Wilson's Disease

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Patient Vignettes

Patient 1

A 26-year-old man presented to a neurologist with a 6-month history of mild arm tremor. He noticed that over the past year, his memory was not as good as it used to be and sometimes he had difficulty focusing mentally on tasks. His family history was notable for two relatives on his mother's side with mild tremor. Laboratory studies were normal as were routine biochemistry panels. The neurologist sitting across the desk discussed the diagnosis of tremor, unknowingly in the midst of an emergency—not an emergency room emergency but a diagnostic emergency. If the appropriate differential diagnosis had been considered, a workup would have led to the diagnosis of Wilson's disease, with institution of appropriate treatment. Instead, the neurologist falsely reassured the patient that he had essential tremor and that it would likely not be more than an inconvenience. Over time though his tremor worsened, and a second opinion was sought at an academic movement disorder center. Again, the diagnosis was delayed, until the patient finally developed worsening tremor, dysarthria, facial dystonia, and incoordination. By the time Kayser-Fleischer rings were seen by an experienced examiner and Wilson's disease was diagnosed, neurologic damage was permanent despite effective anticopper therapy.

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Patient 2

A diagnosis of Wilson's disease was quickly secured in a 23-year-old woman who presented with mild dysarthria and arm tremor. An appropriate workup was performed, and the neurologist described the steps that needed to be taken in order to achieve copper balance. Unbeknownst to either of them, the patient faced an emergency—a hidden therapeutic emergency. The neurologist, unfamiliar with the ability of penicillamine to cause permanent neurologic worsening, reassured the patient about her outcome. Unfortunately, within 2 weeks of beginning penicillamine, her neurologic signs acutely worsened, and she accelerated into a precipitous neurologic decline. She became anarthric with severe generalized dystonia and became functionally completely dependent. Despite attempts to reverse the situation, her condition was permanent. An independent life was destroyed by overly aggressive penicillamine treatment.

Introduction

Wilson's disease (WD) is an autosomal recessive metabolic disorder affecting approximately 1 in 30,000 individuals [1–3]. It is caused by loss of function mutations in the transmembrane ATPase copper transporter encoded by the *ATP7B* gene [4, 5]. Impaired copper transport and excretion due to defects in the hepatic excretory pathway lead to insufficient copper binding to cuproenzymes and reduced elimination of excessive copper into the bile [6, 7]. This ultimately results in chronic copper accumulation in the liver and subsequently in the brain, as well as other organs such as kidneys or cornea. Copper is an essential micronutrient and under physiologic homeostasis is mostly bound to metallothioneins in hepatocytes or ceruloplasmin in plasma. Bound copper is biologically inactive, and only free copper (known as non-ceruloplasmin bound [NCC]) is potentially toxic [6, 7]. Excessive free copper can trigger cytotoxic effects in affected organs, leading to variable clinical phenotypes with predominantly hepatic, neurologic, or psychiatric symptoms.

In contrast to many inherited metabolic conditions, WD is highly treatable with effective therapies reversing clinical manifestations or substantially improving outcomes [8–10]. Untreated, copper overload results in catastrophic neurologic symptoms and eventual death in the vast majority of patients with WD [6, 7]. Delays in initiation of decoppering therapies are associated with worse clinical outcomes and long-term residual neurologic disability [11, 12]. Early recognition of WD is critical for timely initiation of copper removal; for this reason, *the timely diagnosis of WD is a true movement disorder emergency* (patient 1). This is especially challenging as the clinical manifestations are protean, mimicking other movement disorders such as idiopathic Parkinson's disease, essential tremor, or primary dystonia [13].

The first step in WD treatment is to remove excessive copper that is associated with increased plasma NCC levels [1]. This should induce a negative copper

balance with a rapid control of NCC levels, the copper fraction likely responsible for organ toxicity [14, 15]. Currently available options are chelating agents that nonspecifically chelate copper and promote urinary copper excretion. Relatively rapid onset of action favors chelating agents in the acute phase of decoppering treatment when patients are symptomatic [1–3]. However, rapid mobilization of copper from the liver can cause additional elevations in NCC in blood, resulting in further progression of the disease with subsequent neurologic deterioration [11, 16, 17]. Even if appropriate therapy is initiated in a timely manner, this paradoxical worsening is perhaps the most feared complication of chelation therapy. This phenomenon needs to be recognized very early, and the therapy needs to be adjusted to prevent irreversible neurologic deficits. This is also an emergency when treating WD patients: *lack of recognition and prompt management of neurologic deterioration is the second WD emergency* (patient 2). Most patients experiencing paradoxical neurological worsening manifest deterioration in their gait, balance, tremor, speech, and swallowing (due to oropharyngeal dystonia). Worsening of dystonia after chelation treatment may even result in generalized dystonia that is refractory to medical management, i.e., status dystonicus or dystonic storm [18, 19].

Paradoxical worsening with decoppering treatment is a dreaded complication of WD treatment. The choice of the decoppering agent and titration with careful monitoring of copper excretion require experience and guidance from an expert.

First WD Emergency: Timely Diagnosis

Clinical Presentation

Certain clinical phenotypes are suggestive of WD and should prompt further laboratory testing. The diagnosis of WD requires a high degree of clinical suspicion—it bears repeating that the clinician will never diagnose WD if they do not think of it [13]. The historical name for WD, hepatolenticular degeneration, reflects the fact that hepatic and neurologic symptoms are the two major clinical phenotypes in symptomatic patients. WD with hepatic manifestations can be seen in about 40% of all patients, while initial neurologic symptoms and signs are present in approximately 40–50%; primary psychiatric presentations can be seen in about 10% of patients [12, 20–22]. Other systemic manifestations of WD are rare and difficult to recognize without other signs of hepatic or neurologic problems [1, 2]. Aminoaciduria, nephrolithiasis, arthropathy, premature osteoporosis, and cardiomyopathy have been reported as unusual presenting symptoms of WD. Ophthalmologic features are also common, typically asymptomatic, but very useful in supporting the diagnosis. The most important are Kayser-Fleischer (KF) rings caused by asymptomatic copper deposition in Descemet's corneal membrane [23, 24]. Sunflower cataracts, caused by copper deposits in the lens, are another asymptomatic ophthalmologic presentation of WD.

Almost all WD patients with neurologic symptoms and signs have KF rings. KF rings can be visualized at the bedside even in patients with brown irises by illuminating the iris with a light positioned at the side of the eye. KF rings are classically thicker superiorly and inferiorly. They are golden brown to green in color, with a fluffy appearance that blends into the natural color of the iris.

Copper deposits in the cornea and the lens disappear with chelation, but the severity of KF rings does not correlate with clinical deficits. Clinical suspicion for WD should be highest in patients who develop hepatic or neurologic symptoms in adolescence to early adulthood [13, 20–22, 24]. However, the age of first symptoms varies widely from the first decade to the fourth and fifth decades of life. Neurologic symptoms tend to develop approximately one decade later than hepatic presentations, but there is a considerable overlap between these two major phenotypes. Atypical, late-onset WD even in the seventh and eighth decades of life has been described [25–27].

Like other clinical presentations of WD, hepatic symptoms range from asymptomatic liver disease to life-threatening hepatic failure [1, 6, 7]. Asymptomatic patients typically have only biochemical abnormalities with elevation of liver enzymes and histologic findings of steatosis on liver biopsy. Liver involvement in WD may also mimic acute viral hepatitis or autoimmune hepatitis. However, most patients with hepatic symptoms exhibit signs of chronic liver disease with cirrhosis and splenomegaly due to portal hypertension. The hepatic phenotype of WD is frequently associated with Coombs-negative hemolytic anemia that can lead to acute renal failure in extreme cases. Transient episodes of jaundice due to hemolysis may be the initial presentation in patients who do not have any other signs of liver disease. Patients with predominantly neurologic symptoms have frequent mild liver disease, but they tend to have more compensated cholestatic hepatopathy. Liver transaminase enzymes alanine transaminase (ALT) and aspartate transaminase (AST) may be normal [1]. Thus, a normal AST and ALT in patients with suspicious neurologic symptoms does not exclude WD, and further evaluation is warranted.

Presenting neurologic symptoms can be pleotropic and present a significant diagnostic challenge; *WD is the great imitator in movement disorders* [13]. Even though neurologic presentations are very heterogeneous, WD neurologic phenotype can be grouped into dystonic, tremor-dominant or pseudosclerotic, parkinsonian, and hyperkinetic (choreic) subtypes [20–22]. A dysarthric form has been also suggested as another clinical category. However, dysarthria is the most constant neurologic sign in WD, present in 90% of patients. Initial neurologic symptoms are typically subtle and nonspecific. Motor symptoms may include lack of coordination, handwriting change, dysarthria, and drooling [28]. The clinical course is progressive in untreated patients, and they typically develop more noticeable neurologic abnormalities with dystonia, tremor, and parkinsonian syndromes [29]. The most common initial problems are tremor and ataxia, seen in about 40–60% of patients, followed by dysarthria (40–58%), dystonia (15–42%), gait abnormalities (38%), parkinsonism (11–60%), and choreoathetosis (15%) [28, 30–32]. Patients may also

present with new-onset seizures as the first sign of WD in about 5% of cases [29]. However, new onset of generalized tonic-clonic seizures may also indicate the evolution of paradoxical worsening during initiation of chelation therapy, discussed in detail in the following sections. Discrete or unclassified signs were observed in 11.3% of patients, further illustrating the clinical heterogeneity [32].

Behavioral and cognitive changes are commonly associated with neurologic problems and may be detected early in the course of the disease. The pattern of cognitive decline is similar to other basal ganglia disorders [33, 34]. Apathy, reduced attention, bradyphrenia, frontal lobe dysfunction with impaired social judgment, and impulse control behaviors are now commonly recognized, and they represent a significant morbidity for WD patients. Decline in school or job performance may herald cognitive changes. Tremor in WD is highly variable with rest, postural, and action tremor observed [28, 30–32]. Wing-beating tremor is a prototypical WD tremor, proximally generated, appearing when the patient holds semi-flexed outstretched arms in the "wingbeat" posture. Its amplitude increases the longer the patient holds the position, and some patients exhibit a severe flapping tremor as if they are launching into flight. Other patients exhibit a typical postural and action tremor that may easily be misdiagnosed as essential tremor. Dystonia varies from focal to generalized dystonia [28, 30–32]. Advanced WD may produce severe generalized dystonia with secondary contractures and inability to walk. Segmental or focal dystonia affecting the craniofacial region is especially common, causing severe dysphonia, dysarthria, or even a complete loss of speech with dysphagia or inability to swallow. Many WD patients exhibit an exaggerated smile, known as risus sardonicus. Dystonia associated with WD is a prototypical secondary dystonia [13]. Parkinsonism typically manifests as masked facies with hypophonic soft voice, micrographia, and shuffling or freezing gait. Hypokinetic-rigid syndromes tend to be symmetrical, but unilateral tremor can be present leading the examiner to a misdiagnosis of Parkinson's disease.

Dysarthria is typically of a mixed type with prominent dystonic and hypokinetic features [28, 30–32]. Patients with the pseudosclerotic (tremor) subtype may also exhibit signs of cerebellar dysarthria. However, there is a considerable overlap among these groups, and patients with severe WD often display mixed phenotypes. Hyperkinetic movements are more common in younger individuals who developed WD in the second decade. Ataxia is another frequently mentioned sign, but true cerebellar ataxia is rare, and incoordination and balance problems are more commonly caused by extrapyramidal signs and severe wing-beating tremor [32]. Primary psychiatric manifestations have been reported in 10% of newly diagnosed patients without detectable neurologic or hepatic manifestations [35, 36]. Later in the course of the disease, these patients may develop additional neurologic problems, but these initial neurologic signs can be subtle and easily overlooked. Psychiatric symptoms are nonspecific ranging from depression to acute psychotic episodes, leading to common misdiagnoses of bipolar disorder or schizophrenia. Overall, this is a particularly difficult type of WD to diagnose. The analysis of patients initially seen by a psychiatrist showed that the average delay of diagnosis was more than 2 years.

Diagnosis of WD

The definite diagnosis of WD is established by biochemical tests confirming signs of copper overload, including increased urinary copper excretion and elevated values of free copper (NCC) in blood [1, 2]. Even though the diagnosis remains laboratory based, the availability of genetic testing may further increase clinical certainty, especially in patients with biliary obstruction or with borderline biochemical features as can be seen in heterozygous patients [37–39].

Screening tests are recommended as the first step in confirming the diagnosis of WD [1]. Levels of ceruloplasmin plasma, the main copper-binding plasma protein containing more than 90% of total plasma copper, are most frequently used [40]. Loss of function of the *ATP7B* gene impairs copper loading to ceruloplasmin, resulting in low plasma levels. A serum ceruloplasmin level less than 20 mg/dL (200 mg/L or 2.83 μmol/L) is consistent with the diagnosis of WD, but overall the positive predictive value is very low at 5.9% [2]. Even low ceruloplasmin levels cannot confirm the diagnosis, and additional confirmatory tests are needed. Abnormally low ceruloplasmin levels less than 5 mg/dl strongly suggest WD, but it can be also associated with conditions with very low copper plasma values, especially with copper deficiency and aceruloplasminemia [41, 42]. The latter is a rare autosomal recessive condition caused by mutations in the ceruloplasmin gene. Neurologic clinical presentations of aceruloplasminemia may mimic WD but the pathogenesis is caused by iron overload. Another possible cause of low ceruloplasmin is Menkes disease, an X-linked disorder of copper transport from enterocytes to blood and through the blood-brain barrier caused by mutations in the *ATP7A* gene [43]. Heterozygotes carrying one mutated allele of *ATP7B* gene may also have borderline low values requiring further testing. Similarly, low normal ceruloplasmin value does not exclude a diagnosis of WD. Ceruloplasmin is an acute phase reactant causing higher levels, leading to false negative results. Another important cause of higher ceruloplasmin in WD is exposure to estrogens, most commonly from birth control pills [44].

Ophthalmologic evaluation, looking for Kayser-Fleischer rings, is commonly used as a screening test. KF rings may be visible as a golden-brownish pigmentation around the limbus. Some patients may not have a fully formed circle, and increased pigmentation can be seen around 6 and 12 o'clock positions. Definitive detection of Kayser-Fleischer rings should be established by slit lamp examination. They are rarely absent in patients with neurologic presentations. The presence of KF rings can only support the diagnosis of WD, because rarely they may be present in patients with chronic cholestatic liver disease.

Every patient with suspected WD needs to have a 24-h urine copper measurement and this test alone is diagnostic in most patients [1, 2]. Obstructive hepatopathy can cause diagnostic uncertainty, but this is not common for patients with neurologic signs. It is important to completely collect 24-h urine starting after the first morning voiding on the day of the collection day and complete it the next day after the first voiding. Another technical requirement is a copper-free collection vessel. Total creatinine excretion in the 24-h urine collection is typically measured to

support proper urine collection. A 24-h copper value more than 100 μg/24 h (1.6 μmol/24 h) is conventionally considered diagnostic of WD, especially for patients with neurologic or psychiatric phenotypic presentations [1, 2]. Normal values for 24-h excretion are typically below 40 or 50 μg (0.64 or 0.8 μmol)/24 h. Intermediate values between 40/50 and 100 μg/24 h may be seen in heterozygous (carrier) individuals and require further investigation. Affected symptomatic children with WD may also have 24-H urine copper values below the conventional cutoff, and lowering this value in pediatric patients has been suggested [45]. D-Penicillamine challenge has been used in patients with borderline 24-h urine copper values, but this test has been validated only in children with hepatic presentations. Administration of 500 mg of D-penicillamine before urine collection and repeated once 12 h into the collection promotes cupriuria, and values of more than 1600 μg copper/24 h (25 μmol/24 h) are considered diagnostic [46]. Overall, this test is used less commonly with the availability of genetic testing for *ATP7B* mutations.

Serum NCC (non-ceruloplasmin-bound copper) or free copper assay has been proposed as a diagnostic test for WD. It is elevated above 25 μg/dL (3.94 μmol/L) in most untreated patients [1]. Normal values are 10–15 μg/dL (1.6–2.4 μmol/L), and free copper below 5 μg/dL (0.8 4 μmol/L) indicates copper deficiency. Limited availability of this test reduces its clinical utility. The free copper fraction can be also calculated from total plasma copper and ceruloplasmin values. Six copper atoms are bound to one molecule of ceruloplasmin, resulting in approximately 3.15 μg of copper weight per 1 milligram of ceruloplasmin. Thus, free copper can be estimated as a difference between the total copper and ceruloplasmin value multiplied by three. However, this needs to be interpreted with caution, especially when the levels of ceruloplasmin are low [1]. Total copper value alone is not very helpful in the diagnosis of WD because it is very variable. Liver biopsy measuring liver copper content has been considered a gold standard for the confirmation of the diagnosis and may be still required in patients with predominantly hepatic presentation. However, the diagnosis of neurological or psychiatric WD can be confirmed using 24-H urine copper excretion assay. Hepatic copper content more than 250 μg/g dry weight (4.0 μmol/g of tissue) is considered diagnostic for WD [1].

Cloning of the causative gene for WD and the rapid progress in high-throughput sequencing methods increased the importance of genetic testing in the diagnostic process. Identification of both disease-causing mutations confirms the diagnosis. Mutations in the *ATP7B* gene can be found in any of the 21 coding exons and intronic flanking sequences, resulting in a considerable allelic heterogeneity [37, 38]. Many deleterious mutations are private and limited to single families, and most patients are compound heterozygotes. Certain ethnic groups harbor more common mutations, and genetic screening can be prioritized to analyze common mutations first. Targeted mutation analysis for specific mutations, such as multiplex amplification refractory mutation system PCR, can be employed in populations with prevalent common mutations. Otherwise, every exon and adjoining intronic areas need to be sequenced. Genetic testing should be limited to confirmation of diagnosis, family screening, and unclear cases with a high degree of suspicion for

WD. Both mutations need to be known if this test is used for familial screening. Overall rate of detection of mutations in patients with biochemically confirmed disease is approaching 98%, but intronic mutations or mutations in the promoter regions still may be undetected. Whole genome sequencing can be utilized in these cases. However, biochemical laboratory methods detecting copper overload may be sufficient to confirm the diagnosis in these patients.

Most patients manifesting neurologic problems have abnormal magnetic resonance imaging (MRI) findings, and this can help to increase the suspicion for WD [47–49]. However, these MRI changes are nonspecific and WD needs to be confirmed by other laboratory methods. Similarly, a normal MRI of the brain does not rule out WD. The most common finding is hyperintensity on T2-weighted and FLAIR images involving the putamen, striatum, and globus pallidus (Fig. 25.1). Hyperintense signal in the midbrain around the red nucleus and substantia nigra may give the appearance of the "sign of the giant panda" that is most commonly seen in WD patients (Fig. 25.2). MRI structural changes only loosely correlate with neurologic deficits. Nonetheless, MRI monitoring can be very useful to detect clinical deterioration after chelation therapy (see Fig. 25.2) or for clinical improvement if patients respond favorably to decoppering therapies [49].


A normal MRI does not exclude WD.

A scoring system utilizing clinical and laboratory features, including the presence of Kayser-Fleischer rings, neurologic or neuroimaging features, hemolytic anemia, elevated liver function, elevated 24-h urine copper values, reduced ceruloplasmin, and mutation analysis has been developed [2]. The total score is generated by adding values from 0 (normal examination or absent laboratory abnormalities),

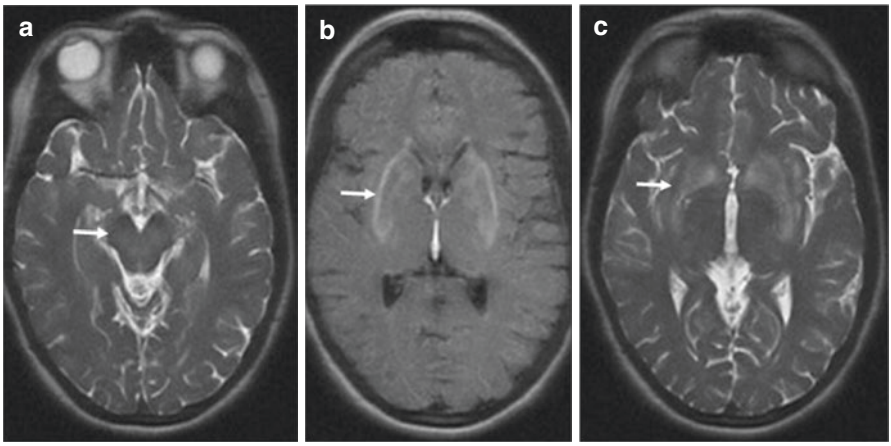

Fig. 25.1 MRI of the brain at the time of diagnosis. The patient was 20-year-old woman who was diagnosed 14 months after exhibiting first symptoms. Faint T2 hyperintensity was observed in upper brainstem (panel **a**). Increased T2 signal in basal ganglia (panels **b** and **c**) is suggestive of WD

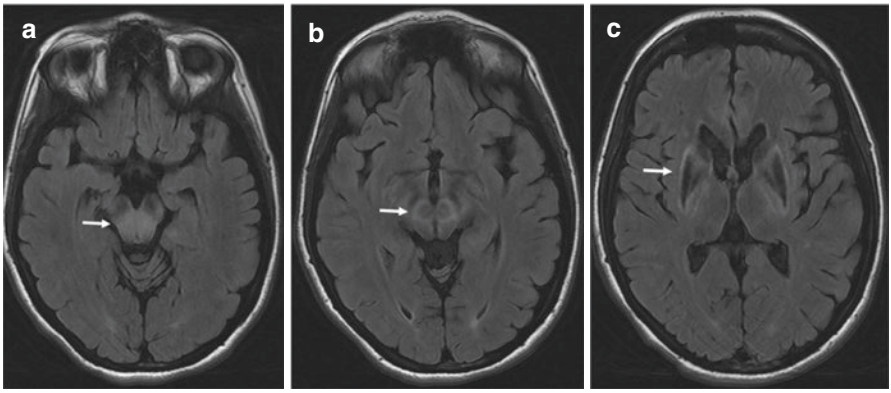

Fig. 25.2 MRI of the brain 8 months after chelation therapy was initiated. She was started on D-penicillamine at an outside institution, and within 1 month she developed severe dystonia with mutism and severe Parkinsonism. This was irreversible and her neurologic deficits were fixed. Flair imaging showed worsening of hyperintensity in the midbrain (panel **a**) with the appearance suggestive of face of the giant panda (panel **b**). Severe cystic changes were detected in basal ganglia (panel **c**)

2 points (abnormal clinical signs or abnormal laboratory tests present) to 4 points if both mutations are detected. Overall score of 4 or more points is highly suggestive for WD, and a score between 2 and 3 points is classified as probable WD where more diagnostic tests are needed [2].

Second WD Emergency: Timely Treatment

The natural history of untreated symptomatic WD is eventual death caused by liver failure or complications from disabling neurologic deficits [1, 2, 29]. Currently published therapeutic guidelines recommend life-long therapy for all patients, regardless of clinical symptoms or severity of their symptoms. Patients diagnosed and treated early may lead essentially normal lives. WD is curable by orthotopic liver transplant, but this approach is mostly reserved for fulminant liver failure, and its role as a rescue therapy for neurologic problems remains controversial [1]. Therapy should be initiated immediately after the diagnosis is confirmed, and a high degree of clinical suspicion for the diagnosis is essential. Average time from symptom onset to correct diagnosis and treatment is still around 1 year [29, 50]. This delay affects the overall success of therapy. Patients presenting with neurologic symptoms had best outcomes when the interval between first symptoms and initiation of therapy was less than 1 month. Only 20% had very favorable outcome with no abnormalities or mild residual symptoms when the diagnosis and treatment was delayed by about half a year [11, 51]. The development of neurologic symptoms is the result of elevated NCC from chronic copper accumulation. Thus, the goals of therapy are to reverse copper overload and establish a negative copper balance during which

NCC values are reduced to normal levels. The tight control of NCC is critical because it is likely the main cause of copper neurotoxicity and can be a trigger of further paradoxical worsening after the therapy is started [14, 15]. Therapy for WD can be divided into an acute chelating phase followed by a chronic maintenance phase after the patients achieve improvement of their copper balance.

WD is treated with chelating agents or zinc salts. Chelators nonspecifically bind copper and promote urinary copper excretion. D-penicillamine and trientine are the two currently available chelating agents [1–3, 10, 52] [another agent, tetrathiomolybdate, has been studied but not yet approved]. Both have rapid onset of action and are used in the acute phase of decoppering therapy. They can also be used for long-term maintenance therapy. Zinc works by a different mechanism of action, as it blocks the absorption of copper from the gastrointestinal tract by triggering increased expression of metallothioneins in the enterocytes [53, 54]. Metallothioneins are cysteine-rich proteins that bind various metal ions, including copper. The dietary copper bound to metallothionein is sequestered within the intestinal cells and prevented from absorption into the blood. Negative copper balance is achieved because copper is removed through the stool after the enterocytes are shed in the intestinal lumen as a part of normal cellular turnover. This is a cumulative effect that can take up to 3 months; thus, the main role of zinc is in the maintenance phase of therapy [53]. The transition to maintenance phase of therapy is based on clinical improvement and laboratory copper values. The typical interval occurs after 2–6 months of chelating therapy, but additional clinical and laboratory improvement can be observed up to 3 months after the initiation of chelation therapy with an ongoing improvement of neurologic symptoms.

D-Penicillamine remains the most frequently prescribed chelator in the treatment of WD around the world, and its major effect is the promotion of the urinary excretion of copper [8, 55, 56]. The starting dose for patients with neurologic symptoms should be 250–500 mg/day with a careful increase by 250 mg every 5–7 days to monitor patients for possible worsening and side effects. The usual maximum dose in neurologic patients is 1500 mg/day. It is dosed three or four times per day either 1 h before meals or 2 h after meals because food reduces its absorption by almost half. Iron supplements and antacids also significantly reduce its absorption. D-Penicillamine has a strong cupreuremic effect and 24-H urine copper assay is used to monitor the therapeutic response [1, 2]. The aim of chelation therapy is to normalize NCC, but this test is not generally available. Calculated NCC based on total plasma copper and ceruloplasmin levels may be imprecise if plasma ceruloplasmin values are low. The dose is adjusted based on 24-H urine copper assay, and excretion of copper may exceed 1000 μg (16 μmol) per day at the initiation of therapy. D-Penicillamine can be also used for long-term maintenance therapy, and this dose is lower than during acute chelation. This dosing is usually 750–1000 mg/day administered in two divided doses with expected daily urine excretion between 200 μg and 500 μg (3–8 μmol). Urine copper levels below 200 μg (3 μmol)/24 h suggest overtreatment with iatrogenic copper deficiency or noncompliance with treatment [8, 9].

Frequent adverse effects are a major disadvantage of penicillamine, and up to one third of patients will eventually stop this therapy. This creates a high risk of noncompliance with a possibility of further worsening of neurologic symptoms. Acute sensitivity reactions include fever, lymphadenopathy, cutaneous eruptions, proteinuria, and signs of bone marrow suppression with neutropenia or thrombocytopenia [1]. Slower rate of dose titration or brief treatment with steroids has been suggested to mitigate these problems, but if alternative medications such as trientine are available, a change of chelating agent may be more suitable. Chronic adverse effects include nephrotoxicity with proteinuria, a lupus-like reaction with hematuria, proteinuria, positive antinuclear antibody, progeric changes in the skin, pemphigoid lesions, lichen planus, aphthous stomatitis, myasthenia gravis-like syndrome, and polymyositis. It also interferes with wound healing, and the therapy needs to be interrupted if surgery is planned. D-Penicillamine also has an antipyridoxine effect, and supplementation of pyridoxine (vitamin B6) or monitoring of pyridoxine levels has been recommended [57].

Trientine is approved by the FDA as second-line therapy for patients who did not tolerate D-penicillamine. It is a chelator with a high affinity for copper, and like penicillamine the bound copper is removed through urinary excretion. Trientine has a lower cupreuremic effect than D-penicillamine, and daily copper excretion in the range of 200–500 μg (3–8 μmoles) is commonly observed in WD patients on trientine [1, 58]. The target dose of trietine during initial therapy is 750–1500 mg/day divided in two or three doses, and it also should be taken before food. Similar to D-penicillamine therapy, trientine should be started gradually in patients with neurologic symptoms, with 250 mg increments every 5–7 days. The typical maintenance dose is 750 or 1000 mg per day, and the dose is adjusted based on 24-copper urine values. Daily urinary copper excretion below 200 μg may indicate either nonadherence to therapy or induction of copper deficiency from overtreatment. Trientine tends to be well tolerated and no significant acute or chronic side effects have been observed. Bone marrow suppression with thrombocytopenia and leukopenia is rare, and it should prompt an evaluation for evolving iatrogenic copper deficiency from overtreatment.

Zinc acetate is approved by the FDA for treatment of WD but other zinc salts, available over the counter, can be used as well [53, 59]. Zinc should be taken on an empty stomach and gastric irritation with nausea is the most common side effect. The severity of gastric intolerance may be influenced by the type of salt, and zinc gluconate can be used to ameliorate gastrointestinal side effects. The typical dose of zinc acetate or zinc gluconate is 50 mg three times per day [54]. The disease control on this therapy is also monitored by 24-h copper urine assay, but given the different mechanism of action, the target copper urine values differ from monitoring parameters of chelation therapies. Zinc does not promote urinary copper excretion, and an effective treatment reduces the overall copper urinary excretion, reflecting the reduction of copper overload. Daily urinary copper excretion of less than 75 μg indicates an adequate control on zinc therapy. The most common use of zinc is for maintenance therapy after chelators have reduced NCC and induced a negative

copper balance. When a patient is crossed over from a chelator to zinc, these two therapies need to overlap for a period of 2–3 months to maximize the effects on metallothionein. This is an especially suitable option for patients with neurologic phenotypes, and some patients with hepatic symptoms only may experience worsening of their disease control on zinc monotherapy.

Third WD Emergency: Paradoxical Treatment-Induced Worsening

The goals of therapy for patients with neurologic presentations are to stop the progression of neurologic disability, followed by gradual improvement of neurologic symptoms. However, treatment with currently available chelating agents is associated with a relatively high risk of deterioration of neurologic symptoms, also known as medication-induced paradoxical worsening [16, 17]. The risk for worsening on chelation therapy is higher for patients with a delayed diagnosis, but some patients deteriorate even if therapy is started in a timely fashion. The main hypothesis explaining this phenomenon is an upsurge of free NCC, caused by copper dissociation from unstable complexes with chelators, triggering a cytotoxic effect in neuronal tissue with subsequent neurologic deterioration. Correlation between the stability of NCC control without additional elevations of NCC values and favorable neurologic outcomes has been reported, but NCC assay is not readily available as a routine clinical test to monitor elevation of NCC after treatment initiation [15]. Paradoxical worsening typically occurs within the first 6 months of therapy as this is the most crucial period of chelation therapy.

The first reports of medication-induced worsening suggested that D-penicillamine has the highest risk, and as many as 20–35% of treated patients with neurologic presentations have experienced further deterioration that is often irreversible [16]. Paradoxical neurologic worsening has been also observed in patients treated with trientine, with reported incidence of 10–15% [58]. This would potentially favor trientine as first-line chelation therapy for patients with neurologic symptoms, based on previous reports of much higher risk in patients treated with D-penicillamine. The severity of presenting neurologic symptoms and the extent of structural changes detected by magnetic resonance imaging with early signal changes in the basal ganglia, thalamus, and brainstem are risk factors for paradoxical worsening (see Figs. 25.1 and 25.2). Recommenced management of paradoxical neurologic worsening is to reduce the dose of the chelating agent. Additional steps include switching to a different chelating agent, especially if paradoxical worsening was induced by D-penicillamine; these patients should be switched to trientine at a lower dose. A temporary interruption of chelation can be also considered if no other treatment options are available.

More recent retrospective studies suggested that D-penicillamine, trientine, and zinc salts have very comparable incidences of paradoxical worsening, and one study found the least frequent deterioration in patients treated with D-penicillamine with the reported risk of 2% of neurologic decline, much lower than previous observations

[11, 60]. The lack of head-to-head comparison between these two chelators and the retrospective nature of most of the studies make it difficult to determine whether there is a superior chelator. Thus, until more conclusive clinical data is available, the selection of first-line chelation therapy for patients with neurologic phenotypes of WD needs to be based on additional factors, including personal experience and availability.

Zinc is considered a second-line therapy after laboratory signs of copper overload have been normalized by chelators. However, zinc has been used in patients with neurologic symptoms who are at risk for paradoxical worsening or who developed this problem on typical chelators [60]. The justification of zinc as first-line therapy in these patients is to lower the risk of paradoxical worsening [61, 62]. The effects of zinc on metallothionein expression are cumulative and there is a delay of several months until zinc is fully effective. That is why some consider first-line therapy with zinc too slow to effectively control neurologic phenotypes of WD. Neurologic worsening has been also observed in patients with neurologic symptoms who were treated with zinc but is more likely caused by undertreatment [60]. Moreover, in initial treatment the doses of zinc need to be higher than for maintenance therapy and this is often poorly tolerated.

Liver transplantation corrects the genetic defect of WD and can be considered a curative procedure, even though it requires life-long immunosuppressive therapy in transplanted patients [1]. The indications for liver transplantation in hepatic forms of WD are generally well established [63]. WD patients who develop acute liver failure are candidates for transplantation because of very high mortality, and liver transplantation is a lifesaving procedure for these patients. Liver transplantation with a wild type of *ATP7B* gene promptly restores copper homeostasis with normalization of extrahepatic copper metabolism, including in the central nervous system. That is why this approach has been also advocated as a rescue therapy for neurologic patients who experienced progressive deterioration of their condition on chelation therapy [64–66]. However, the role of liver transplantation as a treatment for patients with severe neurologic deficits remains controversial. Improvement or even complete resolution after liver transplantation has been reported in some patients with severe and progressive neurologic deficits who did not respond to conventional chelation therapies. These positive outcomes are not universal, and no improvements or further progression has been also observed. The most comprehensive retrospective analysis of 18 patients with WD who underwent liver transplantation because of progressive neurologic deficits showed that four died and a major improvement was seen in eight patients [67]. The rest of the patients had less robust improvement or stabilization of their neurologic function. Thus, at present there are no consensus regarding the role of liver transplant to reverse neurologic deficits and no formal criteria of best candidates for liver transplantation for neurologic phenotypes [68].

Patients who experienced neurologic deterioration while on chelation or zinc typically show progression of orofacial dystonia, progressive dysphagia, and dysarthria. This is associated with a high risk of aspiration, and very close monitoring of swallowing is mandatory in the initial phase of WD treatment [69]. Some patients

may require percutaneous endoscopic gastrostomy feeding to maintain adequate nutrition and reduce the risk of aspiration. An additional life-threating emergency is status dystonicus, reported in a handful of patients after D-penicillamine [18, 19]. This is a potentially life-threatening complication of worsening WD, presenting as an acute and severe generalized dystonia associated with rhabdomyolysis, hyperpyrexia, acute renal failure, and respiratory insufficiency. Treatment options include adjustment or change of chelating agents, as outlined above. Pharmacological therapies include benzodiazepines, baclofen, VMAT2 (vesicular monoamine transporter 2) inhibitors, or a trial with levodopa. Bilateral globus pallidus pars interna (GPi) deep brain stimulation (DBS) can benefit patients in status dystonicus that is refractory to adjustments of decoppering therapies or other pharmacological measures [70]. Outcome of medication-induced status dystonicus in WD varies from mild recovery to a fatal outcome. Similar to other examples of paradoxical worsening, status dystonicus developed within the first 2 months of chelating therapies, further emphasizing that the early stages of acute chelation therapies are most critical.

Conclusion

WD is the prototypical movement disorder challenge—a challenge to diagnose, a challenge to treat, and a challenge to monitor and maintain. However, if the clinician maintains a high index of suspicion for the condition and initiates and monitors chelation carefully, most patients can be effectively managed and live normal and productive lives.

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