half a SD) and display a marked degree of deterioration (one and a half SD) for IQ1. Five of the 19 patients had IQ1 scores lower than 70 (–2 SD).

Table 2 Means, SD and range of three APT IQ indices (Meta indices, expressed as IQ scores (M = 100, SD = 15). IQ1 represents basic motor and speed indices; IQ2 represents attention mechanisms and speed in more complex tasks (IQ3 is equivalent to a conventional IQ index) for 19 symptomatic WD patients

	Mean	SD	Range	Significance
APT IQ1	76.9	35.1	–40–104	$p < 0.01$
APT IQ2	93.2	14.4	65–117	$p < 0.05$
APT IQ3	96.0	16.0	66–118	NS

Differences in the APT variables between the predominantly neurological and the predominantly hepatic patients with treated WD

The predominantly neurological WD patients' performance was significantly higher than that of the predominantly hepatic WD patients on the index of executive consistency (ExecConc) ($z= 3.000$, $p < 0.003$), the alternation task between the right and left index fingers (ARL) ($z= 2.142$, $p < 0.03$). No other significant differences were found between the two groups of WD patients.

Correlations between the APT variables and age, duration, and age at onset in the 19 symptomatic WD patients

The possible roles of age, duration, and age at onset as influential factors on the obtained APT results was examined. The partial correlation coefficients were computerised. ExecSp ($r = –0.52$, $p < 0.07$) and GrReas ($r = –0.46$, $p < 0.05$) were correlated to age, also when controlled for duration. VisoSpat ($r = – 0.50$, $p < 0.03$) was correlated to duration also when controlled for age. TL ($r = –0.48$, $p < 0.05$) and VisoSpat ($r =0.45$, $p < 0.05$) were correlated to age of onset, also when controlled for age.

Gender differences in the 19 symptomatic patients with treated WD

When male and female symptomatic WD patients were compared with respect to age, age at onset and duration of disease no significant differences were found.

The confidence intervals and means of the APT variables, compared to the norms, at a 95 % level for male symptomatic WD patients (n=13) and female symptomatic WD patients (n=6) are illustrated in Fig. 2a and b, respectively. The 13 male symptomatic WD patients had a mean age of 33.2±5.1 years, a mean age at onset of 16.9± 5.9 years, and a mean duration of disease (from age of diagnosis) of 16.4±6.9 years. The 6 female symptomatic WD patients had a mean age of 43.9±11.8 years, a mean age of onset of 20.7±3.0 years, and a mean duration of disease (from age of diagnosis) of 23.1± 8.9 years.

Finally, the possible sex differences (among the 19 symptomatic patients with WD) in strategy and performances in computerised neuropsychological tests were examined. After correction for duration of WD, the 13 male symptomatic WD patients performed significantly higher on the GrReas ($r = 0.54$, $p < 0.02$) with a mean of 45.7±12.0 for males and 21.8±23.0 for females. The 6 female symptomatic WD patients had a significantly higher value of the MFlex ($r = 0.56$, $p < 0.02$) with a mean of 41.6±11.3 for males and 54.7±13.6 for females. When tapping and alternation of the right and left index finger were compared in female and male WD patients, females performed significantly slower in both tasks equally, al-

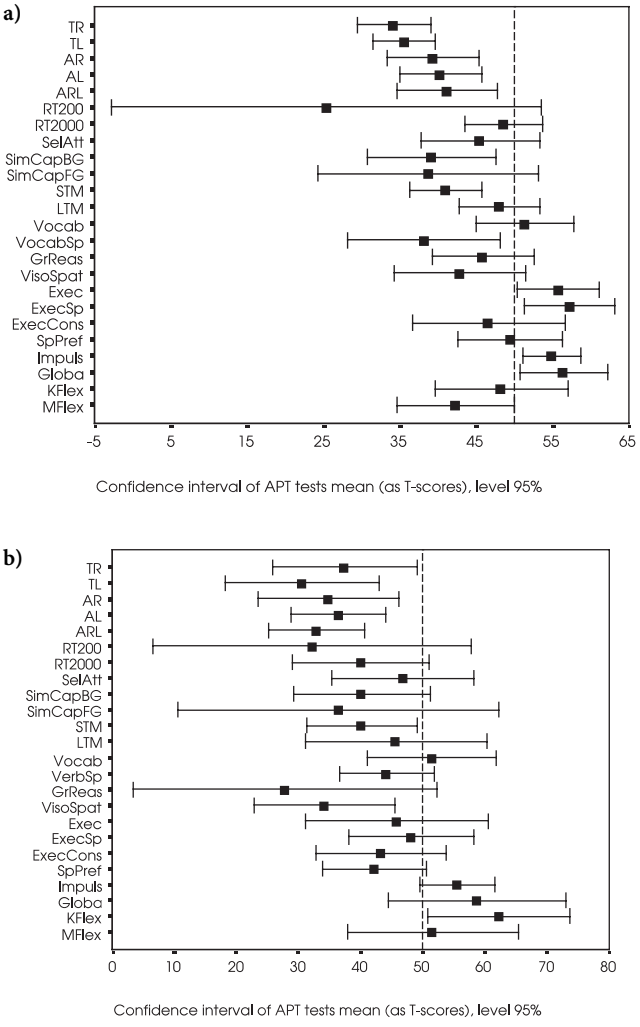

Fig. 2 **A** The neuropsychological profile in the male symptomatic WD patients, expressed as T-scores (Mean=50, SD±10). **B** The neuropsychological profile in the female symptomatic WD patients, expressed as T-scores (Mean=50, SD±10). See Fig. 1 for abbreviations.

though slower with the left hand ($z = -2.200$, $p < 0.03$), and males were equally slow on both hands. In contrast, females had a mostly equal mean of the two-choice (left-right) visual RT (VRT) without and with inhibition (RTI) response, but men had a significantly prolonged RTI left ($z = -1.921$, $p < 0.05$) compared with females.

Discussion

In our study, we found a discrepancy in the degree of prolongation between the simple reaction time (RT200) and the complex reaction time (RT2000), i. e., the RT200 speed was much slower than the RT2000 speed, in both symptomatic and asymptomatic WD patients. In healthy volunteers, there is a high correlation between the simple and complex reaction times. This correlation is lacking in the WD patients. The results are of interest as both the simple and complex reaction times reflect important aspects of the cognitive, executive and behavioural capacity. A similar finding has been reported in schizophrenic patients [48]. The motor functions assessed by the Finger Tapping Alternation tests (five subtasks) were significantly slower in the 19 symptomatic WD patients, which agrees with an earlier report [19]. In the index finger tapping tasks, equal but reduced speed was obtained for the two hands in the male WD patients (also reported in a clinical study of schizophrenic patients [24]). The female WD patients had slower tapping in the left (i. e. non-dominant) index finger. Tarter et al. [45] examined 10 hepatic WD patients, 4 males and 6 females, and found significantly slower tapping by the non-dominant hand but no difference in the dominant hand. This may, considering our results, depend on a preponderance of female WD patients in the sample. The prolonged reaction time as well as the great variability in the mean response time have been reported earlier [19, 28].

The poor performance on the Simultaneous Capacity test illustrates the problems symptomatic WD patients have to handle more than one task simultaneously, suggesting an executive problem in allocating attention resources.

The result of the short-term memory test (STM) in the symptomatic WD patients was significantly inferior as compared to the norms, which is in line with previous findings [16, 31]. The results on the long-term memory test (LTM) and the index of vocabulary (Vocab) were within the norms, which agrees with an earlier study [16]. The results of the Grammatical Reasoning test (GrReas) are significantly lower than in the normal group. There are also reports of impairments of conceptual visuo-spacial function in the literature [45]. In contrast, performance on the PMT (VisoSp) was not significantly lower than the norms probably because of the large variation on performance. However, the results of the memory and cognitive aptitudes tests in our study suggested slight to moderate impairment of the neuropsychological function in WD patients. That used to be associated with impairments of both cortical and subcortical structure.

The results of executive functions based on the Austin Maze test are within the norm. However, when we looked at priorities, strategy and cognitive style, which were included in executive functions, we found a different profile. The WD patients have important problems when handling more than one task simultaneously and they used a global strategy rather than a sequential strategy. Besides, they often showed an impulsive, rather than reflective, style.

Our results suggest that the female symptomatic WD patients displayed more pronounced neuropsychological deficits than the male symptomatic WD patients in the complex tasks – in more basic tasks both sex groups were equally impaired when compared to healthy controls. Due to the small number of female symptomatic WD patients, the results must be taken with caution.

Only two of the 21 WD patients used psychotropic drugs (one SSRI and one major tranquilliser) and there-

fore it is not possible to evaluate the possible influence statistically. However, the profile was not separate in these two patients as compared to the rest of the group. There are no reasons to believe that Trientine or D-penicillamine treatment has a differential effect with respect to neuropsychological functioning and no such tendencies were noted in the present study.

Two trends have been found in the study of neuropsychological functions in WD. Some authors regard WD as a subcortical or frontal dementia disorder [14, 21, 42, 43]. Others are hesitant to use the dementia concept [20, 31] as defined in the previous version of DSM-IIIR or the ICD-10. All these authors agree that there are at least mild neuropsychological impairments in motor-related and memory functions in neurologically impaired WD patients. Makarova and Shekhovtsova [29] reported similar findings. Historically, the term dementia implied an often progressive and always irreversible course of cognitive deficits and psychosocial impairments. In DSM-IV, the definition of dementia is based on cognitive deficits and does not consider prognosis, i. e. dementia may be progressive, static, or remitting. Moreover, new dementia diagnoses have been introduced in DSM-IV, i. e. dementia due to a general medical condition like Huntington's disease, B_{12} deficiency and hypothyroidism. This diagnostic category in the DSM-IV is probably better suited for WD than the dementia diagnoses in the DSM-III-R or in the ICD-10.

However, our results as well as earlier studies about neuronal damage in WD [2, 4, 15, 18, 43, 50] support the hypothesis that impairments of the frontal-subcortical circuits occur in WD, which may cause both cortical and subcortical symptoms. There is a concept that disturbances in the frontal-subcortical circuits may mediate many aspects of human behavioural, as well as some psychiatric disorders (e. g. depression, schizophrenia, and obsessive-compulsive) and components of movement disorders involving basal ganglia [5].

Conclusions

Wilson's disease is associated with a characteristic profile of neuropsychological impairment, in which basic neuropsychological functions and executive functions appear to be the most disturbed. This profile is similar to that found for schizophrenic patients [48]. Schizophrenia is a neuro-psychiatric disorder in which the basal ganglia are strongly incriminated. Thus, our findings have theoretical as well as clinical implications.

Acknowledgement The investigation was supported by the Fredrik and Ingrid Thuring's Foundation, the Märta and Nicke Nasnell Foundation, the Psychiatric and Neurological Research at Uppsala University, the Swedish Medical Research Council and the Swedish Natural Health and Welfare Board.

References

1. American Psychiatric Association (1994) Diagnostic and Statistical Manual of Mental Disorders, 4th edn. Washington, DC: American Psychiatric Association. pp 133–163
2. Berardelli A, Inghilleri M, Priori A, Thompson PD, Fabri S, Fieschi C, Manfredi M (1990) Involvement of corticospinal tract in Wilson's disease. Mov Disord 5:334–337
3. Bull PC, Thomas GR, Rommens JM, Forbes JR, Cox DW (1993) The Wilson disease gene is a putative copper transporting P-type APTase similar to the Menkes gene. Nat Genet 5:327–337
4. Chu NS (1986) Sensory evoked potentials in Wilson's disease. Brain 109:491–507
5. Cummings JL (1993) Frontal-subcortical circuits and human behavioral. Arch Neurol 50:873–880
6. Earl CJ (1961) Anatomical distribution of copper in the brain. In: Cummings JM, Walshe JN, (eds) Wilson's Disease: Some Current Concepts. Oxford: Blackwell, pp 18–23
7. Elithorn A (1955) Preliminary report on a perceptual maze test sensitive to brain damage. J Neurol Neurosurg Psychiatry 18:287–292
8. Elithorn A, Powell J, Telford A (1976) Mental assessment on line. Proc Electronic Display 3:18
9. Gollan JL, Gollan TJ (1998) Wilson's disease in 1998: genetic, diagnostic and therapeutic aspects. J Hepatol 28 Suppl 1:28–36
10. Ghatan PH, Hsieh JC, Wirsén-Meurling A, Wredling R, Ericsson L, Stone-Elander S et al. (1995) Brain activation induced by the Perceptual Maze Test: a PET study of cognitive performance. Neuroimage 2:112–124
11. Grawe RW, Levander S (1995) Smooth pursuit eye movements and neuropsychological impairments in schizophrenia. Acta Psychiatr Scand 92:108–114
12. Grimm G, Madl C, Katzenschlager R, Oder W, Ferenci P, Gangl A (1992) Detailed evaluation of evoked potentials in Wilson's disease. Electroenceph Clin Neurophysiol 82:119–124
13. Hawkins RA, Mazziotta JC, Phelps ME (1987) Wilson's disease studied with FDG and positron emission tomography. Neurology 37:1707–1711
14. Hoogenraad T (1995) Wilson's disease. In: Warlow CP, von Gijn J (eds) Major Problems in Neurology, Vol 30. London: WB Saunders Company, pp 107–108
15. Horoupian DS, Sternlieb I, Scheinberg IH (1988) Neuropathological findings in penicillamine-treated patient with Wilson's disease. Clin Neuropathol 7:62–67
16. Issacs-Glaberman K, Medalia A, Scheinberg IH (1989) Verbal recall and recognition abilities in patients with Wilson's disease. Cortex 25:353–361
17. Jeon B, Kim JM, Jeong JM, Kim KM, Chang YS, Lee SD, et al. (1998) Dopamine transporter imaging with [^{123}I]-β-CIT demonstrates presynaptic nigrostriatal dopaminergic damage in Wilson's disease. J Neurol Neurosurg Psychiatry 65:60–64
18. Kirkham T, Kamin DF (1974) Slow saccadic eye movements in Wilson's disease. J Neurol Neurosurg Psychiatry 37:191–194
19. Knehr CA, Bearn AG (1956) Psychological impairment in Wilson's disease. J Nerv Ment Dis 124:251–255
20. Lang C (1989) Is Wilson's disease a dementing condition? J Clin Exp Neuropsychol 14:569–570
21. Lang C, Müller D, Claus D, Druschky KF (1990) Neuropsychological findings in treated Wilson's disease. Acta Neurol Scand 81:75–81
22. Levander S (1987) Evolution of cognitive impairment using a computerized neuropsychological test battery. Nord Psykiatr Tidskr 41:417–422
23. Levander S (1988) An automated psychological test battery: IBM-PC version. Research report from Department of Psychiatry and Behav Medicine, University of Trondheim, Norway 11:65
24. Levander S, Bartfai A, Schalling D (1985) Regional cortical dysfunction in schizophrenic patients studied by computerized neuropsychological methods. Percept Mot Skills 61:479–495
25. Levander S, Gillner A (1982) Metipranolol and propranolol: no effects of a single oral dose. Psychopharmacology 76:359–366

26. Lezak MD (1983) Neuropsychological Assessment. New York: Oxford University Press, pp 526–527
27. Lishman WA (1987) Organic Psychiatry, 2nd edn. Oxford, UK: Blackwell Scientific Publications, pp 563–567
28. Littman E, Medalia A, Senior G, Scheinberg IH (1995) Rate of information processing in patients with Wilson's disease. J Neuropsychiatry Clin Neurosci 7(1):68–71
29. Makarova VA, Shekhovtsova LF (1989) Psikhometricheskoe Issledovamie Intellekta u Bok'nykh Gepatoserebral'noi Distrofei, Zhurnal Nevropatologii i Pisikhiatrii immeni SS Korsakova 89:22–26
30. McCrea M, Cordoba J, Vessey G, Blei AT, Randolph C (1996) Neuropsychological characterization and detection of subclinical hepatic encephalopathy. Arch Neurol 53:758–763
31. Medalia A, Galynker I, Scheinberg IH (1992) The interaction of motor, memory, and emotional dysfunction in Wilson's disease. Biol Psychiatry 31:823–826
32. Medalia A, Isaacs-Glaberman K, Scheinberg IH (1988) Neuropsychological impairment in Wilson's disease. Arch Neurol 45(5):502–504
33. Medalia A, Scheinberg IH (1989) Psychopathology in patients with Wilson's disease. Am J Psychiatry 146:662–664
34. Meyer BU, Britton TC, Bischoff C, Machetanz J, Benecke R, Conrad B (1991) Abnormal conduction in corticospinal pathways in Wilson's disease: investigation of nine cases with magnetic brain stimulation. Mov Disord Vol 6: No 4:320–323
35. Nyberg P, Gottfries C-G, Holmgren G, Persson S, Roos B-E, Winblad B (1982) Advanced catecholaminergic disturbances in the brain in a case of Wilson's disease. Acta Neurol Scand 65:71–75
36. Nyman H, Bartfai A (2000) Klinisk neuropsychologi. Lund: Studieliteratur, pp 148–159
37. Oertel WH, Tatsch K, Schwartz J, Kraf E, Trenkwalder C, Scherer J, et al. (1992) Decrease of D2 receptors indicated by ^{123}I-Iodobenzamide single-photon emission computed tomography relates to neurological deficit in treated Wilson's disease. Ann Neurol 32:743–748
38. Portala K, Westermark K, v Knorring L, Ekselius L (2000) Psychopathology in treated Wilson's disease determined by means of CPRS expert and self-ratings. Acta Psychiatr Scand 101:104–109
39. Ralf RD, Posner MI, Walker JA, et al. (1984) Cognition and the basal ganglia: separating mental and motor components of performance in Parkinson's disease. Brain 107:1083–1094
40. Reichard P, Berlund A, Britz A, Levander S, Rosenqvist U (1991) Hypoglycaemic episodes during intensified insulin treatment: increasing frequency but no effect on cognitive function. J Intern Med 229:9–16
41. Roh JK, Lee TG, Wie BA, Lee SB, Park SH, Chang KH (1994) Initial and follow-up brain MRT findings and correlation with clinical course of Wilson's disease. Neurology 44:1064–1068
42. Rosselli M, Lorenzana P, Rosselli A, Vergara I (1987) Wilson's disease, a reversible dementia: case raport. J Clin Exp Neuropsychol 9:399–406
43. Scheinberg IH, Sternlieb I (1984) Wilson's disease. In: Smith LH JR (ed) Major Problems in Internal Medicine. Vol XXIII. Philadelphia: WB Saunders Company
44. Snow BJ, Bhatt M, Martin WRW, Li D, Calne DB (1991) The nitrostriatal dopaminergic pathway in Wilson's disease studied with positron emission tomography. J Neurol Neurosurg Psychiatry 54:12–17
45. Tarter RE, Hegedus AM, von Thiel DH, Schade RR, Gavaler JS, Starzl TS (1984) Nonalcoholic cirrhosis associated with neuropsychological dysfunction in the absence of overt evidence of hepatic encephalopathy. Gastroenterology 86:1421–1427
46. Taylor-Robinson SD, Oatridge A, Hajnal JV, Burroughs AK, McIntyre N, deSouza MN (1995) MR imaging of the basal ganglia in chronic liver disease: correlation of T1-weighted and magnetisation transfer contrast measurements with liver dysfunction and neuropsychiatric status. Metab Brain Dis 10:175–188
47. Thuomas KÅ, Aquilonius SM, Bergström K, Westermark K (1993) Magnetic resonance imaging of the brain in Wilson's disease. Neuroradiology 35:134–141
48. Tuninger E (1997) Depot neuroleptic maintenance treatment. Clinical, pharmacological and neuropsychological aspects. Thesis. Lund: Lund University, pp 151–179
49. Waldenström E, Lagerkvist A, Dahlman T, Westermark K, Landegren U (1996) Efficient detection of mutations in Wilson disease by manifold sequencing. Genomics 37:303–309
50. Westermark K, Tedroff J, Thuomas KÅ, Hartvig P, Långström B, Andersson Y, et al. (1995) Neurological Wilson's disease studied with magnetic resonance imaging and with positron emission tomography using dopaminergic markers. Mov Disord 10 (No 5):596–603
51. Williams JB, Walshe JM (1981) Wilson's disease: an analysis of the cranial computerized tomography appearances found in 60 patients and the changes in response to treatment with chelating agents. Brain 104:735–752
52. Wilson RS, Kaszniak AW, Klawans HL, et al. (1980) High speed memory scanning in parkinsonism. Cortex 16:67–72