CHAPTER THIRTEEN

Update on Wilson Disease

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Contents

Abstract

Wilson disease (WD) is an inherited disorder of chronic copper toxicosis characterized by excessive copper deposition in the body, primarily in the liver and the brain. It is a progressive disease and fatal if untreated. Excessive copper accumulation results from the inability of liver to excrete copper in bile. Copper is an essential trace metal and has a crucial role in many metabolic processes. Almost all of the body copper is protein bound. In WD, the slow but relentless copper accumulation overwhelms the copper chaperones (copper-binding proteins), resulting in high levels of free copper and copper-induced tissue injury. Liver is the central organ for copper metabolism, and copper is initially accumulated in the liver but over time spills to other tissues.

WD has protean clinical manifestations mainly attributable to liver, brain, and osseomuscular impairment. Diagnosis of WD is challenging and based on combination of clinical features and laboratory tests. Identification of various high-frequency mutations identified in different population studies across the world has revived interest in developing DNA chips for rapid genetic diagnosis of WD.

All symptomatic and all presymptomatic patients require lifelong decoppering with careful clinical tracking. Decoppering ensures that presymptomatic individuals remain symptom free. With judicious decoppering, given time, even patients

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with severe neurological disability improve and can return to normal life and resume school or work at par with their peers. Treatment regimens and tracking patients using the WD-specific Global Assessment Scale for WD (GAS for WD) are discussed.

1. INTRODUCTION

Wilson disease (WD) is an inherited disorder of chronic copper toxicosis characterized by excessive copper deposition in the body, primarily in the liver and the brain (Walshe, 2009). Excessive copper accumulation results from the inability of liver to excrete copper in bile. Copper toxicosis in WD differs from chronic poisoning from other heavy metals like mercury or lead, because unlike these metals, copper has an essential role in many metabolic processes. Deficiency of copper leads to well-defined clinical and pathological defects (Scheinberg & Sternlieb, 1984). The necessity of copper is exemplified by Menkes disease, an inherited disorder of copper transport that results in relative copper deficiency and failure to incorporate copper in various enzymes. Menkes disease manifests as a progressive multisystemic disease and death in infancy (Tümer and Møller, 2010). Free copper is injurious to cells, and almost all of the body copper is protein bound. In WD, the ever-increasing positive copper balance overwhelms the copper chaperones (copper-binding proteins), resulting in high levels of free copper and copper-induced tissue injury.

The story of WD began with Samuel Kinnier Wilson, while still a registrar at the National Hospital, Queens Square, London, describing a new rare familial disease characterized by progressive lenticular degeneration and liver cirrhosis. The report included exhaustive clinical and pathological description of 12 patients published as a single issue of Brain. Four of the 12 patients were observed by Wilson, while details of two patients were obtained from medical records at the National Hospital. Six of the 12 patients' clinical histories were published earlier; of these, one brother and sister were reported by Gower in 1988 as "Tetanoid Chorea, associated with Cirrhosis of the Liver," one patient was described by Ormerod in 1890, and a further three siblings were described by Homen, of Helsingfors, also in 1890. The disease manifested as progressive involuntary movements, spasticity, dysarthria, and transitory mental symptoms and was fatal in all. All 12 patients had advanced liver cirrhosis (Wilson, 1912).

In contrast to dystonia-dominant syndrome of Samuel Wilson, Westphal and Strumpell independently described cases with pseudosclerosis or a tremor-dominant phenotype of WD (Pfeiffer, 2011).

Wilson believed that WD was a toxin-induced neurodegenerative disorder. Though curious about the presence of unexplained advanced cirrhosis in young people with WD, Wilson surmised that the liver involvement did not contribute to the clinical syndrome or the disease evolution. This is surprising as one of his patients died of hematemesis (Wilson, 1912). Bramwell (1916) drew attention to the role of the liver in the natural history of the disease in a family where 4 of 7 siblings died between 9 and 14 years of liver failure. The name hepatolenticular degeneration was first applied to WD by Hall (1921).

Excess of copper was reported in the liver of a patient dying of WD a year after Wilson's original publication (Rumpel, 1913). In the 1920s, there were other reports of high copper in the brain or liver of patients dying of WD (Glazebrook, 1945; Haurowitz, 1930; Vogt, 1929) and similarity of Kayser–Fleischer rings (KF rings) and sunflower cataracts with copper-containing foreign body (Siemerling & Oloff, 1922). However, the central role of copper was finally acknowledged only in 1948 when Cumings (1948) demonstrated excess copper in the brain and liver of patients with WD. In fact, Cumings not only irrefutably establish that copper played a central role in WD but also suggested that that treatment with the newly developed chelating agent British antilewisite (BAL, dimercaprol) might arrest the progress of the disease (Cumings, 1948). Use of BAL (Cumings, 1951, Denny Brown & Porter, 1951) was soon followed by development and introduction of effective oral chelators as orphan drugs for treating WD (Walshe, 2009).

In what remains a classic monograph, Samuel Wilson described a new invariably fatal disease afflicting the young. Wilson's quest of finding a cure was realized half a century later. Treatment for WD has now been available for over 50 years (Walshe, 1956). Today, with early diagnosis and judicious decoppering, disease progression can be halted and disability reversed. The challenge is to diagnose WD early, preferably before symptom onset, and titrate decoppering effectively.

2. COPPER HOMEOSTASIS

Copper is the third most abundant trace element in humans (after iron and zinc) and serves as a cofactor for many important enzymes including

cytochrome c oxidase, copper–zinc superoxide dismutase (SOD), dopamine beta-hydroxylase, and ceruloplasmin (Bull & Cox, 1994). Though an essential metal, copper can be toxic. Copper exists in two forms, cuprous and cupric ions, which can interchange rapidly. This redox property is essential for the role of copper in its enzymatic activity. However, unbound or free copper can rapidly generate reactive oxygen species and have a deleterious effect on the cell (Rosencrantz & Schilsky, 2011). Therefore, copper homeostasis is tightly controlled, and there is virtually no free copper in the body (Tümer & Møller, 2010).

Daily intake of copper is 1–2 mg, and 98% of the absorbed copper is excreted via the liver into the bile and thereon lost in feces (Lutsenko, Barnes, Bartee, & Dmitriev, 2007). Dietary copper is absorbed in the small intestine by various nonspecific metal transporters and is exported into the portal circulation by Cu-transporting ATPase ATP7A (Menkes protein). ATP7B is present in the enterocytes, but its role is uncertain. In Menkes disease, inactivation of ATP7A in the enterocytes results in overall copper deficiency (Kaler, 1998; Kodama & Murata, 1999). The copper in the portal blood binds to amino acids like histidine or albumin and is then transported to the liver.

Liver is the central organ for copper storage and homeostasis. The liver avidly takes up most of the copper in portal circulation through the CTR1 transporter. Copper is stored in the liver, bound to metallothioneins, and delivered to various intracellular organelles via copper chaperones. Copper in the cytosol is delivered to copper–zinc SOD via copper chaperone of superoxide dismutase (CCS) (Culotta, Yang, & O'Halloran, 2006). Copper enters the mitochondria via COX17 chaperone for incorporation into cytochrome c oxidase, while Atox1 chaperone delivers copper to ATP7B located at the trans golgi complex (TGN) (Lutsenko et al., 2007; Prohaska & Gybina, 2004). ATP7B is a major copper transporter in the liver and plays a vital role in intracellular copper homeostasis. Under normal copper conditions, ATP7B resides at the TGN and facilitates copper incorporation into cuproproteins like ceruloplasmin, which is then secreted into the blood and transports copper to various tissues. Under high copper conditions, ATP7B is transferred to bile canaliculi and facilitates excretion of excess copper into bile. A defect in ATP7B transporter leads to impaired efflux of copper and excessive copper deposition in the liver.

Ceruloplasmin is an alpha-1-acid glycoprotein and is a major copper transporter in blood. Ceruloplasmin is low in 80–95% of the patients with WD. However, low ceruloplasmin is not responsible for WD. Decreased

ATP7B activity leads to impaired incorporation of copper into apoceruloplasmin and low ceruloplasmin levels. Ceruloplasmin has a role in iron metabolism. Mutation in the ceruloplasmin (CP) gene on chromosome 3 leads to aceruloplasminemia, a multisystemic chronic iron toxicosis characterized by absence of ceruloplasmin, and excessive iron deposition in the brain, liver, and pancreas (Harris et al., 1995; Miyajima et al., 1987). CP gene is normal in WD. Ceruloplasmin levels can be low in up to 10–20% of the people heterozygous for WD mutations and in patients with other chronic liver diseases, Menkes disease, and protein malnutrition (Scheinberg & Sternlieb, 1984).

Minute quantities of copper are secreted in saliva and gastric secretion and lost through skin in healthy individuals. Urinary copper excretion is negligible. In WD biliary copper excretion is impaired leading to copper deposition in the liver. Over years, copper gradually accumulates leading to progressive liver dysfunction. Ultimately, the liver can no longer hold more copper, and the unbound toxic metal spills into the blood and other tissues. Urinary copper excretion increases in patients with WD but cannot compensate for impaired biliary excretion of copper or halt the slow relentless increase in positive copper balance in the body (Pfeiffer, 2011).

3. GENETICS OF WD

Wilson described WD as a familial disease but did not consider it hereditary (Wilson, 1912). Genetic origin was proposed by Hall in 1928, and autosomal recessive inheritance was reported in 1953 (Bearn, 1953). The disease was mapped to chromosome 13, and the disease-causing gene *ATP7B* was identified and cloned in 1993 simultaneously by several groups (Bull, Thomas, Rommens, Forbes, & Cox, 1993; Tanzi et al., 1993).

ATP7B is a large gene consisting of 21 exons and is located on chromosome 13 (13q14-q21). The gene encodes for a 1465-amino acid protein consisting of six copper-binding domains, a transduction domain, a cation channel and phosphorylation domain, a nucleotide-binding domain, and eight hydrophobic transmembrane domains. *ATP7B* mutations result in loss of function. Till date, no gain-of-function *ATP7B* mutation has been described (Schmidt, 2009).

The discovery of the *ATP7B* gene was met with great enthusiasm and hope that this would allow early and accurate diagnosis of WD. However, it was soon realized that the disease can be caused by several (>600) mutations and most patients are compound-heterozygous (WD mutation

database—http://www.wilsondisease.med.ualberta.ca/database). Therefore, identification of WD mutation in a given patient is a time-consuming process and offered only on research basis by selected laboratories in the world. While, identification of WD mutation is the gold standard to diagnose WD, previous studies have reported patients with unequivocal WD bearing only one or no WD mutation (Kenney & Cox, 2007; Nicastro, Ranucci, Vajro, Vegnente, & Iorio, 2010). Failure to identify WD mutation in a patient does not conclusively exclude WD.

Majority of the *ATP7B* mutations identified are missense while, minority are deletions/insertions, nonsense, and intronic splice site. Mutations are scattered along the entire length of the *ATP7B* gene. The possibility of other causative genes contributing to WD has been explored, but not realized (Coronado, Damaraju, Kohijoki, & Cox, 2003). With precise clinical diagnosis and rapid whole-gene sequencing, the *ATP7B* mutation detection rate in WD patients is near perfect (~98%) (Aggarwal et al., 2013; Coffey et al., 2013).

In the recent years, there has been resurgence in interest in using genetic analysis to diagnose WD in patients and screen their siblings. DNA chips incorporating few frequent mutations are being developed to allow for rapid diagnosis (Schmidt, 2009). This enthusiasm stems from various high-frequency mutations identified in different population studies. For instance, the p.H1069Q (exon 14) is a common WD mutation accounting for WD in 30–60% of the Caucasian population (Ferenci, 2006). Screening of single-mutation p.H1069Q accounts for two-thirds of the population in northern, central, and eastern Europe and the United States. While, p.R778L and p.R778G mutations (exon 8) among the Chinese and Taiwanese populations enable rapid genetic analysis of WD in these populations (Chuang et al., 1996; Thomas, Forbes, Roberts, Walshe, & Cox, 1995). It is interesting that in countries with varied ethnicity like India, a few mutations likely account for WD in a large proportion of the population. The regional distribution of some of the common WD mutations is summarized in Table 13.1.

Genotype–phenotype correlation in WD is challenging since patients present with varied clinical symptoms. Monozygotic twins with varied clinical phenotypes have been reported (Czlonkowska, Gromadzka, & Chabik, 2009). Compared to a relatively late onset (second to third decade of life) and a predominantly neurological phenotype of mild to moderate disability that could be associated with the most common European mutation p.H1069Q, the two common western Indian mutations (p.C271* and p.E122fs) seem to lead to earlier onset (first and second decade), and more severe disease. The age of onset of WD in Indian patients is earlier than that reported for patients

Table 13.1 High-frequency *ATP7B* mutation spectrum in various world populations

Country	Sample size (*n*)	Nucleotide/ amino acid change	Exon	Domain	Allele frequency (%)	Reference
Austria	125	H1069Q	14	SEPHL	34.1	Ferenci, 2006
		G710S	8		6.4	
		2299insC	8		3.6	
		R969Q	13		3.6	
Bulgaria	89	H1069Q	14	SEPHL	58.75	Todorov et al., 2005
		2304–2305 ins C			11.25	
		3400delC			3.75	
Hungary	42	H1069Q	14	SEPHL	42.8	Firneisz et al., 2002
Germany	82	H1069Q	14	SEPHL	63	Caca et al., 2001
		3400delC	15		9	
		2299ins C	8		4	
Poland	142	H1069Q	14	SEPHL	72	Gromadzka et al., 2005
		3402delC	15		8	
United Kingdom	42	H1069Q	14	SEPHL	17	Curtis et al., 1999
		M769V	8	Tm4	8	
Japan	47	2871delC	13		15.9	Okada et al., 2000
		R778L	8		13.4	
China	40	R778L	8			Gu et al., 2003
	44	R778L	8			Wu, Wang, Murong, & Lin, 2000
India	52	C271*	2	Cu3	20	Aggarwal et al., 2013
		E122fs	2	Cu1	11	
		L795F		Tm4/Td	6	
		T977M		Tm6	6	

Continued

Table 13.1 High-frequency *ATP7B* mutation spectrum in various world populations—cont'd

Country	Sample size (*n*)	Nucleotide/ amino acid change	Exon	Domain	Allele frequency (%)	Reference
	27	C271*	2	Cu3	~9	Santhosh et al., 2006
		G1061E	14	ATP N-binding	~9	
		C271*	2		18.5	Gupta et al., 2005
		G1708-1C	4	Cu6	9.6	
		448_452del5	2	Cu1	5.6	
	43	I1102T	15	ATP loop	6.1	Kumar et al., 2005
		P922H	13	Tm6	5.8	
		P922*	13	Tm6	5.8	
		G1010A-fs	13	Tm6	5.8	

in Europe, Korea, and South America (Deguti et al., 2004; Lee et al., 2011; Stapelbroek et al., 2004; Taly, Prashanth, & Sinha, 2009). Further, the clinical phenotype of Indian patients with WD, is possibly more severe than that observed in western populations (Aggarwal et al., 2013).

Identification of common mutations and exonic hotspots in a given population makes genetic studies promising and a practical diagnostic tool. Genetic diagnosis also plays an indispensable role in diagnosis of asymptomatic siblings of patient wiith WD.

4. CLINICAL MANIFESTATIONS

4.1. Presymptomatic WD

WD is a multisystemic disease characterized by liver, neurological, and osseomuscular involvement. Copper accumulation commences after birth and slowly progresses. The liver and the basal ganglion bears the brunt of copper toxicosis. Patients with WD can remain presymptomatic for decades. It is crucial to be aware of and identify the red flags of WD (Table 13.2) to allow early diagnosis and prompt treatment.

The initial symptoms are often innocuous, for example, asymptomatic elevation of liver enzymes, fleeting jaundice, change in handwriting, drop

Table 13.2 Red flags for Wilson disease

System	Warning symptoms/findings
Neurological	Dysarthria
	Change in handwriting
	Clumsiness
	Difficulty in walking
	Dropping grades at school
	Depression
	Emotional liability
	Aggressive/unruly behavior in school, home, or work
	Hypersexuality
	Running amok
Liver	Incidental unexplained abnormalities on liver function tests
	Unexplained fleeting jaundice
	Repeated jaundice
	Easy bruising
	Unexplained pruritus
	Unexplained anemia
	Unexplained thrombocytopenia
	Liver cirrhosis on ultrasound during episode of acute jaundice
Osseomuscular symptoms	Proximal lower-limb muscle weakness
	Bone pains (dismissed as "growing pains")
	Fleeting arthralgia (ankle, knee, wrist, and elbow)
	Unexplained monoarthritis
	Unexplained limp
	Unexplained fracture
	Back pain
	Joint pain and swelling

Continued

Table 13.2 Red flags for Wilson disease—cont'd

Eye	Incidental diagnosis of Kayser–Fleischer rings (astute optometrist!)
Family history	Wilson disease
	Unexplained liver or neurological disease in family
	Unexplained death in family
General complaints	Unexplained weight loss
	Weight gain (from ascites)
	Failure to thrive
	Menstrual abnormalities in girls

in grades at school, irritability, or recurrent joint pain and swelling. Occasionally, abrupt catastrophic hemolysis and acute liver failure herald the disease, with little time for therapeutic intervention (Scheinberg & Sternlieb, 1984; Taly, Meenakshi-Sundaram, Sinha, Swamy, & Arunodaya, 2007).

4.2. Neurological (extrapyramidal) manifestations

Neurological (motor) manifestations are the most frequent initial symptoms of WD and seen in 40–60% of the patients (Dastur, Manghani, & Wadia, 1968; Scheinberg & Sternlieb, 1984; Taly et al., 2007). Involuntary movements are a common manifestation of WD and are often associated with early onset midline symptoms of dysarthria, dysphagia, and poor axial motor control. It is uncommon for a child with WD to develop marked limb dystonia but have a normal speech and gait. Dysarthria is the most common neurological feature of WD. Of the 100 consecutive patients with WD presenting with neurological symptoms, and seen between 2009 and 2013 at the Wilson Disease Clinic at KDAH, Mumbai, India, 90% had speech involvement. Dysarthria is multifactorial and in most patients it is difficult to delineate the exact neurological mechanism(s) contributing to the dysarthria. Dystonia involving tongue and facial muscles can produce profound dysarthria, while cerebellar involvement can lead to a scanning and explosive quality to speech. Muscular rigidity leads to low-volume speech with inadequate tongue movement and imprecise articulation. In patients with severe neurological disabilty, mutism is common. Decoppering improves dysarthria, though in severely affected patients, the recovery may not be complete (Aggarwal, Nagral, Jankharia, Aggarwal, & Bhatt, 2009). Another frequent midline symptom seen in patients with

WD is dysphagia. Patients with severe neurological disability often require gastric tube feeding for weeks to months.

There are two signs characteristically associated with WD—Wilson facies and KF rings. Wilson facies were described by Wilson in his original publication (Wilson, 1912). They are characterized by a facetious (false) smile, pseudo-laughter, open mouth and drooling saliva, reduced eye blinking, exploratory eye movements, and a dull look (Aggarwal et al., 2009) (Fig. 13.1). Wilson facies give patients with WD a characteristic facial feature, so much so, that they start resembling each other (Fig. 13.1). The "rire spasmodique" of Boudin & Pepin (1959) was described as a fixed smile with open mouth and with a high-pitched cry. To an observant clinician, limb dystonia or a movement disorder with characteristic Wilson facies can be an important diagnostic due to WD. Improvement in WD

Figure 13.1 Collage of Wilson disease patients' facies demonstrating the typical Wilson facies—a diagnostic clinical sign of Wilson disease. As seen in the picture, Wilson facies are characterized by factitious smile, pseudo-laughter, open mouth, dull look, and staring expression in variable combination. The figure also demonstrates hand, nuchal, and truncal dystonia in some of the patients. The patients shown in the picture resemble each other though they carry different Wilson disease-related mutations. With copper chelation, the facies normalize.

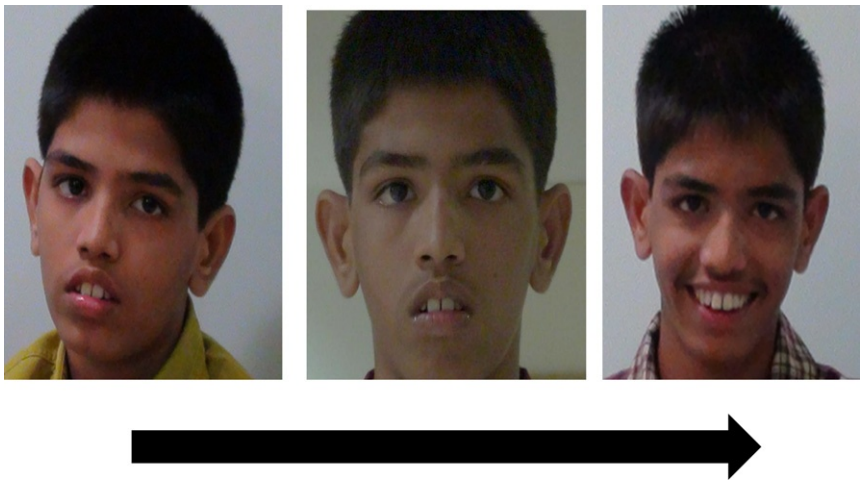

Figure 13.2 Improvement in Wilson facies over 18 months of decoppering.

facies is the earliest clinical sign of treatment (decoppering) response. Wilson facies can be graded as part of the Global Assessment Scale for WD and tracked to monitor decoppering response (Aggarwal et al., 2009) (Fig. 13.2).

In early 1900s, two ophthalmologists, Kayser and Fleischer, independently described the presence of corneal pigmentation in patients with pseudosclerosis (Walshe, 2006). Later, the rings were reported to represent copper deposition. KF rings are copper deposits in the corneal Descemet's membrane, visible as greenish discoloration at the outer corneal circumference. They first appear in the upper corneal limbus, followed by the lower limbus, and then form a complete ring that expands centripetally. KF rings can be seen using a torchlight directed tangentially at the cornea; however, early rings require slit lamp examination. The rings do not impair vision and with decoppering they clear in a sequence opposite to their deposition. Upto 95% of patients with neurologic symptoms and 44–62% of those with liver involvement have KF rings. (Scheinberg & Sternlieb, 1984). Extraocular movement abnormalities are rare and possibly secondary to copper deposition in the midbrain (Scheinberg & Sternlieb, 1984).

A whole range of movement disorders are seen in patients with WD. Patients usually have a mixed movemnt disorder. Four overlapping movement disorder syndromes are commonly recognized (see Pfeiffer, 2011):

1. Dystonic syndrome
2. Postural and action tremor with ataxia and titubation—pseudosclerosis form

3. Akinetic rigid syndrome (parkinsonism)
4. Choriform syndrome

The dystonic and the pseudosclerotic (cerebellar) phenotypes are the most commonly observed. Walsh and Yealland (1992) recorded the onset of WD in 136 patients between 1955 and 1987. Forty-five percent presented with parkinsonism, 32% with pseudosclerotic form, 15% with dystonic type, and 11% with chorea. The profile of neurological impairment observed in a patient cohort seen at the Wilson Disease Clinic, KDAH, Mumbai, India, is detailed in Table 13.3. Dystonia was the most common movement disorder and it was often associated with dystonic tremor and parkinsonism.

Early in the disease, dystonia may be limited to a limb, but if untreated, it invariably becomes generalized. As indicated earlier, speech involvement is an early feature. Interestingly, unlike neurodegeneration with brain iron accumulation, WD is not associated with opisthotonus posturing (Stamelou et al., 2013). Tremor in WD may be resting, postural, or intentional. The pseudosclerotic form is characterized by a typical proximal

Table 13.3 Profile of neurological impairment at diagnosis in 100 symptomatic patients with WD

Neurological feature	% of patients affected
Wilson facies	90.16
Scholastic backwardness	72.13
Depression	22.95
Psychosis	68.85
Dystonia	93.44
Tremor	45.90
Chorea	11.47
Parkinsonism	57.37
Speech impairment	91.80
Swallowing impairment	42.62
Salivation	55.73
Axial	68.85
Kayser–Fleischer rings	85.24

The initial symptom in all patients was neurological. Patients were seen at the Wilson Disease Clinic at KDAH, Mumbai, India, 2009–2013.

wing-beating tremor. Head tremor and isolated tongue tremor are described. Other movement disorders like chorea, myoclonus, and ataxia are infrequent (Prashanth, Taly, Sinha, Arunodaya, & Swamy, 2004; Walsh and Yealland, 1992). There may be regional differences in the WD phenotype. For instance, WD mutations frequent in western India were associated with earlier-onset disease and more severe phenotype than that described with the p.H1069Q mutation, the mutation most frequent in Europe and North America (Aggarwal et al., 2013).

Untreated WD patients continue to deteriorate, and subtle symptoms of dysarthria, behavior abnormalities, and facetious smiles give way to disabling movement disorders. Patients become progressively mute, have difficulty with axial balance, are prone to falls, and soon become bedbound. Without treatment, patients can deteriorate further and die from complications of being bedridden. If, however, decoppering is initiated, the outcomes can be very heartening. Bedbound patients can recover and resume normal life though it may take 1-3 years of judicious decoppering to reverse severe neurological disability. (Aggarwal & Bhatt, 2012).

4.3. Behavioral and cognitive problems

Neuropsychiatric manifestations are described in 20–70% of patients of WD. These may be innocuous or overlooked in the presence of severe extrapyramidal affection. Neuropsychiatric problems maybe the initial symptoms of WD or develop over time. Behavioral or cognitive problems are often ignored in children or attributed to schizophrenia or other primary psychiatric disorders. Neuroleptics are often prescribed, and if an extrapyramidal syndrome develops, it is attributed to neuroleptic related adverse effect (Scheinberg & Sternlieb, 1984; Walshe & Yealland, 1992).

Parents and school teachers are the first to observe subtle changes, like irritability, distractibility, and dropping scholastic performance. Wilson facies correlate with cognitive impairment and improve with decoppering (Fig. 13.2). Cognitive problems can continue for 6–12 months before other symptoms emerge. Aggression, reckless behavior, motor restlessness, running amok, emotional labiality, childlike behavior, impulse control disorders, and hypersexuality are common and different from positive symptoms observed in psychosis from schizophrenia. Antisocial behaviors can cause conflicts with law and lead to great anguish and unhappiness among family members. Expulsion from school or work is not uncommon.

Some of these children need hospitalization and neuroleptics for symptomatic relief. Suicidal attempts are reported (Aggarwal & Bhatt, 2008, Scheinberg & Sternlieb, 1984).

Aggarwal et al. (2009) reported patients with WD who were mute and bedbound at the start of treatment and developed severe psychosis in tandem with recovery of their motor function. The authors hypothesized that in these patients, psychosis was masked by mutism and severe motor disability and manifested once motor function improved. They called this phenomenon as emergent psychosis. Unlike neurological deterioration precipitated by sudden copper chelation, patients with emergent psychosis benefited from continued decoppering. On the contrary, WD patients with serious psychosis, if untreated, eventually developed severe motor disability and mutism that masked their psychosis, a phenomenon termed as concealed psychosis (Aggarwal & Bhatt, 2008; Walshe, 1989; Walshe & Dixon, 1986).

4.4. Hepatic manifestations

Liver failure is the most frequent presenting symptom of WD, and 40–50% of the patients present with liver dysfunction (Scheinberg & Sternlieb, 1984; Walshe, 1962). Symptoms of liver failure generally develop in first two decades but there are wide variations with the youngest reported patient being 2 years old, while the oldest was 74 years old (Pfeiffer, 2011, Czlonkowska, Rodo, & Gromadzka, 2008). Patients with initial liver symptoms present almost a decade earlier than those with initial neurological manifestations. Interestingly, patients with initial neurological disability often have a silent or overt liver disease (Aggarwal et al., 2013; Scheinberg & Sternlieb, 1984). This is not surprising as the liver is the primary target organ for copper deposition, and neurological manifestations likely occur once the liver can no longer accommodate any more copper and this excessive copper spills into the systemic circulation (Pfeiffer, 2011).

The most common mode of hepatic presentation is chronic silent cirrhosis with gradual decompensation from progressive portal hypertension and its complication. Acute viral hepatitis-like symptoms may occur, but there is usually evidence of chronic liver disease (thrombocytopenia or hemolytic anemia from hypersplenism, or cirrhosis on ultrasound) (Scheinberg & Sternlieb, 1984). Hepatitis is often associated with acute rise in serum ceruloplasmin, so a normal ceruloplasmin should be interpreted carefully. Autoimmune-like hepatic presentation is seen in a third of patients

presenting with WD-related liver manifestations, and some respond to immunosuppressants leading to diagnostic confusion (Schilsky, Scheinberg, & Sternlieb, 1991; Sternlieb & Scheinberg, 1972).

The most fearsome manifestation of WD is fulminant hepatic failure and is seen in ~5% of the patients. This is rapidly progressive and invariably fatal unless liver transplant can be performed (Catana & Medici, 2012). Pathologically, most patients have evidence of silent cirrhosis though often not recognized antemortem (Korman et al., 2008). Diagnosis of WD in patients with fulminant hepatic failure is difficult. Urine collection for copper estimation is difficult due to hepatorenal syndrome, while liver biopsy is risky in face of coagulopathy. Further, liver copper and serum ceruloplasmin may be falsely elevated. Clues to diagnosis of WD are evidence of underlying cirrhosis, Coombs-negative hemolysis, and serum copper levels greater than 200 mg/dl (due to massive release of copper from the liver into the circulation) (Roberts & Schilsky, 2008). Unlike in acute fulminant viral hepatitis, in WD, the alkaline phosphates and aminotransferase levels are disproportionately low, while total bilirubin is disproportionately high due to concomitant rise of indirect bilirubin from copper induced hemolysis (Korman et al., 2008; Roberts & Schilsky, 2008).

It is recommended that WD be considered in all children with autoimmune hepatitis and in all adults with atypical autoimmune hepatitis or nonalcoholic steatohepatitis. Further, WD should be suspected in any patient presenting with acute hepatic failure associated with Coombs-negative intravascular hemolysis, modest elevations in serum aminotransferases, or low serum alkaline phosphatase with an alkaline phosphatase to bilirubin ratio of <2 (Roberts & Schilsky, 2008).

4.5. Hematological manifestations

Coombs-negative hemolytic anemia from copper toxicosis and unexplained thrombocytopenia, leucopenia, or pancytopenia from hypersplenism should alert the physician to the possibility of WD (Scheinberg & Sternlieb, 1984).

4.6. Osseomuscular manifestations

Bone and joint involvement (unrelated to penicillamine use) is a common though underrecognized feature of WD (Dastur et al., 1968; Golding & Walshe, 1977). Usually, osseomuscular symptoms are not volunteered, ignored as growing bone pains, or attributed to inadvertent injury. Osseomuscular abnormalities can be the presenting features or evolve later

in the course of WD and are reported in up to 88% of the patients. The spectrum of involvement includes asymptomatic radiological abnormalities, fleeting joint pains, painful mono- or oligoarthropathy or spondylopathy, and nontraumatic fractures. Usually, large joints, like elbow, wrist, knees, and ankles are affected, but small joint pains can also be involved. The mechanism of joint involvement in WD is not clear (Aggarwal, Jankharia, & Bhatt, 2008; Golding & Walshe, 1977). Presence of osseomuscular symptoms in a person with liver or neurological impairment should alert the clinician to the diagnosis of WD.

5. DIAGNOSIS

WD is a multisystemic disease affecting the liver, brain, and osseomuscular system in varying combination with protean clinical manifestations (Dastur et al., 1968; Gill, Shankaran, & Desai, 1994; Taly et al., 2007, Walshe, 1962). A clinician is unlikely to see more than one patient in a lifetime of practice and no two WD patients are alike (Weiner & Lang, 1989). In a study cohort, patients consulted on an average of six doctors including specialists (range 2–11) before WD was diagnosed, contributing to a mean diagnostic delay of 2 years (Aggarwal et al., 2009). It is not unusual for families to have lost one or more child before WD is diagnosed in a younger sibling. In the posttreatment era, diagnostic failure has been the principal cause of death in WD (Członkowska, Tarnacka, Litwin, Gajda, & Rodo, 2005; Prashanth et al., 2004; Walshe, 2007). Maintaining a high degree of suspicion is the key to early diagnosis. Unexplained jaundice, alterations in liver function tests, neurological symptoms and osseomuscular problems, in a child or young adult should prompt consideration of WD (Table 13.2). Siblings of all patients with WD should be screened for the disease and kept under surveillance till adulthood unless WD is definitely ruled out by genetic analysis.

Genetic analysis is the gold standard for diagnosis of WD but has remained an impractical diagnostic tool as there are over 600 WD mutations described and many new continue to be reported. One or more disease-causing genes cannot be identified in 20% of the patients with clinically definite WD (Schmidt, 2009). This number of mutation-negative patients is likely to decrease with the ability to rapidly sequence and screen the whole *ATP7B* gene for WD mutations (Aggarwal et al., 2013; Coffey et al., 2013). While identification of WD mutations confirms WD, inability to find mutations does not conclusively exclude the disease. Recent studies from various parts of the world suggest that despite there being considerable genetic

heterogeneity in various populations, a single or few *ATP7B* mutations may account for WD in a majority of patients in a given cohort (Table 13.1). Various research groups are therefore working on developing DNA chips targeting population-specific mutations to allow for rapid diagnosis of WD in that particular population. If WD mutations are identified in a patient, all of the patient's siblings should be screened for them.

Presently, diagnosis of WD is based on the combination of clinical features and laboratory tests. The presence of family history of WD, Wilson facies, and KF rings are important clinical clues for diagnosing WD. Constellation of neurological symptoms (extrapyramidal and behavioral problems), liver disease, and osseomuscular affection in young adults is uncommon and if present, it serves as a clinical marker of WD. Neurological symptoms are usually volunteered, but parents should be quizzed about subtle and often forgotten episodes of fleeting jaundice, incidental finding of raised liver enzymes, or innocuous features of osseomuscular involvement (Table 13.2). Diagnosis of WD in patients presenting with extrapyramidal syndrome or behavioral problems is usually straightforward and aided by the presence of KF rings, Wilson facies, abnormalities on brain scan, and clinical or subclinical liver disease. However, presymptomatic patients and those with pure liver disease often pose a diagnostic dilemma and necessitate careful consideration.

Serum ceruloplasmin, 24-h urinary copper excretion, liver function tests, brain imaging, and in select cases liver biopsy help establish the diagnosis of WD. Each of these tests has confounding features and test results need to be interpreted with caution (Table 13.4). Serum (total) copper or indices like serum non-ceruloplasmin-bound (free) copper (derived by simultaneous measurement of serum copper and serum ceruloplasmin levels) (Roberts & Schilsky, 2008) are difficult to measure reliably, may not reflect total body copper content, and may be confusing to interpret (Mak & Lam, 2008). Urine copper exertion measurement after penicillamine challenge has been standardized only for the pediatric population (Martins da Costa et al., 1992). Moreover, it is contentious if the penicillamine challenge adds to the diagnostic yield of basal urinary copper excretion (Gaffney, Fell, & O'Reilly, 2000; Scheinberg & Sternlieb, 1984). Measurement of incorporation of radioactive copper in ceruloplasmin is a research tool. Diagnostic algorithms proposed by American Association for Study of Liver Diseases (AASLD) (Roberts & Schilsky, 2008) and Ferenci's scoring (Ferenci et al., 2003) are useful in guiding investigations and interpreting test results.

Table 13.4 Diagnostic tests for WD and clues in interpretation of test results (Roberts and Schilsky, 2008; Scheinberg & Sternlieb, 1984)

Investigation	Value/finding supporting diagnosis of WD	Confounders		Precautions and test interpretation	Screening siblings
		False-positive results	False-negative results		
Kayser–Fleischer rings KF rings	Present	• Chronic cholestatic liver • Copper foreign body in eye	• 38–56% patients with WD-related liver disease • 5% patients with WD-related neurological disease	• Examination best done by experienced ophthalmologist/clinician • Can be viewed by torchlight shinned tangentially on the cornea • Early rings require slit lamp examination • Taking a picture of KF rings helps reconfirm their presence and track treatment response	If present in a normal sibling, confirms WD
Wilson facies	Present		• Absent in patients with pure liver involvement from WD • 5% patients with WD-related neurological disease		Cannot use as sole screening test to diagnose WD

Continued

Table 13.4 Diagnostic tests for WD and clues in interpretation of test results (Roberts and Schilsky, 2008; Scheinberg & Sternlieb, 1984)—cont'd

Investigation	Value/finding supporting diagnosis of WD	Confounders		Precautions and test interpretation	Screening siblings
		False-positive results	False-negative results		
Serum ceruloplasmin	<50 mg/L	• 20% of heterozygotes (people with 1 *ATP7B* mutation and 1 normal *ATP7B* allele) • Values are normally low till up to 6 months of age • Conditions of protein loss (renal, enteric, nutritional, etc.) • Menkes disease • Absent in aceruloplasminemia	• 5–15% of WD • Acute inflammation • Hyperestrogenemia like pregnancy, estrogen supplements, or treatment	• Can be evaluated enzymatically by their copper-dependent oxidase activity toward these substrates, or immunologic assays. Immunologic assays use may overestimate ceruloplasmin concentrations because they do not discriminate between apoceruloplasmin and holoceruloplasmin. Modestly low values need further investigation • Normal values do not exclude WD	Cannot use as sole screening test to diagnose WD

Basal 24-h urinary copper	>100 μg of copper/ 24 h	• Autoimmune hepatitis • Primary sclerosing cholangitis • Acute liver failure • Chronic active liver disease	• Ensure 24-h urinary collection • Avoid contamination with tap water • Measurement of 24-h urine volume and total creatinine excretion in the sample help assess completeness of urine sample collection	Cannot use as sole screening test to diagnose WD
Hepatic parenchymal copper	Copper content of 250 μg/g dry weight of liver. This is the best biochemical evidence of WD	Distribution of copper in liver is uneven	• Liver biopsy has a small but definite risk of complication, therefore it is reserved for symptomatic patients in whom simpler & safer tests have not helped establish definite diagnosis of WD. • Use disposable suction or cutting needle for liver biopsy and place	Not recommended

Continued

Table 13.4 Diagnostic tests for WD and clues in interpretation of test results (Roberts and Schilsky, 2008; Scheinberg & Sternlieb, 1984)—cont'd

Investigation	Value/finding supporting diagnosis of WD	Confounders		Precautions and test interpretation	Screening siblings
		False-positive results	False-negative results		
				sample in copper-free container • Ensure adequate specimen (1–2 cm core recommended) • Copper content of <40–50 μg/g dry weight in untreated patients rules out WD • Transjugular liver biopsy is preferred if coagulopathy is a concern • Values (copper content of <70–250 μg/g dry weight of the liver): further testing is necessitated especially if there is active liver disease or other features of WD	

MRI brain in patients with neurological symptoms	Symmetrical hypersensitivities in the basal ganglion and brain stem on MRI T2W and FLAIR sequences	Leigh's disease, hypoxic ischemic encephalopathy, Japanese B encephalitis, methyl alcohol poisoning, osmotic disequilibrium syndrome, glutaric academia	MRI may be normal in patients with WD with neurological symptoms	MRI brain is preferred brain imaging MRI abnormalities may be seen before onset of neurological symptoms	Not recommended for screening

6. TREATMENT

WD is an inherited disorder of chronic copper toxicosis and is invariably fatal if not treated (Scheinberg & Sternlieb, 1984). The goal of WD treatment is decoppering with clinical tracking and this needs to be continued lifelong.

Copper starts accumulating in excessive amounts after birth, being sequestered initially in the liver and later spilling into brain and other body tissues. Symptoms from brain or liver failure usually occur with in the first two decades of life, and the disease progresses rapidly unless decoppering is initiated. Presymptomatic patients, (those who have WD mutations but as yet have not developed symptoms), become ill over time, unless copper accumulation is halted. All symptomatic and all presymptomatic patients require lifelong decoppering (Sternlieb & Scheinberg, 1968). Individuals heterozygous for WD mutation (one mutated and one normal *ATP7B* genes) have normal copper metabolism and do not necessitate treatment or monitoring.

Decoppering ensures that presymptomatic individuals remain symptom free. With judicious decoppering, given time, even patients with severe neurological disability improve and can return to normal life and resume school or work at par with their peers (Aggarwal & Bhatt, 2012; Scheinberg & Sternlieb, 1984, 1995; Walshe, 1989; Walshe & Dixon, 1986). Improvement and reversal of brain imaging abnormalities follow adequate decoppering (Aggarwal & Bhatt, 2012) (Fig. 13.3). KF rings and sunflower cataracts disappear. Liver failure stabilizes and is associated with clinical, biochemical, and histological improvement (Scheinberg & Sternlieb, 1984).

BAL was the first drug demonstrated to chelate copper in patients with WD (Cumings, 1951, Denny Brown & Porter, 1951) This was a major breakthrough and earned WD the distinction of being the first neurometabolic disease that could be treated. A few years later, Walshe conceived that penicillamine, the metabolite of penicillin, excreted in urine, had the requisite molecular structure that could chelate copper. He swallowed 1 g of penicillamine and, having survived 24 h without any ill effects, deemed the drug safe. Subsequent administration of penicillamine to patients with WD led to expected cupriuresis and clinical improvement. Introduction of penicillamine and later trientine as oral decoppering drugs, by Walshe, forever changed the natural history of the disease (Walshe, 2009).

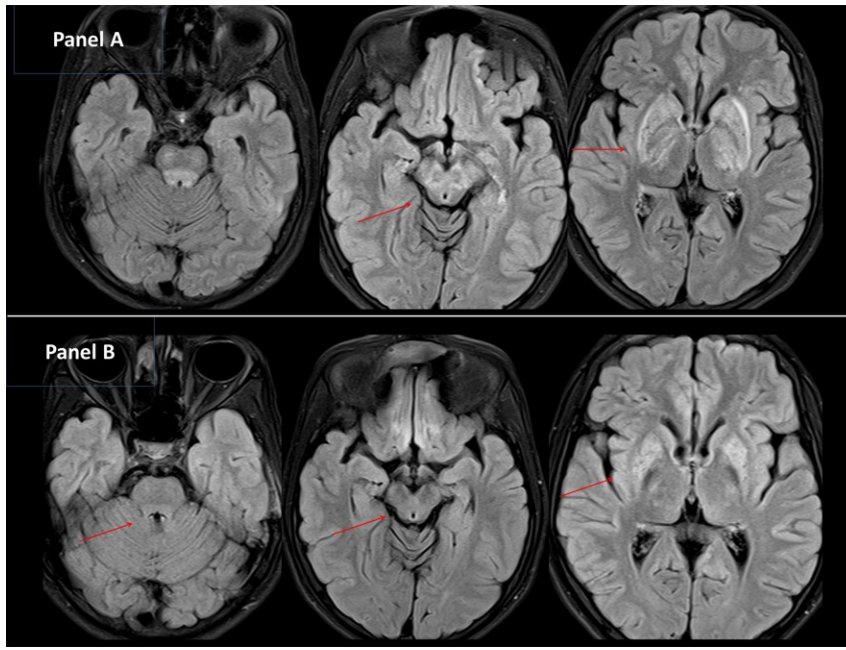

Figure 13.3 (A) Brain MRI of patient with Wilson disease shown in Fig. 13.2. The MRI demonstrates symmetrical hyperintensities on FLAIR-weighted images in the pons, midbrain, and basal ganglia (caudate, putamen, and globus pallidus). (B) Serial scan after 18 months of decoppering shows decrease in FLAIR hyperintensities, associated with atrophy of the caudate and putamen nuclei.

Copper is ubiquitous in water and food, and dietary restrictions are neither essential nor sufficient to prevent copper overload. In symptomatic patients, foods with high concentrations of copper, like shellfish, nuts, chocolate, mushrooms, and organ meats, should be avoided, for the first few years of initiation of decoppering. Once symptoms regress (indicating adequate decoppering), these dietary restrictions can be relaxed. Copper content of most municipal drinking water supplies is low and need not be tested (Pfeiffer, 2011; Roberts & Schilsky, 2008). In general, copper levels of 0.1 ppm in drinking water should prompt use of bottled or boiled water (Brewer et al., 2001). Domestic water softeners increase copper content of water (Yarze, Martin, Muñoz, & Friedman, 1992). Copper-containing vitamins or supplements should be avoided.

Globally, the largest experience of WD treatment is with penicillamine. It continues to be the most extensively used decoppering drug for WD, due to its wide availability and low cost. In much of the developing world,

penicillamine is the only copper chelator available. Presently, trientine is available only in the United States and the United Kingdom; other countries need to import the drug. Trientine's relatively short shelf life and the need to store the drug in cool temperatures pose a problem in warm regions and add to the cost of therapy. Ammonium tetrathiomolybdate is an experimental drug and is not easily available (Pfeiffer, 2011; Roberts & Schilsky, 2008).

Penicillamine (dimethyl cysteine) is an avid copper chelator and the gold standard for treatment of WD. It is recommended for treatment of symptomatic and presymptomatic patients. Penicillamine should be administered on an empty stomach as food decreases the bioavailability of penicillamine by 50%. The drug is usually given in two or three divided doses to ensure compliance with fasting. It is best to supervise drug intake in children till they are older and symptom free and can be trusted to take the medication unsupervised. The aim of treatment with decoppering is to start slow and go slow. Penicillamine is initiated at doses of 125–250 mg per day. Dosage is gradually increased every 2–3 weeks by 125–250 mg, up to 1–3 g/day, under close clinical monitoring (see succeeding text). Clinical improvement is seen after few months of initiation of treatment. Patients with severe disability may require 2–3 years of decoppering to normalize. Once the positive copper balance in the body has been chelated, doses of the decoppering drugs can be reduced and patients can be maintained on a maintenance phase. Daily doses of penicillamine may be reduced to 250–750 mg in the maintenance phase. Penicillamine is a pyridoxine antagonist and 20 mg of pyridoxine should be supplemented. Other metal supplements should be avoided while patients are on penicillamine. Normal pregnancies are reported while on penicillamine (Scheinberg & Sternlieb, 1984).

Penicillamine-induced neurological worsening is seen in up to 10% of the patients and can resolve with downtitration of the drug followed by slower uptitration with close clinical monitoring (see succeeding text).

Hypersensitivity reactions occur 10–20% patients, within the first few weeks to months of commencing penicillamine. However, the incidence is much lower, if penicillamine is initiated gradually. The reactions include fever, rash, and lymphadenopathy, and usually. Resolve with short-course steroids. Penicillamine should be preferably discontinued. Once the hypersensitivity reaction has resolved, penicillamine may be reintroduced or substituted by trientine. Most patients with WD have thrombocytopenia (or uncommonly) concomitant leucopenia and anemia, from hypersplenism (liver cirrhosis). Rarely, platelet and leucocyte count may drop further as a hypersensitivity reaction to penicillamine, but these recover by

downtitrating the penicillamine dose and a short-course of steroids. Late reactions are observed after years of penicillamine therapy. These include drug-induced systemic lupus erythematosus, nephrotic syndrome, Goodpasture's nephritis, hemolytic anemia, and thrombocytopenia. Symptoms of lupus and proteinuria from nephropathy resolve with steroids and penicillamine withdrawal. An alternative decoppering drug should be substituted and rechallenge with penicillamine is best avoided. There are case reports of myasthenia gravis and optic neuritis following penicillamine use. Long-term use of penicillamine may also lead to easy bruising or recurrent subcutaneous bleeding due to penicillamine-induced inhibition of collagen and elastin cross-linking. Elastosis perforans serpiginosa, pemphigus, and aphthous stomatitis are rare (Scheinberg & Sternlieb, 1984; Walshe, 2009).

Trientine (triethylene teramine dihydrochloride) was introduced by Walshe in 1968 as an alternative to penicillamine. It is designated as an orphan drug and approved by FDA for treatment of penicillamine-intolerant patients with WD. Trientine likely leads to less cupriuresis compared to penicillamine, but its continued administration is therapeutically effective (Walshe, 1973, 1982). Being a gentler chelator, trientine is less likely to lead to neurological deterioration following initiation of treatment.

Trientine has a polyamine-like structure, and copper is chelated by forming a stable complex with the four constituent nitrogen atoms in a planar ring. It lacks a sulfhydryl group and is therefore, possibly less immunogenic. Trientine has a poor gastric abortion; most of the absorbed drug is metabolized and only a small percentage is excreted in urine (Roberts & Schilsky, 2008; Walshe, 1973).

Trientine is useful in patients intolerant to penicillamine and those with renal or autoimmune disease. It is also an attractive initial therapy for the initial treatment for symptomatic WD, given its gentler chelation and less likelihood to cause neurological deterioration. Trientine has also been used as initial therapy in patients with decompensated liver disease.

Trientine has lesser adverse effects than penicillamine, and long-term use in penicillamine-intolerant patients is safe. Penicillamine-induced systemic lupus erythematosus and elastosis perforans serpiginosa can be reactivated following substitution of penicillamine with trientine (Walshe, 1982). *De novo* hypersensitivity reactions and lupus without prior penicillamine use have not been described. Neurological worsening is described with trientine but is likely less frequent than with penicillamine. Trientine-induced copper deficiency has led to reversible sideroblastic anemia and iron overload in the liver (Roberts & Schilsky, 2008). Normal

pregnancies are reported in patients on treatment with trientine. Ingestion of 30 g of trientine, in a suicidal attempt, did not lead to apparent ill effects (Scheinberg & Sternlieb, 1984).

Doses of 750–2000 mg/day of trientine in 2–3 divided doses, are typical and may be reduced to 750–1500 mg/day in the maintenance phase. Doses are titrated as for penicillamine. The drug is best administered fasting. Coadministration of iron supplements should be avoided as trientine chelates iron and forms toxic complexes with iron.

BAL (dimercaprol) is no longer used for treatment of WD but may have application in ill patients who are intolerant to oral decoppering drugs. BAL is administered admixed peanut oil as deep intramuscular injections. The injections are painful, associated with waning decoppering effect and high incidence of adverse effects (Walshe, 2009; Walshe & Munro, 1995).

Zinc inhibits intestinal absorption of copper, by inducing metallothionein, a cysteine-rich protein present in many tissues including intestine, liver, and brain. Oral zinc is absorbed by the enterocytes and bound to the induced metallothionein, trapping the metal within the enterocytes. The metallothionein has a higher affinity for copper than for zinc and sequesters dietary copper, preventing its absorption into the portal circulation. The bound zinc and copper are stored in the enterocytes and excreted in feces when the cells are sloughed. Reabsorption of copper secreted in the salivary and gastric circulation is similarly impaired resulting in a mild negative copper balance. Zinc-induced metallothionein in hepatocytes may be beneficial in liver disease (Lee, Northup, & Berg, 2006; Marcellini et al., 2005).

Zinc does not chelate copper stored in the body. The negative cooper balance induced by zinc-mediated impairment of copper absorption is too small for zinc to be an effective as monotherapy in symptomatic patients (Scheinberg & Sternlieb, 1984). Neurological and hepatic deterioration, with fatal outcome, has been reported following use of zinc in symptomatic individuals (Lang, Rabas-Kolominsky, Engelhardt, Kobras, & Konig, 1993; Walshe & Munro, 1995). Zinc has been used as monotherapy in presymptomatic individuals, who have been diagnosed with WD but do not yet have any symptoms (Marcellini et al., 2005). It has also been used as "maintenance therapy" in patients who have been decoppered with penicillamine or trientine (Brewer et al., 1998, Sinha & Taly, 2008). Hepatitis and emergence of symptoms have occurred following institution of zinc in presymptomatic patients (Castilla-Higuero, Romero-Gomez, Suarez, &

Castro, 2000; Mishra, Kalra, & Seth, 2008). Caution should be exercised in using zinc, and any evidence of clinical deterioration should prompt replacement of zinc with a decoppering drug (penicillamine/trientine) (Subramanian, Vanek, & Bronstein, 2002).

Zinc is administered as acetate, sulfate, or gluconate salts. Dosing is based on the amount of elemental zinc present in the formulation and should be given fasting. Doses of 50 mg three times a day are typical. It is generally well tolerated with few serious adverse effects and is safe for use during pregnancy. Gastric irritation is common and a dose-limiting adverse effect. Zinc acetate is better tolerated than zinc sulfate. Zinc can rarely lead to sideroblastic anemia. Zinc has not been associated with neurological worsening (Roberts & Schilsky, 2008).

Symptomatic treatment with levodopa–carbidopa, anticholinergics, dopamine blockers, neuroleptics, and targeted botulinum toxin injections has been shown to benefit some patients with WD.

A dreaded complication of WD is fulminant liver failure. This has 100% mortality unless patients can receive a liver transplant. The role of liver transplant in patients with WD-related neurological disability is not yet well defined. Following liver transplant, biliary copper excretion is normalized, and patients no longer require decoppering therapy (Catana & Medici, 2012, Pfeiffer, 2011). Neurological worsening is described following liver transplant, possibly from massive mobilization from the native liver during operation (Litwin, Gromadzka, & Czlonkowska, 2008).

7. TRACKING WD

There are numerous deeply entrenched myths among clinicians about problems encountered in treating WD and expected outcomes (Table 13.5). It is well established that WD is treatable, but so profound is the fear of neurological worsening and drug-related adverse effects that many a clinician are hesitant in administering decoppering drugs in recommended doses and often withdraw treatment at first sign of clinical worsening. Therefore, it cannot be emphasized enough that WD is treatable and WD-related neurological disability is reversible. Following decoppering, liver impairment also stabilize. Inadequate treatment or noncompliance leads to progressive increase in positive copper balance in the body, worsening symptoms, and, if unchecked, death. Decoppering is best titrated with objective clinical monitoring.

Table 13.5 Myths regarding Wilson disease treatment

S. No.	Myth
1	Patients with WD require strict copper-free diets
2	Kayser–Fleisher rings do not regress or resolve with treatment
4	Severe WD-related neurological disability is not reversible
5	Dystonia is not reversible
6	Penicillamine is not a safe drug
7	Neurological worsening with decoppering is permanent or not reversible

Decoppering is a slow process and it takes 1–3 years of aggressive decoppering to remove excessive copper in symptomatic patients. Once adequate decoppering has been achieved, signaled by disappearance of KF rings, neurological recovery, and liver stabilization, patients can be switched to a maintenance phase of decoppering. Maintenance decoppering is aimed at preventing ongoing copper accumulation and reoccurrence of symptoms. Doses of decoppering drugs during the maintenance phase of treatment are much less than those required during the initial decoppering phase (see penicillamine in the preceding text).

Decoppering treatment needs careful titration. Rapid decoppering can lead to neurological worsening from sudden excessive mobilization of copper from liver into blood and thereon into the brain. Too slow, copper chelation increases risk of further clinical deterioration and death.

WD progress and treatment response are best measured by careful clinical assessment. In our WD Clinic, we track patients using the multisystemic, validated WD-specific scale, the Global Assessment Scale for WD (GAS for WD). GAS for WD is a two-tier scale that can be administered by the patient's bedside. Tier 1 measures WD-related disability across four domains: liver (L), cognition and behavior (C), motor (M), and osseomuscular (O). Each domain is scored on an ascending six-point scale (0–5). Tier 2 assesses WD-related neurological dysfunction across 14 items. Each item is graded on an ascending five-point scale (0–4) and summed to obtain the total tier 2 score (0–56) (Aggarwal, 2009).

After initiating treatment, patients are assessed at weekly intervals to track neurological worsening, drug-related adverse effects, and compliance. Decoppering is started at low doses and slowly titrated up (see penicillamine in the preceding text). Generally, no clinical benefit is seen in the first few months of initiation of therapy, though some patients may show

improvement in GAS for WD scores within first 2 weeks. Clinical deterioration while on treatment may represent ongoing disease progression, decoppering-induced neurological worsening, noncompliance, or intercurrent illness. Unlike, ongoing disease progression, drug-induced neurological worsening is reflected by an abrupt change in GAS for WD scores. Once compliance is confirmed, neurological worsening is managed by simply downtitrating the decoppering drug. Once the GAS for WD scores return to baseline, decoppering can again be gradually escalated, albeit at a slower pace. Neurological worsening should be differentiated from the phenomenon of emergent psychosis (see earlier text) (Aggarwal et al., 2009).

Improvement in WD facies is the earliest clinical change, seen within 3–5 months of commencing treatment. Reduction in KF rings is observed only after 8–12 months. Complete neurological recovery may take 12–36 months (Aggarwal, 2009). Once it is assured that the patient is tolerating decoppering drugs well and GAS for WD scores are steadily improving, patients' visits can be spaced out to once in 4–12 weeks. Any clinical worsening should prompt careful assessment for neurological worsening or noncompliance.

After clinical recovery, patients may be switched to a maintenance phase with 6–12 monthly follow-up. Worsening of GAS for WD scores on follow-up or reappearance of KF rings, neurological signs, or biochemical liver derangements should signal noncompliance. Patients should be warned about possibility of rapid clinical deterioration if they are non compliant. (Walshe & Dixon, 1986).

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