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Psychopathology in Wilson's Disease

BY

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ABSTRACT

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Wilson's disease (WD), hepatolenticular degeneration, is an autosomal recessive disorder caused by mutations in the ATP7B gene, and is characterised by abnormal metabolism and deposition of copper in the liver, brain and other organs.

The main aim of this thesis was to investigate the occurrence of psychopathology, as well as personality traits and neuropsychological function in Swedish patients with treated WD. The research subjects were 29 patients with confirmed WD, investigated at the Department of Internal Medicine at Uppsala University Hospital between 1996 and 2000.

The treated WD patients showed prominent psychopathology as determined by the Comprehensive Psychopathological Rating Scale. The spectrum of psychopathological symptoms is not typical of classic psychiatric syndromes, and includes symptoms from Anxiety, Depression and Obsessive-Compulsive disorders as well as Negative Symptoms. In self-assessment, the WD patients tended to underestimate the presence of psychopathological symptoms.

The treated WD patients differed in their sleep pattern from the control group, as measured with the Uppsala Sleep Inventory. The spectrum of self-reported symptoms suggests an altered REM sleep function.

The treated WD patients had significant deviations in personality traits, especially in aggressivity-hostility related scales and Psychic anxiety, compared to healthy controls, as measured with the Karolinska Scales of Personality.

The deviations were not related to age, age at onset or duration of WD. The symptomatic WD patients displayed a specific profile of moderate neuropsychological impairment, as determined by the Automated Psychological Test battery.

Finally, an attempt was made to search for, possible genotype-phenotype relationships in some ATP7B mutations.

Key words: Wilson's disease, psychopathology, personality traits, neuropsychological impairment, sleep, CPRS, KSP.

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LIST OF PAPERS

This thesis is based on the following original papers, which will be referred to in the text by their Roman numerals:

I Portala K, Westermark K, von Knorring L, Ekselius L. Psychopathology in treated Wilson's disease determined by means of CPRS expert and self-ratings. *Acta Psychiatrica Scandinavica.* 2000; 101: 104-109.

II Portala K, Westermark K, Ekselius L, von Knorring L. Personality traits in treated Wilson's disease determined by means of the Karolinska Scales of Personality (KSP). *European Psychiatry.* 2001; 16: 362-371.

III Portala K, Westermark K, Ekselius L, Broman JE. Sleep in patients with treated Wilson's disease. A questionnaire study. *Nordic Journal of Psychiatry.* Accepted.

IV Portala K, Levander S, Westermark K, Ekselius L, von Knorring L. Pattern of neuropsychological deficits in patients with treated Wilson's disease. *European Archives of Psychiatry and Clinical Neuroscience.* Accepted.

V Portala K, Waldenström E, von Knorring L, Westermark K. Psychopathology and personality traits in patients with treated Wilson's disease grouped according to gene mutations. Manuscript.

ABBREVIATIONS

AL	Alternation with left fingers
APT	Automated Psychological Test
AR	alternation between the right index and middle fingers
ARL	alternation between the right and left index fingers
BMI	Body Mass Index
BSA	Brief Anxiety Scale
CPRS	Comprehensive Psychopathological Rating Scale
CPRS-S-A	CPRS Self-rating Scale for Affective Syndromes
Exec	Executive Index
ExecCons	Executive consistency index
ExecSp	Executive speed index
GAF	Global assessment of functioning
Global	Global/ sequential Index
GrReas	Grammatical reasoning test
HE	Hepatic Encephalopathy
HD	Huntingdon's disease
Impulse	Impulsive Index
KFlex	index of strategy flexibility (global vs. sequential) in the k-test
KSP	Karolinska Scales of Personality
LTM	Long-term Memory
MFlex	index of strategy flexibility in the Perceptual Maze test
MADRS	Montgomery-Åsberg Depression Scale
MMSE	Mini-Mental State Examination
MRT	Magnetic Resonance Imaging
OCD	Obsessive Compulsive Disorder
NS	Negative Symptoms
PD	Parkinson's disease
PCR	Polymerase Chain Reaction
PINA	Pineal Night-Specific ATPase
pPS	Sjögren´s syndrome
PMT	Perceptual Maze test
PS	Positive Symptoms
REM	Rapid Eye Movement
RT200	Simple reaction time
RT2000	Complex reaction time
SCapBG	Simultaneous capacity in background task
SCapFG	Simultaneous capacity in foreground task
SpPref	Speed preference index
STM	Short-term memory
TL	Tapping with left index finger
TR	Tapping with right index finger
USI	Uppsala Sleep Inventory
VerbSp	Index of word decoding speed
VisoSpat	Performance in the visuo-spatial test
Vocab	Index of vocabulary
WD	Wilson's disease

Idea is a word by which I understand the form of any thought, that form by the immediate awareness of which I am conscious of that said thought; in such a way that, when understanding what I say, I can express nothing in words, without that very fact making it certain that I possess the idea of what these words signify.

There are diverse degrees of reality or (the quality of being an) entity. For substance has more reality than accident or mode; and infinite substance has more than finite substance. Hence there is more objective reality in the idea of substance that in that of accident; more in the idea of an infinite than in that of a finite substance.

Descartes
(Chávez-Arvizo E, 1997)

To the memory of my grandparents,
(dziadkom)

CONTENTS

INTRODUCTION

Historical background

"Progressive lenticular degeneration: A familial nervous disease associated with cirrhosis of the liver" was the title of the thesis published in 1912 by S A Kinnier Wilson in Brain. It took about a century of continuous work to uncover some of the secrets of the disorder now known as Wilson's disease (WD). Owing to this work, the primary morbid disease can be treated quite effectively if it is diagnosed.

Epidemiology

WD is a rare disease. Reliable data on its prevalence are scarce and estimates have changed over the years (Scheinberg & Sternlieb, 1984). In most European countries the prevalence at birth is between 12 and 18 per million. However, Sweden seems to have a lower prevalence according to a recent study (Olsson et al., 2000), which reported a figure, of around 10 per million. In Japan, where consanguineous marriages are much more common than in Europe, a prevalence at birth of 33 per million has been reported (Saito, 1988), and in Costa Rica a prevalence of 60 per million (Herra et al., 1990) has been found. It should be pointed out that, because of the high mortality rate associated with delayed diagnosis, prevalence rates at a certain point in time are much lower than the rates at birth. In Ireland, for example the point prevalence for patients being treated for WD in 1986 was 3.6 per million, whereas the birth prevalence was 17 per million births (Reilly et al., 1993).

Etiology

Genetics

Wilson's disease is a monogenic disease. It is an autosomal, recessive disorder of copper metabolism caused by mutations in the APT7B gene (gene map locus 13q14.3-q21.1.). Thus far, more than 200 different mutations have been detected (http://www.medgen.med. ualberta.ca/database.html.). The APT7B gene encodes a membrane bound, copper-transporting P-type ATPase (Bull et al 1993, Tanzi et al 1993, Yamaguchi et al 1993). This protein is a member of the CPx-ATPase family that is conserved from bacteria to humans (Solioz & Vulpe 1996). The APT7B gene is expressed in the liver and brain. The predominant WD mRNA transcript produced in the human liver encodes the full-length protein, but several alternative splicing forms have been detected, particularly in brain (Petrukhin et al., 1994). Borjigin at el., (1999) have identified a pineal night-specific ATPase (PINA), a splice variant of the ATP7B gene in rats. The full-length protein defects in liver result in reduced excretion of copper into bile, and consequently in the accumulation of copper and organ damage in the liver, brain and other organs (Gollan & Gollan 1998).

Pathogenetic mechanisms

The gene that causes WD has been isolated and cloned, and it codes for a copper-transporting APTase. Since both the biliary excretion of copper and the incorporation of copper into ceruloplasmin are reduced in WD, this metal-transporting APTase is probably needed to make copper available for both processes (Danks, 1991). However, the precise relationship between the primary defect and the pathogenesis of WD is still unknown. Over the years, several hypotheses have been put forward regarding the basic defect in WD.

Copper homeostasis vs. toxicity

Copper is an essential element for the activity of a number of physiologically important metalloenzymes, such as tyrosinase and cytochrome oxidase, and it plays a role in many processes, including mitochondrial energy generation, melanin formation, scavenging of oxygen radicals and the cross-linkage of collagen and elastin (Zucker & Gollan, 1992). Copper is a co-factor of Cu/Zn-superoxide-dismutase, which plays a key role in the cellular response to oxidative stress by scavenging reactive oxygen species. Furthermore, copper is a constituent of dopamine-beta-hydroxylase, a critical enzyme in the catecholamine biosynthetic pathway.

Copper homeostasis is determined principally by a balance between the rates of intestinal absorption and biliary excretion. Metallothionein, a cysteine-rich zinc- and copper-bindning protein, plays an important role in the regulation of copper-absorption (Bremmer 1980; Coustis 1983). Howeve, the mechanisms regulating the excretion of copper via the bile and stool are not completely understood. It is known that hepatic lysosomes are involved, and it is probable that degeneration products of cearuloplasmin in the bile have a regulatory function (Brewer & Yuzbasiyan-Gurkan, 1992; Verbina et al., 1992; Zucker & Gollan, 1992).

Under normal conditions, only small amounts of copper (0.05-0.10 mg l^{-1}) are loosely bound to albumin in plasma, whereas the bulk of the plasma copper (0.90-0.95 mg l^{-1}) is tightly bound to the protein ceruloplasmin. Therefore, the total plasma copper concentration is 1.0 mg l^{-1} and the ceruloplasmin level is about 300 mg l^{-1}. Ceruloplasmin contains 0.3% copper, corresponding to 0.9 mg l^{-1}. Thus, the plasma free copper concentration can be calculated to be 0.1 mg l^{-1}.

In patients with WD, the total copper concentration is 0.70 mg l^{-1}, and the ceruloplasmin concentration 120 mg l^{-1} (corresponding to 0.4 mg l^{-1}). The concentration of free copper in the plasma of WD patients can be calculated to be 0.3 mg l^{-1} (Hoogenraad, 1996). As a result of the positive copper balance, copper accumulates first in the liver and later in the brain and other organs. Excess copper is toxic by inducing free radical formation, cell injury, inflammation and finally cell death. It is also harmful to mitochondria and inhibits a large number of enzymes, e.g. glutathione reductase (Scheinberg and Sternlieb 1984).

Enzyme-related malfunctions may contribute to severe neurological symptoms and neurological diseases: copper is a component of cytochrome c oxidase, which catalyses the reduction of oxygen to water, the essential step in cellular respiration. Evidence is increasing to indicate that oxidative cell injury exist in a variety of neuro-psychiatric disorders, such as

schizophrenia, Down's syndrome, Parkinson's disease, and Alzheimer's disease, etc. (For review see: Mahadik et al., 2001; Fiskum, 1996; Simonian & Coyle, 1996). Moreover, experimental, clinical and epidemiological observations in neurodegenerative disorders (Alzheimer's disease) and in the genetically inherited copper-dependent disorders (Menkes and Wilson's disorders) provided a rationale for a link between severely dysregulated metal-ion homeostasis and the selective neuronal pathology (For review see: Mercer, 2001; Rotilo et al., 2000; Strausak et al., 2001).

Animal model of Wilson's disease

Long-Events Cinnamon rats (LEC rats) provide a good animal model for studying the pathogenesis of WD. These rats, a strain of a mutant rat isolated from LE rats, are afflicted by copper toxicosis, which is inherited in an autosomal recessive fashion (Okayasu et al., 1992; Yamada et al., 1992). A rat model has been used to study therapeutic strategies (Kolberg, 1992;) as zinc, and to compare effects of tetrathiomolybdate, penicillamine and trientine (McQuaid & Mason, 1991).

Liver pathology

Wilson (1912) regarded pathological changes in the liver as a *conditio sine qua non* for the diagnosis of progressive lenticular degeneration. Scheinberg and Sternlieb (1984) distinguished three stages of hepatic damage in WD (the early stage, the intermediate stage, and the late stage), and correlated liver abnormalities with these stages ranging: from a practically normal state to massive necrosis with complete disappearance of parenchymal tissue.

The hepatic copper level is reliable both as a diagnostic criterion for WD and for monitoring of treatment (Dahlman et al., 1995; Hoogenraad et al., 1987). Samples from needle biopsies can be analysed by flameless atomic absorption (Wawschinek & Beyer, 1982) or by destructive neutron activation (Tjoe et al., 1977). The normal copper level in the liver is less than 50 μg per g dry weight. In WD patients the concentration is almost invariably in excess of 250 μg per g dry weight.

Neuropathology

Macroscopy: atrophy and cavitation

The brain usually shows no external abnormality in WD. The ventricular system is often enlarged due to atrophy of basal ganglia. The lenticular nuclei show symmetrical atrophy and discoloration. The consistency of the putamen is often softer than normal. Cyst formation is often found in the putamen and sometimes in the external capsule, claustrum and frontal lobes (Schulman, 1968). Therefore, the distribution of neuronal damage in the brain caused by copper disposition, and/or encephalopathy due to hepatic dysfunction in WD, are highly variable, and may include brainstem nuclei, dentate nucleus, pons as well as a certain degree of general brain atrophy (Scheinberg & Sternlieb, 1984).

Microscopy: gliosis and abnormal protoplasmic astrocytes

The widespread abnormalities of glial cells are the most conspicuous microscopic finding in WD patients. Both gliosis (Konovalov, 1960) and astrocytosis (with Alzheimer type II glia and Opalski cells) occur frequently (Horoupian et al., 1988).

Pathobiochemistry

An abnormal metabolism of neurotransmitters, probably due to an increase in the activity of copper-containing enzymes like dopamine ß-hydroxylase (Barkhatova et al., 1995), with increased noradrenaline in the striatum, has been reported (Nyberg et al., 1982; Kish et al., 1990). Moreover, Nijeholt (1978) reported a decrease both of 5-hydroxyindole acetic acid (5-HIAA, a 5-HT metabolite) and homovanillic acid (HVA, a metabolite of dopamine) in the lumbar CSF of WD patients before and during treatment with penicillamine.

Hepatic encephalopathy

Hepatic encephalopathy (HE) is seen in acute liver failure and in cirrhosis with portosystemic shunting. In both disorders portal blood bypasses the liver, making it possible for noxious substances from the intestine to reach the brain without being metabolised by the liver. The clinical profile is complex and includes mental and neurological disturbances. In early phases, the encephalopathy is reversible, but the brain lesions later become irreversible (Sherlock & Dooley, 1993). It is intriguing that the neuropathological features of HE are practically identical to those of hepatolenticular degeneration (Finlayson & Superville, 1981). The prominent histopathological findings in both conditions are the presence of Alzheimer type II astrocytes in the grey matter of the brain (Norenberg et al., 1990) and relatively spared neurones. However, oedema is more common in HE than in WD. Furthermore, patients with advanced liver disorders show testicular atrophy and hormonal changes characterised by feminisation, as described in both alcoholic and non alcoholic disease (Dykes, 1969; Boiesen, 1979). The pathogenesis of HE is not known exactly. The main theories concerning the pathogenetic mechanism are accumulation of toxic products like ammonia in the brain, chronic HE-disturbed brain energy metabolism, deranged balance and/or metabolism of neurotransmitters like monoamines, and glutamine, glutamate, γ-aminobutyric acud (GABA), and α-ketoglutarate, and direct effects on neuronal membranes. (For overviews see e.g. Conn & Lieberthal, 1979; Butterworth, 1994; Crossley et al., 1983; Mousseau & Butterworth, 1994)

Neurophysiology

Impairments of a descending frontobulbar saccadic pathway (slow saccadic eye movements) (Kirkham & Kamin, 1974), corticomotoneuronal pathways (EMG) (Berardelli et al., 1990), somatosensory, and auditory and visual pathways at the brainstem level (evoked potential) (Chu, 1986; Grimm et al., 1992) 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 (Cummings, 1993).

Neuroimaging

Neuroimaging findings in WD suggest a complex pathogenesis involving both efferent (loss of D2 receptors in striatum) (Oertel et al., 1992; Westermark et al., 1995) and afferent nigrostriatal dopaminergic projections (Snow et al., 1991). Furthermore, there are dopamine transporter abnormalities (Jeon et al., 1998). In addition, Hawkins et al. (1987) demonstrated a reduction of glucose metabolism in all brain regions except thalamus.

Clinical manifestations

In the majority of patients, the first symptoms appear in the late teens or twenties but has been described in patients as early as 3 years or as late as 60 years of age. Scheinberg and Sternlieb, (1984) estimated that the first manifestations of WD are caused by hepatic disturbances in about 40% of patients (usually with onset in childhood or adolescence), in another 40 % the first symptoms are neurological (usually with onset in early adulthood), and the remainder present with psychiatric, haematological, renal or osteochondrotic symptoms.

Four clinical subgroups, hepatic, neurological, mixed (hepatic and neurological) as well as an asymptomatic group (diagnosed by family screening) have been described by Dening and Berrios (1989c) and later verified by Oder and colleagues (1993). WD may present under a variety of clinical conditions, most commonly liver disease and neuropsychiatric disturbances. However, the frequency and the time point when patients with WD exhibit psychopathological symptoms vary from study to study. The diagnosis is usually made based on clinical findings and/or Kayser-Fleischer corneal rings and laboratory abnormalities, e.g. low serum ceruloplasmin and increased amounts of urinary and liver copper.

Hepatic aspects

As has been mentioned earlier Scheinberg and Sternlieb (1984) distinguished three clinical stages of WD. *The early (asymptomatic) stage* is characterised by the asymptomatic accumulation of copper in hepatocytes. In *the intermediate, symptomatic (hepatic) stage*, the copper is redistributed and bound in the lysosomes of the hepatocytes. The acute release of copper may occur, with hepatic necrosis, and increased plasma levels of free (non-ceruloplasmin-bound) copper may temporarily effuse to the bloodstream, causing haemolysis. *The late symptomatic (extrahepatic) stage* is characterised by continuously increased free copper levels and chronic copper toxicosis, giving rise to liver cirrhosis and toxic accumulation of copper in extrahepatic tissues such as the brain. In this stage, the Kayser-Fleicher rings appear (Dobyns et al., 1979).

Neurological manifestations

Typically, WD is a movement disorder. Its manifestations are diverse and include tremors (postural, intentional, action and rest tremors), dysarthria (focal, segmental and oromandibular dystonia, dystonic- tics, dysphonia and contractures), choreoathetosis, hypokinesia (dysarthria), rigidity (hypomimia, bradykinesia, parkinsonian gait) and ataxia. Moreover, features of neurological WD may also include intellectual deterioration, abnormal eye movements and epilepsy. However, it may be difficult to differentiate the clinical picture

of WD from that of more common diseases, such as idiopathic dystonia, Parkinson's disease or multiple sclerosis (Hoogenraad, 1996).

The onset of neurological symptoms is usually insidious. A single symptom may exist for many months before other manifestations appear. Short periods of spontaneous amelioration of neurological manifestations are rare but have been described (Scheinberg & Sternlieb, 1984). Without treatment the neurological symptoms almost invariably became worse. In some patients deterioration is rapid and death can occur within six months of the appearance of the first symptoms. In other patients progression is much slower, and several decades may pass before total incapacity and death ensue (Schouwink, 1961).

Psychopathology

The frequency and the time point when patients with WD exhibit psychiatric and psychological symptoms vary from study to study. Scheinberg and Sternlieb (1984) stated that almost every patient with clinically manifest WD suffers from psychiatric disorders at some time during the course of his/her disease. Dening and Berrios (1989a) retrospectively, assessed 195 cases of WD and found that 51% of these patients displayed psychopathological features.

As early as 1912, S. A. Kinnier Wilson, in his original article, described prominent psychopathology in eight of the twelve reported cases. Since then a wide variety of psychiatric disturbances have been reported. These include anxiety (Goldstein et al., 1968; Walker, 1969; Scheinberg et al., 1968), affective (Scheinberg & Sternlieb, 1984; Goldstein et al., 1968; Walker, 1969; Lishman, 1987; Dening & Berrios, 1989a), and psychotic disorders (Scheinberg & Sternlieb, 1984; Walker, 1969; Lishman, 1987; Dening & Berrios, 1989a; Dening & Berrios, 1989b).

Moreover, personality changes, incongruous behaviour, aggression, irritability and antisocial / psychopathic personality have often been reported in patients with WD (Kaul & McMahon, 1993; Akil et al., 1991; Dening & Berrios, 1989a; Dening & Berrios, 1989b; Goldstein et al., 1968). Oder and colleagues (1993) described an organic personality syndrome when investigating neuropsychiatric symptoms and structural brain lesions in WD patients. Furthermore, family members often reported increased aggression in WD patients (Akil et al., 1991).

Cognitive impairment (Scheinberg & Sternlieb, 1984; Goldstein et al., 1968; Borsein & Lean, 1985; Oder et al., 1991; Goldstein et al, 1968) has often been reported in patients with WD. Early studies (Akil & Berewer, 1995; Medalia et al, 1988; Rathbun, 1996) reported motor impairments and relatively good cognitive performance in WD patients. Confusion, with disorientation to time and/ or place, can occur in WD patients with acute hepatic failure (Doering et al., 1979). These patients are easily distracted, have slow thought processes and a limited concentration span. Delirium with perceptual disorders, illusions and hallucinations may accompany the confused state (Adams & Foley, 1953).

The malignant neuroleptic syndrome in WD is a rare but potentially fatal complication of treatment with neuroleptic drugs. Kontaxakis and colleagues (1988) described its induction following treatment with chloromazine and haloperidol in a 19-year-old man who presented with agitation, delusions and hallucinations. The condition improved when the above drugs were withdrawn and dantrolene, bromociptine and amantadine were given. Several months later, and about 2 years after the initial psychiatric symptoms, the diagnosis of WD was made and decoppering treatment initiated (Kontaxakis et al., 1988).

Treatment

Without treatment, WD is fatal, but with proper therapy, the disease progress can be halted and symptoms often improve. The treatment is aimed at removing excess accumulated copper and preventing its reaccumulation and it has to be life-long. The treatment of patients with WD may take many forms, from drug therapy and advice about diet to liver transplantation. Three options are available for drug therapy in WD: chelating agents (penicillamine, trientine), zinc and tetrathiomolybdate (Scheinberg and Sternlieb 1984, Czlonkowska et al., 1996; Brewer et al 2000). Outcome is mainly determined by the amount of damage that has occurred before the institution of treatment. In patients with irreversible liver damage, liver transplantation is indicated and the only option in the presence of fulminate liver failure (Schilsky et al 1994).

It is important to emphasise that management of the whole patient is an important not only anti-copper therapy. Today, most patients with WD, once diagnosed and treated, often face a life where their physical impairment is minor to moderate. On the other hand, the psychopathological component of the disease has become more apparent and now forms the next challenge in the management of the disease.

AIMS

The primary incitement leading to this research project was clinical observations suggesting the occurrence of psychopathological symptoms among the treated WD patients at the Dept. of Internal Medicine at the University Hospital in Uppsala. Since there is inconsistency in the literature and a lack of conclusive descriptions of the psychopathology in patients with treated WD, it was deemed important to describe the psychopathology, without a predetermined hypothesis about the type of psychopathology, as well as the neuropsychological functioning of patients with treated WD. Furthermore, it was important to elucidate if their sleep patterns and personality traits deviated from those in the general population. As WD is a genetically determined disorder, it was thought to be important to try to elucidate possible genotype –phenotype relationships. However, the number of subjects with each separate mutation was too small to permit firm conclusions.

Thus, the main purpose of this thesis was to investigate the occurrence and severity of psychopathological symptoms in Swedish patients with treated Wilson's disease.

The more detailed aims of the present research were as follows:

1. To examine the occurrence and severity of psychopathological symptoms in patients with treated WD (study / paper I).

2. To evaluate the clinical utility of a self-assessment in patients with treated WD (study / paper I).

3. To elucidate the personality traits of patients with treated WD in comparison to healthy volunteers (study / paper II).

4. To examine general sleep habits and sleep disturbances among patients with treated WD, and in comparison with an age- and sex matched control group (study / paper III).

5. To explore the degree and the pattern of neuropsychological impairment among a series of treated WD patients (study / paper IV).

6. To attempt to evaluate whether there are differences in psychopathology or personality traits in the WD patients grouped according to APT7B gene mutations (study / paper V).

METHODOLOGY

SUBJECTS

The population

The data in the present thesis are based largely on about 60% of the known Swedish population of patients with WD, who were from different areas in Sweden and who were investigated in conjunction with their regular visits to the Dept. of Internal Medicine at the Uppsala University Hospital between 1996 and 2000.

The inclusion criteria

The main inclusion criterion in the project was confirmed diagnosis of WD in Swedish patients, visiting, the Dept. of Internal Medicine at the Uppsala University Hospital. The diagnosis of WD was based on clinical symptoms, low levels of plasma ceruloplasmin, increased serum free and urinary copper concentrations, and mostly on the occurrence of Kayser-Fleischer rings at slit-lamp examination, and/or on increased copper concentrations in liver biopsies. Genetic charting, using PCR (polymerase chain reaction) was also performed in all patients. The detailed procedures are found in Waldenström et al., (1996).

The WD samples in studies I - V

In total, 29 patients (11 females and 18 males), from 27 families with genetically confirmed WD participated in the project. For demographic details of the WD samples, see **Table 1**. The participating WD patients, dropouts and reasons for dropout in studies I to V, are presented in **Appendix 1**. For demographic details on an individual level see **Appendix 2**.

Table 1. Descriptions of the included series of WD patients in each study as regarding sex, mean age, mean age at onset and mean duration (from diagnosis) of WD.

Study (Paper)	**N**	**Females/ Males**	**Age** (years) Mean ± SD	**Age at onset** [a] (years) Mean ± SD	**Duration of WD** (years) Mean ± SD
I	26	10 / 16	34.7 ± 8.5	18.3 ± 5.2	17.4 ± 8.3
II	25	10 / 15	35.2 ± 8.3	18.0 ± 5.2	18.1 ± 7.6
III	24	11 / 13	35.1 ± 8.7	17.8 ± 5.1	17.2 ± 9.0
IV	21	7 / 14	35.3 ± 9.2	18.1 ± 5.4	20.3 ± 5.1
V	12	5 / 7	37.5 ± 9.8	18.8 ± 5.4	17.7 ± 8.2

[a] - two cases diagnosed by family screening, i.e. no onset of symptoms, were excluded from calculations.

At the time of the first investigation or visit (patients in studies I, II, V and some patients in study III), all patients, except the recently diagnosed patient (No.25, Appendix 2) were in a mainly copper-depleted state and received pharmaceutical treatment for WD, except for two who were liver transplanted (No. 12, No.20). Eight patients were on D-penicillamine, sixteen had triethylene tetramine dihydrochloride (Trientine) and three were on zinc acetate. Three of the 29 subjects (No. 4, No. 23, No. 24) received psychotropic drugs (citalopram, nefazodone, venlafaxin and flupentixol). A wide spectrum of illness symptoms was encountered, ranging from a mute and bedridden patient (No. 8) to individuals who had never been symptomatic (No. 10, No 29). Twenty-five WD patients (not including liver transplanted patients No. 11, No. 20) showed no signs or mild signs of liver involvement and two (diagnosed 10 months earlier, No. 14, No. 24) had liver cirrhosis.

In study V, three groups of patients homozygous for three different mutations in exon 14 (His1069Gln), in exon 13 (Thr977Met) and in exon 8 (Trp779Stop) and one group compound heterozygous (exon 14:19) for His1069Gln and Arg1319Stop, were compared with respect to the psychopathological symptoms determined by means of the CPRS. Individual data regarding the aforenamed patients are given in **Appendix 1**and **2**.

Comparison group in study II

The comparison group comprised 200 men and 200 women drawn from the general population (Bergman et al, 1982).

Comparison group in study III

From the random sample of 3558 individuals, selected citizens in central Sweden with at sex distribution of 1:1 and an age range of 30–65 years (Hetta et al., 1985), all women in the age range 30-50 years and all men in the age range 30-40 years, were used for selection of a random sample of 72 individuals. The random sample of 33 women (age range 30 -50 years) and 39 men (age range 30-40 years) was drawn from the large group (1746 individuals) in the study cited above and served as a control group. The difference in age ranges in women and men in the control was due to a shift in the same direction for age ranges in male and female patients with WD. The mean age (±SD) of the control group was 37.2±5.2 years.

Comparison group in study IV

Norm data are based on data collected since the early 1980s (Levander, 1988) which has been continuously updated. The number of healthy volunteers varies for the different tests, from approximately 250 up to several thousand. No data from the general population are available.

METHODS

The diagnostic instruments used in studies I to V are presented in **Table 2**. Studies I to V were approved by the Ethics Committee of the Medical Faculty at Uppsala University.

Table 2. Instruments and statistic in studies I-V.

Study / Paper	Instruments	Statistics used
I	CPRS Expert rating CPRS-A Self rating MMSE GAF	Descriptive Spearman's Rank Correlation Coefficient Wilcoxon Matched-Pair Signed-Rank Test Mann-Whitney U Test
II	KSP	Descriptive Mann-Whitney U Test Spearman's Rank Correlation Coefficient Kruskal-Wallis One Way ANOVA
III	USI	Descriptive Chi-square Mann-Whitney U Test Spearman's Rank Correlation Coefficient Student's t-test
IV	APT	Descriptive Mann-Whitney U Test Spearman's Rank Correlation Coefficient Partial correlations
V	CPRS Expert rating KSP PCR	Descriptive

The Comprehensive Psychopathological Rating Scale, CPRS

The Comprehensive Psychopathological Rating Scale (CPRS) (Åsberg et al., 1978) comprises 65 items (40 reported items and 25 observed items) concerning psychopathological symptoms. One item is a global measurement of illness and one item takes into account the assumed validity of the rating performed. All 65 items concerning psychopathological symptoms are colloquially formulated, and are presented in stages ranging from 0 to 3 by half point steps, where 0 indicates absence of the particular symptom. A rating of 1 is a description that could apply to a pathological deviation from the individual's own norm, but might equally well be considered a normal variation in a group of people. A rating of 2 indicates clearly pathological symptoms and 3 indicates the most severe degree. Many sub-scales have been derived from the CPRS. Six such sub-scales have been used in the present study: a 10-item Brief Anxiety Scale (BSA) (Tyrer et al., 1984), a 10-item depression rating scale - the Montgomery-Åsberg Depression Rating Scale (MADRS), an 8-item Obsessive Compulsive Symptoms Scale (OCD), an 18-item Positive Symptoms Scale (Åsberg et al., 1978), a 5-item Negative Symptoms Scale (NS) (Lindström, 1996), and a 5-item Retardation Symptoms Scale (RS) (Beck-Friis, 1993). Beck-Friis (1993) reported significant negative regressions between low melatonin and high score of the retardation symptoms vs. items. The list of CPRS items and sub-scales is presented in **Appendix 3**. Furthermore, a 19-item anxiety scale (CPRS-A) has been derived (Svanborg et al., 1994).

The CPRS Self-rating Scale for Affective Syndromes, CPRS-S-A

The CPRS-S-A is related mainly to anxiety and affective symptoms and it has been demonstrated to have good validity and reliability (Svanborg et al., 1994). The same authors later included six items (Depersonalisation, Lack of appropriate emotion, Feeling controlled, Disrupted thought, Ideas of persecution and Commenting voices) regarding psychotic symptoms (CPRS-S-A-modified). The modified CPRS-S-A has not yet been validated. The 25-item modified CPRS-S-A was used in study I, for the item list see **Table 5**.

Global assessment of functioning, GAF

The GAF considers psychological, social and occupational functioning on a hypothetical continuum of mental health-illness. The 100-point scale ranges from 100 to 1, 100 indicating the highest level, 70-40 a mild level, and less then 40 a major impairment of function in several areas of life (American Psychiatric Association, 1996).

Mini-Mental State Examination, MMSE

The MMSE consists of 11 items (scores range from 0 to 30, scores below 24 indicate a significant cognitive impairment) (Dick et al., 1984).

The Karolinska Scales of Personality, KSP

The KSP is a self-reported inventory consisting of 135 questions grouped into 15 scales (Schalling et al., 1987), see **Appendix 4**. It was constructed for research purposes and focuses on personality traits assumed to have a biological basis and to be related to vulnerability to psychopathology. The scales are constructed on a rational-theoretical basis rather than on empirical-statistical grounds. Following their construction, the scales later underwent psychometric evaluation. Two factors have been composed: Aggression factor (Indirect aggression + Verbal aggression + Irritability) and the Hostility factor (Suspicion + Guilt). The scales have been demonstrated to have long-term stability (Gustavsson, 1997).

Uppsala Sleep Inventory, USI

The USI is a questionnaire designed for studies of sleep disturbances and related symptoms and has been validated against polysomnography (Hetta et al., 1998). The USI has been used in epidemiological studies of sleep in the Swedish population (Hetta et al., 1985) as well as in studies of various diseases (Gudbjörnsson et al., 1993; Hultgren et al., 2000; Edéll-Gustafsson, 1999), and comprises 87 questions concerning demographic and social characteristics, sleep habits and sleep difficulties.

Demographic and social characteristics
The questions were mainly categorical (yes/no answers) concerning demographic and social characteristics. Marital status was defined as married or cohabiting or as not married or cohabiting. Occupational status was defined as regularly employed or not regularly employed, and if employed, whether the job involved, day- or night-time work. To obtain more complete descriptions of WD patients, the authors included additional categories of occupational status in the WD group (student, unemployed, vocational rehabilitation, and maternity and sick- leave level as well as disability pension).

Patterns of sleep
There were quantitative questions about the time the respondent usually went to bed, the length of time it usually took to fall asleep, number of nocturnal awakenings, total sleep time, estimated need for sleep, the time the respondent usually got up, and daytime napping, with the answers expressed as continuous variables.

Sleeping difficulties
The questions concerned symptoms and severity of sleeping difficulties, rated on a five-point scale (1= no problems, 2= minor problems, 3= moderate problems, 4= severe problems, 5= very severe problems), and how often sleeping difficulties occurred (1= never, 2= seldom, 3= sometimes, 4= often, 5= very often). In addition, some categorical questions (yes/no) about sleep problems were also included (“ Do you think that you have sleep problems? ”).

Sleeping medication and consulting a physician because of sleeping difficulties
There were questions about whether the individual had ever consulted a physician because of sleeping difficulties or had ever used sleeping pills, and these were answered by either yes or no.

The neuropsychological test battery

The Automated Psychological Test (APT) system (Levander, 1988) is one of the most often used computerised neuropsychological tests in Scandinavia (Nyman & Bartfai, 2000). The different tests of the APT set have been applied to evaluate cognitive and motor impairments in somatic (Reichard et al., 1991) and psychiatric diseases (Gråwe & Levander, 1995; Levander 1987), and in neuroimaging,-psychology (Ghatan et al., 1995), and to study various CNS effects of drugs (Levander et al., 1982; Tuninger, 1997). The clinical version of the APT used in the present study comprised eleven separate tests (presented in **Appendix 5**) and assessed five essential types of neuropsychological functions: motor functions, basic neuropsychological functions, specific cognitive functions, memory, and executive functions.

Manifold sequencing

Genomic DNA was isolated from whole blood collected in EDTA according to standard procedures. Each of the 21 exons (in total 4.4 kb) was amplified using PCR (polymerase chain reaction). Exon 2, 1234 bp, was amplified in four overlapping fragments. Primers were designed using the OLIGO program (Research genetics) from adjacent intron sequence data. Sequencing was performed using a solid support (Lagerkvist et al., 1994), now available as AutoLoad Solid Phase Sequencing Kit (Amersham Pharmacia Biotech, Uppsala, Sweden). Primer data and detailed procedures are found in Waldenström et al., (1996).

Statistical methods

Statistical analyses were performed on the Apple Macintosh using the SPSS 6.1 vs. 10.0 statistical package (SPSS Inc.1995 vs. 2000).

Although, the sample size in the present study is relatively large compared to the frequency of WD, the statistical analyses were done conservatively due to the small number of included patients. Moreover, as most variables were not normally distributed, parametric statistical tests were not used, with some exceptions in studies III and IV. Probability levels lower than 0.05 were considered as significant.

Differences in the distribution of continuous or ordinal data between two or more groups in studies I-IV were analysed with the Mann Whitney U-test or with the Kruskal-Wallis one-way ANOVA test, respectively.

In Study I, agreements between self-ratings and expert ratings were estimated by the Wilcoxon Matched-Pairs Signed-Ranks test and Spearman's rank correlation coefficient. Inter-rater reliability for CPRS ratings was estimated by means of Spearman's rank correlation' coefficients.

In Study II, the raw scores of the KSP were transformed into T-scores (x – mean of healthy

volunteers/ SD of healthy volunteers x 10 + 50). Correlations between the KSP variables and age, age at onset and duration of WD were sought by means of Spearman's rank correlation' coefficients.

In study III, the categorical questions with a yes or no answer were analysed by chi-square analysis. The quantitative questions were analysed with Student's *t* -test.

In Study IV, to reduce the number of output variables in the APT system, the raw ATP data were transformed into a standardised set of meta indices, and expressed as T- scores (M=50, SD±10). The correlation between simple (RT200) and complex reaction time (RT2000) was estimated by means of Spearman's rank correlation coefficient. Correlations between the APT and age, age at onset, and duration of disease were sought by means partial correlations, controlled for confounding variables.

RESULTS AND DISCUSSION

GENERAL PSYCHOPATHOLOGY

Fourteen of 29 patients (46%) had exhibited psychiatric symptoms (personality disturbances, anxiety symptoms, affective symptoms and psychosis-like syndromes) at the time of diagnosis. Only five (two in the project) of the 14 patients had seen a psychiatrist at the time of diagnosis. Eight patients (28%) had seen a psychiatrist before the time of inclusion in the present study.

PSYCHOPATHOLOGY AS DETERMINED BY THE CPRS, STUDY I

RESULTS

The CPRS expert ratings

The total CPRS scores ranged from 2.50 to 59.00 (median 29.50; mean 29.42± 15.51), scores for reported items ranged from 0 to 44.00 (mean 19.04; SD±12.39), and scores for observed items ranged from 2.50 to 18.00 (mean 10.38; SD±5.01). The global assessment of mental illness ranged from 0 to 3 (mean 1.62; SD±0.80) and the assumed reliability of the ratings ranged from 1 to 3 (mean 2.73; SD±0.53). The rating of 65 CPRS items ranked according to frequency in 26 WD patients, as well as means, SDs, and ranges, are presented in **Table 3.** There were no significant differences between patients with predominantly hepatic or predominantly neurological symptoms at the time of diagnosis.

Most commons items

Twelve items with scores of 1 or more were present in more than fifty percent of the subjects. These were: Reported Autonomic disturbances (in 73% of the patients), Observed muscular tension (73%), Fatigability (62%), Reduced sexual interest (62%), Lack of appropriate emotion (62%), Concentration difficulties (62%), Observed Autonomic disturbances (62%), Reduced sleep (54%), Aches and pains (54%), Hostile feeling (54%), Apparent sadness (54%), and Failing memory (54%). The frequencies for all WD patients are presented in **Table 3**.

Gender differences

There were some CPRS items that were scored significantly higher by females than by males e.g. Autonomic disturbances ($p < 0.01$), Rituals ($p < 0.05$), Feeling controlled ($p < 0.05$), and Labile emotional responses ($p < 0.05$).

Table 3. Ratings of 65 CPRS items ranked according to frequency in 26 WD patients.

CPRS items (No.)	Frequency of patients with scores ≥1	Mean	±SD	Range
Reported				
Autonomic disturbances (23)	73%	1.06	±0.67	2.00
Fatiguability (15)	62%	1.12	±0.82	2.50
Reduced sexual interest (21)	62%	0.98	±0.84	2.50
Concentration difficulties (16)	62%	0.87	±0.73	2.00
Reduced sleep (19)	58%	1.02	±0.85	2.50
Aches and pains (24)	58%	0.88	±0.84	2.50
Hostile feeling (4)	54%	0.96	±0.90	2.50
Failing memory (17)	54%	0.77	±0.68	2.00
Loss of sensation or movement (26)	50%	0.75	±0.67	2.00
Worrying over trifles (9)	50%	0.62	±0.67	2.00
Inability to feeling (5)	50%	0.75	±0.71	2.00
Muscular tension (25)	46%	0.85	±0.90	2.50
Lassitude (14)	46%	0.75	±0.78	2.00
Inner tension (3)	46%	0.75	±0.76	2.00
Sadness (1)	42%	0.67	±0.65	1.50
Rituals (12)	38%	0.44	±0.55	1.50
Morbid jealousy (35)	35%	0.44	±0.59	2.00
Indecision (13)	31%	0.52	±0.71	2.00
Derealisation (27)	31%	0.42	±0.48	1.50
Hypochondriais (8)	27%	0.46	±0.66	2.00
Pessimistic thoughts (6)	27%	0.44	±0.62	2.00
Delusional mood (33)	27%	0.40	±0.63	2.00
Ideas of grandeur (32)	27%	0.37	±0.48	1.50
Compulsive thoughts (10)	24%	0.31	±0.53	1.50
Reduced appetite (18)	23%	0.29	±0.51	1.50
Phobias (11)	19%	0.37	±0.66	2.00
Visual hallucinations (39)	19%	0.29	±0.51	2.00
Disrupted thoughts (30)	19%	0.25	±0.49	1.50
Ideas of persecution (31)	15%	0.25	±0.47	1.50
Other delusions (36)	12%	0.12	±0.33	1.00
Feeling controlled (29	8%	0.15	±0.37	1.50
Other auditory hallucinations (38)	8%	0.15	±0.37	1.50
Ecstatic experiences (34)	8%	0.15	±0.31	1.00
Depersonalisation (28)	8%	0.12	±0.36	1.50
Suicidal thoughts (7)	7%	0.15	±0.51	1.00
Increased sleep (20)	4%	0.06	±0.29	1.50
Other hallucinations (40)	4%	0.04	±0.20	1.00
Commenting voices (37)	0	0.06	±0.16	0.50
Elation (2)	0	0	0	0
Increased sexual interest (22)	0	0	0	0

Observed items	Frequency of patients with scores ≥1	Mean	±SD	Range
Muscular tension (63)	73%	1.17	±0.68	2.00
Lack of appropriate emotion (45)	62%	0.96	±0.69	2.00
Autonomic disturbance (46)	62%	0.83	±0.63	2.00
Apparent sadness (41)	58%	0.91	±0.58	2.00
Slowness of movement (60)	50%	0.69	±0.71	2.00
Specific speech defects (55)	46%	0.83	±0.63	3.00
Perseveration (58)	46%	0.69	±0.65	2.00
Pressure of speech (53)	46%	0.60	±0.68	2.00
Perplexity (50)	31%	0.48	±0.59	2.00
Labile emotional responses (44)	31%	0.40	±0.53	1.50
Agitation (61)	27%	0.41	±0.67	2.00
Reduced speech (54)	27%	0.37	±0.56	1.50
Hostility (43)	27%	0.35	±0.49	1.50
Distractability (48)	23%	0.35	±0.46	1.50
Flight of ideas (56)	15%	0.31	±0.57	2.00
Withdrawal (49)	15%	0.29	±0.43	1.50
Blank spells (51)	12%	0.13	±0.33	1.00
Overactivity (59)	8%	0.12	±0.29	1.00
Involuntary movement (62)	4%	0.15	±0.60	3.00
Mannerisms and postures (64)	4%	0.12	±0.59	3.00
Elation mood (42)	4%	0.08	±0.39	2.00
Disorientation (52)	4	0.04	±0.20	1.00
Incoherent speech (57)	0	0.10	±0.20	0.50
Hallucinatory behaviour (65)	0	0	0	0

Table 4. The means, SDs, and ranges of 7 sub-scales of the CPRS, as well as frequencies of WD patients with scores ≥1/ sub-scale item are presented. To make comparison of the sub-scales easier, the means of each sub-scale (mean of the sub-scale / number of the sub-scale items) have been calculated.

Mean of sub-scale / N of items	CPRS scales [N of items]	Frequency of patients with scores ≥1/ item	Mean	±SD	Range
0.82	BSA [10]	36%	8.2	±4.79	18.0
0.74	RS [5]	31%	3.7	±2.60	10.0
0.72	DS [17]	27%	12.4	±8.15	27.5
0.66	MADRS [10]	27%	6.6	±4.87	16.0
0.62	OCD [8]	27%	4.6	±4.14	14.0
0.56	NS [5]	8%	2.8	±1.87	8.0
0.05	PS [13]	0%	3.9	±3.43	14.0

BSA- Brief Scale for Anxiety; DS- Depression Rating Scale; MADRS- Montgomery-Åsbery Depression Rating Scale; OCD- Obsessive Compulsive Disorders scale; NS- Negative Symptom Rating Scale; PS- Positive Symptoms; RS- Retardation Syndromes Scale.

CPRS sub-scales

The means, SDs, and ranges of 7 sub-scales of the CPRS as well as the frequencies of WD patients with scores ≥1 / item in the sub-scales are presented. For ease of comparison of the sub-scales, which have differing numbers of items, the means of each sub-scale have been calculated (mean of the sub-scale / number of the sub-scale items) and are presented in **Table 4**. A list of items included in each sub-scale is presented in **Appendix 3**.

The CPRS –A Self-rating

The total scores for the modified CPRS-S-A covering 25 items, ranged from 0 to 34.00 (median 4.25; mean 6.73±7.98), and for the CPRS-S-A (19 items), ranged from 0 to 28.50 (median 4.50; mean 6.15±6.67). Agreement between interview-based ratings and self-ratings estimated by Spearman's rank correlation coefficients was low. Means (M), standard deviations (±SDs), differences (D) determined by Wilcoxon's matched-pairs signed ranks test and agreement (A) determined by Spearman's rank correlation coefficients (r_s) as well as p-values for differences between CPRS self-assessments and CPRS interview-based ratings for each item are shown in **Table 5**.

Table 5. Means (M), standard deviations (±SDs), differences determined by Wilcoxon's matched-pairs signed ranks test and agreement determined by Spearman's rank correlation coefficients (r_s). * p<0.05, **p<0.01, ***p<0.001

CPRS-S-A items (No. in the CPRS)	CPRS-S-A Self-Assessment M±SD	CPRS Expert M±SD	Differences Z	Agreement r_s
1. Mood (1)	0.10 ±0.25	0.60±0.63	3.15**	0.28
2. Feeling of uneasiness (3)	0.40 ±0.69	0.67±0.73	1.82	0.45*
3. Irritability and anger (4)	0.44 ±0.74	0.85±0.85	2.34*	0.54**
4. Sleep (19)	0.60 ±0.75	0.94±0.84	2.48*	0.76***
5. Appetite (18)	0.19 ±0.46	0.25±0.47	0.89	0.23
6. Ability to concentrate (16)	0.48 ±0.65	0.79±0.71	1.87	0.47*
7. Ability to make decisions (13)	0.16 ±0.37	0.41±0.63	2.50*	0.37
8. Initiative (14)	0.34 ±0.58	0.65±0.71	2.53*	0.75***
9. Emotional involvement (5)	0.17 ±0.35	0.65±0.63	3.05**	0.50*
10.Pessimism (6)	0.33 ±0.56	0.39±0.55	0.86	0.36
11.Concern for health (8)	0.45 ±0.64	0.40±0.64	0.31	0.34
12.Worry over trifles (9)	0.36 ±0.61	0.52±0.60	1.15	0.15
13.Phobias (11)	0.31 ±0.59	0.39±0.68	2.36*	0.48*
14.Obssessive thoughts (10)	0.23 ±0.42	0.22±0.47	0.08	0.59**
15.Compulsive behaviour (12)	0.18 ±0.38	0.40±0.55	2.11**	0.74***
16.Physical discomfort (23)	0.50 ±0.64	1.00±0.66	2.91**	0.45*
17.Aches and pains (24)	0.70 ±0.67	0.81±0.83	0.63	0.56**
18.Panic attacks (not in the CPRS)	0.25 ±0.55	0.75±0.76	2.79***	0.45*
19.Zest of life (7)	0.13 ±0.30	0.10±0.25	0.25	0.11
20.Depersonalization (28)	0.13 ±0.24	0.12±0.36	0.00	0.38
21.Lack of appropriate emotion(45)	0.19 ±0.57	0.96±0.69	2.96**	0.04
22.Feeling controlled (29)	0.06 ±0.22	0.15±0.37	1.35	0.34
23.Disrupted thoughts (30)	0.13 ±0.34	0.25±0.49	0.94	0.47*
24.Ideas of persecution (31)	0.06 ±0.22	0.25±0.47	2.20*	0.58**
25.Commenting voices (37)	0.02 ±0.10	0.06±0.16	1.35	0.55**

GAF and MMSE

The distribution of GAF scores ranged from 35 to 90 (median 70; mean 68.80±11.90) for the year preceding the examination and from 50 to 90 (median 70; mean 70.65±9.94) for the time of investigation. The distribution of MMSE scores evaluated in 25 patients (excluding one case with severe dystonia and muscle contractures) ranged from 27 to 30 (median 30; mean 29.52+0.96).

DISCUSSION, STUDY I

The main finding of the present study was that the patients with WD had prominent psychopathology despite the fact that they were all treated for WD. The total burden of the psychopathological symptoms seen on the interview-based CPRS was in the same range as that of patients with moderately severe to severe depressive disorders (mean 32.9; SD±2.7) (Perris et al., 1979), and more pronounced than in patients with neurofibromatosis and psychiatric diseases (mean 16.1; range 1.5 – 30) or neurofibromatosis without psychiatric symptoms (mean 4.8; range 0 - 12.5) (Zöller, 1997), or primary hyperparathyroidism pre-operatively (mean 17.2; SD±9.0) or post-operatively (mean 4.4; SD±3.1) (Joborn et al., 1988) or in healthy controls (mean 4.4; SD±2.0 (Joborn et al., 1988).

In earlier studies, it has been claimed that psychiatric symptomatology is related to neurological symptoms (Dening & Berrios, 1989b; Oder et al., 1991). In the present study, psychiatric symptomatology did not differ between the group of patients with predominantly neurological symptoms at the time of diagnosis and those with predominantly hepatic symptoms.

Schizophrenia-like psychosis and other forms of psychosis have been reported in WD (Davison & Bagley, 1969; Dening & Berrios, 1995b; Beard, 1959). However, more recent reports indicate that this is an infrequent problem, at least after the acute phase (Akil et al., 1995; Oder et al., 1991). In the present study, which included treated patients, only a few psychotic (e.g. positive) symptoms were noted, although it seemed appropriate to cover the symptomatology by means of a comprehensive rating scale to avoid preconceived assumptions.

The most common psychiatric symptoms in our patients, based on the CPRS expert (interview), included twelve symptoms. However, only six of them (Reported autonomic disturbances, Fatiguability, Concentration difficulties, Reduced sleep, Observed muscular tension, and Apparent sadness) were found to be derived from the 17 -item Depression Scale (Montgomery, 1978), three (Concentration difficulties, Reduced sleep and Apparent sadness) were derived from the common depression scale, the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery, 1979), and one (lack of appropriate emotion) was derived from the Negative Symptoms scale (Lindström et al., 1996). Thus, the typical symptomatology found in patients with WD cannot easily be described only by means of common rating scales for depressive symptoms.

In the present study, we were able to describe, by means of a comprehensive psychopathological rating scale used without assumptions about the symptomatology to be expected, a symptom profile that might be typical of patients with treated WD. However, studies confirming the present findings are needed. According to our findings, this profile of symptoms seems to be typical of patients with treated WD, regardless of whether the somatic symptoms were predominantly hepatic or neurological. The latter finding was somewhat unexpected but might indicate that the psychiatric symptoms in patients with predominantly hepatic symptoms have previously been underestimated. Our results are, however, in line with those of Dening and Berrios (1989b).

There were no significant differences between sexes apart from a few items; females consistently scored higher than males concerning autonomic disturbances, rituals, feelings of being controlled and labile emotional responses. It is known that females are more prone to admit to depressive symptomatology than males (Streiner, 1995).

In the present study, agreement between expert-based ratings and self-ratings was low. Patients with WD had a tendency to underestimate the presence of psychopathological symptoms. However, the low correlation between self-rating and expert rating could be explained in part by methodological problems concerning the items covering psychotic symptoms in the modified CPRS-S-A. Pronounced differences were also present in the earlier validated part of the CPRS-S-A scale (Svanborg & Åsberg, 1994). For almost all items, the experts scored higher than the patients in their self-assessments. This finding is of clinical importance since it means that expert evaluations ought to be carried out regularly in order for the psychopathology to be revealed and adequately treated.

The typical psychopathological symptom profile in treated WD is not typical of classic psychiatric syndromes and thus the clinical picture may be missed if selected, specific rating scales, e.g. depression rating scales or schizophrenia rating scales, are used. Thus, a comprehensive psychopathological rating scale or a special rating scale designed for the typical symptomatology in WD ought to be used. The problems involved when pre-selected, specific psychiatric rating scales or only self-rating scales are used may explain the inconsistencies in the literature and the often obscured/missed/delayed diagnosis when WD patients present with psychiatric symptomatology.

PERSONALITY TRAITS AS DETERMINED BY THE KSP, STUDY II

RESULTS

Differences in the KSP personality variables between patients with treated WD and healthy controls.

All patients with treated WD (N=25), the predominantly hepatic patients with treated WD (hepatic, n=9) and the predominantly neurological patients with treated WD (neurological, n=10) were compared directly with the healthy volunteers by means of the Mann-Whitney U test, and the results are presented in **Table 6.**

Correlations between KSP scores and age, age at onset, and duration of WD

None of the 15 separate scales in the KSP correlated significantly with age, age at onset or duration of WD.

Gender differences in patients with treated WD

Male WD patients had significantly lower scores than male healthy volunteers on scales measuring Detachment, Somatic Anxiety, Psychic Anxiety, Suspicion, Guilt, Indirect Aggression, Verbal Aggression, Irritability, and on the Aggression and the Hostility factors. Female WD patients had results that were more similar to those of female healthy volunteers. The confidence intervals for the means of the KSP scores at the 95% significantly level, for male and female WD patients are presented in **Figures 1a and 1b,** respectively.

When male and female WD patients were compared, females (n=10) scored significantly higher than males (n=15) on the scale measuring Guilt (49.3±8.5, 39.9±9.1, $z= -2.60$, $p < 0.01$). A sex difference in the same direction was found among healthy volunteers. Female patients with WD scored higher on the scale measuring Suspicion (51.3±11.8, 40.5±10.0, $z= -1.90$, $p < 0.05$) and on the Hostility factor (50.4±12.5, 38.5±9.2, $z= -2.4$, $p <0.01$) than the males. The opposite is usually found in healthy volunteers, where females tend to have lower scores on Suspicion and the Hostility factor than males. Furthermore, female WD patients scored higher than male WD patients on Detachment (49.7±9.5, 44.9±11.2). In healthy controls, females usually have lower scores on Detachment than males.

Table 6. Means and SDs of the KSP variables as T-scores (M=50, SD±10) in the three groups of WD patients (all WD, N=25; predominantly hepatic, n=9; predominantly neurological, n=9) compared to healthy volunteers, respectively, by means of the Mann-Whitney U test, significance levels * $p \leq 0.05$; ** $p < 0.01$; *** $p < 0.005$.

KSP variable	All WD pat M ±SD	Predominantly hepatic M ±SD	Predominantly neurological M ±SD
1. Impulsivity, sensation seeking and social withdrawal scales:			
Impulsiveness	51.6 ± 15.4	49.7 ± 17.5	56.5 ± 15.5
Monotony Avoidance	49.8 ± 12.5	49.9 ± 14.5	53.8 ± 10.5
Detachment	46.9 ± 10.6	48.4 ± 11.6	44.0 ± 9.4
2. Psychopathy versus conformity scales:			
Socialization	49.2 ± 14.7	46.0 ± 19.1	50.3 ± 14.0
Social Desirability	52.9 ± 15.7	48.6 ± 11.9	52.1 ± 20.0
3. Anxiety – related scales			
a) Nervous tension and distress:			
Somatic Anxiety	47.2 ± 8.8	46.7 ± 9.4	46.2 ± 8.7
Muscular Tension	53.1 ± 11.8	53.6 ± 14.7	55.3 ± 11.5
b) Cognitive-social anxiety:			
Psychic Anxiety	45.1 ± 11.5 *	43.1 ± 10.0 *	43.5 ± 12.9
Psychasthenia	50.0 ± 13.8	50.5 ± 11.4	46.9 ± 14.6
Inhibition of Aggression	49.5 ± 12.9	47.8 ± 13.1	46.4 ± 14.0
4. Hostility-related scales:			
Suspicion	44.9 ± 11.8 *	46.0 ± 14.1	44.2 ± 11.9
Guilt	43.7 ± 9.9 ***	43.9 ± 12.5	43.8 ± 10.4 *
5. Aggressivity-related scales:			
Indirect Aggression	47.6 ± 11.3	45.2 ± 11.6	49.2 ± 12.0
Verbal Aggression	42.9 ± 12.4 **	42.3 ± 9.2 *	44.7 ± 13.9
Irritability	43.2 ± 13.1 ***	43.1 ± 14.2 *	43.2 ± 13.4
Aggression factor	43.2 ± 12.1 **	42.1 ± 11.0 *	44.9 ± 13.2
Hostility factor	43.2 ± 12.1 ***	44.3 ± 15.5	42.9 ± 12.2 *

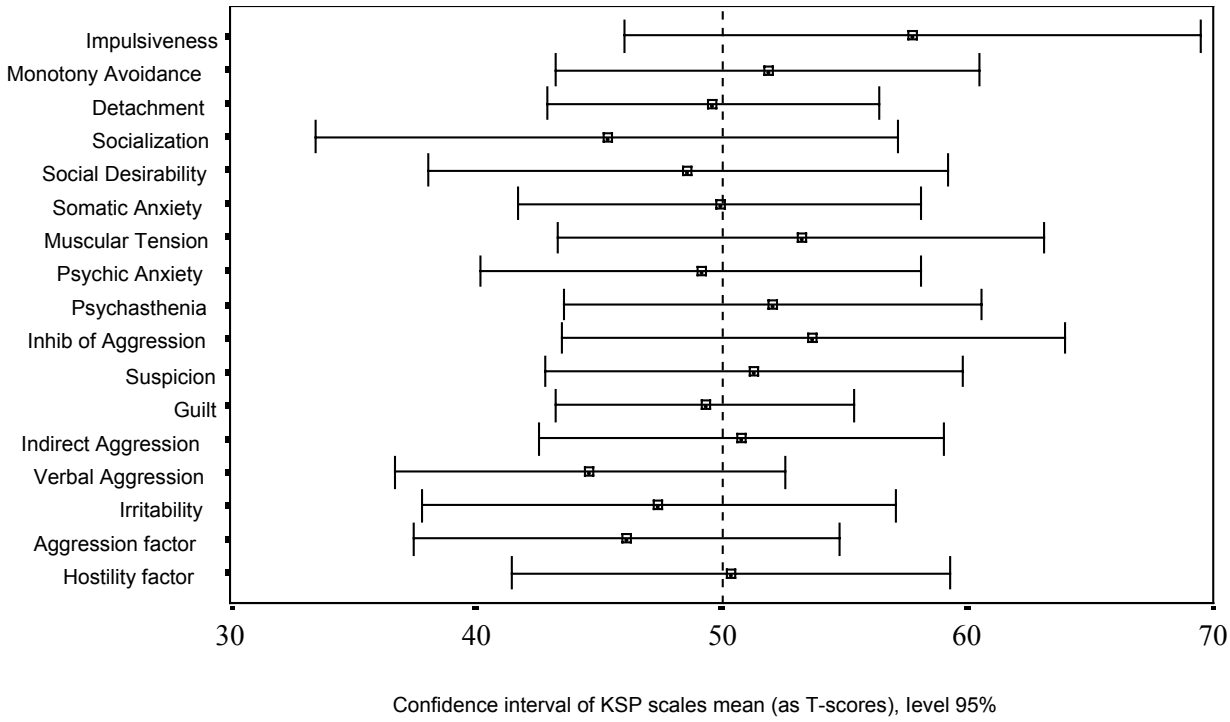

Figure 1a. The male WD patients (N=15).

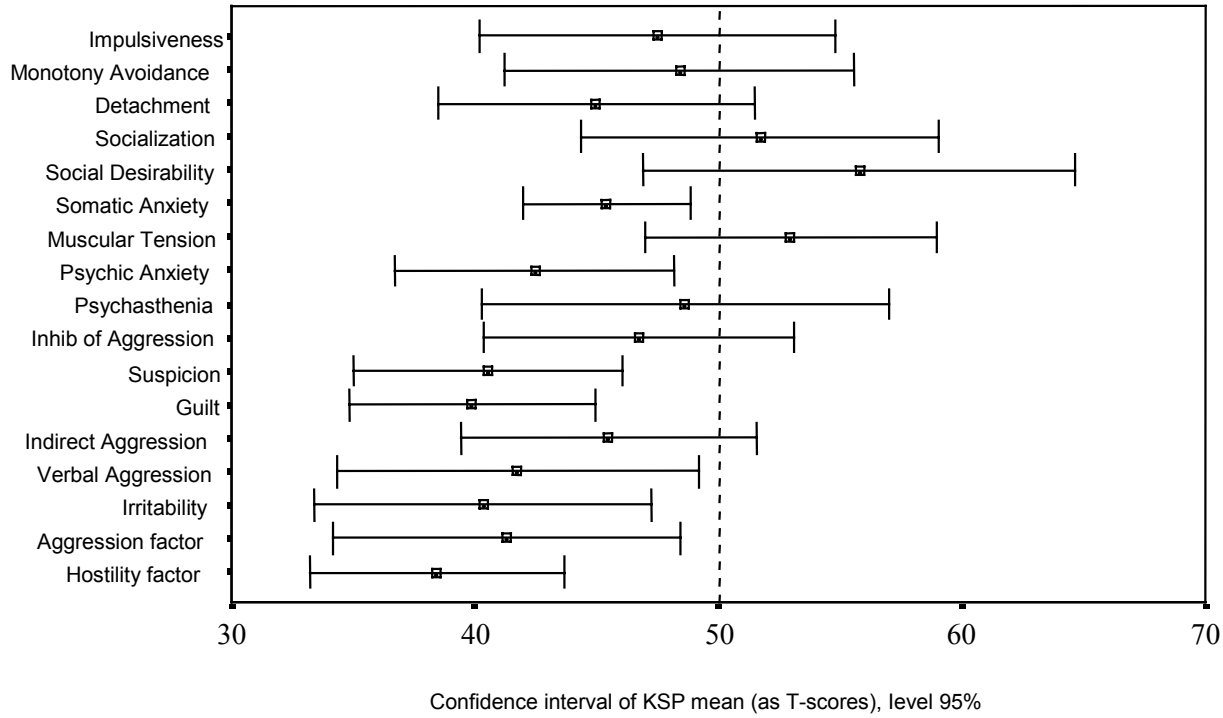

Figure 1b. The female WD patients (N=10).

DISCUSSION, STUDY II

Our main finding is that the patients with treated WD showed significant deviations on several KSP scales, especially aggressivity and hostility related scales, compared to healthy controls when investigated by means of a self-report inventory. Previously, only one study has been reported in which personality traits in WD patients have been investigated using a semi-structured interview, i.e. the Personality Assessment Schedule (PAS) (Dening & Berrios, 1989a), but the authors did not present any detailed personality profile. They claimed that it is difficult to evaluate personality traits in patients with WD because the patients differ in age, age at onset and duration of the disease. In our study, none of the 15 KSP scales correlated significantly with age, age at onset or duration of disease. Other studies have focused on personality disorders, investigated by means of the Minnesota Multiphasic Personality Inventory (MMPI) (Goldstein et al., 1968), the Assessment of an Organic Personality Syndrome (Oder et al., 1993), or a clinical interview (Akil et al., 1991; Walker, 1969). Goldstein et al. (1968) reported some improvement on the MMPI during long-term therapy for WD. Akil et al. (1991) used clinical interviews to diagnose personality disorders and included subjective reports, data from medical records, as well as reports by family members. They reported personality changes that, included aggression and irritability.

However, it is difficult to compare our results with those of other studies that have used different methods. Our main finding is that aggression and hostility levels are low in WD patients when determined by self-reports. In studies where family members were interviewed, aggression and irritability were often reported as prominent features (Akil et al., 1991). Interestingly, the evaluation of patients with WD by experts (Paper I) and family members (Akil et al., 1991) differs from the evaluation in self-report inventories (Paper I).

Furthermore, low scores on aggression-related scales are not found only in patients with WD. This has previously been demonstrated in patients with chronic pain (von Knorring et al., 1987) and in those on long-term dialysis (Björvell & Hylander, 1989), respectively.

It is interesting that both the predominantly hepatic and the predominantly neurological WD patients had lower scores on the Psychic Anxiety Scale than healthy controls. Moreover, the predominantly hepatic WD patients evaluated themselves as less aggressive than healthy controls, and the predominantly neurological WD patients evaluated themselves as less withdrawn (they scored low on the Detachment scale) than healthy controls. In contrast, in the PET study of healthy humans by Farde et al. (1997) and by Laasko et al. (2000), subjects who had low dopamine D2 receptor density in striatum and low dopamine transporter binding in putamen (as WD patients have) scored high on the Detachment scale of the KSP.

Gender differences on the KSP have been reported (af Klinteberg et al, 1987; von Knorring et al., 1984; von Knorring et al., 1987). The most consistent results concern the anxiety-related scales, where females usually score higher than males, and the Detachment scale (Bergman & Bergman 1982), where males score higher than females. It has been shown that there is a relationship between aggressive behaviour and high levels of testosterone in males (Dabbs et

al., 1987). Interestingly, a correlation between high levels of testosterone and aggression – irritability could also be demonstrated in females with PMS (Eriksson et al.,1992), and in adult women with a history of prenatal virilisation due to congenital adrenal hyperplasia (CAH), who have had high scores on the Detachment scale (Helleday et al., 1993). It has been reported that male as well as female WD patients have abnormal steroid levels (Frydman et al., 1991; Kaushansky et al., 1987; Walker, 1969), and women with WD can have oligomenorrhea or amenorrhea, which may be caused by ovarian dysfunction. Kaushansky et al. (1987) found low estradiol values, high total testosterone levels with normal free testosterone, and mildly elevated androstenedione in four female WD patients. Hypogonadism can usually be observed in men with cirrhosis, but increased androgen levels in male WD patients have also been reported (Frydman et al., 1991). No agreement has been reached on the cause of these abnormalities (Hoogenraad, 1996). The mechanisms behind the gender differences observed in the present study, i.e. that female WD patients scored significantly higher than male WD patients on Suspicion and Guilt, as well as on the Hostility factor, and higher on Detachment, are presently unknown. It should also be noted that only 10 female patients were included in the study. Thus, the less pronounced differences between WD females and control females than between WD males and control males might be a Type II error. Since data from the literature may suggest a possible connection with hormonal factors, further characterisation of the hormonal status of WD patients and a possible impact on their personality traits will be the subject of four future studies.

Patients with treated WD have significant personality trait deviations compared to healthy controls, especially regarding aggression-hostility related scales. Our results differ from those obtained by clinical interviews with WD patients and from interviews with family members (Akil et al., 1991). Thus, future studies on personality traits in WD patients, comprising a larger patient series, if possible, should use structured interviews and self-report instruments. Also, the results obtained should be correlated to endocrine profiles and the density of dopamine D2 receptors or dopamine transporters in order, to precisely determine the nature of the personality deviations and the extent to which patients themselves are aware of the deviations in their personality traits.

SLEEP PATTERN AS DETERMINED BY USI, STUDY III

RESULTS

Demographic and social characteristics

About half the WD patients were married or cohabiting, which is significantly fewer than in the reference group (50% and 82%, respectively; $\chi 2=9.5$, $p< 0.001$). Fifty percent of the WD patients were regularly employed compared to 89% in the control group ($\chi 2=18.5$, $p < 0.0001$). The WD patients were significantly taller than the controls (179.8±10.5 cm and 172.7±9.2 cm, respectively; $t=3.1$, $p< 0.01$). There was no significant difference in weight. Consequently, the WD patients had a significantly lower BMI than the controls (21.6±2.9 and 24.3±3.4, respectively; $t=3.6$, $p< 0.0001$)

Quantitative sleep variables

There was no significant difference in nocturnal sleep time, but WD patients went to bed and woke up later than the controls. WD patients took significantly longer time to fall asleep than the controls. Furthermore, the WD patients had a significantly greater number of awakenings per night compared with the controls. In addition, 36% of the female WD patients and 23% of the male WD patients estimated that they were awake for more than 30 minutes a night. Moreover, the WD patients thought they require significantly more sleep than the controls. The quantitative sleep variables and differences in the general sleep variables, means and standard deviations in both groups, as well as results of the Student's *t* test analyses are presented in **Table 7**.

Sleeping difficulties in pre-sleep and sleep periods

In the pre-sleep period and at the moment of awakening, the WD patients reported significantly more problems with "being temporarily paralysed" than the controls. During the sleep period, WD patients reported significantly more nocturnal awakenings, and significantly less snoring and fewer nightmares as compared to the controls. In the WD group nightmares were strongly correlated to number of awakenings, $r_s=0.60$, $p < 0.002$, and palpitations, $r_s=0.70$, $p < 0.0001$, but this was not the case in the controls. In the controls the variable "remembering having dreamt" was strongly correlated to nightmares ($r_s=0.43$, $p < 0.0001$), while this was not so in the WD group. In both the WD and the control group snoring was correlated to BMI, $r_s=0.46$, $p=0.039$ and $r_s=0.31$, $p=0.009$, respectively.

Daytime function

The WD patients complained significantly more than the controls over not feeling rested following sleep and they suffered from fatigue during the daytime. Moreover, the WD patients took naps significantly more often during the daytime than the controls.

The most frequent problems in WD patients

The USI includes two questions about "being temporarily paralysed" when falling asleep or awakening (sleep paralysis), and one question about the sudden onset of muscle weakness during wakefulness (cataplexy). Both sleep paralysis and cataplexy are relatively rare phenomena. In **Table 8** we therefore, present the frequencies for those symptoms in the WD group and in both the controls (N=72) and the large sample (N=1764). All three variables are more frequent in the WD group.

Table 7. Differences in the general sleep variables in the WD group and the reference group determined by means of Student's *t* tests. Means, standard deviations, *t* values and significance levels *p< 0.05, **p< 0.01, ***p < 0.001, ****p < 0.0001are given in the Table.

General sleep variables concerning sleep	**Wilson's disease (WD)** N=24 M ± SD	**Control group (CG)** N= 72 M ± SD	**t - test** WD vs. CG 2-tail sign t -value	p
Bedtime (hours)	23,06±1,24	22,24±00,42	2.05	*
Time until a wakening (hours)	6,48±1,36	6,06±0,42	-1.95	ns
Time until falling asleep (min)	23±21	13±14	2.18	*
Sleep time (hours)	7.0±1.5	7.1±0.9	0.37	ns
Need to sleep (hours)	8.0±1.1	7.3±0.8	-2.86	**
Number of awakenings	2.0±1.8	0.9±1.0	-2.98	**
Nocturial awakenings	1.2±1.1	0.2±0.5	-4.30	****
Getting out of bed for reasons other than nocturial	0.7±1.0	0.2±0.5	-2.19	*

Table 8. Relative frequency of being "temporarily paralysed" during the daytime (cataplexy), the pre-sleep period and at awakening (sleep paralysis) in the different groups: the large sample, the controls and the WD group.

	The large sample N=1764	**Controls N=72**	**WD N=24**
Sleep paralysis in pre-sleep period	9.6 %	2.8 %	20.8 %
Sleep paralysis at awakening	13.0 %	8.3 %	25.0 %
Cataplexy	17.6 %	19.4 %	29.2 %

Other problems pertaining to sleep disturbances

The WD patients were also asked if their work capacity had been affected by the way they sleep. Of the 21 WD patients, who answered this question, nine said yes. These comprised four of nine female WD patients and five of 12 male WD patients. In addition, only one male patient had previously been in contact with a doctor because of sleep problems.

Gender differences

Two variables, i.e. palpitations and nightmares during the sleep period, were scored significantly higher by the WD women (n=11) than the WD men (n=13). No gender differences were found for these variables in the controls. However, snoring, slumbering unwillingly during the daytime and taking naps differed significantly between women and men in the controls, but not in the WD group. For details see **Table 9.**

Table 9. Gender differences in the sleep related variables in patients with treated WD and in the reference group determined by means of Mann- Whitney U tests (M-W test). * $p < 0.05$, ** $p < 0.01$.

	Wilson's disease				**Control Group**			
	Female n=11 M±SD	Male n=13 M±SD	M-W test F vs. M Z	P	Female n=33 M±SD	Male n=39 M±SD	M-W test F vs. M Z	P
Palpitations (sleep)	1.9±1.1	1.0±0.0	-2.66	**	1.4±0.7	1.2±0.6	-1.56	ns
Nightmares	2.3±1.1	1.1±0.5	-3.04	**	2.1±0.9	1.9±0.7	-1.33	ns
Snoring aloud	1.7±0.7	1.9±1.0	-0.11	ns	2.0±1.0	2.6±1.0	-2.62	**
Slumber unwillingly during the daytime	1.4±0.9	1.2±0.8	-1.27	ns	1.2±0.6	1.6±1.0	-2.20	*
Taking naps	2.9±1.3	2.4±1.0	-0.87	ns	1.6±0.9	2.1±1.1	-2.18	*

DISCUSSION, STUDY III

In the present study, 42% of the WD patients thought that they had sleep problems. In contrast, in our recent unpublished study of a large random sample, only 25% of the respondents gave that response.

Although there were no significant differences in sleep time during the night between the WD patients and the control group. WD patients had a significantly greater number of nocturnal awakenings compared to the control group. Moreover, 59% of the WD patients reported that

they were frequently awake for more than 30 min during the night, and nocturia was cited as a frequent cause. However, it was only in the WD group that the number of nocturnal awakenings was correlated to nightmares. WD patients reported a significantly more frequent occurrence of "being temporarily paralysed" (sleep paralysis) than the control group. While WD patients reported not feeling rested after sleep, often taking naps, and suffering from fatigue, they did not report sleepiness during the daytime. In our previous report (Paper I) we pointed out that, WD patients tend to underestimate the presence of psychopathological symptoms. Analogously, it could be that the same trend may occur in self- ratings of sleep problems. All symptoms cited as occurring in the WD group, including autonomic and motor disturbances as well as impaired daytime function, contained features of an altered REM-sleep function.

An unexpected result was that the WD patients snored significantly less than the control group. However, this could be explained by the findings that snoring was correlated to body mass index (BMI), and that the WD patients had a significantly lower BMI than the control group.

The Uppsala Sleep Inventory (USI) has previously been used to investigate the sleeping habits of outpatients with primary Sjögren´s syndrome (pSS), rheumatoid arthritis (Gudbjörnsson et al., 1993) and ankylosing spondylitis (Hultgren et al., 2000), as well as patients with coronary artery disease (Edéll-Gustafsson, 1999). The sleep pattern in patients with treated WD seems to most closely resemble the sleep pattern in patients with primary Sjögren´s syndrome. Similarities were: a sleep deficit, being awake for longer periods during the night, being more disturbed by nocturnal awakening, not feeling rested following sleep, taking naps, and fatigue during the daytime. In contrast to patients with pSS, however, the WD patients did not report problems such as nocturnal pain, muscular tension and restless legs during the pre-sleep and sleep period.

Movement disorders such as Parkinson's disease (PD) and Huntington's disease (HD), and progressive supranuclear palsy, frequently cause EDS (expressive daytime sleepiness) as a result of sleep fragmentation (Bergonzi et al., 1974). However, movement disorders may influence sleep in many ways. Periodic limb movements in sleep and restless legs syndrome frequently occur in HD. In PD, sleep disturbance is reported by approximately 75% of patients and is characterised by an increased number of awakenings, decreased delta and REM sleep, and a scarcity of sleep spindles (April,1966). Sleep in patients with Alzheimer's type of dementia has more sleep fragmentation, and sleep efficiency may be reduced to 60% of normal with an increase in REM latency and a reduced duration of REM sleep, probably due to degeneration of the sleep-regulating mechanisms (Reynolds et al., 1988).

As has been mentioned before, WD patients may have impairments at the brainstem level, disturbances in monoaminergic neurones (REM-off neurones), the PINA mutation (circadian function, suprachiasmatic nuclei), and the spectrum of sleep / wake symptoms they report, suggests an altered REM sleep function. That is in line with a previous case report by Firneisz et al. (2000). Future studies are required to elucidate the mechanisms behind the sleep disturbance in WD. They should include objective methods of assessing sleep and wakefulness e.g. polysomnography and multiple sleep latency tests.

NEUROPSYCHOLOGICAL FUNCTION DETERMINED BY APT, STUDY IV

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 WD patients are illustrated in **Figure 2**. The 19 symptomatic WD patients had a significantly poorer 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 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 correlation is approximately 0.70 (50% shared variance). The two asymptomatic patients had similar but less pronounced impairments, especially in RT200 and Global strategy.

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 better than that of the predominantly hepatic WD patients on the index of executive consistency (ExecConc) ($z= 3.00$, $p< 0.003$), and the alternation task between the right and left index fingers (ARL) ($z= 2.14$,$p < 0.03$). No other significant differences were found between the two groups of WD patients.

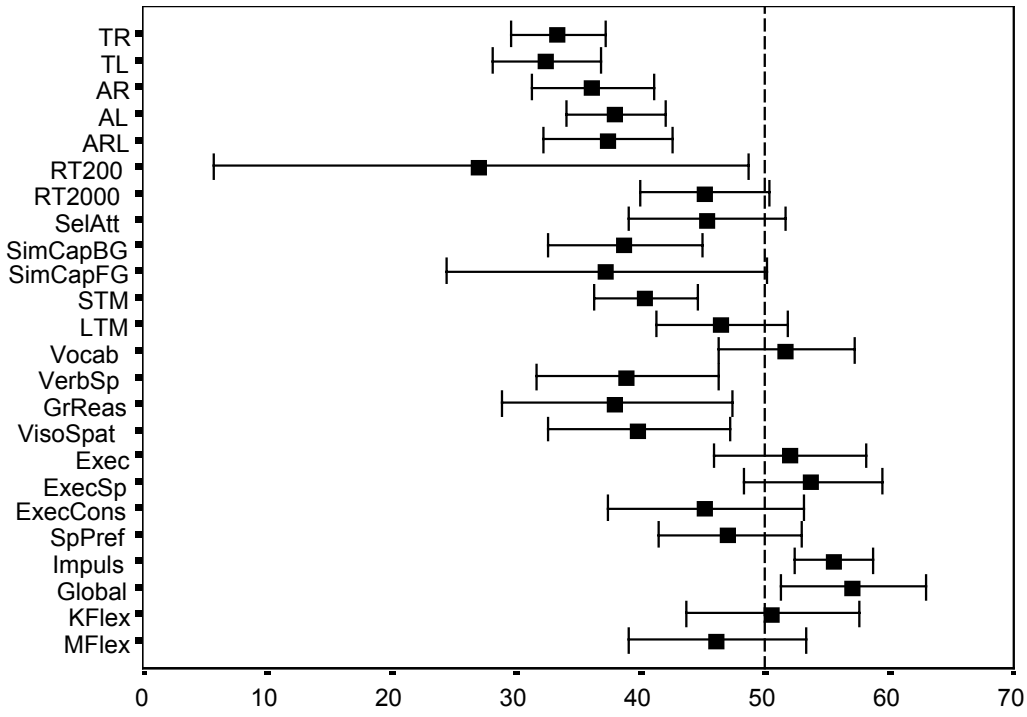

Figure 2. The neuropsychological profile in the symptomatic WD patients (n=19). See abbreviations and Appendix 6.

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' concerning the obtained APT results in patients with treated WD were examined. Partial correlations were calculated between age and the APT variables. Two negative ExecSp ($z = -0.52$, $p < 0.04$), GrReas ($z = -0.46$, $p < 0.05$) correlations remained significant even after correction for duration. Duration (after correction for age) was found to be negatively correlated with VisoSpat ($z = -0.51$, $p < 0.03$) and SCapBG ($z = -0.49$, $p < 0.05$). Age at onset (after correction for age) was found to be positively correlated with MFlex ($z = 0.58$, $p < 0.02$).

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 female symptomatic WD patients (n=6) and male symptomatic WD patients (n=13) are illustrated in **Figures. 3a** and **3b**, respectively.

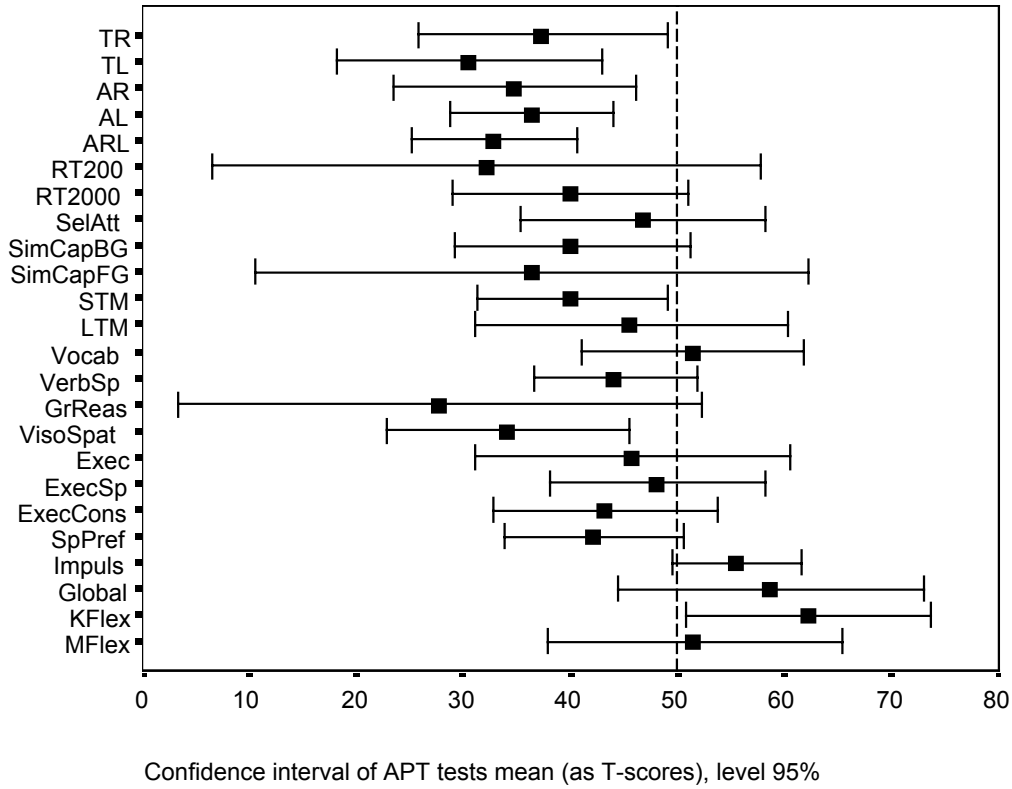

Figure 3a. The neuropsychological profile in the female symptomatic WD patients.

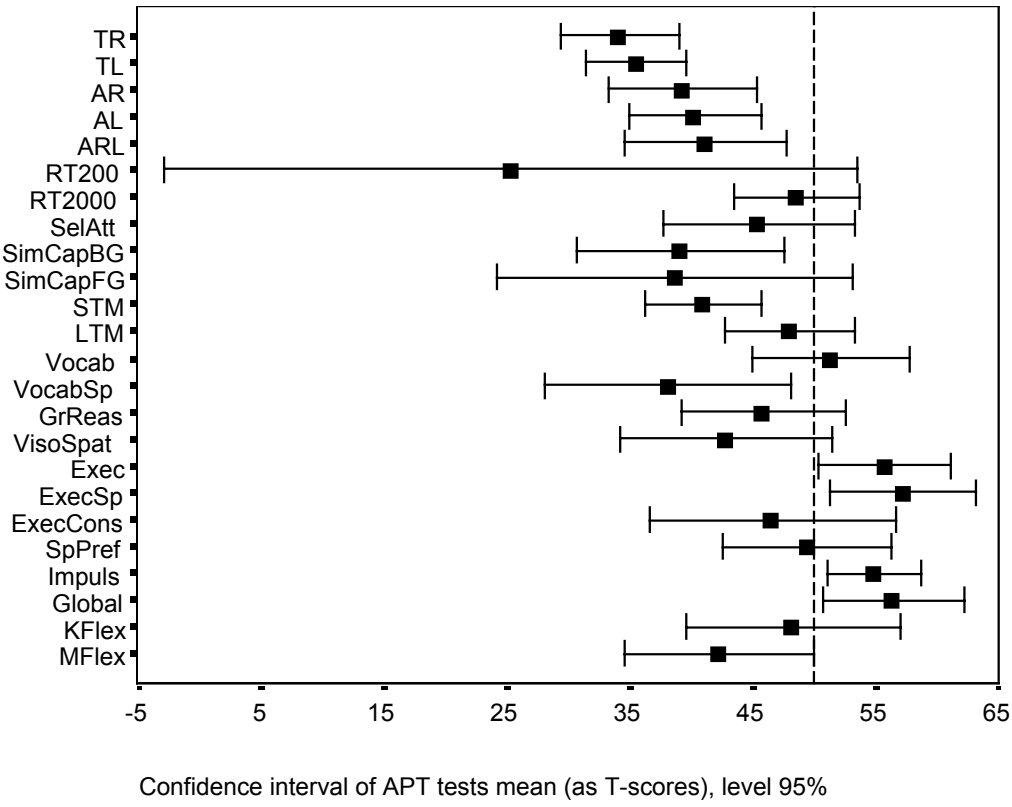

Figure 3b. The neuropsychological profile in the male symptomatic WD patients.

DISCUSSION, STUDY IV

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 cognitive, executive and behavioural capacities. A similar finding has been reported in schizophrenic patients (Tuninger, 1997). The motor functions assessed by the Finger Tapping Alternation tests (five subtasks) were significantly slower in the 19 symptomatic WD patients, which is in accord with an earlier report (Knehr, 1956). Littman and colleagues (1995) reported a prolonged reaction time as well as great variability in the mean response time in predominantly neurological WD patients.

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

The results of the short-term memory test (STM) for the symptomatic WD patients were significantly inferior as compared to the norms, which is in line with previous findings (Issacs-Glaberman et al., 1989; Medalia et al., 1992). The results on the long-term memory test (LTM) and the index of vocabulary (Vocab) were within the norms, which is accord with an earlier study (Issacs-Glaberman et al., 1989). The results of the Grammatical Reasoning test (GrReas) were significantly lower than in the normal group. There are also reports of impairments of conceptual visuo-spacial function in the literature (Tarter et al., 1984). However, in our study, performance on the PMT (VisoSp) was not significantly lower than the norms because of the large variation in performance.

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

We found 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 sexes were equally impaired when compared to healthy controls. Due to the small number of female symptomatic WD patients, the results must be interpreted with caution.

Only two of the 21 WD patients used psychotropic drugs (one SSRI and one major tranquillizer), and therefore it is not possible to evaluate the possible influence statistically. However, the profile was not different in these two patients as compared to the rest of the group. There is no reason to believe that Trientine or D-penicillamine treatment has a differential affect with respect to neuropsychological functioning, and no such tendencies were noted in the present study.

In the past, some authors have discussed the disturbances in WD as being subcortical or frontal (Hoogenraad, 1996; Lang et al., 1992; Rosselli et al., 1987; Scheinberg & Sternlieb, 1984). Today, however, it is generally accepted that there are parallel segregated circuits that link the frontal lobe and the subcortical structures. In other words, depression, schizophrenia, and obsessive-compulsive disorder may be mediated by frontal-subcortical circuits. (Cummings, 1993). The present results are in line with disturbances in frontal-subcortical circuits also being present in WD.

In summary, Wilson's disease is associated with a characteristic profile of neuropsychological impairment, in which basic neuropsychological functions and executive functions appear to be most disturbed. This profile is similar to that found for schizophrenic patients (Tuninger, 1997). Schizophrenia is a neuro-psychiatric disorder in which the basal ganglia are strongly incriminated. Thus, our findings have theoretical as well as clinical implications.

GENOTYPE-PHENOTYPE CORRELATION , STUDY V

RESULTS

Genotype-phenotype correlation concerning psychopathology in patients homozygous or compound heterozygous for WD gene mutations.

Concerning psychopathological symptoms, the homozygous patients with the Trp779Stop mutation had the lowest scores on the total CPRS, due to less pronounced reported CPRS items and a low variability as compared to patients homozygous for the His1069Gln and Thr977Met mutations, respectively, and to those compound heterozygous for His1069Gln/ Arg1319Stop. The three patients with His1069Gln/Arg1319Stop mutations had the highest scores on the total CPRS, both reported and observed items. See **Figure 4**.

Genotype-phenotype correlation concerning personality traits in patients homozygous or compound heterozygous for WD gene mutations.

When personality traits determined by means of the KSP were examined the patients homozygous for the Trp779Stop mutation, had the highest scores on psychopathy related scales, i.e. the Social desirability scale and the Socialization scale, as well as the lowest scores on impulse vs. sensation seeking and social withdrawal, i.e. Impulsiveness, Monotony Avoidance and Detachment scales. The patients with His1069Gln/Arg1319Stop mutations had the lowest scores on psychopathy related scales with values below those of healthy volunteers. See **Figure 5.**

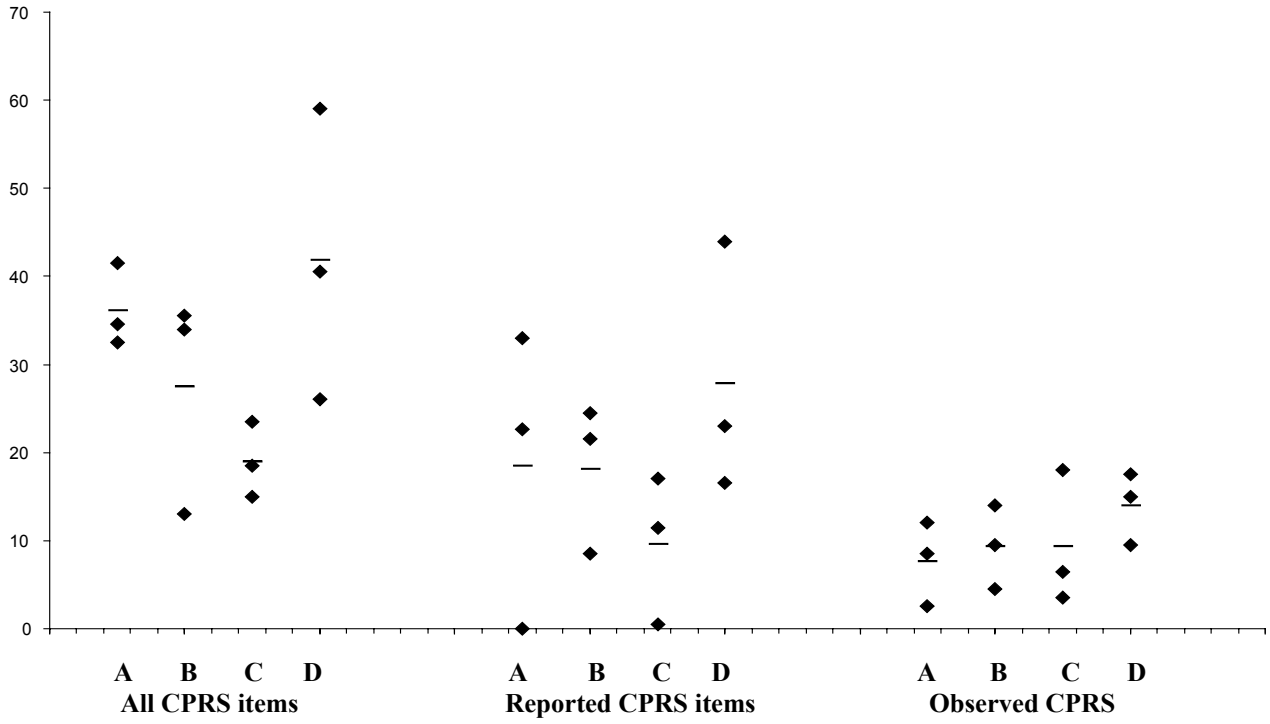

Figure 4. Symptomatology as estimated by means of the Comprehensive Psychopathological rating Scale (CPRS) in patients with treated WD with four separate mutations (N=12) A= His1069Gln, B=Thr977Met, C=Trp779Stop,

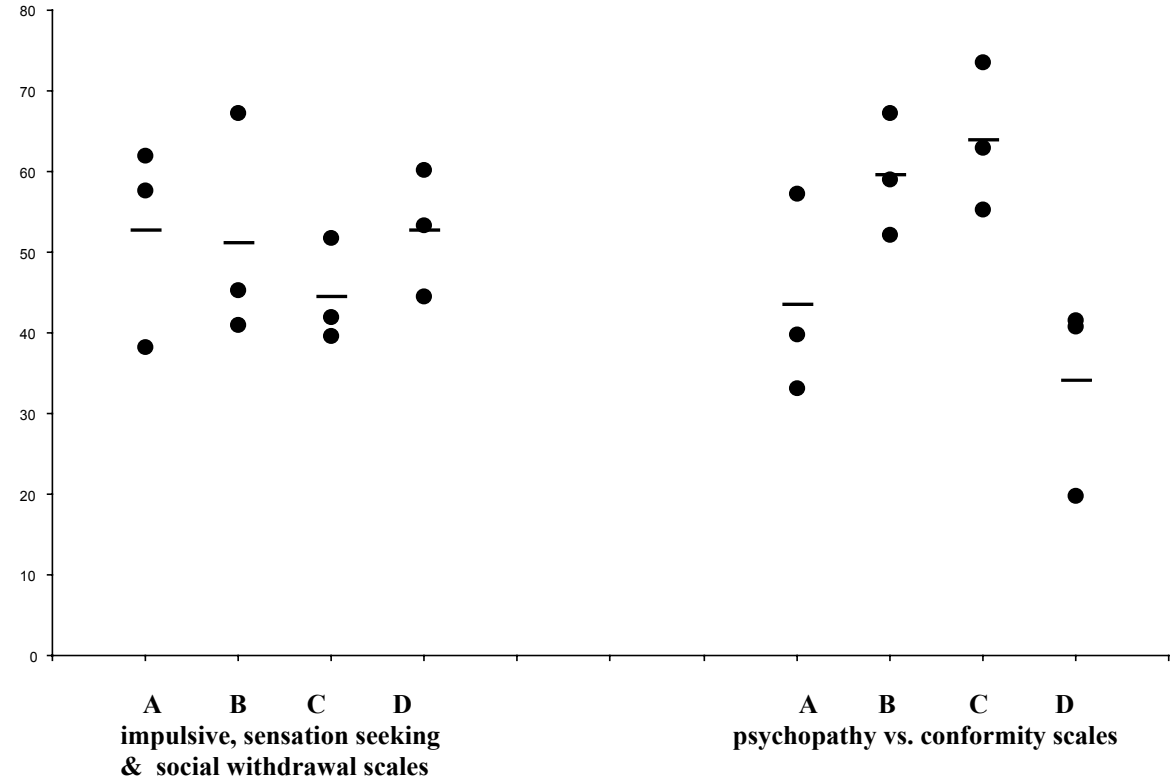

Figure 5 Personality scales according to the Karolinska Scales of Personality (KSP) in patients with treated WD with four separate mutations (N=12) A= His1069Gln, B=Thr977Met, C=Trp779Stop, D=His1069Gln/Arg1319Stop, — = Mean.

DISCUSSION, STUDY V

In the Wilson literature, there exist a number of publications (for review see Riordan & Williams 2001; Thomas et al., 1995; Waldenström et al., 1996; Loudianos et al., 1996; Shah et al., 1997; Czlonkowska et al., 1997; Schiefermeier et al., 2000) where attempts have been made to find a correlation between genotype and phenotype regarding age of onset, severity and type of WD (hepatic, neurologic, mixed). The interpretations of the results of these studies have encountered considerable difficulties since Wilson's disease is a rare disease, the patient materials are small but the number of mutations is large; more than 200 are known at present

Mutations in the WD gene are known to result in a deficient copper transporting P-type ATPase and subsequently to the accumulation of copper mainly in the liver and brain. Although Thr977Met seems to be a conserved amino acid substitution, it has been shown to render ATP7B completely without activity in a yeast system (Forbes & Cox, 1998). Trp779Stop is postulated to give a prematurely terminated protein, without functional domains. This mutation is in exon 8, that has been shown to be absent in an alternative splice variant (where also exons 6, 7 and 12 are lost) that has a normal reading frame, giving rise to a shorter protein. Yang et al., (1997) have shown that this protein is mainly present in the cytosol whereas the normal ATP7B is in the *trans*-Golgi apparatus. These alternative splice variants of *ATP7B* are expressed in the brain (Petrukhin et al., 1994) and could be an explanation for differences in central nervous system manifestations, as tentatively shown in this study. Whether this shorter protein has any functional activity in human is unknown, so the relationship between personality traits and psychopathology and the function of a truncated WD gene products can only be speculated on at present.

The patients described in the present study deviated from healthy volunteers both regarding several personality traits and concerning several psychopathological symptoms, as earlier described (Paper I & II). All of them had been on treatment for WD for several years and according to clinical and laboratory examination, in a copper depleted state. Thus, the full-blown psychopathology and the most pronounced personality trait deviations related to the genotype may, at least in part, have been mitigated as a result of the ongoing treatment.

The results from the present study may suggest a correlation between genotype and phenotype in WD but obviously, larger patient materials are required in order to obtain statistically significant results. Despite these shortcomings, our results support the notion that patients with WD resulting from a homozygous stop codon in exon 8 gives rise to a different phenotype as compared to the other mutations. Further studies are required to support this observation but in the case of a rare disease like WD every contribution, however small, could eventually make it possible to perform large meta-anlyses in order to obtain reliable data on the issue of correlations between genotype and phenotype in WD.

MAIN CONCLUSIONS

1. The patients with treated WD presented prominent psychopathology, when determined by means of the CPRS, that is in the same range as in patients with moderate to severe depressive disorders. The spectrum of psychopathological symptoms is not classic psychiatric syndromes but includes symptoms from Anxiety, Depression and Obsessive-Compulsive disorders as well as Negative Symptoms.

2. In the self-assessment, the patients with treated WD tended to underestimate the presence of psychopathological symptoms.

3. The patients with treated WD had significant deviations in personality traits, especially in aggressivity-hostility related scales and Psychic Anxiety, compared to healthy controls when investigated by means of a self-report inventory, the KSP. The deviations were not related to age, age at onset or duration of the disease.

4. The patients with treated WD differed in their sleep pattern from the control group, as measured with the Uppsala Sleep Inventory. The spectrum of self-reported symptoms suggests an altered REM sleep function.

5. The patients with treated WD patients displayed a specific profile of moderate neuropsychological impairment, as tested with the Automated Psychological Test battery (APT). The WD patients had a significantly lower level of performance than the norms on all finger tapping tasks, the simple reaction time test, 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 had significantly higher scores on the index of impulsive errors, and used a significantly more global processing mode in the test of selective attention.

6. There were some differences in psychopathology and personality traits in the treated WD patients grouped according to APT7B mutations (His1069Gln/His1069Gln, Thr977Met/Thr977Met, Trp779Stop/Trp779Stop and His1069Gln/Arg1319Stop). It was mainly the patients homozygous for the Trp779Stop mutation who tended to differ with respect to psychopathology and personality traits.

REFLECTION

As in many other studies, the present efforts resulted in some answers, summarised in the main conclusions and indicated the importance of taking gender into account when considering WD patients (this should be verified though further research) and many new questions arose such as:

How does this monogenic disorder present with such a wide spectrum of phenotypes concerning psychopathology and neuropsychological dysfunction?

What kinds of mechanisms are behind all these symptoms?

Will the biological model of WD, i.e. LEC rats, provide us with some answers?

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APENDIX 1. WD patients' participating in studies I – V. Study I consisted of interview - based ratings (I) and self-based ratings (S).

Pat. No	**Study I** N=26		**Study II** N=26	**Study III** N=24	**Study IV** N=22	**Study V** N=27
	I	**S**				
1	x	x	x	x	x	x GP
	x	x	x	x	x	x GP
3	x	x	x	0	x	x GP
4	x	x	x	x	x	x
5	x	x	x	x	x	x GP
6	x	x	x	x	x	x GP
7	x	x	x	x	x	x GP
8	x	x	x	x	Ex	x GP
9	0	0	0	0	0	x GP
10	x	x	x	x	x	x GP
11	x	x	x	x	x	x
12	x	x	x	x	x	x
13	x	x	x	0	x	x
14	x	x	x	x	x	x
15	x	x	x	x	x	x GP
16	x	M	x	x	0	x GP
17	x	x	x	x	x	x GP
18	x	x	x	x	x	x
19	x	x	x	x	0	x
20	x	x	x	x	x	x
21	x	x	x	x	x	x
22	x	x	x	x	x	x
23	0	0	0	x	0	0
24 †	x	D	D	0	D	D
25	x	x	x	0	x	x
26	0	0	0	x	0	0
27	x	x	x	x	x	x
28	x	x	x	x	0	x
29	x	x	x	x	x	x

x= included; 0= not a patient at the Dept. of Intern. Medicine at time of the specific study; M= patient missed participation in part of the study; D= patient deceased, missing data; Ex= patient excluded due to severe general dystonia with contractures of hands and feet); GP= patients investigated for genotype-phenotype relationships

APPENDIX 2. Description of the series of patients participating in studies I – V as regarding family membership, age, sex, and year of birth (19--), ethnic background, age at onset, clinical symptoms at onset / diagnosis, and homozygous and compound heterozygous for mutations in the WD gene (APT7B).

Pat No.	Family No.	Sex & year of birth	Ethnic back-ground	Age at onset	Symptom at onset / diagnosis	Exon in APT7B		Mutation in APT7B	
Patients homozygous for mutations in the WD gene									
1	1	F 48	NE	21	H+N	14	14	His1069Gln	His1069Gln
2	2	M 54	NE	24	N+P	14	14	His1069Gln	His1069Gln
3	3	M 59	NE	23	H	14	14	His1069Gln	His1069Gln
4	4	M 60	NE	24	H+P	14	14	Frameshift	Frameshift
5	5	F 40	NE	25	H+N+P	13	13	Thr977Met	Thr977Met
6	6	M 66	NE	24	H+N+P	13	13	Thr977Met	Thr977Met
7	7	M 67	NE	13	H	13	13	Thr977Met	Thr977Met
8	8	M 64	NE	18	N+P	8	8	Trp779Stop	Trp779Stop
9	9	M 71	NE	14	N	8	8	Trp779Stop	Trp779Stop
10	10	F 66	NE	family screening		8	8	Trp779Stop	Trp779Stop
11	11	M 58	K	15	N	8	8	Gly710Ser	Gly710Ser
12	11	M 61	K	13	H	8	8	Gly710Ser	Gly710Ser
13	12	M 66	A	21	N+P	8	8	Arg778Leu	Arg778Leu
Patients compound heterozygous for mutations in the WD gene									
14	13	M 67	NE	9	N	19	?	Arg131Stop	?
15	14	F 44	NE	22	H+P	14	19	His1069Gln	Arg1319Stop
16	15	F 62	NE	12	H+P	14	19	His1069Gln	Arg1319Stop
17	15	M 64	NE	11	H	14	19	His1069Gln	Arg1319Stop
18	16	M 63	NE	10	N	14	18	His1069Gln	Frameshift
19	17	F 62	NE	24	N	14	15	His1069Gln	Val1106Asp
20	18	M 75	NE	20	N	14	13	His1069Gln	Thr977Met
21	19	F 68	NE	16	H+P	14	13	His1069Gln	Thr977Met
22	20	F 48	NE	21	H+N+P	14	13	His1069Gln	Ile967Phe
23	21	F 64	NE	16	H+P	14	13	His1069Gln	Gly1000Arg
24	**22** †	M 74	NE	21	N	14	8	His1069Gln	Trp779Stop
25	23	M 64	NE	12	N	14	?	His1069Gln	?
26	24	M 78	K	14	H+P	8	17	Ala751Val	Thr1220Met
27	25	F 67	NE	19	H+P	6	15	Gly626Ala	Val1106Asp
28	26	F 61	NE	21	N+P	2	16	Gln289Stop	Trp289Stop
29	27	M 69	NE	family screening		2	?	Gln289Stop	?

Abbreviations used: M/F –male / female, NE –North European, K –Kurdish, H – hepatic, N –neurological, P –psychiatric, C –cohabiting or married, NC –not cohabiting or not married, E –regularly employed, R –vocational rehabilitation, U – unemployed, St –student, Ml –maternity leave, Sl –sick leave, D –disability pension.

APPENDIX 4. List of CPRS items and sub-scales

	Reported items		Observed items
D,M,O	1. Sadness	D,M,O	41. Apparent sadness
	2. Elation		42. Elation mood
B,D,M,O,	3. Inner tension		43. Hostility
B,D	4. Hostile feeling		44. Labile emotional responses
D,M,R	5. Inability to feel	N	45. Lack of appropriate emotion
D,M	6. Pessimistic thoughts	B	46. Autonomic disturbance
D,M	7. Suicidal thoughts		47. Sleepiness
B	8. Hypochondriasis		48. Distractability
B,D,O	9. Worrying over trifles	N	49. Withdrawal
O	10. Compulsive thoughts		50. Perplexity
B	11. Phobias		51. Blank spells
O	12. Rituals		52. Disorientation
D,N,O	13. Indecision		53. Pressure of speech
D,M,O,R	14. Lassitude	N,R	54. Reduced speech
D,R	15. Fatiguability		55. Specific speech defects
D,M,O	16. Concentration difficulties	P	56. Flight of ideas
	17. Failing memory	P	57. Incoherent speech
D,M	18. Reduced appetite		58. Perseveration
B, D,M	19. Reduced sleep	P	59. Overactivity
	20. Increased sleep	N,R	60. Slowness of movement
	21. Reduced sexual interest	D,P	61. Agitation
	22. Increased sexual interest		62. Involuntary movement
B,D	23. Autonomic disturbances	D	63. Muscular tension
B	24. Aches and pains		64. Mannerisms and postures
B,D	25. Muscular tension	P	65. Hallucinatory behavior
	26. Loss of sensation or movement		66. Global rating of illness
P	27. Derealisation		67. Assumed reliability of the rating
P	28. Depersonalisation		
P	29. Feeling controlled		
P	30. Disrupted thoughts		
P	31. Ideas of persecution		
P	32. Ideas of grandeur		
P	33. Delusional mood		
	34. Ecstatic experiences		
	35. Morbid jealousy		
P	36. Other delusions		
P	37. Commenting voices		
P	38. Other auditory hallucinations		
P	39. Visual hallucinations		
P	40. Other hallucinations		

B =(BSA) items in Brief Scale for Anxiety; D = (DS) items in Depression Rating Scale; M= (MADRS) items in Montgomery-Åsbery Depression Rating Scale; O = items in CPRS-OCD scale; N = items in Negative Symptom (NS) Rating Scale; P = items in Positive Symptoms (PS); R= items in Retardation Symptom

APPENDIX 5. The grouping of 15 KSP scales (Schalling, 1993) and descriptions of high scores for each scale.

KSP variable	Description of high scores
A. Impulsivity, sensation seeking and social withdrawal scales:	
Impulsiveness	Acting on the spur of the moment, non-planing, impulsive
Monotony Avoidance	Avoiding routine, need for change and action (sensation seeking)
Detachment	Avoiding involvement with others, withdrawn, "schizoid
B. Psychopathy versus conformity scales:	
Socialization	Positive childhood experiences, good school & family adjustment
Social Desirability	Socially conforming, friendly, helpful (or "faking good")
C. Anxiety – related scales	
1) Nervous tension and distress:	
Somatic Anxiety	Autonomic disturbances, restless, panicky
Muscular Tension	Tense and stiff, not relaxed
2) Cognitive-social anxiety:	
Psychic Anxiety	Worrying, anticipating, lacking self-confidence, hypersensitive
Psychasthenia	Easily fatigued, feeling uneasy when urged to speed up and when facing new tasks
Inhibition of Aggression	Lacking ability to speak up and lack of self-aggression in social situations
D. Hostility-related scales:	
Suspicion	Suspicious, distrusting people's motives
Guilt	Remorseful, ashamed of bad thoughts
E. Aggressivity-related scales:	
Indirect Aggression	Sulking, slamming doors when angry
Verbal Aggression	Getting into arguments, telling people off when annoyed
Irritability	Irritable, lacking patience

APPENDIX 6. List of APT tests

APT tests	Meta indices of APT variables	
A. Motor and Basic neuropsychological functions		
1. Finger Tapping and Alternations Test		
- right index finger tapping	**TR**	
- left index finger tapping	**TL**	
- right index-middle finger alternation	**AR**	
- left index-middle finger alternation	**AL**	
- right - left index finger alternation	**ARL**	
2. Reaction Time Tests (RT)		
- simple auditory and simple visual RT	**RT200**	simple RT
- two-choice (left-right) visual RT - two-choice visual RT with auditory signals for response inhibition	**RT2000**	complex RT
3. *K* – Test	**SelAtt**	Selective Attention
4. Simultaneous Capacity Test (SCap)		
- Background task	**ScapBG**	
- Foreground task	**ScapBG**	
B. Memory and cognitive aptitude tests		
5. Digit Span Test	**STM**	short-term memory
6. Associative Learning Test		
7. Long-term memory Test	**LTM**	
8. Word Recognition Test		
	Vocab	index of vocabulary
	VerbSp	index of word decoding speed
9. Grammatical Reasoning Test	**GrReas**	
10. Perceptual Maze Test (PMT)	**VisoSpat**	visuo-spatial ability
C. Executive functions		
11. Austine Maze Test	**Exec**	executive index
	ExecCons	executive consistency index
	ExecSp	executive speed index
D. Index of performance		
	SpPref	speed preference
	Impuls	impulsive vs. reflective cognitive style
	Global	global vs. sequential strategy
	KFlex	flexibility of strategy in k-test
	MFlex	flexibility of strategy in PMT

Errata

Comprehensive summary

Page 1, last paragraph, page 2, first paragraph, page 8, last line, page 40, last paragraph APT7B	should be ATP7B
Page 25, Fig. 1a. male...patients Fig. 1b. female...patients	should be Fig. 1a. female...patients Fig. 1b. male...patients
Page 33, first paragraph z=	should be r=

Paper IV

Page 10, last line r=-50	should be r=-0.50
Page 11, line 16 and 17: ”First, the Mann-Whitney...”	The sentence should be omitted
Page 11, third paragraph z=	should be r=