a diagnosis of WD and excluding other neurological disorders. Evaluation of the extrapyramidal system should include observation for posturing of the extremities or torso (i.e., dystonia), irregular dance-like movements (chorea), determination of tone (parkinsonism and dystonia), and evidence of tremor at rest, with posture or action, or as a rubral wing-beating tremor. The pyramidal system is primarily evaluated by checking reflexes and tone (hyperreflexia and spasticity). Cerebellar function is typically evaluated by having the patient perform finger to nose and heel/knee/shin testing. Gait should be evaluated for speed and fluidity: widened stance may be evident with cerebellar involvement. Cognitive evaluation utilizing the Montreal Cognitive Assessment (MoCA)[38] or Folstein Mini Mental Status Examination (MMSE) could be repeated every 3–6 months, when abnormal at the outset, to monitor changes with treatment. In those with possible altered cognition, a comprehensive neuropsychiatric evaluation can be obtained at baseline and followed over time.

Specialized neurological rating scales such as the Unified Wilson's Disease Rating Scale (UWDRS)[39] and the Global Assessment for Wilson's Disease[40] were developed for research purposes. These rating scales, or selected portions of them, help in evaluating quantitatively disease progression and response to therapy. Elements of the UWDRS focused on the patient's symptoms along with the MoCA and/or MMSE may help with monitoring changes in cognition objectively.

Psychiatric manifestations of WD

Psychiatric symptoms are wide-ranging. They can occur initially or develop despite WD treatment. Importantly, psychiatric disease may be intrinsic to or independent of WD. Psychiatric features of WD are more common than generally acknowledged. Approximately two thirds of patients had psychiatric symptoms at the beginning of their illness, with or without hepatic or neurological findings[41,42]; approximately 71% also experienced neuropsychological symptoms over time.[42] Presence of more than one psychiatric condition is common: a cross-sectional study of 50 patients using Structured Clinical Interview for DSM Disorders found that 40% met criteria for at least three psychiatric diagnoses.[42]

The purely psychiatric presentation frequently results in delayed diagnosis. The average time between the onset of psychiatric symptoms and WD diagnosis was 2.4 years.[43] Up to 20% of patients with WD had seen a psychiatrist prior to their WD diagnosis.[44] In adults, the most common conditions include mood disorders (depressive or bipolar spectrum), psychotic disorders, sleep disturbances, and subtle cognitive dysfunction.

Depressive disorders

The most common type of depression in WD is major depressive disorder (MDD), an episodic illness recurrent in many cases.[43] The prevalence of depression in patients with WD varies broadly (4%–47%) depending on the assessment instrument.[45,46] The mechanisms of depression in WD appear similar to those in MDD, namely, alteration of serotoninergic transmission in the thalamus–hypothalamus and midbrain–pons region, notably with low density of the presynaptic serotonin transporter.[47] In contrast, dysthymic disorder (dysthymia) is a chronic depressive disorder of at least 2 years' duration in adults, differing slightly from MDD clinically. Patients with WD may have dysthymic disorder[45]: its distinction from MDD has treatment implications.

Bipolar disorders/bipolar spectrum

Bipolar presentations in WD range from a full manic episode to mild mood instability or impulsivity. Prevalence of bipolar disorder in patients with WD is approximately 18%–39%.[43] Features of a full manic episode include abnormally and persistently elevated, expansive, or irritable mood; persistently increased goal-directed activity or energy; inflated self-esteem or grandiosity; decreased need for sleep; being more talkative or wanting to keep talking; flight of ideas or subjective racing thoughts; distractibility; and prolonged (at least 1 week) increase in goal-directed but risky activities. Bipolar disorder in WD significantly impacts quality of life.[48] Patients with WD may present with various degrees of mood instability that do not meet criteria for mania or hypomania but nevertheless impair quality of life.[46,49]

Psychotic disorders

Psychosis in WD includes frank delusions and/or thought disorder or disorganized thinking.[44,50–54] Cases were reported where patients carried the diagnosis of schizophrenia for years prior to their WD diagnosis.

Sleep disturbances

Severe sleep disturbances, which can rarely be a presentation of WD, are a long-term issue. Overall, patients with WD had a lower sleep quality,[55] with frequent nocturnal awakening, occasional sleep paralysis or catalepsy,[56] and worse daytime somnolence than controls.[57,58] Rapid eye movement sleep behavior disorder (RBD) was reported, associated with more nightmares and violent dreams than in patients without