



Neurologic impairment in Wilson disease

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Abstract: Neurologic symptoms in Wilson disease (WD) appear at an older age compared to hepatic symptoms and manifest in patients with misdiagnosed liver disease, in patients when the hepatic stage is clinically silent, in the case of non-compliance with anti-copper treatment, or with treatment failure. Neurologic symptoms in WD are caused by nervous tissue damage that is primarily a consequence of extrahepatic copper toxicity. Copper levels in brain tissues as well as cerebrospinal fluid (CSF) are diffusely increased by a factor of 10 and its toxicity involves various mechanisms such as mitochondrial toxicity, oxidative stress, cell membrane damage, crosslinking of DNA, and inhibition of enzymes. Excess copper is initially taken-up and buffered by astrocytes and oligodendrocytes but ultimately causes dysfunction of blood-brain-barrier and demyelination. Most severe neuropathologic abnormalities, including tissue rarefaction, reactive astrogliosis, myelin palor, and presence of iron-laden macrophages, are typically present in the putamen while other basal ganglia, thalami, and brainstem are usually less affected. The most common neurologic symptoms of WD are movement disorders including tremor, dystonia, parkinsonism, ataxia and chorea which are associated with dysphagia, dysarthria and drooling. Patients usually manifest with various combinations of these symptoms while purely monosymptomatic presentation is rare. Neurologic symptoms are largely reversible with anti-copper treatment, but a significant number of patients are left with residual impairment. The approach for symptomatic treatment in WD is based on guidelines for management of common movement disorders. The vast majority of WD patients with neurologic symptoms have abnormalities on brain magnetic resonance imaging (MRI). Pathologic MRI changes include T2 hyperintensities in the basal ganglia, thalami and white matter, T2 hypointensities in the basal ganglia, and atrophy. Most importantly, brain damage and neurologic symptoms can be prevented with an early initiation of anti-copper treatment. Introducing population WD screening, e.g., by exome sequencing genetic methods, would allow early treatment and decrease the neurologic burden of WD.

Keywords: Wilson disease (WD); copper toxicity; neuropathology; neuroradiology; magnetic resonance imaging (MRI); clinical scales

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Introduction

Historically, the neurologic symptoms of Wilson disease (WD) were first noted in 1912 by Wilson who provided detailed accounts of the clinical presentation of 12 patients

with WD, including descriptions of various movement disorders, drooling, dysarthria and psychiatric symptoms (1). The disease was initially coined 'hepatolenticular degeneration'. Only later it became clear that neurologic symptoms are typically preceded by liver involvement and

are not inevitable when proper treatment is initiated in the early phase of the disease (2,3). Approximately 50% of patients with neurologic symptoms have liver cirrhosis at the time of diagnosis. It is not clear whether there are WD patients with neurologic symptoms without any liver involvement (4). The first symptoms of WD are usually hepatic. Later in the natural course of untreated disease, in the case of poor compliance with anti-copper treatment or treatment failure, neurologic and other WD symptoms usually occur. Neurologic symptoms in WD are, thus, considered as a manifestation of more advanced disease stage that typically occurs in patients with misdiagnosed liver disease or when the hepatic stage is clinically silent (5). The term neuro-WD was introduced to emphasize the significance of neurologic symptoms and their dominant influence on disability in some WD patients. Although this paper is focused on neurologic symptoms, it is important to note that brain damage in WD frequently leads also to psychiatric impairment (6). Neuro-WD is thus a representative neuropsychiatric disorder.

Pathophysiology

Although ATP7B is expressed in the human central nervous system (CNS) (7), its dysfunction in the brain apparently does not lead to overt clinical symptoms. According to the current paradigm, nervous tissue damage leading to neurologic and psychiatric symptoms in WD is primarily a consequence of extrahepatic copper toxicity. This paradigm is supported by several observations: (I) copper concentration in the brain tissue and cerebrospinal fluid (CSF) is increased by a factor of 10 in WD compared to healthy subjects (8,9) and (II) anti-copper treatment leads to an improvement of neurologic symptoms that is paralleled with disappearance of magnetic resonance imaging (MRI) abnormalities and lowering of copper concentrations in the CSF (10,11). Excess copper is toxic to the brain tissue. It may cause cell injury and inflammation via various mechanisms including mitochondrial toxicity, oxidative stress, cell membrane damage, crosslinking of DNA, and inhibition of enzymes as has been shown in *in vitro*, animal, and post mortem human studies (12-16). Astrocytes, being part of the blood-brain barrier, can partially buffer toxic effects of "loosely bound" blood copper. It has been documented that astrocytes can upregulate synthesis of metallothionein and glutathione, which are peptides with the capacity to detoxify copper (17,18). Upon chronic copper intoxication, astrocytes increase in numbers and

undergo morphological changes, but their copper storage capacity is ultimately exhausted. Among brain cells, oligodendrocytes appear to be particularly sensitive to copper toxicity; hydropic swelling of myelin sheaths and demyelination can be one of the earliest consequences of cerebral copper overload (19). Accordingly, MRI studies in *de novo* WD patients provide indirect evidence of cytotoxic edema and myelin damage (20,21). Another factor contributing to cerebral dysfunction in WD is hepatic encephalopathy which occurs in patients with severe liver damage and portal hypertension with portosystemic shunting. Neurologic symptoms in hepatic encephalopathy are likely caused by accumulation of neurotoxic substances that are normally cleared from blood by the liver, e.g., ammonia and manganese (22,23).

Neuropathologic findings

Pathologic changes in WD are typically observed in the central grey matter nuclei and white matter tracts in the brainstem. The underlying cause of high susceptibility of these brain regions to copper toxicity is unknown (24,25). Macroscopically, most severe abnormalities are present in the putamen, which is typically shrunken, soft, and brown-yellowish discolored. In the most severe cases, there is a putaminal necrosis with iron-laden macrophages surrounding the necrotic cavity (26). Cavitation can be infrequently found also in the thalamus, dentate nucleus or white matter. The latter was more common before anti-copper treatment became available and is only rarely described in treated patients (27,28).

Upon microscopic examination, tissue rarefaction of various severity, astrocytes with abnormal morphologies, loss of myelination, and iron-laden macrophages are found predominantly in the central grey matter (*Figure 1*). Specific type of astrocytes, referred to as Alzheimer type II glia, with swollen pale nuclei and little cytoplasm are frequently found in the basal ganglia and less commonly also in the cortex. These astrocytic population is not specific for WD, it has been associated with hepatic encephalopathy (25). Reactive astrocytes, also referred to as Alzheimer type I glia, are enlarged cells with cytoplasm immunoreactive for glial fibrillary acidic protein (GFAP) and metallothionein and with histochemical positivity for copper deposits (18). Opalski cells are large cells of ambiguous origin with foamy cytoplasm, which are considered to be specific for WD. It is not clear whether these cells are derived from the astrocytic or histiocytic cell line (29). In addition to astrocytes, cells

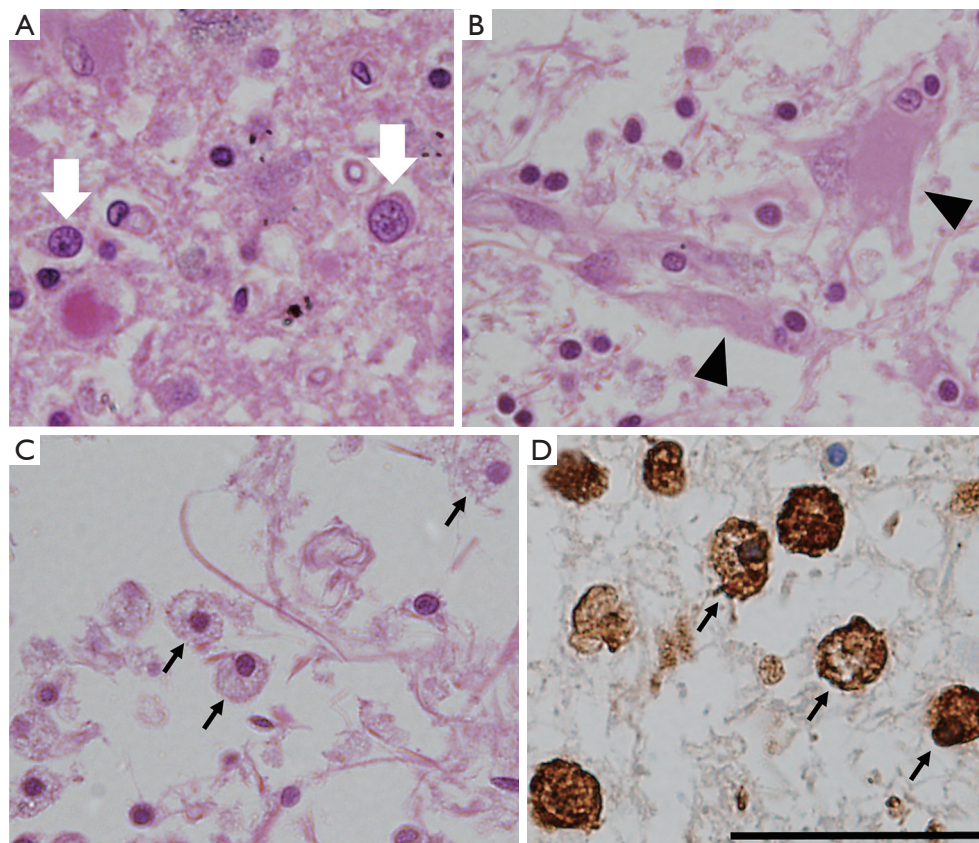


Figure 1 Neuropathological abnormalities in WD. (A) Hematoxylin-eosin (HE) staining showing disorganization of tissue with Alzheimer type 2 gliosis (white arrows); (B) severe tissue rarefaction with reactive gliosis (black arrowheads show swollen reactive astrocytes) (HE staining); (C) severe tissue rarefaction and macrophages (black arrows) (HE staining); (D) ferritin immunostaining showing cells with macrophage morphology strongly positive for ferritin (black arrowheads). All images are from the putamen, scale bar represents 50 μm . WD, Wilson disease.

with oligodendrocyte morphology were also shown to accumulate copper (30). Oligodendrocyte rarefaction is typically present in the bundles passing through lentiform nucleus, the entire dentato-rubro-thalamic pathway, and fibers of the pontocerebellar pathway. Demyelination of pontine fibers may lead to pathology resembling central pontine myelinolysis (29). Neuronal dysfunction usually follows glial abnormalities and, when present, is pathologically manifested by axonal swelling and spheroid formation. Neuronal loss is observed in more severe cases (31).

Neurologic symptoms and their treatment

Neurologic symptoms of WD typically occur between the ages 20–40 years, however the range is very large (32–34). The youngest WD patient with neurologic symptoms

was aged 6, and the oldest 72 years (32,35,36). The most common neurologic symptoms of WD are movement disorders including tremor, dystonia, parkinsonism, and ataxia, which are frequently associated with dysphagia, dysarthria and drooling (33,34). In most cases these symptoms overlap, fluctuate and can be aggravated by several factors (e.g., emotions, stress, general health conditions, concomitant disorders as well as drugs). All these factors cause difficulties with symptom classifications as well as with implementation and using neurological scoring systems. Nevertheless, there are several propositions of neurologic phenotypes classifications (37–42) (Table 1) and a few scales quantifying severity of neurologic symptoms (43,44). WD belongs to the group of treatable neurometabolic disorders. In most cases, neurologic symptoms diminish or even disappear during the correct

Table 1 Neurologic symptoms in Wilson disease—historically proposed classifications

The first author (year of proposition)	Classification
Hall <i>et al.</i> , 1921 (37)	<ul style="list-style-type: none"> • Classic form (progressive rigidity and tremor) with domination of rigidity and bad prognosis • Tremor form (Strumpell-Westphal, pseudosclerotic form) occurring in adults with a relatively good prognosis • Torsion spasms (currently dystonic form)
Konovalov <i>et al.</i> , 1960 (42)	<ul style="list-style-type: none"> • Arrhythmic-hyperkinetic form (hyperkinesias and dystonia) • Tremulous form (ataxia and postural tremor) • Tremulous-rigid form (rigidity and resting tremor—currently parkinsonian)
Denny-Brown <i>et al.</i> , 1964 (38)	<ul style="list-style-type: none"> • Juvenile form (onset before second decade of life, hyperkinetic/dystonic symptoms with putaminal lesions) • Pseudosclerotic form (dominant intention and postural tremors with lesions in the cerebral cortex, thalamus, subthalamic regions, nucleus dentatus)
Marsden <i>et al.</i> , 1987 (39)	<ul style="list-style-type: none"> • Hyperkinetic-dystonic form (dystonia and choreoathetosis) • Ataxic form (postural and intentional tremor, ataxia) • Parkinsonian form (rigidity, rest tremor, hypokinesia)
Oder <i>et al.</i> , 1993 (41)	<ul style="list-style-type: none"> • Dyskinetic form (dystonia and choreoathetosis) • Pseudosclerotic (ataxia and postural tremor) • Pseudoparkinsonian form (rigidity, resting tremor, abnormal cognition)
Czlonkowska <i>et al.</i> , 1996 (40)	<ul style="list-style-type: none"> • Dystonic form • Tremor form • Rigidity-tremor form • Rigidity form

anti-copper treatment (32,45). However, symptoms with varying severity persist in about 40–50% patients even after long-term anti-copper treatment leading to decreased quality of life and requirement for symptomatic treatment (32,45,46). It should be emphasized that no controlled clinical trials have been performed, which document the efficacy of symptomatic treatment of neurologic symptoms. Only several naturalistic studies and clinical experience of expert centers indicate that such treatment may partially improve disabling neurologic symptoms of WD (46,47). It is also important to note that unless neurologic symptoms are severely disabling upon diagnosis, it is preferable not to start symptomatic drugs together with anti-copper therapy as symptomatic drugs may obscure its effects.

In carefully selected patients, deep brain stimulation (DBS) may be a last resort treatment of neurologic symptoms that are refractory to pharmacotherapy (48). However, DBS should not be considered sooner than

2–3 years after treatment initiation, while positive effects of anti-copper treatment may be expected. Below, we present a clinical description of the most common neurologic symptoms of WD as well as possible options for their symptomatic treatment (*Table 2*).

Tremor

The most characteristic neurologic symptom of neuro-WD is tremor. It occurs in up to 55% of patients as the first neurologic symptom and in almost 90% patients during the course of the disease (33,34,49). Tremor in WD may be resting, postural (with “wing beating” features), action or intention. It may have features of dystonic, rubral, parkinsonian, and essential tremor, or have a mixed presentation. The phenotype of tremor can also change during the disease progression, especially in untreated patients. Usually, it first affects distal upper extremities,

Table 2 The options for symptomatic treatment of WD neurologic symptoms

WD neurologic symptoms	Possible therapeutic interventions
Tremor (the treatment depends mostly on the type of tremor—described in the text)	<ul style="list-style-type: none"> • Beta-blockers (propranolol) • Barbiturates (primidone) • Benzodiazepines (most commonly—clonazepam) • Anticholinergics (trihexyphenidyl or biperiden) • Presynaptic gamma-aminobutyric acid agonist (baclofen) • BTX injections • Neurosurgical treatment—Vim DBS or thalamotomy
Dystonia (the treatment depends mostly on type of dystonia—described in the text)	<ul style="list-style-type: none"> • Anticholinergics (as in WD tremor treatment) • Presynaptic gamma-aminobutyric acid agonist (baclofen) • Benzodiazepines (as in WD tremor treatment) • Levodopa or dopamine agonists (e.g., ropinirole or pramipexole) • Dopamine depleting drugs • Antiepileptics drugs (mostly used carbamazepine, oxcarbazepine or gabapentin); • BTX injections • Neurosurgical treatment—DBS of GPi, pallidotomy or thalamotomy
Parkinsonism (therapeutic test with levodopa suggested to establish dopaminergic responsiveness)	<ul style="list-style-type: none"> • Levodopa • Dopamine receptors agonists • Neurosurgical treatment—DBS or neuroablative lesions of GPi or STN
Chorea	<ul style="list-style-type: none"> • Dopamine depletion agents (tetrabenazine)
Dysphagia	<ul style="list-style-type: none"> • Behavioral therapy • Dietary modifications • Stopping the drugs influencing arousal • Neuromuscular electrical stimulation • Tube feeding (percutaneous gastrostomy) if needed
Dysarthria	<ul style="list-style-type: none"> • Speech therapy • Augmentative communications devices if needed
Drooling	<ul style="list-style-type: none"> • Non-Pharmacological methods • Anticholinergics • Adrenergic alfa-2 receptor agonists • BTX (injection in parotid and submandibular glands)

BTX, botulinum toxin; DBS, deep brain stimulation; GPi, globus pallidus internus; STN, subthalamic nucleus; Vim, ventral intermediate nucleus of the thalamus; WD, Wilson disease.

as unilateral or bilateral asymmetric tremor. During WD progression, the head, legs, as well as whole body may be affected by tremor. The symptomatic treatment depends on the particular phenotype of tremor (47). In the case of

essential tremor-like phenotype, i.e., postural, and kinetic tremor affecting predominantly hands, the treatment with non-selective beta-blockers (preferentially propranolol) is the first option to alleviate the symptoms. Further

possibilities of treatment include barbiturates (primidone), benzodiazepines (BZD) or neurosurgical treatment—DBS of ventral intermediate nucleus of the thalamus (Vim DBS) or thalamotomy (46,47). Dystonic tremor can be treated additionally with anticholinergics or botulinum toxin (BTX) injections.

Dystonia

Dystonia has been reported in 11–65% of neuro-WD patients in different cohorts and is the most severe and refractory symptom (33,34,49,50). Dystonia can involve different body parts and can be focal (e.g., “risus sardonicus”, cervical dystonia, “starfish” hand), segmental (trunk dystonia—“Pisa” sign), multifocal, or even generalized (status dystonicus). However, the most common presentation of dystonia in WD is abnormal face expression, which can present as: (I) “risus sardonicus” (due to dystonic spasm of the risorius muscle) or (II) “vacuous smile” (due to dystonic dropped jaw). In untreated WD, focal dystonia usually spreads to other body regions during disease progression, eventually affecting axial muscles and leading to abnormal posture and gait disturbances. Dystonic muscle activity may interfere with eating, speech, and various physical activities leading to immobilization and increased mortality (49,50). The options for symptomatic treatment of dystonia in WD is not different from other etiologies: BTX, anticholinergics, benzodiazepines, baclofen, dopamine agonists, antiepileptic drugs (oxcarbazepine or gabapentin), or neurosurgical treatment—DBS of globus pallidus internus (GPi) or pallidotomy. The latter is reserved for generalized dystonia or status dystonicus not responding to pharmacotherapy. BTX injection directly into affected muscles is the first-line treatment for focal dystonia. Pharmacotherapy is recommended for multifocal and generalized dystonia. In the case of severe disabling dystonia, all these treatments, even in combination, should be considered (46,47,50).

Parkinsonism

Parkinsonism is a clinical syndrome, which consists of bradykinesia, rigidity, resting tremor, along with postural imbalance. Drooling, hypomimia, dysarthria, micrographia, and shuffling gait are manifestations of these symptoms in specific muscle groups. Parkinsonism has been reported in 19–62% of WD patients (33,34,47). As for other causes of parkinsonism, levodopa or dopamine agonists should be tried

in patients with disabling symptoms. Further, in cases with severe symptoms, DBS or neuroablative procedures of the subthalamic nucleus (STN) or GPi could be considered (46,47).

Cerebellar ataxia

Cerebellar ataxia has been reported in almost 30% of neuro-WD patients, mostly in combination with other neurologic symptoms (33,46,47). Symptoms of impaired cerebellar function can be distinguished as: (I) ataxic gait (wide stance and wide-based gait with impaired tandem walking); (II) intentional tremor; (III) dysdiadochokinesis; (IV) impaired coordination of fine hand movements; (V) ataxic speech (described below). There is no proven effective pharmacotherapy for the symptomatic treatment of ataxia. Physiotherapy targeted at gait and balance control, as well a speech therapy could be of some benefit (46,47).

Chorea

Chorea as well as athetosis occur relatively rarely in WD, in approximately 6–16% of neurologic patients. They occur very sporadically as an isolated neurologic symptom of WD, more commonly in young patients. Data about the efficacy of symptomatic treatment of choreoathetosis in WD are very limited; presynaptic monoamine depletory drug, tetrabenazine, could be considered in cases with severe chorea (46,47).

Dysarthria

Dysarthria is apparently the most frequent neurologic symptoms of WD. It occurs in almost every neurologic patient. Speech disturbances as a clinical symptom of WD are caused by the damage of basal ganglia (leading to dystonic and parkinsonian features), cerebellar nuclei and their tracts (leading to cerebellar features) and possibly also cortico-bulbar tracts (leading to pseudobulbar features) (34,47,51). Based on the predominant characteristic of speech abnormality, several types of dysarthria in WD can be distinguished including: (I) mixed unclassified (due to involvement of several brain structures); (II) ataxic (cerebellar); (III) dystonic (hyperkinetic); and (IV) hypokinetic. Treatment of dysarthria in WD is not specific but is based on general rules for dysarthria management and the approach depends mostly on the specific type of speech disturbance. Treatment involves relaxation techniques in the case of dystonic dysarthria, techniques improving

speech rate in the case of cerebellar ataxia, and loudness and articulation in the case of hypokinetic dysarthria. In patients with severe dysarthria or anarthria, alternative and augmentative communication devices such as tablets or smartphone application can be recommended (47).

Dysphagia

Dysphagia, defined as difficulty in any phase of swallowing, occurs in about 18% of WD patients and in 50% of patients with neurologic symptoms (33,34,52). Any phase of the swallowing act can be affected including oral, preparation/chewing, oral transit, and swallowing itself. Dysphagia may emerge due to impairment of muscle tone (e.g., in oro-facial dystonia), incoordination, slowness and weakness of deglutition muscles. As dysphagia may lead to aspiration, pneumonia, and malnutrition, the assessment of neuro-WD patients should always include examination of swallowing and nutritional status using questionnaires, body weight measurement, and biochemical markers. In the case of persistent or progressive severe dysphagia, feeding via percutaneous gastrostomy (PEG) should be considered (46,47).

Drooling

Drooling, along with dysarthria and “wing beating” tremor, belongs to the most prominent and characteristic symptoms of WD (32-34,53). Defined as involuntary flow of saliva from the mouth, drooling affects approximately 70% of neuro-WD patients. Very often it is the consequence of dysphagia and/or the inability to retain saliva within the mouth due to orofacial dystonia. This typically occurs in patients with “open mouth smile”. Medical interventions that may reduce drooling are as follows: (I) non-pharmacological, such as chewing gum or sucking on hard candies, which reduce hypersalivation by triggering automatic swallowing; (II) pharmacological, such as anticholinergic drugs or BTX injection in parotid and submandibular glands to decrease saliva production (46,47).

Gait and posture disturbances

Gait and posture disturbances have been reported in 44–75% of neuro-WD patients (33,34,54). Gait disturbances are consequent to cerebellar dysfunction which leads to ataxia and incoordination and to movement disorders including dystonia, parkinsonism and chorea. Gait disturbances occur especially when motor control of legs and axial muscles

are affected. The symptomatic treatment is based on pharmacotherapy for specific movement disorders as well as on rehabilitation of postural control and gait (46,47).

Other neurologic symptoms

Additionally to the typical neurologic symptoms of WD described above, other neurologic symptoms may occur in the course of WD including myoclonus (55,56), tics, headache, taste and olfactory dysfunction (57-59), neuropathies (60), epilepsy (61,62), restless leg syndrome (63), sleep disturbances (64-66), and other abnormalities (34). However, the frequency of these symptoms, except of epilepsy which has 10-fold greater frequency in WD compared to general population, is rare and their presentation is not specific for WD (32,34,45).

Neuroimaging

Brain MRI is nowadays the most widely used neuroimaging method in the differential diagnosis of neurological WD. More than 90% WD patients with neurological symptoms have pathology on brain MRI (67,68) which, when fully developed, is reasonably specific for WD (*Figure 2*). Negative or inconspicuous MR finding alone should however not exclude WD in a patient with neurologic symptoms. Neuroimaging abnormalities are also present in approximately 40–70% of hepatic, and even in 20% of presymptomatic WD cases (68,69). The most prominent findings in untreated patients are symmetric hyperintensities in T2-weighted image in the deep grey matter (DGM) nuclei and mesencephalic and pontine white matter (70-76). The prevalence of T2 lesions in brain structures varies across studies but the most commonly lesioned site appears to be putamen (45–85%), followed by caudate nucleus (30–60%), anterolateral thalamic nuclei (30–60%), pons (10–80%) and mesencephalon (20–70%) (67,77-84). Importantly, tectal plate hyperintensity and central pontine myelinolysis-like lesions as well as concurrent involvement of the brainstem, basal ganglia, and/or thalamus are highly suggestive of WD (77). These T2 hyperintense lesions are partly reversible upon anti-copper treatment (11,85-88) and presumably reflect edema and demyelination caused by copper toxicity. Presence of cytotoxic edema as an early WD pathology was supported by findings on diffusion-weighted imaging (DWI) showing restricted diffusion in areas affected by T2 hyperintensities in some patients (83,89,90). In the

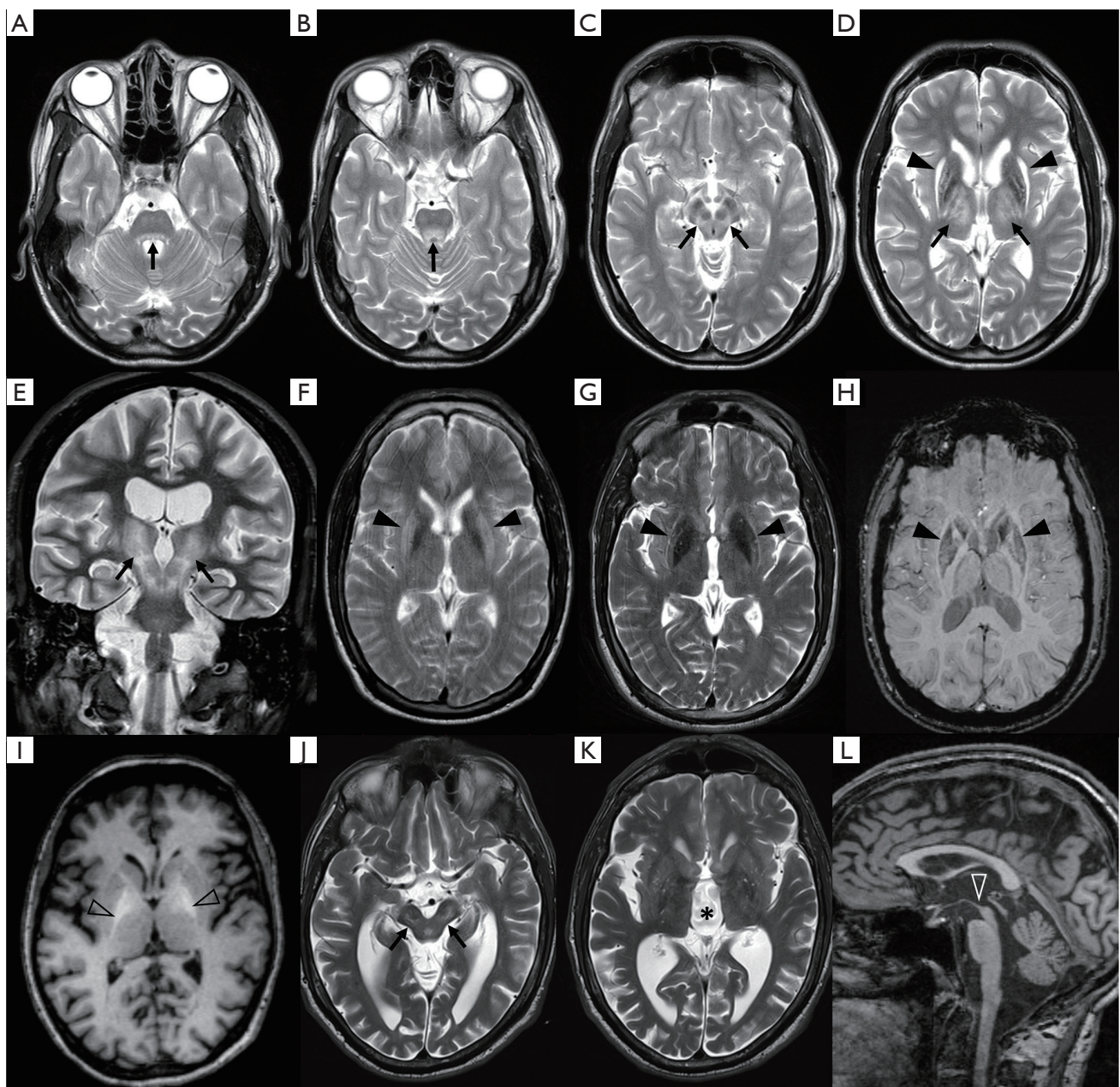


Figure 2 MRI findings in WD. (A-E) T2 hyperintensities at different levels of the dentato-rubro-thalamic pathway (black arrows) in a single WD patient; (A,B) at the level of tectal plate; (C) in the white matter fibers surrounding red nucleus, and (D) in the anterolateral group of thalamic nuclei; (D) shows also severe damage to the putamina with atrophy and mixed, hyperintense and hypointense, signal abnormalities; (E) coronal slice of the same patient showing continuous affliction of the continuous nervous pathway. (F) T2w image acquired at 1.5 Tesla scanner showing profound T2 hyperintensity in the putamen; (G) same patient examined at 3 Tesla scanner showing mixed T2 signal in the putamen; (H) SWI in the same patient showing definite hypointensity in the striatum and globus pallidus (black arrowheads); (I) T1 hyperintense signal in the globi pallidi (empty arrowheads); (J-L) typical pattern of brain atrophy in WD, severe mesencephalic atrophy is shown in (J) (black arrows) along with (K) 3rd ventricle enlargement (asterisk); (L) mesencephalic atrophy is best assessed on the mid-sagittal slice (white arrowhead). MRI, magnetic resonance imaging; SWI, susceptibility weighted imaging; WD, Wilson disease.

case of more severe tissue pathology, T2 hyperintensity corresponds to gliosis or rarefaction that may, particularly in the putamen, progress to necrosis manifesting as cavitation on MRI (91,92). The latter changes are typically visible also as hypointensities on T1-weighted images. Structural disorganization of the DGM in WD was further documented by a novel diffusion-weighted imaging (DWI) technique, neurite orientation dispersion and density imaging (NODDI). Using this method, WD patients were shown to have lower intracellular compartment, lower orientation dispersion index and higher isotropic volume fraction as well as higher mean diffusivity throughout DGM nuclei compared to healthy subjects (93). These results indicate increased extracellular volume and reduced neurite density, i.e., rarefaction of the nervous tissue in WD.

From the early disease stages, hypointensities may be seen along with T2 hyperintensities in the DGM on T2-weighted images (94-99). These hypointensities are better visualized with T2*-weighted (i.e., dependent on effective T2 relaxation time) or susceptibility weighted imaging (SWI). As validated in a post mortem MRI histopathology correlation study, these hypointense lesions are caused by abnormal iron accumulation (26) and may even progress after anti-copper treatment initiation (100,101). When using scanners with higher magnetic field and imaging techniques sensitive to paramagnetic species such as T2*-weighted or SWI, hypointense lesions become prominent and may overshadow T2 hyperintensities. The clinical significance of cerebral iron accumulation in WD is not clear.

There is a wide range of reported prevalence of demyelinating changes in the hemispheric white matter (5-60%). Demyelination in neuro-WD may affect splenium of the corpus callosum (102), internal capsule (103), and cerebellar white matter including superior and middle peduncles containing dentato-rubro-thalamic and ponto-cerebellar tracts respectively (79,103-105). Continuous or patchy lesions in the superior cerebellar peduncle, caudal mesencephalic tectum, rostral mesencephalic tegmentum (surrounding nuclei ruber) and anterolateral thalami likely represent lesions in the entire dentato-rubro-thalamic tract (106-108). Interestingly, quantitative analysis of diffusion tensor imaging (DTI) parameters showed markers of altered tissue microstructure, i.e., increased mean diffusivity and decreased fractional anisotropy, even in normal appearing lobar white matter (21,109,110) as well as in the thalamus with normal signal on T2-weighted images (111); this DTI metric was shown to improve with treatment (112). These results suggest widespread reversible pathology of the white

matter beyond lesions visible on T2-weighted images that is consistent with impaired myelination. Importantly, white matter lesions visible on T2-weighted images were also reported to improve on anti-copper therapy (113). The above-mentioned signal changes are typically symmetrical. In the early stages, however, signal changes may sometimes be asymmetrical in correlation with clinical symptoms (114). WD patients may rarely exhibit extensive, sometimes asymmetric, cortico-subcortical lesions, typically affecting the frontal lobe (61,115), which are associated with an unfavorable prognosis.

Atrophy is the ultimate and mostly irreversible consequence of degenerative changes induced by copper toxicity. However, improvement of atrophy has been also reported in few patients (11). Atrophy is present in approximately 30-45% of newly diagnosed neurological WD patients and it appears to be more prevalent in men compared to women (68,87). Tissue loss may progress on treatment and some degree of atrophic changes can be eventually observed in up to 70-90% of chronically treated patients (103,116,117). A specific pattern of atrophy is present in a subgroup of WD patients with predominant involvement of putamina and other DGM structures leading to profound enlargement of 3rd ventricle along with shrinkage of mesencephalon. The degree of mesencephalon atrophy in WD is comparable to findings commonly seen in progressive supranuclear palsy (118,119). Non-specific atrophy of the cerebellum and frontoparietal cortex is also common in neuro-WD.

As in other liver disorders with cirrhosis and portosystemic shunt, WD patients with severe hepatic manifestation may present with symmetrical hyperintense lesions in the globus pallidus in T1-weighted images. These lesions are likely caused by manganese deposits and indicate hepatic encephalopathy (80). With improvement of liver function, these changes typically disappear (120,121).

In addition to MRI markers, several independent studies have shown that transcranial sonography (TCS) consistently shows hyperechogenicity of lenticular nuclei in neuro-WD (122-125). TCS could be thus a cheap screening test for the differential diagnosis of WD and other neurodegenerative disorders (123). A longitudinal case study showed that TCS hyperechogenicity does not change with anti-copper therapy and is likely not suited for treatment monitoring (100).

Several studies have examined dopamine transporter (DAT) and D2 dopamine-receptor single photon emission computed tomography (SPECT) with the result that

parkinsonism in WD is associated with both, pre- and post-synaptic lesions in the nigrostriatal pathway (126-128) and that it may improve with therapy (129). Therefore, DAT-SPECT cannot be reliably used in differential diagnosis between WD and Parkinson's disease. Reduction in DAT binding was significantly associated with the degree of midbrain atrophy in WD (119). Perfusion SPECT and fluorodeoxyglucose positron emission tomography (PET) have been also used to study brain metabolism and perfusion in WD to find decreased cerebral blood flow and glucose consumption in DGM, cerebellum and cortex (130,131). The latter abnormalities may improve on treatment (132-134).

Scales for neurologic and imaging severity

Clinical rating scales designed and validated for assessment of severity of specific diseases are helpful in routine clinical monitoring of patients and are necessary for clinical trials with novel drugs. In addition to clinical scales, (semi)quantitative analysis of MR images may serve as surrogate marker of the type, reversibility, and extent of brain damage in *de novo* patients before anti-copper treatment initiation. Such MRI markers will be also helpful as outcome measures in clinical trials. While universal disability scales such as Schwab and England Activities of daily living score can be used for WD clinical scoring (11), standardized quantitative assessment of disease severity and monitoring of treatment effects is hampered by the large clinical variability of WD. Therefore, scales designed for assessment of specific syndromes such as tremor, ataxia, parkinsonism or dystonia are not capable of capturing the distinctive and complex spectrum of WD symptoms (135). Several scales were created to score neurologic WD severity in studies comparing clinical symptoms with results of paraclinical examinations (136). The first scale specifically developed and validated to assess the whole spectrum of neurologic clinical symptoms in WD was the unified Wilson disease rating scale (UWDRS) consisting of three parts: consciousness, historical review of activities of daily living adapted from the Barthel index, and neurological examination (44). The majority of items in the latter was taken from established scales focused on specific syndromes: parkinsonism [unified Parkinson's disease rating scale (UPDRS)] (137), dystonia [Burke-Fahn-Marsden dystonia rating scale (BFMDRS)] (138), Huntington disease [unified Huntington disease rating scale (UHDRS)] (139), tremor [clinical rating scale for tremor (CRST)] (140),

and ataxia [International Cooperative Ataxia Rating Scale (ICARS)] (141). The severity of neurologic impairment was shown to correlate with the degree of disability in activities of daily living as assessed by the UWDRS (135). Hepatic and psychiatric subscales were later added to the scale. All UWDRS items show excellent inter-rater agreement in validation studies (44,142). A second WD specific scale is the global assessment scale (GAS) for WD; it has a two-tier design with tier 1 being a global disability measure of the disease burden across hepatic, psychiatric, motor and osseo-muscular systems, and tier 2 being neurological assessment (43). Except of the hepatic subscore, all items from tier 1 were shown to correlate with the severity of neurologic impairment. The neurologic assessment in GAS for WD is considerably shorter and focused more on disability compared to the one included in UWDRS, which is reflected in higher interrater variability of the latter scale. Direct comparison of these scales confirmed excellent correlation between neurologic UWDRS and the GAS for WD tier 2 sub-scores (143). In this study, the "minimal UWDRS" score consisting in nine items from the historical review of activities of daily living was suggested for routine clinical monitoring of WD patients (143). It is however not clear whether this score, which is based only on the patient's history, has any advantage over simpler universal scales, e.g., modified Rankin scale, and whether it would have enough sensitivity to pick up subtle clinical changes occurring after initiation of anti-copper treatment.

It has been suggested that brain MRI could be helpful not only in the WD diagnosis but also in treatment monitoring and outcome prediction. In order to quantify MRI severity and monitor treatment effects on brain parenchyma, several scales with variable complexity were developed. All scales are represented by a total severity score based on the sum of pathology in predefined structures, typically basal ganglia, thalami, and brainstem. The simplest score considers only the presence or absence of T2 hyperintensities in six regions and represents the number of affected areas (144). Other authors suggested adding atrophy as another item and assessing the overall grade of the severity of change in signal intensity on the scale 0 (normal) to 3 (severe) in addition to the extent of the pathology (79). In another scale, grading was done separately for each assessed structure taking into account signal change and associated atrophy as follows: "0" = no abnormality, "1" = change in signal intensity with no atrophy, "2" = change in signal intensity with mild or moderate atrophy, and "3" = change in signal intensity with severe atrophy (103). Yet, a more complex scale considers

the presence of T2 hyperintensities, T2 hypointensities, T1 hyperintensities (only in the globus pallidus), and a semi-quantitative assessment of global atrophy classified as absent ("0"), slight ("1") or severe ("2") (117,123). Development of a reliable and valid MR severity scale is hampered by several factors: (I) there are no MRI histopathology correlation studies to accurately determine the pathological basis of T2 hyperintensities, (II) pathology not visible on routine MRI scans may significantly contribute to clinical disability, (III) it is not clear whether and how specific pathological findings on MRI contribute to disability. It can be assumed that while mild T2 hyperintensities represent changes reversible with treatment, T1 hypointensities and atrophy as markers of tissue loss and T2 hypointensities as a marker of iron depositions represent irreversible changes likely associated with worse prognosis. These assumptions should be first validated and, if confirmed, they should be taken into account in future MR severity scales.

Concluding remarks and outlook

Neurologic symptoms in WD are largely reversible with anti-copper treatment but most patients have at least minor residual neuropsychiatric impairment and approximately 20% of patients have unfavorable outcome with severe disability or death (145,146). The prognosis of WD is much better when treatment is started before neurologic symptoms develop. Thus, population screening for WD is well justified but there are no biochemical markers with sufficient sensitivity/specificity and acceptable costs (147). With improving reliability and decreasing costs of next generation sequencing, it is likely that newborn genetic screening of treatable metabolic disorders including WD will be feasible in the upcoming years (148). Gene therapy has been recently tested in animal WD models with promising results (149). Combination of genetic newborn screening and gene therapy would be the ultimate solution for WD.

Development of novel anti-copper drugs with a lower risk of neurologic worsening is also desirable. Tetrathiomolybdate has shown promising results with respect to neurological complications in pilot studies (150-152) and a randomized controlled trial with this compound is currently being performed. For future clinical studies, it would be advantageous if there was one universally accepted and well-validated scale for the assessment of clinical severity (153). Also, identification of MRI markers related to the degree of CNS damage would help to define outcome measures for WD clinical trials.

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Footnote

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