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Chapter 11

# Cognitive and psychiatric symptoms in Wilson disease

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**Abstract**

Wilson disease – can present with such a variety of psychiatric and cognitive symptoms that it has been named the "great masquerader." Symptoms may include cognitive deficits, impairment of executive function, mood disturbance or psychosis. These impairments may occur in different stages of the disease and with varying intensity in individual patients. This chapter reviews the literature and authors' clinical experiences of the assessment, mechanism, and prevalence of cognitive and psychiatric pathology occurring in Wilson disease. Evidence of pharmacologic and nonpharmacologic treatments is also discussed.

## INTRODUCTION

Wilson disease (WD) can present with such a variety of psychiatric and cognitive symptoms that it has been named the "great masquerader" (Soltanzadeh et al., 2007). Psychiatric symptoms have been considered a part of the clinical presentation in WD since the disease was first described in 1912. Eight out of 12 cases in Wilson's monograph had psychiatric symptoms (Kinnier-Wilson, 1912). Irreversible cognitive decline was considered common in WD and psychiatric textbooks often cited this disorder as one of the classic examples of subcortical dementia. Cognitive problems and psychiatric symptoms were considered inseparable from the neurologic findings. Studies published in the last three decades started to point out that cognitive, psychiatric, and neurologic findings can present and evolve separately in the course of WD. Longitudinal observations have challenged the general view that cognitive impairment is irreversible in WD. Successful symptomatic treatment of psychiatric symptoms has been described even in severe cases. In addition, improved diagnostic tests make it easier to reach the diagnosis of WD when the initial presentation is atypical.

## PHYSIOLOGIC BASIS FOR PSYCHIATRIC AND COGNITIVE SYMPTOMS IN WILSON DISEASE

Copper is considered essential for normal brain function (Madsen and Gitlin, 2007) and its role in various psychiatric illnesses has been explored for decades. As early as the 1940s, copper was postulated to play an essential role in schizophrenia (Beard, 1959), although the relationship between peripheral copper levels and the copper effects in the brain has never been clarified. Studies showed increased levels of copper in plasma and hair of patients with acute schizophrenia compared to controls (Yanik et al., 2004; Rahman et al., 2009). Copper serum values were also elevated in criminal schizophrenic men compared to noncriminal subjects (Tokdemir et al., 2003). More recently, Wolf et al. (2006) showed that patients with schizophrenia had serum copper levels that were increased by 23% and serum ceruloplasmin elevated by 20% compared to controls.

The exact mechanism of how copper participates in the course of psychiatric illness is not known. It was postulated that excess of serum copper may affect dopamine activity through several enzymes which are copper-dependent (dopa-decarboxylase,

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beta-hydroxylase, and monoamine oxidase) (Jeon et al., 1998).

In addition to its role in the dopamine system, serotonin abnormalities have been described in WD, in particular abnormalities of the presynaptic serotonin transporter (SERT) density. A significant negative correlation was found between severity of depression in WD and SERT density in the thalamus–hypothalamus region (Eggers et al., 2003) and hypothalamus (Hesse et al., 2003). More details about brain pathology in WD and pathogenesis are presented in Chapters 8 (on brain pathology) and 5 (on pathogenesis).

Brain lesions identical to those in WD occur in patients with other varieties of cirrhosis in which copper metabolism is not affected (Duchen, 1984). One study (Rathbun, 1996b) assessed simultaneously cognitive domains in a cohort of 34 WD patients, 25 with neurologic and/or hepatic symptoms and 9 asymptomatics, and measured urinary copper. There was no significant correlation between the copper level and degree, frequency, and nature of neuropsychologic variables in either symptomatic or asymptomatic patients. Since the diverse pathologies of WD have been usually directly linked to copper toxicity, the absence of any significant correlation in Rathbun's sample has heuristic implications for additional clinical and experimental studies. This finding might suggest that direct copper toxicity may not be the mediating factor in cognition in WD patients. Possible mechanisms may consist of brain damage secondary to copper toxicity or alternative biochemical influences produced from pathologically involved organs such as the liver (Rathbun, 1996b).

In another study (Goldstein et al., 1968) of 17 WD patients who underwent decoppering treatment, psychologic tests showed no specific changes, suggesting the lack of a direct relationship between copper toxicity and cognition. These findings contradict other studies which showed that effective decoppering therapies arrested or reversed psychiatric, neurologic, and hepatic symptoms (Cartwright, 1978).

## EVALUATION OF COGNITIVE IMPAIRMENT AND PSYCHIATRIC SYMPTOMS IN WILSON DISEASE

### Clinical assessment

Before reviewing the literature on cognitive functioning and psychiatric symptoms in WD it is worth discussing the challenges in measuring these findings.

Cognitive function is a general term, used both in clinical and common language, usually to determine the correct, logical, and effective reasoning, manifested in verbal statements or behavior. In any assessment of cognition it is difficult to separate one function/ability from the other, because they co-occur and influence each other. Conscious, aim-directed, intelligent behavior is based on many fundamental cognitive abilities such as perception, memory and learning, language abilities, reasoning, praxis, and construction. The distinction between testing cognitive function, verbal abilities or behaviors is often artificial and intended to facilitate description and measurement. In psychology as well as in neuroscience, each cognitive function is usually divided into more specific subsystems, with characteristics of their parameters (e.g., speed, precision).

Differentiation of cognitive function uses various criteria developed by general and clinical psychology based on theoretic models and empiric research.

In the dynamic organization of the brain, cognitive function is inseparably linked with volition, motivation, and affective systems, as well as with the system controlling intentional, aim-directed behavior, which is the executive system. The latter, being a theoretic construct, includes a series of abilities such as inhibitory control, working memory, cognitive flexibility, problem solving, and planning. It is rare to find a patient who has defects in just one aspect of executive functioning. Rather, defective executive behavior involves a cluster of deficiencies of which one may be dominant. Such pathology is very sensitive to prefrontal damage and to prefronto-subcortical loop impairment, which usually occur in WD. Therefore it is very difficult, in relatively short clinical assessment, to identify at what level of hierarchically organized cognitive behavior the primary pathology arises.

During the neuropsychologic assessment clinicians pay great attention to differentiate primary from secondary cognitive deficits, specifically those impairments due to alteration of consciousness, physical illness, affective impairment, speech disorders, and sensorimotor deficits. The latter frequently occur in WD population.

The quality of psychometric evaluation of the cognitive state depends on the characteristics of the tests, their reliability, sensitivity, temporal stability, and predictive validity. However, tests are rarely designed for a specific clinical population that may have its own specific limitations (e.g., motor impairment or dysarthria that occurs in WD). This reduces the reliability of the evaluation because some of the variables (e.g., even mild extrapyramidal movement or dysarthria) are in practice difficult to control for.

Many inconsistencies concerning cognitive dysfunctions in WD originate from the differences between the assessment tools used by different researchers. Some researchers prefer screening tools which are less sensitive. Other authors use highly sensitive tests, but assess selectively a narrow aspect of cognitive functioning (e.g., divided attention or information-processing speed). In

the presence of movement disorders typical for WD, measurement of cognitive abilities might be altered when tests chosen by a researcher engage manual skills. The rarity of WD underlines the weaknesses of some studies resulting from small groups of participants, which are, in addition, diverse as to the severity and duration of the disease, its treatment duration, the characteristics of the clinical picture, and the severity of the pathology of the liver and brain. This reduces the reliability of generalizations about the entire WD population and makes it impossible to predict development or reversibility of specific dysfunctions in the individual patient (treated vs. nontreated).

Methodologic difficulties limiting the reliability of cognitive assessment in WD were summarized by Frota et al. (2013): "Despite being present in the first patients described by Wilson in 1912, cognitive impairment has been little studied and is still a matter of controversy until today."

Due to the fact that the psychiatric, cognitive, and neurologic symptoms were often described together as one entity, it was difficult to distinguish them until the late 1970s, when investigators started assessing the symptoms in more detail. Structured psychiatric measures started being used to specifically describe mood, psychotic or behavioral symptoms. All the limitations described above in relation to cognitive testing apply to an extent to psychiatric measures: many scales have not been validated in this specific population, results could be skewed by motor or verbal deficits, and limited longitudinal follow-up does not allow accounting for normal variations in mood or anxiety.

## Laboratory data and neuroimaging

### Copper and ceruloplasmin levels

At this time there is not enough information about the correlation between specific psychiatric symptoms and levels of copper or ceruloplasmin (Dening and Berrios, 1989).

### Electroencephalogram (EEG)

Small studies have suggested that the beta EEG generator was more anteriorly localized in patients with more pronounced psychiatric symptoms and cognitive deficits (Dierks et al., 1999). Other studies have described abnormalities on EEG in patients with WD; however, no clear correlation between EEG findings and psychiatric symptoms has been established (Arendt et al., 1994a).

### Neuroimaging

The most common finding on the brain magnetic resonance imaging (MRI) in WD is T2 hyperintensity signal lesions in basal ganglia, as well as in thalamus, brainstem, and cerebellum (see Chapter 10 for further details). Neuroimaging can provide important information for treatment-resistant illness, such as a case with rapid deterioration on computed tomography (CT) scan of the brain (bilateral putamen necrosis 15 months after diagnosis of WD) (Awada et al., 1990). However, there are no studies looking at correlations between MRI studies and specific psychiatric presentations in WD.

There are few studies correlating cognitive functions with MRI findings in WD. Seniów and coworkers (2002) compared cognitive functioning in 50 WD patients with different type and degree of neurologic symptoms, 17 WD neurologically asymptomatic (some of them with very mild hepatic dysfunction), and 50 healthy controls. Multifocal brain pathology with cortex atrophy revealed on MRI was associated with more severe cognitive impairment than pathology within selective basal ganglia lesions.

Hegde et al. (2010) examined 12 treated Indian WD patients with neurologic symptoms to assess their cognitive abilities in relation to MRI findings. The researchers measured sustained attention, focused attention, mental speed, motor speed, category fluency, working memory, planning and problem solving, concept formation, abstract thinking, cognitive flexibility, verbal learning, visuoconstructive ability, and visual memory. Patients with changes in the putamen had cognitive impairment in more than six examined domains, while those without signal changes in the putamen had deficits in fewer than four domains. A deficit in visual and verbal learning was confirmed in all patients with pathology of putamen.

### Event-related potentials (ERP)

It has been earlier shown that ERPs may reflect cognitive decline in patients with dementia (e.g., Lai et al., 2010). Gunther and coauthors (2011) assessed cognitive functioning of 35 WD patients by dividing them into two groups: 25 with neurologic symptoms /basal ganglionic and/or cerebellar/ and 10 with hepatic or asymptomatic type of WD. Results of cognitive measurement tools (Structured Interview for the Diagnosis of Dementia of the Alzheimer Type, multi-infarct dementia, and dementias of other etiology (SIDAM) and Mini Mental State Examination (MMSE)) were correlated with auditory ERPs for a neurophysiologic assessment of cerebral information processing underlying cognition.

The auditory P300 ERPs were studied using the Nihon Kohden Neuropack μ device. Binaural auditory stimuli were presented in a random series. Twenty percent of stimuli were rare target tones of 2000 Hz; the remaining 80% were frequent tones of 1000 Hz at 75 dB. For each patient analysis was performed twice.

For each set of signal-averaged data 30 target responses were required and series mode rejection was performed. The P300 was measured by quantifying its amplitude and latency. Results of ERPs were compared between the two WD groups and in regard to the literature, about P300 studies (Lai et al., 2010). Patients with a neurologic course of the disease by trend showed lower amplitudes, delayed latencies of P300, and lower values in the cognitive tests.

In structured interview SIDAM concerning cognitive functioning, the median of neurologic patients was only mild, reduced to 52 of a possible 55 points. The nonneurologic group had a normal median result of 54.5 points. The median for all participants was reduced to 53 points. In the neurologic group the median in MMSE was minimally decreased to 29 of 30, which represents normal values.

Median amplitude and latency of P300 were 326 ms and 9 μV within normal range in all patients. There were only slight differences between the median of the neurologic and nonneurologic group, showing a reduced amplitude with 7.8 μV and delayed latency of 333 ms in the neurologic group, compared to 11.3 μV and 305.5 ms in the nonneurologic group. The authors concluded that the neurologic WD group – as compared to the nonneurologic group – only by trend showed reduced cognitive functioning, lower amplitudes, and delayed latencies of P300, but all median results were still within a normal range in both WD groups. Therefore, WD did not influence significantly the auditory ERPs in this study. The examined cohort was formed of patients with very discrete mental deficits; therefore it might not be a representative WD sample. Furthermore, the applied tests were not sufficiently sensitive to reveal mild cognitive impairments usually present in neurologic WD patients, and it might have been more useful if they were assessed using specific neuropsychologic tools (Seniów et al., 2002).

### Genetic studies

Genetic studies looking at correlations between various genes and psychiatric aspects of patients with WD are promising, although limited at this time to small studies and to limited psychiatric symptoms. Twenty-six patients with WD were evaluated via the Comprehensive Psychopathological Rating Scale (CPRS) and Karolinska Personality Scales (KPS) and findings were analyzed against the gene mutations present in *ATP7B*. Patients with the Trp779Stop mutation scored the lowest on CPRS, while heterozygous patients had the highest score on CPRS. When the results of personality testing were studied, those homozygous for Trp779Stop mutation had the highest scores on the psychopathy versus conformity scale and socialization scale, and low scores on the impulsiveness, avoidant, and detachment scales. Patients homozygous for Thr977Met scored high on the psychopathy versus conformity scale as well. Patients with heterogeneous mutation His1069Gln/Arg1319Stop had the lowest score on the psychopathy versus conformity scale. Of note, there was low agreement between the interview-based ratings and self-ratings. The significance of the correlations of psychiatric findings with *ATP7B* genotype is unclear, as the authors noted, because the cohort size was small and, at the time of study publication, there were at least 300 gene sequence variants known to occur in WD (Portala et al., 2008).

## COGNITIVE FUNCTION IN PATIENTS WITH WILSON DISEASE

The literature review presented in Table 11.1 summarizes the types of cognitive deficits disclosed in various psychometric tests in WD groups. Groups are numerically and clinically diverse as WD population is very heterogeneous. The reversibility of cognitive dysfunctions under the influence of treatment is difficult to predict. Cognitive impairment can be more easily recognized in the neuropsychiatric form of WD or in end-stage liver WD than in mild hepatic WD (Ferenci et al., 2015) and therefore mixing of these patients during examination blurs pathologic specifics. In such a diverse and dynamic disease, prediction of a specific pattern of cognitive pathology is doubtful, as sickness pathology overlaps with the highly individualized premorbid abilities.

When assessing cognition in WD, patients at the extreme end of the intelligence spectrum are the most difficult to categorize. The highly intelligent may appear average and not impaired and may continue fulfilling their social roles. There are also WD patients with such severe intellectual impairment that they are even excluded from clinical trials. These patients could usefully be described in methodologically correct case studies, based largely on observation of their behavior, nonstandardized simple clinical tasks, and interviews with the family.

The solution for a reliable assessment of cognitive functioning WD patients with specific disease symptoms, including somatic, motor, cognitive, emotional symptoms, and speech dysfunction, requires implementation of an interdisciplinary, multicenter study with standardized measurement tools of cognitive-behavioral variables. Only in such a model could the data be compared and generalized. Describing the real state of a heterogeneous patient population requires experimental, prospective, randomized studies, including large groups, and this is not easy to implement in a rare disease at a single medical center. The selection of cognitive tests must

*Table 11.1*

**Review of research studies on cognitive functioning in the Wilson disease population**

| Authors and year | Study design/ participants (*n*) | Measurement tools | Conclusions/cognitive deficits |
|---|---|---|---|
| Medalia et al. (1988) | Comparative study<br>WDN = 19<br>WDA = 12<br>The whole group = 35<br>Healthy controls = 15 | Wechsler Adult Intelligence Scale-R (with exclusion of two subtests: Vocabulary and Object Assembly);<br>Wechsler Memory Scale;<br>Dementia Rating Scale;<br>Wisconsin Card Sorting Test;<br>Boston Naming Test;<br>Trail Making Test;<br>Animal Naming Test | The WDN patients, as compared to the WDA, and the controls, revealed mild and selective cognitive dysfunctions: the lower IQ, a worse memory quotient, worse scores in Dementia Rating Scale (although test scores were still within the low area of norms) |
| Lang et al. (1990) | Comparative study<br>WDN (11) + WDH (6) = 17<br>Healthy controls = 17 | Chosen subtests from Wechsler Adult Intelligence Scale-R: Digit Span, Picture arrangement, Arithmethics;<br>Multiple Choice Vocabulary Test;<br>Raven's Progressive Matrices;<br>Short-term memory, Attention and Perceptual Speed;<br>Benton Visual Retention Test – multiple choice version;<br>Chosen subtests from German Intelligence Test: verbal fluency, logical reasoning, visual perception, and spatial imaginary;<br>two subtests from German Intelligenz Struktur Test, assessing perception and visual-spatial imaginary | The WDN patients, as compared to the healthy individuals, had diminished logical reasoning<br>The whole WD group – lower speed in perceptual tasks |
| Medalia et al. (1992) | Comparative study<br>WDNP = 16<br>WDH (5) + WDA (3) = 8 | Wechsler Memory Scale;<br>Minnesota Multiple Personality Inventory (MMPI);<br>The Sickness Impact Profile (SIP) | The WDNP group:<br>lower scores on Wechsler Memory Scale.<br>more psychopathologic features in MMPI;<br>more subjective complaints regarding the impact of WD on everyday functioning (SIP) |
| Arendt et al. (1994b) | Comparative study<br>WDN = 19<br>Healthy controls = 19 | Multiple Choice Vocabulary Test;<br>Ravens Progressive Matrices;<br>The Short Cognitive Performance Test | WDN, as compared with the healthy, did not reveal any significant cognitive impairment<br>All WDN complained about depressed mood |
| Littman et al. (1995) | Comparative study<br>WDN = 17<br>Healthy controls = 17 | Memory scanning task;<br>Visual scanning task<br>(tasks based on the Sternberg fixed-set paradigm) | WDH did not slow down information processing<br>Motor deficits had a clear impact on cognitive tests performance |
| Rathbun (1996b) | Comparative study<br>WDN + WDH = 25<br>WDA = 9<br>The whole WD group = 34<br>Without control group (test results compared with Indian norms) | Wechsler Adult Intelligence Scale-R;<br>Hooper Visual Organization Test;<br>Ravens Progressive Matrices;<br>Benton Visual Retention Test;<br>Symbol Digit Substitution (written and oral versions);<br>Peabody Picture Vocabulary Test-R;<br>Wechsler Memory Scale;<br>Purdue Pegboard Test | Symptomatic (neurologic and hepatic) patients, as compared to asymptomatic patients, were slightly lower results in all cognitive tests, except visual-spatial task |

*Continued*

*Table 11.1*

**Continued**

| Authors and year | Study design/ participants (*n*) | Measurement tools | Conclusions/cognitive deficits |
|---|---|---|---|
| Seniów et al. (2002) | Comparative study<br>WDN = 50<br>WDA = 17<br>The whole WD group = 67<br>Healthy controls = 50 | Wechsler Adult Intelligence Scale;<br>Rey's Auditory Verbal Learning Test;<br>Benton Visual Retention Test (multiple choice version);<br>Raven's Progressive Matrices | The WDN group, as compared to the controls, showed a mild impairment in all tested cognitive functions<br>The WDA patients had no deficits in any measured cognitive functions |
| Hegde et al. (2010) | WDN = 12<br>Without control group (test results compared with the norms) | Digit Vigilance Test;<br>Color Trial Test and Triads Test;<br>Digit Symbol Substitution;<br>Finger Tapping Test;<br>Animal Names Test;<br>Rey's Auditory Verbal Learning Test;<br>Rey's Complex Figure Test.<br>Verbal N-back Test;<br>Tower of London;<br>Wisconsin Card Sorting Test | The WDN group had deficits in: psychomotor speed, verbal working memory, sustained and focused attention, verbal learning, visuoconstructive ability, verbal memory, mental speed, verbal fluency, set-shifting ability, visual memory<br>Only 1 patient (with normal MRI) did not reveal any cognitive deficits |
| Xu et al. (2010) | Comparative study<br>WDS = 20<br>Healthy controls = 38 | Clinical Dementia Rating Scale;<br>Memory abilities-experimental computer tasks;<br>Perceptual learning tasks in situation with low vs high external noise | 7 WDS patients had no deficits in general cognitive functioning, 13 patients revealed mild to moderate impairment<br>All patients had deficits in both forms of category learning and in perceptual learning but only in high external noise; in low external noise these functions were relatively spared |
| Frota et al. (2013) | Comparative study<br>WDN = 18<br>WDA = 2<br>The whole WD group = 20<br>Healthy controls = 20 | Mini Mental State Examination;<br>Digit span forward and backward task;<br>Memory Test of Figures;<br>Clock Drawing Test;<br>Verbal Fluency Test;<br>CERAD naming test;<br>Stroop Test;<br>Frontal Assessment Battery;<br>Mattis Dementia Rating Scale;<br>Wisconsin Card Sorting Test;<br>Hooper Visual Organization Test;<br>Block Design (a subtest from WAIS) | The WDN patients had various isolated cognitive impairments, especially concerning executive functions<br>Only 10% of WD patients did not reveal any executive disturbances |

| | | | |
|---|---|---|---|
| Ma et al. (2013) | Comparative study<br>WDN = 30<br>Healthy controls = 30 | Mini Mental State Examination;<br>Wechsler Adult Intelligence Scale-R;<br>Verbal Fluency Test;<br>Digit Span Test (forward and backward);<br>The Stroop Test;<br>Wisconsin Card Sorting Test;<br>Decision Making Tasks (under risk condition) | The WDN patients had worse results in a task that requires decision making in a situation of risk and in tests: Verbal Fluency, Digit Span, The Stroop Test, Wisconsin Card Sorting Test (all tests are sensitive for frontal damage) |
| Wenisch et al. (2013) | Comparative study<br>The whole WD group = 31<br>WDN = 18<br>WDH + WDA = 13<br>Without control group (compared with test norms) | Chosen subtests from Wechsler Adult Intelligence Scale-III: Information, Similarities, Digit Span, Digit Symbol;<br>Symbol Search;<br>Raven's Progressive Matrices;<br>California Verbal Learning Test;<br>Modified Taylor Complex Figure-recall;<br>Chosen subtests from Wechsler Memory Scale: Letter-Number Sequencing, Visual Span;<br>Wisconsin Card Sorting Test;<br>Stroop Test;<br>Test Uwagi D2;<br>Baddeley's Double Test Task;<br>Trial Making Test | In all WD patients verbal intelligence and episodic memory and visuospatial functions were preserved<br>In WDN patients pathology concerned more executive functions: working memory, abstract reasoning, and inhibitory process |
| Han et al. (2014) | Comparative study<br>WDN = 35<br>Healthy controls = 35 | Wechsler Adult Intelligence Scale-R;<br>Attention Network Test;<br>Short-term memory and attention span (digits repetition forward and backwards);<br>Verbal fluency task | The WDN patients had diminished alertness to what may secondarily disturb more complex attention subsystem and intellectual skills<br>The other measured cognitive functions did not differ significantly from those in healthy individuals |
| Iwański et al. (2015) | Comparative study<br>WDN = 33<br>WDH + WDA = 34<br>Healthy controls = 43 | Test of Everyday Attention | The WDN patients had deficiency in all attention subsystems (sustained, selective, divided, switching); however relatively the most disturbed was attention switching<br>WDH + WDA group – an isolated deficit of sustained attention |

WD, Wilson disease; WDS, WD symptomatic; WDA, WD clinically asymptomatic; WDH, WD hepatic; WDN, WD neurologic; WDNP, WD neuropsychiatric.

be carefully matched with the typical symptoms of WD (accurate tests, responsive to change, reliable, functional, acceptable and understandable by the patient, and results that are not significantly influenced by neurologic symptoms). In clinical research it is worth determining in advance whether the measurement of cognitive functioning is done at the level of: (1) impairment; (2) disability; or (3) participation (e.g., social, cultural, economic). Such proceedings are recommended by the World Health Organization (1980) for neurorehabilitation. There is a need for more research to assess the impact of pharmacologic or behavioral treatment on cognitive functioning. It is also important to assess the preserved functions and well as the impaired ones.

The failure of strenuous attempts to find the typical profile of cognitive and affective dysfunctions in WD patients appears discouraging. Sometimes it may be more valuable to describe individual patients and their preserved cognitive resources. It is important that rehabilitation programs are conducted in parallel with pharmacotherapy in order to assess outcomes.

A few decades ago cognitive dysfunction in the neurologic form of WD was sometimes called subcortical dementia. This implied that the disease – especially if left untreated – frequently resulted in gradual intellectual deterioration which met the criteria for dementia (Cummings and Benson, 1984). However it seems that, when properly treated, the majority of WD patients reveal only selective, mild cognitive deficits, that do not meet the current criteria of dementia (Seniów et al., 2002; Frota et al., 2009; Wenisch et al., 2013). There is a relatively good prognosis for maintenance of cognition in asymptomatic patients with treated WD (Medalia et al., 1988; Seniów et al., 2002). None (Lang et al., 1990) or only mild and isolated cognitive deficits may occur in some individuals with WD with the hepatic form without overt encephalopathy (Tarter et al., 1987; Szutkowska-Hoser et al., 2005). They may include slightly diminishing visuopractic abilities, psychomotor speed, learning, and arithmetic skills.

## PSYCHIATRIC PRESENTATIONS IN WILSON DISEASE

Psychiatric symptoms have been described in all stages of WD. A particular focus has been placed on the presence of psychiatric symptoms at the initial stages of the disease, in the absence of hepatic or neurologic manifestations, since it has been linked with delays in diagnosis. A meta-analysis of the case reports when the psychiatric disease was the initial presentation of WD showed that average time between psychiatric symptoms and diagnosis of WD was 2.42 years (SD 2.97) (Zimbrean and Schilsky, 2014). In comparison, the median time between initial symptoms and when the diagnosis of WD was first established was 1.5 years for neurologic WD and 0.5 years for hepatic disease (Oder et al., 1991). Cohort studies have reported that up to 64.8% of patients with WD reported psychiatric symptoms at their initial presentation (Akil et al., 1991) and up to 20% of patients had seen a psychiatrist prior to the formal diagnosis of WD (Dening and Berrios, 1989). Table 11.2 summarizes the case studies in which psychiatric presentations occurred in patients with WD disease prior to any neurologic or hepatic manifestation.

Studies have indicated that up to 64.8% of patients had psychiatric symptoms in the beginning of illness (with or without hepatic or neurologic findings), while up to 70.7% of patients experienced neuropsychologic symptoms at some point in the course of the disease (Pan et al., 2005). The presence of multiple psychiatric conditions is common. A cross-sectional study of 50 patients using the Structured Clinical Diagnostic Interview (SCID) found that 40% met criteria for more than three psychiatric diagnoses (Svetel et al., 2009). Table 11.3 summarizes the prevalence of psychiatric symptoms in WD.

### Mood disorders

The occurrence of depressive symptoms has been well documented in patients with WD. The prevalence of major depressive disorder has been reported to be between 4% (assessed by the SCID: Shanmugiah et al., 2008) and 47.8% (assessed by Advanced Neuropsychiatric Tools and Assessment Schedule: Carta et al., 2012a). It is important to note that depression was often described in the beginning of the illness, therefore it could not be explained by the psychosocial consequences of a chronic medical disease. In one of the three prospective studies looking at psychiatric symptoms in the course of WD disease, depression remained present in a significant part of the group: 1 in 3 patients had depression on initial evaluation and 1 in 4 continued to have depression at follow-up (Dening and Berrios, 1990). At least two systematic studies have documented a high prevalence of bipolar disorders in WD patients: a cross-sectional study in which each patient was examined by two psychiatrists using SCID diagnosed bipolar disorder in 18% of 50 patients (Shanmugiah et al., 2008). A more recent case-control study of 23 patients using Mood Disorder Questionnaire (a screening instrument for mania or hypomania) showed that 30% of those studied met criteria for bipolar disorder, while 39% met criteria for mania or hypomania (Carta et al., 2012a).

*Table 11.2*

**Psychiatric symptoms as the initial presentation of Wilson disease**

| Author and year | Age (years) | Gender | Psychiatric symptom | Neurologic symptom | Days from onset of psychiatric symptoms to diagnosis | Psychiatric treatment |
|---|---|---|---|---|---|---|
| Carr and McDonnell (1986) | 13 | M | Behavioral problems, academic decline | Involuntary limb and head movement | 1460 | No details |
| Chung et al. (1986) | 30 | F | Psychosis | Parkinsonism | 14 | Haloperidol, chlorpromazine |
| Bouix et al. (1987) | 24 | M | Concentration problems, poor academic performance, catatonia, conversion | Dysarthria | 3650 | |
| Awada et al. (1990) | 20 | F | Catatonic schizophrenia | Parkinsonism, dystonia | 480 | No details; psychiatric hospitalization |
| Buckley et al. (1990) | 16 | F | Personality change | Neuroleptic malignant syndrome | 90 | Amitriptyline, clomipramine, perphenazine |
| Saint-Laurent (1992) | 18 | M | Psychosis (three episodes) | Parkinsonism | 4380 | Neuroleptics, chelation |
| Davis and Borde (1993) | 12 | M | Irritability, academic problems, catatonia | Tremor, drooling | 365 | Benzodiazepines, chelating agents |
| Gwirtsman et al. (1993) | 22 | F | Anorexia nervosa | None | 1825 | Eating disorder behavioral treatment |
| Garnier et al. (1997) | 39 | M | Psychosis | Akathisia, dysarthria, resting tremor | 180 | Neuroleptics, D-penicillinamine, zinc, antiparkinsonian |
| Shah and Kumar (1997) | 23 | M | Schizophrenia | Dysarthria, ataxia, tremor | 60 | Electroconvulsive therapy, haloperidol |
| Walter and Lyndon (1997) | 21 | M | Major depressive disorder | Drooling, motor retardation | 84 | Tricyclic antidepressants, mianserine, lithium, decoppering agents |
| Keller et al. (1999) | 38 | M | Major depressive disorder then mania after antidepressants were started | Extrapyramidal symptoms | 180 | Antidepressants, interpersonal therapy, neurorehabilitation |
| Muller et al. (1998) | 23 | M | Psychosis, depression | Parkinsonism, dysphagia | 1215 | Haloperidol, pipamperone, bipiriden, alprazolam |
| Muller (1999) | 13 | M | Suicide attempts, mania, psychosis | | 2555 | Zuclopenthixol |
| Stiller et al. (2002) | 18 | M | Depression | Stuttering | 2190 | Psychotherapy |

*Continued*

*Table 11.2*

**Continued**

| Author and year | Age (years) | Gender | Psychiatric symptom | Neurologic symptom | Days from onset of psychiatric symptoms to diagnosis | Psychiatric treatment |
|---|---|---|---|---|---|---|
| Stiller et al. (2002) (2) | 19 | M | Psychosis, schizophrenia | Dysarthria | 730 | Antipsychotics |
| Campos Franco et al. (2003) | 58 | M | Depression, psychosis | | $6 \times 365$ | |
| Rodrigues and Dalgalarrondo (2003) | 26 | M | Depression with psychosis | Bradykinesia | 600 | Electroconvulsive therapy, risperidone, amytriptyline, thiaridazine |
| Sagawa et al. (2003) | 17 | F | Psychosis (olfactory paranoia) | Dysarthria and finger tremor, rigidity | 2430 | |
| Shah and Vankar (2003) | 11 | M | Psychosis | Muttering, tremor | 30 | Alprazolam, risperidone, divalproex |
| Smit et al. (2004) | 21 | M | Depression | Bradykinesia | 30 | Fluoxetine |
| Chan et al. (2005) | 35 | F | Depression, suicide attempt | Parkinsonism | 1460 | Electroconvulsive therapy, selective serotonin reuptake inhibitors, haloperidol, eventually chelation |
| Krishnakumar and Riyaz (2005) | 11 | F | Major depressive disorder | Abnormal movements | 270 | Thioridazine |
| Chand and Murthy (2006) | 18 | M | Mania | Extrapyramidal symptoms | 120 | Lithium |
| Lin et al. (2006) | 10 | M | Attention deficit disorder, violent rages | Drooling, seizures | 600 | Carbamazepine, Penicillamine, vitamin $B_6$, and zinc supplement |
| Jukic et al. (2006) | 26 | F | Psychosis | Choreoathetosis | 7 | Haloperidol |
| Barbosa et al. (2007) | 16 | M | Academic decline, aggression, irritability | Jerks of four limbs, unsteady gait, impaired coordination, action tremor of upper limbs, difficulty in swallowing solid foods | 730 | Haloperidol, chlorpromazine |
| Benhamla et al. (2007) | 59 | M | Major depressive disorder with psychosis | | 7 | Elavil, haloperidol |
| Kumawat et al. (2007b) | 17 | M | Obsessive-compulsive disorder | None | 180 | Fluoxetine |

| | | | | | | |
|---|---|---|---|---|---|---|
| Machado et al. (2008) | 26 | M | Manic episode | Tremor in the upper limb (1 year later) | 1215 | Lithium initially; after chelation treatment, patient was asymptomatic without psychiatric medications for years |
| Aggarwal and Bhatt (2009) | 18 | M | Irritability, personality change, behavioral disturbance | Dysarthria, dystonia, abnormal limb posture | 1095 | No details |
| Aravind et al. (2009) | 41 | M | Mania (four episodes) | Rigidity, bradykinesia, dysphagia, dysarthria | 1825 | Valproic acid, chlorpromazine |
| Habek et al. (2009) | 45 | F | Generalized anxiety disorder | None | 7 | No psychotropic medications; penicillamine only |
| Tatay et al. (2010) | 23 | M | Bipolar I | Tremor | 365 | Lithium, risperidone |
| Alva-Moncayo et al. (2011) | 13 | M | Inexpressive face, indifference | Dystonia, bradykinesia, stiffness | 730 | No details |
| Silva et al. (2011) | 5 | M | Attention-deficit hyperactivity disorder | Diadocokinesia | 365 | Methylphenidate |
| Nayak et al. (2012) | 19 | M | Catatonia | | 14 | Electroconvulsive therapy, olanzapine trifluoperazine 15 mg/day, trihexyphenidyl 6 mg/day |
| Aljukic et al. (2013) | 18 | M | Behavioral problems (lack of interest in the surroundings, decreased interactions with family) | Aphasia, drooling, tongue protrusion and cogwheel rigidity | Unspecified "prior history" | Clozapine, pyridoxine |
| Araujo-de-Freitas et al. (2014) | 31 | M | Depression, psychotic symptoms after 6 months | Drooling, cogwheeling | 195 | Various antidepressants initially; escitalopram with paliperidone, mirtazapine |
| Yigit et al. (2014) | 25 | M | Psychosis; persecutory delusions, auditory and visual hallucinations | | Days | No details |
| Basu et al. (2015) | 19 | F | Paranoia, catatonia | | 365 | Risperidone, olanzapine, aripiprazole, quetiapine initially for psychosis without improvement; lorazepam when catatonia developed |
| Zimbrean and Schilsky (2015) | 38 | F | Depression initially, mania and psychosis after diagnosis of Wilson disease | Perioral numbness | 365 | Escitalopram, quetiapine, clonazepam |

*Table 11.3*

**Prevalence of psychiatric problems in Wilson disease**

| Author and year | Type of study | *n* | Measure | Findings | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Psychiatric symptoms | Depression | Mania/ hypomania | Anxiety | Psychosis | Personality changes | Other |
| Medalia and Scheinberg (1989) | CSec | 24 | MMPI | Patients with neurologic impact scored higher on the Schizophrenia and depression scale | | | | | | |
| Dening and Berrios (1990) | P | 129 | AMDP system | 51% had psychopathologic features<br>20% had seen a psychiatrist prior to the diagnosis of WD | 15% | | | Rare | | 15% irritability<br>15% "incongruent behavior" |
| Akil et al. (1991) | R | 41 | CE | 64.8% had psychiatric symptoms in the beginning of the illness | 27% | | | | 45.9% | Catatonia, cognitive changes, anxiety, psychosis |
| Oder et al. (1991) | P | 45 | HDS<br>ZDS<br>ADS<br>MMSE | | 26.6% mood symptoms; 31.1% affective instability | | | 6.7% psychosis | | 15.5% past suicide attempts; 20% impaired social judgment 24.4% belligerence |
| Huang and Chu (1992) | R | 71 | CE | Mean age for onset of symptoms $25.3 \pm 2.4$ for WD with psychiatric features | | | | 11.3% Schizophrenia; was the initial diagnosis for 4.2% | 38.0% | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Rathbun (1996a) | CSec | 34 | MNB | | 26% | | 20% | 2.0% |
| Portala et al. (2000) | CSec | 26 | CPRS KSP | Autonomic disturbances, muscular tension, fatigability, decreased sexual interest, lack of appropriate emotion, concentration difficulties, reduced sleep | | | | |
| Bono et al. (2002) | CR | 21 | CE | 19% had initial psychiatric symptoms | | | | |
| Pan et al. (2005) | R | 41 | CE | 70.7% had neuropsychologic symptoms | | | | |
| Soltanzadeh et al. (2007) | R | 44 | CE | 44% had psychiatric or sleep problems | | | | |
| Srinivas et al. (2008) | R | 15 out of cohort of 350 | CE | 4.2% had psychiatric findings; 33.3% of psychiatric symptoms improved with decoppering treatment alone | | 2.5% Bipolar | | 1.4% Schizophrenia 0.8% Schizoaffective, sensitivity to neuroleptics |
| Shanmugiah et al. (2008) | CSec | 50 | SCID, two psychiatrists | 24% met diagnosis of a psychiatric disorder | 4% MDD 2% dysthymia | 18% had bipolar disorder | | |

*Continued*

*Table 11.3*

**Continued**

| Author and year | Type of study | *n* | Measure | Findings | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Psychiatric symptoms | Depression | Mania/ hypomania | Anxiety | Psychosis | Personality changes | Other |
| Svetel et al. (2009) | CSec | 50 | SCID NPI | 40% had >3 psychiatric diagnoses; 14% had two psychiatric diagnoses; 18% had one psychiatric diagnosis; 70% had one psychiatric symptom | Depression 36% | | Anxiety 62% | | | Irritability 26%; disinhibition 24%; apathy 24% |
| Mercier-Jacquier et al. (2011) | R | 19 | CE | 21% had psychiatric disorders | 15.7% depression | | | | | One anorexia nervosa, two impulsivity |
| Netto et al. (2011) | CSec | 24 | PSQI | | | | | | | PSQI worse in WD than in controls ($p = 0.03$) |
| Nevsimalova et al. (2011) | CSec | 55 | ESS RBD-SQ MSLT (24) | | | | | | | Lower sleep duration, decreased sleep efficiency, and increased wakefullness |
| Carta et al. (2012a) | CC | 23 | ANTAS MDQ | 30% Bipolar disorder | 47.8% MDD | 39% mania/ hypomania | 8.7% Panic disorder | | | |

CPRS, Comprehensive Psychopathologic Rating Scale; MMSE, Mini Mental Status Examination; MMPI, Minessota Personality Inventory; HDS, Hamilton Depression Scale; ZDS, Zeissen Depression Scale; ADS, Adjective Depression Scale; MNB, Michigan Neuropsychological Battery; KSP, Karolynskaya Scale of Personality; SCID, Structured Clinical Diagnostic Interview; CE, clinical examination; ANTAS, Advanced Neuropsychiatric Tools and Assessment Schedule; MDQ, Mood Disorders Questionnaire; PSQI, Pittsburg Sleep Quality Index; ESS, Epworth Sleepiness Scale; RBD-SQ, rapid eye movement behavior disorder questionnaire; MSLT, Multiple sleep latency test; MDD, major depressive disorder; CSer, case series; CSec, cross-sectional; CC, case control; CR, case registry; R, retrospective; P, prospective.

### Anxiety

Between 20% and 62% of patients with WD are reported to have significant anxiety symptoms (Rathbun, 1996a; Svetel et al., 2009), while 8.7% of patients met criteria for panic disorder (Carta et al., 2012a).

### Psychotic symptoms

In a Chinese group, 11% of patients with WD met criteria for schizophrenia (Huang and Chu, 1992). The typical presentation is a patient with psychotic symptoms who is started on antipsychotic medications and develops significant neurologic symptoms, which are interpreted as being side-effects related to antipsychotics. When these side-effects take an unusual presentation, neurologic consultation is requested, and this sometimes leads to the diagnosis of WD. These particular cases are associated with significant delays in diagnosis and treatment. Cases have been reported in patients who spent years in psychiatric facilities only to be diagnosed with WD and have their psychiatric symptoms resolved when chelation therapy was instituted. Up to 4.2% of patients seen in WD clinic were reported to present with initial symptoms of psychosis (Huang and Chu, 1992).

Psychotic symptoms may also occur during the treatment phase of WD in up to 40% of cases (McDonald and Lake, 1995; Aggarwal and Bhatt, 2012). Cases of new-onset psychosis and euphoria have been reported post liver transplantation for WD (Al-Hilou et al., 2012). One patient developed acute neuropsychiatric presentation (major depressive disorder with psychotic features, suicide attempt, involuntary placement of his arms, speech disturbance) immediately after general anesthesia and was subsequently diagnosed with WD and treated accordingly (Dikmen et al., 2008).

### Sleep disturbances

Poor quality of sleep, frequent nocturnal awakening, and other sleep disturbances like sleep paralysis or cataplexy have been described (Portala et al., 2002). Patients with WD tend to have worse daytime somnolence compared to controls (Netto et al., 2011). Another study compared 55 patients with WD disease with age- and sex-matched controls, and the results showed that patients with WD tended to have lower sleep time, decreased sleep efficiency, and increased wakefulness. Case reports have described the development of excessive somnolence confirmed on multiple sleep latency test (Amann et al., 2015); in one case, severe hypersomnia developed late in the course of the illness, 3 years after initiation of depression, and after 2 years of cognitive impairment (Kim et al., 2011).

### Other psychiatric symptoms

Other psychiatric symptoms reported in WD are obsessive compulsive disorder, both in the beginning of illness (Kumawat et al., 2007a), but also associated with treated WD (Sahu et al., 2013) and catatonia (Davis and Borde, 1993; Nayak et al., 2012; Basu et al., 2015).

Probably more significant, in addition to well-constituted psychiatric syndromes discussed above, patients with WD may present at various points in their lives with behavioral changes that do not meet criteria for specific psychiatric disease: irritability (prevalence 15–25%: Dening and Berrios, 1990; Svetel et al., 2009), impaired social judgment or disinhibition (Oder et al., 1991; Svetel et al., 2009), apathy (Svetel et al., 2009), "belligerence" (Oder et al., 1991), or "incongruent behavior" (Dening and Berrios, 1990). Personality changes are described in up to 57% of patients with WD (Dening and Berrios, 1990; Akil et al., 1991). Due to the atypical presentation, these patients rarely receive psychiatric or psychologic assistance, and their quality of life suffers.

## TREATMENT OF PSYCHIATRIC SYMPTOMS IN WILSON DISEASE

One approach to treatment of psychiatric symptoms in WD is to expect that primary treatment (namely decoppering therapy) will improve the psychiatric symptoms by addressing the primary disease process, without any additional intervention needed. Up to one-third of patients with psychiatric symptoms will improve with decoppering treatment alone (Modai et al., 1985; Bachmann et al., 1989; Srinivas et al., 2008). In support of this approach is the finding that D-penicillamine treatment is believed to impact brain metabolism (De Volder et al., 1988), although the clinical correlation of this finding has not yet been fully investigated.

Liver transplantation did not always improve the neuropsychiatric symptoms, as improvement was noted only in a minority of patients (Geissler et al., 2003; Boeka et al., 2011; Al-Hilou et al., 2012). One case, however, reported resolution of psychosis in a patient with WD disease after liver transplantation (Sorbello et al., 2011). At this time liver transplantation is not recommended for WD patients with psychiatric symptoms in the absence of liver disease due to the lack of prospectively studied outcomes for this subset of patients.

A second approach involves treating psychiatric symptoms with specific interventions. Multiple modalities of symptomatic treatment for psychiatric presentations in WD have been described in the literature, including biologic approaches and psychotherapy. At this time, in the USA there are no treatments approved

by the Food and Drug Administration for psychiatric symptoms in WD; however, an increasing body of evidence supports the use of psychotropics and/or psychotherapy when symptoms are causing significant functional impairment. Examples of such situations include psychotic episodes, mania, or severe depression. The use of psychotropic medications in WD is supported by multiple cases that describe efficacy of these treatments, but also by the evidence regarding neurotransmitter abnormalities (such as abnormalities of SERT in patients with WD and depression: Eggers et al., 2003; Hesse et al., 2003), which provide a theoretic basis for the use of psychotropic agents.

The use of lithium (Loganathan et al., 2008; Tatay et al., 2010; Rybakowski et al., 2013), divalproex (Shah and Vankar, 2003; Aravind et al., 2009), serotonin reuptake inhibitors (Smit et al., 2004; Kumawat et al., 2007b), trycyclic antidepressants (Buckley et al., 1990; Benhamla et al., 2007), methylphenidate (Silva et al., 2011), benzodiazepines (Muller, 1999; Shah and Vankar, 2003; Zimbrean and Schilsky, 2015), haloperidol (Chung et al., 1986), risperidone (Shah and Vankar, 2003), quetiapine (Kulaksizoglu and Polat, 2003), and clozapine (Krim and Barroso, 2001) with good treatment results has been described in patients with WD. Anecdotal successful use of cyproterone for hypersexuality associated with psychosis in a patient with WD has been described (Volpe and Tavares, 2000).

Lithium is an attractive choice as a mood stabilizer considering that it is not metabolized by the liver and does not carry the risk of extrapyramidal side-effects. With the cognitive impact of lithium still being debated (Pfennig et al., 2014), it is prudent to monitor cognitive abilities during lithium therapy in patients with WD. Another interesting choice of psychotropic medication is quetiapine, which has the advantage of reduced risk of extrapyramidal side-effects. Neuroleptic malignant syndrome has been reported during therapy with the use of various neuroleptics in WD (Kontaxakis et al., 1988; Buckley et al., 1990; Chroni et al., 2001; Czlonkowska et al., 2005). Acute focal dystonic symptoms induced by clomipramine have been described (Litwin et al., 2013). We have however to remember that psychotropic medications must be used in WD with great caution, understanding metabolic disorders and potential adverse events which may cause rapid and severe clinical deterioration (see Table 11.4).

Another biologic treatment effective for mood symptoms in patients with WD is electroconvulsive therapy (Negro and Louza Neto, 1995; Shah and Kumar, 1997; Rodrigues et al., 2004; Avasthi et al., 2010; Vaishnav et al., 2013). Cognitive-behavioral therapy (Kumawat et al., 2007a) and interpersonal therapy (Keller et al., 1999) have been used independently or in association with other interventions, with good results.

*Table 11.4*

**Precautions in prescribing psychotropic medications to patients with Wilson disease**

| |
|---|
| Avoid medications with potential hepatotoxic effect (e.g., valproic acid, duloxetine) |
| Whenever possible, preference should be given to medications with minimal hepatic metabolism (e.g., lithium, gabapentin) |
| When prescribing neuroleptics, preference should be given to those with reduced risk for causing extrapyramidal side-effects (e.g., quetiapine) in minimal effective dose |
| Unless there is evidence of an independent psychiatric condition separate from Wilson disease or repeated recurrence of psychiatric symptoms, consideration should be given to tapering off psychotropic medications once full remission of symptoms has been achieved |
| Consider monitoring of cognitive status when treating patients with Wilson disease with psychotropic agents that can impact cognition (e.g., benzodiazepines, lithium) |

## Significance of psychiatric symptoms in Wilson disease

Some authors have hypothesized that psychiatric symptoms indicate a more severe or advanced disease, may signal irreversible brain damage, or are secondary to metabolic disturbances produced by the liver disease, such as hyperammonemia associated with hepatic encephalopathy (Rathbun, 1996a). The presence of psychiatric symptoms in general in WD has been associated with lower quality of life (Svetel et al., 2011; Petrovic et al., 2012). In particular, the presence of bipolar disorders in patients with WD has been associated with a poorer quality of life (Carta et al., 2012b) and with higher frequency of brain damage (Carta et al., 2015). Presence of psychiatric symptoms is feared to lead to nonadherence with medical treatment, which further worsens the overall prognosis of WD (Mrabet et al., 2013).

# CONCLUSION

Cognitive, emotional, psychotic, and other less specific psychiatric problems are common in the WD population and can occur at any stage of the illness. These symptoms can greatly impair a patient's quality of life and delay proper diagnosis. Improvement or resolution of psychiatric WD symptoms is – besides hepatic and neurologic symptoms – usually the goal of treatment. Dementia, understood as severe and irreversible cognitive impairment, preventing independent functioning, is not expected in properly treated WD patients. New

psychotropic medications allow safer symptomatic treatment and can improve a patient's quality of life, and should be considered (however, with caution) independently of primary treatment of WD.

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