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Wilson's disease: A master of disguise

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ABSTRACT

Wilson's disease (WD), in contrast to many neurogenetic metabolic diseases, can be very effectively treated in acute and chronic stages of the disease. However, early recognition is paramount because delays in treatments have much higher risk of unfavorable clinical outcomes. Identification of WD remains challenging because it is a great imitator and requires a high index of suspicion for correct and timely diagnosis. Initial neurologic problems can be seen in approximately 40%–50% of patients and the rest has either hepatic or primarily psychiatric manifestations. Neurologic and neuropsychiatric problems in WD are quite nonspecific and we discuss the most common clinical problems associated with early and late stages of the disease. Many patients with neurologic symptoms do not have any obvious hepatic symptoms. Most common neurologic abnormalities include dysarthria, dystonia, tremor and Parkinsonism. In spite of its phenotypic heterogeneity, laboratory abnormalities, reflecting abnormal copper homeostasis, are very specific and the diagnosis of WD remains laboratory based. We review most important challenges and pitfalls in laboratory evaluation of WD, including emerging role of genetic testing. Pharmacologic treatments need to be life-long and are focused on restoration of negative copper balance without inducing iatrogenic copper deficiency. The gold standard of therapy is chelation of excessive copper. Chelators may induce further clinical deterioration in some treated patients. We also review most promising novel therapeutic approaches that appear to better control non-ceruloplasmin or free copper because elevation of free copper may be responsible for paradoxical neurologic worsening.

1. Introduction

Wilson's disease (WD) is an inherited metabolic disorder caused by biallelic mutations in the *ATP7B* gene [1,2]. The loss of function of copper transporter ATP-ase results in an impaired excretion of copper into the bile and subsequent accumulation of copper in the liver, and later in the brain and other organs [3–5]. Moreover, amassed copper is not incorporated into copper binding proteins, such as ceruloplasmin. Excessive free copper leads to cytotoxic effects in hepatic and central nervous tissues, accounting for the disease phenotypes because WD typically present with hepatic, neurologic or psychiatric problems.

Mutations in the *ATP7B* gene are the only known cause of WD. Carrier frequency is estimated at 1:90 to 1:100 with the disease prevalence between 1:30,000 and 1:40,000, given 25% risk of inheritance of two mutations [6–8]. Several populations with higher prevalence have been identified, such as in Sardinia where the disease frequency is estimated from 1:10,000 to 1:7,000 [9]. More than 600 disease causing mutations have been identified in the *ATP7B* gene [10,11].

2. Clinical presentation of Wilson's disease

Clinical features associated with symptomatic WD are non-specific and highly variable, requiring a high index of suspicion for prompt diagnosis [3–5]. Most patients develop symptoms in adolescence to early adulthood. Neurologic symptoms tend to develop later by approximately one decade than hepatic presentation. However, the age of onset may vary considerably with atypical late onset observed even in the 7th and 8th decades of life, adding significant diagnostic challenge because clinical symptoms are similar to other common, age-related conditions [12–14].

Initial signs and symptoms of WD are hepatic in approximately 40% of patients, neurologic in about 40%–50% and primarily psychiatric manifestation can be seen in about 10% of patients [3–5,15,16]. WD may be also diagnosed in presymptomatic individuals through recommended screening of siblings of affected probands or in asymptomatic individuals when routine laboratory test detects otherwise unexplained abnormalities of liver function panels. Patients presenting with liver disease may range from an asymptomatic state to life-threatening hepatic failure [17,18]. Most patients with hepatic symptoms exhibit signs of chronic liver disease with cirrhosis and

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splenomegaly due to portal hypertension. Hepatic phenotype of WD is frequently associated with Coombs-negative hemolytic anemia [17].

Incipient neurologic symptoms are typically subtle and non-specific. Subjective difficulties in concentration are particularly common [19,20]. Motor symptoms include lack of coordination, handwriting changes, and slurred speech with drooling [15,16]. Somatization or psychogenic condition is often misdiagnosed before the correct diagnosis is reached with potentially catastrophic consequences because of delayed therapy. In untreated patients the course is progressive and more pronounced neurologic abnormalities emerge with dysarthria, dystonia, tremor and parkinsonian manifestations being most common [19–23]. Analysis of heralding WD symptoms confirmed a considerable heterogeneity and the most common initial problem was dysarthria (57.6%), followed by dystonia (42.4%), abnormal gait (37.8%), tremor (36.2%), Parkinsonism (17.3%), choreoathetosis (15.3%), and seizures (4.7%) [19,20]. However, another recent study of newly diagnosed patients showed that most patients (62.3%) exhibited tremor and ataxia, followed by dystonia in 15.1% and parkinsonism in 11.3% patients. Discrete or unclassified signs only were observed in 11.3% of patients, further illustrating considerable clinical heterogeneity of these patients [21].

Even though neurologic presentation is indeed very pleomorphic, WD neurologic phenotype has been grouped into dystonic, pseudosclerotic (tremor), parkinsonian and hyperkinetic (choreic) subtypes [24]. Additional category of dysarthric form has been also suggested but dysarthria is the most constant neurologic sign in WD because almost 90% have some form of speech abnormalities in the course of the disease [19–21].

Dysarthria is often of a mixed type with dystonic and hypokinetic features. Patients with pseudosclerotic subtype may also exhibit signs of cerebellar ataxia and cerebellar dysarthria. However, there is a considerable overlap among these groups and patients with severe WD display very mixed phenotype. Many patients with neurologic symptoms do not have any obvious hepatic symptoms [3–5].

Tremor is another common neurologic sign present in 22%–55% of patients diagnosed with WD [3,4,15,21]. The wing-beating tremor with proximal tremor, appearing when the patient holds semi-flexed outstretched arms has been suggested as a hallmark type of tremor in WD. These patients experience increasing amplitudes with a longer duration of posture holding and this may progress into a severe flapping tremor with large amplitudes. However, many patients exhibit a regular typical postural and action tremor that can be easily confused with essential tremor [5]. Additional very common neurologic finding in symptomatic WD patients is dystonia that is detected in approximately 10%–65% of all patients [4,18–21]. Dystonic symptoms vary from focal to generalized dystonia. Segmental or focal dystonia in craniofacial region is especially very symptomatic with severe dysphonia, dysarthria, risus sardonicus with forced, often exaggerated smile and dysphagia with a complete loss of speech and inability to swallow. Advanced WD may also lead to generalized dystonia, causing debilitating symptoms with secondary skeletal changes and inability to walk [18–21]. Dystonia associated with WD is a prototypical secondary dystonia and hyperkinetic jerks are less common than in idiopathic dystonias. Hypokinetic-rigid syndrome is present in 20–60% of patients who typically present with masked face with hypophonic, soft voice, micrographia and shuffling or freezing gait [18–22]. Parkinsonian symptoms tend to be symmetrical but unilateral tremor can be observed and this needs to be distinguished from idiopathic Parkinson's disease [20,21].

Other neurologic signs are less frequent and rarely present in isolation. Hyperkinetic movements are more common in younger individuals who developed WD in the second decade and up to one fifth of these patients exhibit choreoathetosis [20–24]. Ataxia is another frequently mentioned symptom but a true cerebellar ataxia is rare and incoordination and balance problems are more commonly caused by extrapyramidal symptoms [21]. Tremor in WD may have some cerebellar features with dysmetria and intention tremor. Generalized tonic-clonic seizures have been reported in 6% of patients but they are rarely presenting symptom and may herald paradoxical worsening during the initiation of chelation therapy [24].

The third most common type of presenting symptoms are psychiatric and behavioral symptoms. There is a growing recognition of early occurrence of psychiatric symptoms and up to one thirds of these patients may manifest subtle psychiatric symptoms before developing other clinical problems that lead to the diagnosis of WD [25]. Psychiatric symptoms are also very nonspecific and can range from depression to acute psychotic episodes [26]. Frank psychosis is present in about 10% of these patients and is frequently misdiagnosed as schizophrenia or bipolar disease [27]. Behavioral and personality changes are commonly associated with cognitive changes. The pattern of cognitive decline is similar to other conditions with prominent basal ganglia pathology. Apathy, reduced attention, bradyphrenia, and executive dysfunction with impaired social judgment, and impulse control behavior are now commonly recognized and they represent a significant morbidity for WD patients [28,29]. Overall, approximately half of all patients with manifesting WD have active psychiatric problems [25]. They are usually accompanied by additional neurologic signs but these initial neurologic signs can be very subtle and easily overlooked or attributed to the use of neuroleptics that were used to treat the psychiatric condition. However, clearly some patients, estimated between 10 and 20%, may present with truly isolated psychiatric symptoms without any neurologic or hepatic manifestations [25,27,28].

Other systemic manifestations of WD, including aminoaciduria, nephrolithiasis, arthropathy, premature osteoporosis and cardiomyopathy, are rare and very difficult to recognize as WD without other features of the disease [5]. The most important exemptions to this rule are ophthalmologic features. Even though they are mostly asymptomatic, they may be useful in supporting the diagnosis. They are reviewed in details in the diagnostic tests section.

3. Diagnosis of Wilson's disease

The definite diagnosis of WD can be established only by laboratory assays of impaired copper homeostasis, including increased urinary copper excretion and elevated values of non-ceruloplasmin-bound copper or free copper (NCC) in blood. Suggestive clinical symptoms, as outlined above, should prompt further laboratory testing to confirm or exclude this diagnosis. Two sets of diagnostic algorithms have been published and are widely accepted, including the scoring system for the diagnosis of WD [30,31].

Screening tests are recommended as the first step in the diagnosis of Wilson's disease and serum ceruloplasmin less than 20 mg/dL (1.49 μmol/L) may be consistent with the diagnosis but overall the positive predictive value is very low at 5.9% [32]. Ceruloplasmin is the main copper binding plasma protein with more than 90% of total copper bound to it. However, even low levels cannot conclusively confirm the diagnosis and additional confirmatory tests are needed [30,31]. Ceruloplasmin is also an acute phase reactant and this is a common reason for false negative data that may lead to missed diagnosis of WD. Additional important cause of higher ceruloplasmin is elevated estrogen levels, most commonly induced by birth control pills or estrogen replacement therapy. Abnormally low ceruloplasmin level less than 5 mg/dl (0.37 μmol/L) is strongly suggestive of WD but such a low value can be also found in conditions with very low copper plasma values, especially with copper deficiency and aceruloplasminemia [32]. Neurologic clinical presentation of aceruloplasminemia may mimic WD but the pathogenesis is actually iron overload and other copper laboratory parameters are within normal limits [33]. Another possible cause of low ceruloplasmin is Menke's disease, an X-linked disorder caused by mutations in the *ATP7A* gene [34]. Carriers of one mutated allele of *ATP7B* gene tend to have borderline low values requiring further testing.

Ophthalmologic evaluation is also commonly used screening test

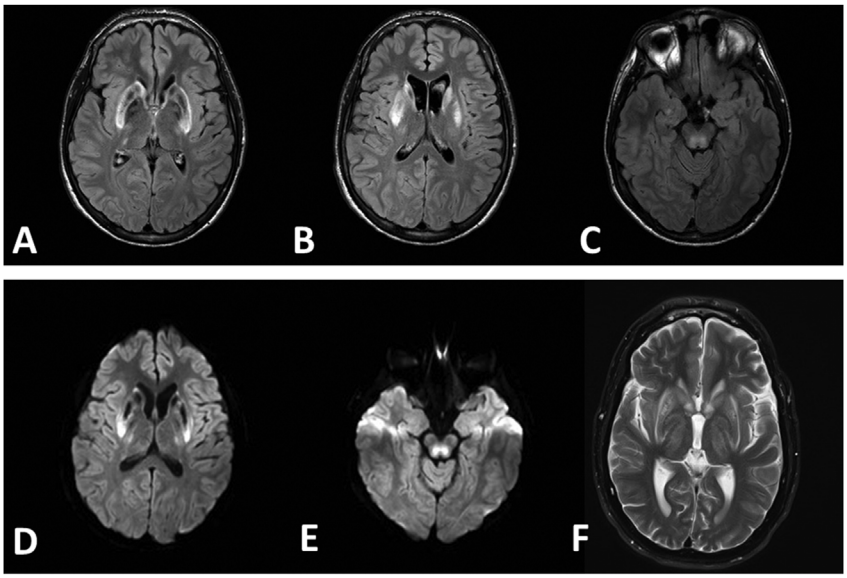

Fig. 1. A–C: MRI study of a 24 year old man showing extensive signal changes in basal ganglia and involving the midbrain (FLAIR sequence) at the time of diagnosis with severe dystonia and parkinsonims. D–E: MRI study of a 20 year old woman with severe worsening after D-penicillamine therapy resulting in mutism and inability to swallow with extensive signal changes in basal ganglia and brainstem (FLAIR sequence). F: Signal changes in basal ganglia in a 19 year old man at the time of diagnosis with severe tremor and dysarthria (T-2 weighted sequence).

[30,31]. The most important findings are Kayser-Fleischer rings that are caused by asymptomatic copper deposition in Descemet's corneal membrane. They may be visible by naked eye 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 position. Definitive detection of Kayser-Fleischer rings should be established using slit lamp examination. This examination can also detect asymptomatic sunflower cataracts that are caused by copper deposits in the lens [35]. The presence of rings can only support the diagnosis because rarely they can be seen in patients with chronic cholestasis. Additionally, they may be absent in some fully symptomatic patients and almost half of patients with an isolated liver disease does not have fully formed rings [36]. Their absence is rare in patients with neurologic presentation and only about 10% of these patients have a normal slit lamp examination [16]. Copper deposits in the cornea and the lens disappear with chelation but there is no correlation between their presence and the severity of clinical deficits [30].

24-h urine copper assay can confirm the diagnosis of WD in patients with neurologic symptoms who typically do not have advanced obstructive hepatopathy [30,31]. It is important to completely collect 24 h urine starting after the first morning voiding in the day of the collection day and complete it the next day after the first voiding, and the collection vessel must be free of copper. Total creatinine excretion in the 24-h urine collection is typically measured to support proper urine collection. The 24-h copper values more than 100 μg/24 h (1.6 μmol/24 h) is conventionally considered diagnostic of WD [3,30]. This is definitely true for patients with neurologic or psychiatric phenotypic presentations who have no signs of chronic cholestasis [3]. Normal values for 24-h excretion are below 40 or 50 μg (0.64 or 0.8 μmol)/24 h. The 24-h urine copper values below this cutoff exclude WD. Intermediate values between 50 and 100 μg/24 h may be seen in heterozygous (carrier) individuals and require further investigation [3,37]. 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. 24-hour urine copper test can be also used for therapy monitoring [38–41].

Liver biopsy has been considered a gold standard for the confirmation of the diagnosis and may be still required in patients with predominantly hepatic presentation [30,31]. However, the diagnosis of neurological or psychiatric WD is sufficient based on diagnostic values of 24-H urine copper excretion [5].

Serum NCC (non–ceruloplasmin bound) 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 but may be also seen in acute liver failure [30,31]. 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 [42]. This test with a direct measurement of NCC has still a limited clinical availability. 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 one milligram of ceruloplasmin [40]. 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 [30]. Total copper value alone is not very helpful in the diagnosis WD because it is very variable and typically parallels the main copper binding protein ceruloplasmin [32].

Genetic testing with sequencing of the *ATP7B* gene confirms the diagnosis if both disease causing mutations are identified. Allelic heterogeneity in WD is considerable and many mutations are private, limited to single families and the vast majority of patients are compound heterozygotes [11]. Thus, unless familial mutations are known or the patient is from the region where certain mutations are very common, all exons and promoter region must be sequenced. Targeted mutation analysis for specific mutations, such as multiplex amplification refractory mutation system PCR, can be employed in populations with prevalent common mutations. 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 [11]. Thus, at present negative genetic testing alone does not absolutely exclude WD and other biochemical laboratory methods may need to be utilized [43].

Neuroimaging with magnetic resonance imaging (MRI) can detect structural abnormalities in the vast majority of WD patients with neurologic presentation. The most common finding is hyperintensity on T-2 weighted and FLAIR images involving putamen, striatum and globus pallidus [44,45] (Fig. 1). Hyperintense signal in the midbrain around the red nucleus and substantia nigra may give the appearance of “panda sign” that is most commonly seen in WD patients. However, these changes are non-specific and WD needs to be confirmed by other laboratory methods. MRI changes correlate with neurologic deficits and clinical improvement with chelation therapy also followed improvement of serial MRIs [46]. Structural changes also correlate with cognitive decline in these patients. Functional assessment of dopaminergic innervation using single photon emission computerized tomography (SPECT) in striatum can detect abnormalities in both presynaptic and

postsynaptic dopaminergic markers [47]. This pattern is relatively specific for WD because neurodegenerative striatonigral degeneration usually shows either pre or postsynaptic deficits only. Glucose uptake in basal ganglia is also reduced in WD but this is very non-specific finding and it does not differentiate between WD and other neurodegenerative conditions.

4. Treatment of Wilson's disease

Untreated fully symptomatic WD can be potentially fatal and unless they undergo liver transplant, all patients require life-long therapy, regardless of clinical symptoms or severity of their symptoms. The treatment goals in WD are to reverse copper overload and establish a negative copper balance during which copper values are reduced to normal levels. This includes the management of NCC or free copper levels that has emerged as a crucial factor in reducing copper toxicity, and thus preventing and reversing potentially devastating neurologic symptoms.

Treatment outcomes are best if the interval between first symptoms and initiation of therapy is less than one month [24]. If diagnosed and treated early, patients may lead essentially a normal life with a normal life expectancy. When delay in the diagnosis was increased to 1–6 months, only about one fifth of patients achieved a favorable outcome with very minor disability [48]. However, average time from the symptom onset to a correct diagnosis and appropriate treatment is still on average around one year between the onset and diagnosis [49].

The current standard of care treatments for WD are chelator therapies with D-penicillamine and trientine (also known as triethylenetetramine), which non-specifically chelate copper and promote urinary copper excretion [30,31]. Chelators bind to the circulating NCC or free copper pool and do not directly bind stored copper in the liver tissue. This may also account for the delayed recovery and patients with neurologic involvement often fully or partially recover within four years since the initiation of chelation therapy [50]. The residual neurologic deficit present after this period tends remain chronic unless non-adherence further worsens neurologic disability.

Paradoxical worsening after the start of chelation therapy is most feared complication and it is observed mostly in patients with neurologic involvement [49–54]. This has been observed even after an appropriate therapy is initiated in a timely manner. The presumed mechanism behind this worsening is a rapid mobilization of copper from the liver leading to elevations in blood unbound copper, resulting in ongoing cytotoxic effect in neuronal tissue with subsequent neurologic deterioration in treated patients. This is more commonly associated with therapy with D-penicillamine and 20–35% of treated patients with neurologic presentation may experience further deterioration that is often irreversible [49,50,53]. The highest reported rate of worsening associated with chelation with D-peniciallmine was 50% [51]. The same phenomenon is also observed with trientine therapy but its incidence is lower with 10–15% patients experiencing progression of their neurologic symptoms [52]. A recent retrospective analysis of WD patients showed no statistical difference between the rate of neurologic complications between D-penicillamine (6 patients from 295) and trientine (4 from 38), and the frequency of neurologic deterioration was much lower than in other studies [54]. However, overall only 55% of treated patients had experienced neurologic improvement, suggesting that either undertreatment or the methodologic differences how to assess neurologic worsening may account for this difference from other studies [54].

The target dose of D-penicillamine during the initial therapy is 1000–1500 mg/day given in 2–4 divided dosages that need to be taken 1–2 h before food to achieve an adequate absorption. The starting dose for patients with neurologic symptoms should be 250–500 mg/day with a careful increment by 250 mg every 5–7 days to monitor patients for a possible worsening and side effects [30,31]. The dose is adjusted based on 24-H urine copper assay and excretion of copper may surpass 1000 μg (16 μmol) per day early in the therapy. Dosing in the pediatric patients is 20 mg/kg/day. The maintenance dose is lower than during acute chelation and 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) [30,31].

The target dose of trientine during the initial therapy is 750–1500 mg/day divided in two or three doses and it also should be taken before food [30,31,52]. Similarly to D-penicillamine therapy, trientine should be also 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 [30,31]. Trientine has lower cupreuremic effect than D-penicillamine and daily copper excretion should be in the range of 200–500 μg (3–8 μmoles). The occurrence of neurologic worsening should prompt the reduction of the dose of the used chelator, even though there are no firm guidelines for this situation at present [30,31,54].

The selection of the first line chelator in WD patients with neurologic symptoms remains somewhat controversial because there is no head to head comparison between D-penicillamine and trientine. Even though trientine has been approved for patients who do not tolerate D-penicillamine, the use of trientine as the first line therapy for WD patients with neurologic symptoms has been favored by some because of possibly lower risk of paradoxical worsening [55]. However, until we have more conclusive clinical data, the selection of the first line therapy needs to be based on additional factors, including personal experience and the availability of chelators in different regions of the world.

Chelators are also associated with frequent adverse effects. Up to one third of all patients on penicillamine discontinue this therapy because of poor tolerability [30,54]. Lymphadenopathy, neutropenia or thrombocytopenia, myasthenic reaction, lupus-like syndrome and proteinuria with nephrotoxicity are most common adverse effects. Trientine is better tolerated but patients need to be monitored for proteinuria [30].

Additionally, zinc salts are used to induce negative copper balance but its mechanism of action is different from chelators. It is a potent inducer of metallothioneins, which block dietary uptake of copper in enterocytes [56]. Given the delay of several months in its peak efficacy zinc is used mainly for maintenance treatment. Typical dose of zinc acetate or zinc gluconate is 50 mg three times a day [30,56].

Shellfish, nuts, chocolate, mushrooms, and organ meats, especially liver tend to have very high copper concentration and should be avoided until the patients achieve negative copper balance [30]. Dietary restrictions alone are insufficient to treat copper overload in WD. Well controlled patients may be more liberal with their diet.

Bis-choline tetrathiomolybdate (WTX101) is currently under investigation as a novel therapeutic agent to treat WD [57]. Unlike chelators that non-specifically bind copper in the circulation and promote the excretion of copper via urine, bis-choline tetrathiomolybdate forms a tripartite complex with copper and albumin and directly reduces copper content in the liver with the elimination of excess copper via biliary excretion. The tripartite complex with copper and albumin is stable and bound copper trapped in this complex cannot redistribute to the brain. This is in contrast to chelators where bound copper is less stable and may be released as a free copper. The results of phase II study with once-daily WTX101 treatment induced rapid and sustained reduction of NCC copper and this was also associated with favourable clinical outcomes with improvement of neurologic deficits and disability [58]. Furthermore, WTX101 demonstrated a favourable safety profile and paradoxical neurologic worsening was not observed in this clinical trial. This compound appears to be superior to other chelators and phase III study is currently ongoing.

Chelators and zinc do not restore copper homeostasis. Liver transplantation can correct the genetic defect causing WD but it requires a life-long immunosuppressive therapy in transplanted patients. The indications for liver transplantation in hepatic disease in WD are generally established with proposed scoring systems for adults and children

[30,31]. However, the role of liver transplantation as a treatment of neurologic deficits remains controversial [59,60]. Liver transplantation corrects the hepatic metabolic defects of WD and also affects the normalization of extrahepatic copper metabolism, including in the central nervous system. Improvement or even a complete resolution after liver transplantation have been reported in some patients with severe and progressive neurologic deficits who did not respond to conventional chelation therapies and they did not require liver transplant because of failing liver functions [60]. These positive neurologic outcomes are not universal and no improvements or further progression have been also observed. At present there is no consensus regarding the role of liver transplant to reverse neurologic deficits.

In summary, timely diagnosis of WD with its pleomorphic clinical phenotype remains the main challenge and a high index of suspicion is needed to reduce the rate of misdiagnosis. Delays in initiation of decoppering therapies are associated with less favorable clinical outcomes and long term residual neurologic disability.

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