Wilson’s Disease

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Wilson’s disease (WD) or hepatolenticular degeneration is an autosomal recessive disorder with impaired hepatic excretion of copper. The disease has a penetration of 100% and therefore all homozygous individuals express clinical symptoms at some time or the other. The protein manifestations of the disease can take the patient to a psychiatrist, neurologist, hepatologist and ophthalmologist in addition to an internist. In 1883, Westphal gave an account of a disease, which was possibly Wilson’s disease. The first authentic report was by Samuel Alexander Kinner Wilson of 12 cases, which he termed as ‘progressive lenticular degeneration’. This was later called as Wilson’s disease. Keyser and Fleischer described the corneal deposits in Wilson’s disease in the early 19th century. In 1921, Hall described the autosomal recessive nature of inheritance of the disorder. Subsequently, advances in the fields of genetics and molecular biology have provided interesting insights into the genetics and pathogenesis of WD.

Copper Metabolism

Chief sources of copper in the Indian diet are nuts, water and food cooked in copper utensils. Normal copper intake in human diet is about 1-5 mg/day, which is transported into the epithelial cells of the upper small intestine by a copper transporter protein, where it is incorporated into various intracellular proteins like the superoxide dismutase and cytochrome oxidase etc., thereby reducing free copper ions in intestinal epithelial cells. Copper ions in excess to those attached to copper transporter protein get incorporated into the Golgi apparatus and are excreted from the body when the intestinal epithelial cells are shed off.

Hepatic copper homeostasis and Wilson’s disease

About 25-60% of the total ingested copper is absorbed and transported to the hepatocytes, bound with albumin, with the help of the transporter protein. Less than 40 microgram are excreted in the urine. The copper absorbed into the hepatocyte binds to the copper binding protein, ceruloplasmin. Copper in excess to the binding capacity of ceruloplasmin, gets bound to apometallothioneins and is excreted in the bile. From the hepatocytes copper is either (a) released into the blood, bound to ceruloplasmin from the basolateral surface of hepatocytes or (b) excreted into biliary canaliculi. Both these processes are brought about by WND, an intrahepatic copper transporter protein. Abnormalities/absence or reduction of WND protein results in impaired excretion of copper, with accumulation of copper in liver and copper-induced hepatotoxicity; the main features of Wilson’s disease (WD).

Role of Ceruloplasmin

Ceruloplasmin, a copper carrier protein transports Cu-ceruloplasmin complex into blood from the basal portion of the hepatocytes. Normal serum ceruloplasmin levels are 20-40 mg/dl. The production of ceruloplasmin is normal in WD patients, but low levels seen are due to its accelerated degradation. Other conditions with low ceruloplasmin level are hypoproteinemnic states like nephrotic syndrome, malnutrition and severe hepatic disorders and congenital absence of ceruloplasmin. Features of WD are not seen in these disorders because WND protein is normal, and also the Cu-ceruloplasmin complex formation. High ceruloplasmin levels are seen in acute liver disease, therapy with estrogen and pregnancy. The major regulatory control mechanism in copper metabolism is biliary excretion of non-absorbable copper which is 1-2 mg/day in normal and is reduced to 20-40% in Wilson’s disease. In WD the defect in excretion of copper leads to its accumulation in liver resulting in copper-induced hepatotoxicity and neurological symptoms.

Molecular Genetics of Wilson’s Disease

Wilson’s disease is inherited as an autosomal recessive disease with a frequency of about 1 in 40,000 live-births. The gene locus for WD is located on chromosome 13 and is linked to the gene for the enzyme esterase D and retinoblastoma gene on the same chromosome. The gene (80kb) was cloned in 1994 by Petrukhin et al and was named as WND gene. Mutations in this gene consist of small deletions, insertions and point mutations. All the patients of WD have mutations in the same gene. Clinical heterogeneity observed in WD patients is probably due to allelic heterogeneity (multiple different mutations seen at the same locus). Patients having the same genetic mutations may present in different ways, and the clinical features may not be similar even in identical twins. Patients with nonsense mutations have severe impairment of function and so are responsible for childhood onset severe hepatic disease. Missense mutations on the other hand cause relatively minor
clinical presentations.\textsuperscript{11}

**Pathology And Pathophysiology**

Deficiency of WND protein leads to failure of incorporation of copper into ceruloplasmin. Copper-free ceruloplasmin, has a shorter half-life and therefore undergoes rapid degradation, resulting in low serum copper levels in WD patients. The hallmark of Wilson’s disease is reduced excretion of copper from the liver with intrahepatic copper deposition in the face of normal or raised serum copper concentration. Copper deposition in liver levels causes lowering of hepatic glutathione resulting in lipid peroxidation, disruption of cell membrane, mitochondria and even DNA. Hepatocellular damage further leads to release of free copper into circulation, which gets deposited in the extrahepatic sites such as Descemet’s membrane in cornea (with formation of Keyser-Fleischer ring) and in the basal ganglia leading to neuro-psychiatric manifestations. In brain the basal ganglia have a special predilection for copper deposition. In about 10\% of cases there is deposition of copper in the cerebral cortex and brain stem as well.

**Pathology**

**Liver**

The hallmark of hepatic changes is microvesicular and macrovesicular fatty changes, fibrosis and cirrhosis. Copper can be demonstrated in liver biopsy sections by rhodamine and rubeanic acid staining. Electron microscopy studies show increased matrix density, matrical inclusions with widened intramembranous and intercristal spaces in mitochondria in the early stage of the disease, and disappear as the disease progresses, or following treatment.\textsuperscript{12}

**Brain**

Wilson’s disease affects both the grey and white matter of the brain, with relative sparing of cerebellum. The corpus striatum is affected most severely, with neuronal loss, fissures and cavitations. In early stage the putaminal cavities and small and perivascular in distribution, but increase in size as the disease advances with cavitation in caudate nucleus. Other grey nuclei like the thalami, subthalamic nuclei, substantia nigra etc. may also be involved in later stages. The damaged cells are large, with abundant cytoplasm and small nucleus and are called Opalski’s cells, characteristic of hepatolenticular degeneration. Changes in white matter consist of loss of myelin with sudanophillic myelin breakdown products, to frank cavitation.

**Clinical Features**

The onset of symptoms can occur between 6-40 years and about 50\% of patients are symptomatic by the age of 15 years. Usually patients present with neuropsychiatric symptoms with concurrent abnormalities of hepatic function. Other common symptoms are drooling, dysphagia, and progressive dementia in a child. In general, about one-third of the patients present with features suggestive of hepatic dysfunction, a third present with neurological symptoms, and other with predominantly neuropsychiatric symptoms. Disturbance of hepatic functions is practically always present in patients who have extrahepatic manifestations.

**Hepatic presentation**

Hepatic involvement is invariably seen in WD. Walshe et al reported evidence of current or past hepatic involvement in 40\% of symptomatic patients. Patients who present with predominately hepatic symptoms are generally young.\textsuperscript{13} The mode of hepatic presentation can be in the form of fulminant hepatic failure of cirrhosis. Fulminant hepatic failure, seen in younger patients, presents with jaundice, hypoalbuminemia, ascites, coagulation defects, hyperammonemia and even frank hepatic encephalopathy. Release of stored copper from the damaged hepatocytes results in disruption of red blood cell membrane causing Coomb’s negative hemolytic anaemia. Excessive hemolysis causes hyperbilirubinemia disproportionate to serum transaminase levels. The combination of high serum bilirubin (> 10 gm/dl) increased hepatic aminotransferase levels (> 200 IU/l) and prolonged prothrombin time (> 12 sec) is usually associated with a poor prognosis in patients with fulminant hepatitis.\textsuperscript{14} Older patients usually have milder and chronic form of hepatic failure. They usually have portal hypertension, cirrhosis, features of hypersplenism like thrombocytopenia and leukopenia.\textsuperscript{15}

**Psychiatric and behavioural abnormalities**

The psychiatric manifestations of WD are markedly variable and are often overlooked leading to missed or delayed diagnosis. Schwartz et al report these symptoms in a third of their patients and in 20\% patients they precede other symptoms. Akil and Brewer report psychiatric symptoms in as many as two-thirds of their patients.\textsuperscript{16} The psychiatric manifestations can be categorized into five groups namely behavioural/personality disorders, affective disorder, cognitive disorders, psychoses, and anxiety. Of these the commonest is behavioural problems. The common cardiac problems are ECG abnormalities varying from minor ST segment changes to frank AV block and cardiomyopathy. Renal involvement is in the form of aminoaciduria, proteinuria. Patients can have osteopenia, arthralgias and rhabdomyolysis. Hypoparathyroidism, coagulopathy, sunflower cataracts are uncommon presentations seen in the form of irritability, decreased threshold for anger, temper tantrums, and aggression. The second most common psychiatric manifestation is depression, which can be severe enough to interfere with normal functioning of the patient and may lead to suicidal ideations. Patients also complain of deteriorating academic performance, which result in expulsion from jobs or schools. Increased sexual preoccupation has also been observed with decreased sexual inhibitions. Psychoses and significant cognitive impairment is unusual in patients with WD.\textsuperscript{17}

**Neurological symptoms**

The mean age of onset of neurological symptoms is about 21 years (range being 5-50 years), a little older than those
who have initial hepatic presentation. About 97% of patients with neurological symptoms have KF ring. The symptoms are very subtle to begin with and are usually in the form of mild tremors, speech problems, micrographia and excessive drooling of saliva. Dysarthria giving way to dysphagia and other movement disorders increases in severity with time. Common neurological signs are dysarthria (97%), dystonia (65%), dysdiadochokinesis (58%), rigidity (52%), gait and posture abnormalities (42%), tremors (32%) and pyramidal signs (spasticity and brisk deep tendon reflexes). Some patients have motor impersistence and frontal lobe release reflexes. Among movement disorders chorea is rare. Fixed contractures at the joints are late features in disease. Ultimately, patients become bed-ridden. The patients with neurological symptoms are classified into four symptomatic categories depending upon the predominant neurological symptom. The parkinsonism patients (45%) have prominent bradykinesia and paucity of expression. The pseudosclerotic type (24%) patients are characterized by tremors and cerebellar signs, patients in dystonic subgroup (15%) present with increased limb tone and abnormal movements and postures of limbs and choreic group (11%) is characterized by choreoathetoid movements (Table 3). Most patients who present with neurological symptoms will also have some degree of hepatic impairment.

Other manifestations

Almost every organ system can be affected in Wilson’s disease. The disease can affect kidneys, endocrine glands, heart, musculoskeletal system, and the hemopoietic system in addition to liver and brain and cause symptoms pertaining to these systems.

Diagnosis of Wilson’s disease

Due to absence of characteristic signs and symptoms of the disease, a high level of index of suspicion of Wilson’s disease is the key factor in early and correct diagnosis. Every young patient with a movement disorder of unexplained origin should be screened for WD. The doubt is further strengthened if there is a background history of recurrent jaundice. The diagnosis is virtually certain if a patient with neurological disorder demonstrates Keyser-Fleischer’s (KF) ring. However confirmation of the diagnosis rests on demonstration of abnormal copper metabolism in patients with suspected WD. The mainstay of diagnosis is the measurement of ceruloplasmin, urine copper, serum copper, and hepatic copper clouds. A classical ring is golden brown in colour but can be greenish brown or bronze in colour. Similar rings may be seen in patients with a longstanding cholestasis, like primary biliary cirrhosis, chronic active hepatitis etc., but the diagnosis of WD is betrayed by the unique clinical and biochemical features. Sunflower cataracts are green, golden brown granular deposits in the lens of the eye that are seen in as many as 17% of patients with WD.

Table 1: Stages of KF ring in Wilson’s disease (Weibers et al, 1977)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>No identifiable KF ring</td>
</tr>
<tr>
<td>Stage 1</td>
<td>KF ring at superior poles only</td>
</tr>
<tr>
<td>Stage 2</td>
<td>KF ring at superior and inferior poles</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Full circle corneal rings encompassing the entire periphery of each cornea</td>
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Serum ceruloplasmin

The most important step in the diagnosis of WD is estimation of levels of circulating oxidase active ceruloplasmin, which is low in about 95% of patients with Wilson’s disease (20 mg/dl). About 20% of the heterozygotes also have low levels of ceruloplasmin (Table 2). In about 5-10% of patients of WD the levels may be normal, especially during pregnancy and in patients taking estrogen containing drugs.

Table 2: Causes of low serum ceruloplasmin level

1. New borns and infants (upto 6 months)
2. Severe malnutrition
3. Nephrotic syndrome
4. Protein losing enteropathies
5. Congenital aceruloplasminemia
6. Severe hepatic insufficiency
7. Acute hepatic infection

Table 3: MRI findings in Wilson’s disease

<table>
<thead>
<tr>
<th>Sign on neuroimaging</th>
<th>Description of the sign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bright claustrum sign</td>
<td>Increased signal intensity of the claustrum. Seen in 75% of symptomatic patients.</td>
</tr>
<tr>
<td>Peripheral putamen sign</td>
<td>Peripheral lateral rim of hyperintensity of the putamen on T2 weighted images. Seen in 86% patients.</td>
</tr>
<tr>
<td>Ventral nucleus of thalamus sign</td>
<td>If the thalamus involved, the signal alteration is seen in the ventral nuclear mass of the thalamus. Seen in 54% patients.</td>
</tr>
<tr>
<td>Head of the giant panda sign</td>
<td>Increased signal intensities in the midbrain tegmentum (except for the red nuclo). Preservation of signal in the lateral pares reticularis of substantia nigra, and hypointensities of the superior colliculi</td>
</tr>
</tbody>
</table>

Urinary copper excretion studies

Estimation of 24-hours urinary copper excretion is almost always elevated above 100 µg/24 hrs in symptomatic
patients. It is important that the sample should be properly collected and should be free from contamination. When the diagnosis of WD is suspected, value of urinary copper less than 50 µg/24 hour virtually excludes the diagnosis of WD. Values falling between 50-100 µg/24 hours need confirmation by other tests. Cupriuresis induced by penicillamine treatment offers no advantage over the simple 24-hours urinary copper estimation. This can be used as a cost-effective screening test for the evaluation of cooperative patients suspected of WD.

Serum free copper and total copper levels

Total serum copper level (70-150 mg/dl) includes both free fraction and the fraction bound to ceruloplasmin. Measuring total serum copper level can be very misleading as it may be low in WD patients (< 80 µg/dl), reflecting low levels of ceruloplasmin. Free serum copper level in normal adults ranges between 5-12 µg/dl. This fraction of copper is loosely complexed to albumin and accounts for 10% of total copper. It is consistently elevated in untreated WD and other cholestatic liver diseases. This test is useful in the diagnosis of WD. The copper content of ceruloplasmin is 0.03%.

Hepatic copper estimation

Determination of hepatic copper levels by percutaneous liver biopsy is the final test for the diagnosis of WD. The test is particularly useful in the detection of presymptomatic individuals, especially when all other tests for copper metabolism are normal. In symptomatic patients of WD the levels are 250 µg/g of dry weight of liver. The levels may be falsely low in early WD, presymptomatic individuals, patients with extensive fibrosis of liver and if the sample is collected in normal saline prior to fixation. The results should be interpreted cautiously in the presence of other hepatic diseases.

Radiolabeled copper incorporation studies

This test assays the hepatic copper metabolism directly. Patients are given radiolabeled copper (64Cu or 67Cu) orally, and blood samples are collected 1, 2, 4, 24 and 48 hours after the intake. In all normal individuals the radioactivity disappears from serum, promptly after oral ingestion due to prompt hepatic clearance. There is reappearance of radioactivity in normal and heterozygous individuals in the serum. The reappearance of radioactivity is slow in heterozygotes and is absent in patients of WD. This test is useful when serum ceruloplasmin is normal and liver biopsy is contraindicated.

Genetic testing

Linkage analysis can be used in family studies for presymptomatic siblings. In most families, a correct diagnosis can be made using micro-satellite markers, which flank the genetic locus on chromosome 13 if the tissue from the proband is available. The problem in genetic diagnosis is the large number of mutations seen in WD and hence it cannot be used as a screening test in the absence of blood from an affected family member.

Neuroradiology of Wilson’s disease

While none of the radiological tests are characteristic of WD suspicion, they can support the diagnosis in suspected cases of WD.

a) CT Scan

CT scan may show generalized cerebral atrophy, with basal ganglia having low attenuation signals. Walshe et al reported ventricular dilatation in 73% patients, cortical atrophy in 63% patients, brain stem atrophy in 55%, basal ganglia hypodensity in 45%, and posterior fossa atrophy in 10% patients. The CT may be normal in about 20% patients. Similar results were seen in an Indian study. In our series, we found basal ganglions hypodensities as the commonest abnormality (10/21 CT scans) followed by brain stem hypodensity (6/21) and hypodensity in thalami. Three out of 21 scans were normal. (Fig. 1a, b, c)
b) Magnetic resonance imaging (MRI)

MR is more sensitive than a CT scan in detecting subtle signals intensity alterations in the basal ganglia, in the patients as well as presymptomatic individuals. There is symmetrical and wide-spread involvement of the deep gray nuclei, subcortical white matter and the brain stem in symptomatic patients. The lesions demonstrate high signal intensity on T1W and low intensity in T2W images. Putamen is affected earliest and most severely particularly along its lateral region. Many radiological signs have been described in WD patients on the MRI. The increased signal intensity of the putamen—the bright putamen sign is seen in 75% of patients. Increased signal intensities in the midbrain tegmentum, with normal signal of the red nucleus, give the appearance of the head of a giant panda sign on MRI.

c) Positron emission tomography (PET)

PET studies show diffusely reduced glucose metabolism in Wilson’s disease. This is more profuse in the caudate nucleus, lenticular nuclei, and frontal and parietal cortex. The thalami do not show any difference when compared to normal controls.

TREATMENT

WD is a treatable disorder and treatment should be instituted in the symptomatic as well as asymptomatic heterozygous individuals as soon as the diagnosis is confirmed. Though D-penicillamine holds the mainstay of treatment, emergence of new drugs with safer adverse effects profile has made treatment of WD easy and safe.

In principle treatment of WD requires the following

1. Patient/family education to emphasise proper compliance and genetic implications.
2. Specific medical treatment: copper-chelating agents, zinc, tetrathiomolybdate, diet, liver transplant, peritoneal dialysis.
3. Symptomatic treatment for psychiatric, medical, hepatic and neurological manifestations.
4. Screening for asymptomatic individuals and their treatment.

An overview of various drugs is essential in order, before evaluating their role in the treatment.

COPPER CHELATING AGENTS

D-penicillamine

D-Penicillamine was introduced in 1956 by Walshe as a copper chelating agent for the treatment of WD. The dose is 1000 mg/day in two or four divided doses and must be spaced from food. It should be started in low dose and the dose should be increased slowly over a period of 4 to 6 months. Penicillamine is a toxic drug and the incidence of initial hypersensitivity is as high as 30%. Patients may develop fever, rashes, arthralgias and severe urticarial rashes. These effects can be overcome by the concurrent administration of steroids, reducing the dose of the drug or by temporarily stopping the drug and restarting it at a lower dose. Other side effects are bone marrow suppression, and proteinuria and hepatic toxicity. Goodpasture’s syndrome, lupus like reaction and myasthenic syndrome can occur in rare cases. The most dreaded side effect of penicillamine is worsening of neurological features, which is observed in as high as 50% patients, and about half of these patients never recover. The incidence of this complications can be reduced by starting treatment in low dose and increasing it slowly. Zinc or trientine, can be used as an effective adjunct in the initial phase of treatment. 26,27 Pyridoxine supplement should be given as D-penicillamine has an anti-pyridoxine action.

Trientine

Trientine was introduced in 1968 for patients who could not tolerate penicillamine. It chelates copper and increases its urinary excretion. It is also shown to decrease intestinal copper absorption.28 The standard dose is 1000 mg/day in two or four equal divided doses to be given spaced from meals. Common side effects are bone marrow suppression, proteinuria and initial neurological deterioration. Treatment should be monitored with regular blood counts, urinalysis and urinary copper excretion. 28

DRUGS REDUCING COPPER ABSORPTION AND REDUCING COPPER FROM TISSUES

Zinc

Zinc is a useful drug in the treatment of Wilson’s disease. It acts by inducing metallothionein (MT) synthesis in the intestinal cells and blocking the absorption of copper from the intestines. This results in its binding to copper present in food and body secretions thereby preventing it from gaining access to the blood or getting deposited in tissues.
Copper thus complexed to metallothionine is excreted in the stool as the intestinal cells are shed off. The dose required to induce a negative copper balance in the body is about 150 mg/day divided in two or three equal doses. The drug is almost free of side effects, only side effect being mild gastric intolerance. Acetate salt of zinc is less likely to cause this side effect. The drug works well with other anti-copper agents but the two should be spaced about one hour apart. Therapy with zinc can be monitored by 24-hour urinary copper and zinc estimations.29,30

**Tetrathiomolybdate**

Tetrathiomolybdate (TM) was introduced for the treatment of WD in 1980’s. TM works in two ways: (a) it forms a tripartite complex between itself, copper and the available protein in the gut, when given with the food. This complex is insoluble, non-toxic and stable so it cannot be absorbed by the intestine, and (b) the absorbed TM forms complexes with albumin and circulating copper in the blood thereby making circulating copper unavailable to cellular uptake and removes copper from toxic pool. TM is the most active and potent anti-copper agent available at present. The major side effect reported is mild and reversible anaemia, which is usually as a result of overzealous treatment, resulting from rapid depletion of copper from the body.31

**Diet**

As copper utensils are used in some parts of India for cooking, this should be stopped. Copper rich food items such as organ meat, shell fish, nuts, chocolates and mushrooms should also be avoided.

**Liver Transplant**

An occasional patient requires liver transplantation. Indications for the procedure are: (a) fulminant hepatic failure, (b) decompensated hepatic failure with coagulopathy, encephalopathy and jaundice and (c) refractory portal hypertension. Severe neurologic WD is not an indication for liver transplant. Surgical mortality is 20-30%.32

**Short Term Measure**

These include haemodialysis and plasma exchange and are indicated in severely ill patients who cannot wait for 2-6 months for the action of copper removing agents to become effective.

**Starting Treatment in WD**

Almost all asymptomatic, and most symptomatic patients with WD are likely to improve if anti-copper treatment is instituted early without neurological sequel. As newer drugs become available, it becomes confusing to choose the best drug to initiate therapy. D-penicillamine has been in use since 1955 and has been useful in the treatment of fairly advanced stage of the disease with reversal of neurological, ophthalmic and hepatic abnormalities. The only deterrent to its use is troublesome and some times fatal deterioration of neurological symptoms. This phenomenon is seen with almost all forms of therapies currently available but is particularly severe with penicillamine. There are no predictors of initial deterioration and therefore all patients must be monitored very closely, especially in early part of thereby and the treatment should be started in a small dose and the dose increased slowly.

Zinc can be used to initiate therapy in WD patients.29-31 Though there are no major adverse effects, the onset of effect is slow and the patients may deteriorate during this time. Tetrathiomolybdate (TM) has fast action and lowers serum copper levels with virtually no adverse effects or deterioration of neurological status. Mild clinical deterioration in only two of the 51 patients of WD treated with TM has been reported. It is therefore, recommended to use TM for 6-8 weeks and then switch over to zinc therapy for maintenance. TM is not available in India and therefore one has to initiate therapy with penicillamine. In our centre we start treatment with low dose penicillamine and increase it over a period of four to six months to maximum dose. We institute zinc therapy along with penicillamine keeping adequate spacing between the drugs. We and other Indian authors have observed good results in patients treated with zinc.29

**Initial Hepatic Disease**

In patients who present with mild form of hepatic disease orthoptic hepatic transplantation is the optimum choice. But patients with severe disease or chronic active hepatitis must be stabilized with a chelating agent preferably trientine, TM or D-penicillamine with zinc before hepatic transplantation can be contemplated.32

**Maintenance Therapy**

Most authorities use zinc as the drug of choice for maintenance of patients of WD. It is almost 100% effective, very safe and can be given for a very long time without any adverse effects. It is used in doses of 150 mg per day in three divided doses. Alternatively, penicillamine and trientine can be used together for maintenance therapy. Maintenance therapy should be continued throughout life.

**Presymptomatic Patients**

The family members especially the siblings of patients with WD should be screened for WD. The therapy of choice for presymptomatic individual is zinc in dose of 150 mg per day in three divided doses. These patients can also be treated with penicillamine and trientine, but as they do not have symptoms, subjecting them to a toxic drug is not advisable.

**Pregnancy**

Penicillamine and trientine have both been found to be teratogenic in animals and penicillamine has been found to be so in humans as well.33 Such patients should receive zinc, which has been studied extensively and has been found to
be free of significant teratogenic effect. Anti-copper treatment should not be stopped in pregnant females.

**COMPLIANCE AND FOLLOW UP**

The issue of a proper compliance to the treatment cannot be overemphasized. Dropouts are common in the maintenance phase of treatment, which can cause symptomatic deterioration. A relapse is more difficult to treat. It is seen in about 10-25% of patients. To prevent this, patients should have regular and lifelong follow up.

**PROGNOSIS**

The symptoms start improving in about four to five months in most patients but the process is slow and continuous. Some degree of improvement is expected in the patients up to 18 months. A similar response is seen in patients whose initial presentation is hepatic. The symptoms thereafter plateau and the deficits persisting after about two years of regular treatment are usually permanent.

**CONCLUSION**

Hepatolenticular degeneration or Wilson’s disease, an autosomal recessive disorder, results from a defect in copper excretion with resultant copper accumulation in various tissues of the body like liver, cornea and brain. The disease, which was inevitably fatal at one time, is completely treatable disorder now. D-penicillamine, the gold standard in the treatment of WD, should be used with caution, since initial deterioration in the neurological status is common. The newer drugs, like trientine, tetrathiomolybdate and zinc appear to be less toxic and effective. Treatment is initiated with a copper-chelating agent along with zinc and maintained with zinc lifelong. Patient education regarding the importance of proper compliance, and positive attitude towards the disease is important. The importance of positive attitude cannot be overemphasized as it helps the patients to maintain adequate physical activity, so that when the recovery occurs, the body will be ready for it.

**REFERENCES**


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