CLINICAL PICTURE:

A 30 years old female patient presented clinically with oro-facial dyskinesia, parkinsonian manifestations (with rigidity and hypokinesia). Slit lamb examination of the cornea revealed Kayser-Fleischer rings. Serum ceruloplasmin was reduced and urinary excretion of copper was increased. Liver biopsy revealed increased concentration of copper.

RADIOLOGICAL FINDINGS:

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Figure 1. Wilson's disease has a relatively characteristic appearance, particularly on high field strength MR imaging studies. Signal hyperintensity on T2-weighted and FLAIR images exists in the putamen symmetrically and bilaterally, presumably representing chronic gliotic and edematous changes. Within the putaminal high signal intensity, irregular areas of low signal intensity are also frequently observed on the T2-weighted images. These areas of low signal intensity are somewhat characteristic of Wilson's disease and most likely represent increased iron accumulation, occurring secondary to the increased copper distribution in the putamen. Central atrophy is also noted. Notice the signal hypointensity that is observed in the corticospinal tract bilaterally. The signal hypointensity is anatomically mapping the corticospinal tract bilaterally.

Figure 2. Wilson's disease has a relatively characteristic appearance, particularly on high field strength MR imaging studies. Signal hyperintensity on T2-weighted and FLAIR images exists in the putamen symmetrically and bilaterally, presumably representing chronic gliotic and edematous changes. Within the putaminal high signal intensity, irregular areas of low signal intensity are also frequently observed on the T2-weighted images. These areas of low signal intensity are somewhat characteristic of Wilson's disease and most likely represent increased iron accumulation, occurring secondary to the increased copper distribution.
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Our results showed that abnormal white matter on MR images is a common finding in Wilson disease. Light microscopic studies confirm active involvement of supratentorial and infratentorial white matter with pathologic alterations varying from capillary endothelial swelling, gliosis, and demyelination to spongy degeneration or even loss of neurons (8–13). In histologic studies central pontine myelinolysis is also found in Wilson disease (9, 12, 14). Demyelination, edema, and gliosis can explain the signal intensity changes of white matter on the MR images. We considered that part of the white matter abnormalities could be located in both extrapyramidal and pyramidal tracts, although Wilson disease is in general considered to be an extrapyramidal disease.

The corticospinal or pyramidal tract contains projection fibers from the cerebral cortex, which extends into the corona radiata, the posterior limb of the internal capsule (20), the center of the cerebral peduncle of the mesencephalon, rounded foci in the base of the pons, the medulla oblongata, and the spinal cord (15). Light microscopic findings in Wilson disease support active involvement of the deep pyramidal cell layers of the cerebral cortex, where the corticospinal tract originates (8–10, 12). Imaging studies in amyotrophic lateral sclerosis have described abnormal signal intensity in the posterior third quarter of the posterior limb of the internal capsule (20), coinciding with abnormalities in our patient and one case with Wilson disease reported in literature (6). Although we did not notice abnormal signal intensity in the medulla oblongata and spinal cord, neuropathologic studies on Wilson disease reported amyotrophic lateral sclerosis–like spinal lesions without gliosis and secondary degeneration of the pyramidal tracts in the spinal cord (9, 10). Abnormal muscle responses evoked by transcranial stimulation, which was not significantly correlated with clinical symptoms, in patients with Wilson disease indicated (sub)clinical involvement of the corticospinal tract (21, 22).

In the literature, occurrence of subtle pyramidal signs in Wilson disease varied from “occasionally” to about 20% (21–25). In fact, the historical dichotomy of extrapyramidal and pyramidal motor systems proved inadequate: new results show extensive interconnection and cooperation of the motor systems in the control of movement (16). In addition, the clinical distinction between subtle pyramidal and extrapyramidal symptoms can be difficult in the presence of a great spectrum of neurologic abnormalities (22).

In the MRI T2 images a mixture of T2 hypointensities and hyperintensities are observed mainly in the basal
Wilson disease is a rare autosomal recessive inherited disorder of copper metabolism. The condition is characterized by excessive deposition of copper in the liver, brain, and other tissues. The major physiologic effects of copper deposition include the formation of T2 hyperintense and hypointense zones in the basal ganglia and the corticospinal tract. These signal abnormalities are primarily due to cavitations, astroglial proliferation, and spongy degeneration. T2 hypointensity in the basal ganglia is associated with extrapyramidal symptoms and signs, while T2 hyperintensity in the corticospinal tract is associated with pyramidal tract involvement. Copper deposition is also associated with increased iron concentration in some areas of the brain, which may induce observable MRI signal changes. The pathophysiology and anatomical distribution of copper and iron deposition in Wilson disease are different, with copper deposition leading to extrapyramidal symptoms and iron deposition being asymptomatic. In brain, the basal ganglia show the most striking alterations, with a brick-red pigmentation and spongy degeneration of the putamen frequently leading to the formation of small cavities. Microscopic studies reveal a loss of neurons, axonal degeneration, and large numbers of protoplasmic astrocytes, including giant forms known as Alzheimer cells. The cortex of the frontal lobe may also show spongy degeneration and astrocytosis. Copper is deposited in the pericapillary area and within astrocytes, where it is located in the subcellular soluble fraction and bound not only to cerebrocuprein but also to other cerebral proteins. Copper is uniformly absent from neurons and ground substance.
aberration is excessive absorption of copper from the small intestine and decreased excretion of copper by the liver. The genetic defect, localized to chromosome arm 13q, has been shown to affect the copper-transporting adenosine triphosphatase (ATPase) gene (ATP7B) in the liver. Patients with Wilson disease usually present with liver disease during the first decade of life or with neuropsychiatric illness during the third decade. The diagnosis is made by measurement of serum ceruloplasmin, urinary copper excretion, and hepatic copper content, as well as the detection of Kayser-Fleischer rings.

The estimated total body copper content is 50-100 mg, with an average daily intake of 1-2 mg/d. Copper is an important component of several metabolic enzymes, including lysyl oxidase, cytochrome c oxidase, superoxide dismutase, and dopamine beta-hydroxylase. Intestinal copper absorption and transport into hepatocytes is intact in Wilson disease. After copper reaches the hepatocyte, it is incorporated into copper-containing enzymes, including ceruloplasmin. Excess copper may be rendered nontoxic by forming complexes with apo metallothionein to produce copper-metallothionein, or it may be excreted into bile.

In Wilson disease, the processes of incorporation of copper into ceruloplasmin and excretion of excess copper into bile are impaired. The transport of copper by the copper-transporting P-type ATPase is defective in Wilson disease secondary to one of several mutations in the ATP7B gene. The excess copper acts as a promoter of free radical formation and causes oxidation of lipids and proteins. In the earliest stages of hepatocellular injury, ultrastructural abnormalities involving the endoplasmic reticulum, mitochondria, peroxisomes, and nuclei have been identified. Initially, the excess copper is stored in the liver and causes damage to the hepatocytes. Eventually, as liver copper levels increase, it is released into the circulation and deposited in other organs.

Fulminant Wilson disease leads to rapidly progressive liver failure, encephalopathy, coagulopathy, and, eventually, death if emergent liver transplantation is not performed. The fulminant presentation of Wilson disease is more common in females than males (4:1). Wilson disease manifests as liver disease in children and adolescents, peaking at ages 10-13 years, and as neuropsychiatric illness in young adults aged 19-20 years.

The worldwide incidence is 10-30 million cases, with increased rates in areas of consanguinity. The heterozygote carrier rate is 1 case per 100 persons, corresponding to a gene frequency varying between 0.3-0.7%. The frequency ranges worldwide from 1 case per 30,000 population in Japan to 1 case per 100,000 population in Australia. The increased frequency in certain countries is due to high rates of consanguinity.

Wilson disease is an autosomal recessive disorder; the gene is located on the long arm of chromosome 13 at the esterase D locus. The world-wide prevalence of the disease is about 30/ million, with a gene frequency of 1:180. Although most patients show markedly diminished serum ceruloplasmin concentrations, the localization of the gene for ceruloplasmin to chromosome 3 indicates that failure to form the copper protein is not the primary defect. Studies with radioisotopes indicate that the dynamic turnover of copper is disturbed. After intravenous administration of Cu to a normal person, there is a rapid rise of serum copper content followed by an equally rapid fall and, commencing at about 6 hours postinfusion, a secondary slow rise as ceruloplasmin enters the serum. In Wilson disease, the initial rise is more extensive, the secondary rise is not observed, and no radioactivity enters the globulin fraction where ceruloplasmin is normally found. This phenomenon is also noted in patients who have nearly normal ceruloplasmin concentration and in children who lack the protein, which is an indication that the rate of copper transfer from the albumin into the globulin fraction is reduced.

In addition to these abnormalities, plasma levels of nonceruloplasmin copper are increased, and the biliary excretion of copper is reduced. Equally unexplained are the low to low-normal levels of plasma iron-binding globulin. These abnormalities also, occur in asymptomatic carriers and suggest that Wilson disease may also involve a disorder of iron metabolism; ceruloplasmin directly affects the transfer of iron from tissue cells to plasma transferrin.

Another metabolic feature is a persistent aminoaciduria. This is most marked during the later stages, but may be noted in some asymptomatic patients. The presence of other tubular defects (e.g., impaired phosphate resorption in patients without aminoaciduria) suggests that a toxic action of the metal on renal tubules causes the aminoaciduria. The most plausible explanation of the copper accumulation and other features of Wilson disease is that there is a defect of an energy-mediated secretory mechanism for the metal in hepatocytes, possibly in hepatic lysosomes, and that a similar defect prevents copper from entering the ceruloplasmin compartment.
The abnormalities in copper metabolism result in a deposition of the metal in several tissues. Anatomically, the liver shows focal necrosis that leads to a coarsely nodular, postnecrotic cirrhosis; the nodules vary in size and are separated by bands of fibrous tissue of different width. Some hepatic cells are enlarged and contain fat droplets, intranuclear glycogen, and clumped pigment granules; other cells are necrotic and there are regenerative changes in the surrounding parenchyma.

Electron microscopic studies have shown that copper is sequestered by lysosomes that become more than normally sensitive to rupture and therefore lack normal alkaline phosphatase activity. Copper probably initiates and catalyzes oxidation of the lysosomal membrane lipids, resulting in lipofuscin accumulation. Within the kidneys the tubular epithelial cells may degenerate and the cytoplasm may contain copper deposits.

In brain, the basal ganglia show the most striking alterations. They have a brick-red pigmentation; spongy degeneration of the putamen frequently leads to the formation of small cavities. Microscopic studies reveal a loss of neurons, axonal degeneration, and large numbers of protoplasmic astrocytes, including giant forms known as Alzheimer cells. The cortex of the frontal lobe may also show spongy degeneration and astrocytosis. Copper is deposited in the pericapillary area and within astrocytes, where it is located in the subcellular soluble fraction and bound not only to cerebrocuprein but also to other cerebral proteins. Copper is uniformly absent from neurons and ground substance.

Lesser degenerative changes are seen in the brain stem, the dentate nucleus, the substantia nigra, and the convolutional white matter. Copper is also found throughout the cornea, particularly the substantia propria. In the periphery of the cornea the metal appears in granular clumps close to the endothelial surface of the descemet membrane. The deposits in this area are responsible for the appearance of the Kayser-Fleischer ring. The color of this ring varies from yellow to green to brown. Copper is deposited in two or more layers, with particle size and distance between layers influencing the ultimate appearance of the ring.

In Wilson disease, an abnormal striatum depicted on MR images correlated with pseudoparkinsonian signs, an abnormal dentatothalamic tract correlated with cerebellar signs, and an abnormal pontocerebellar tract correlated with pseudoparkinsonian signs.

On the other hand the presence of portosystemic shunt was strongly associated with abnormality of the globus pallidus.

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**CLINICAL**

- **History:**

Consider hepatic Wilson disease in the differential diagnosis of any unexplained chronic liver disease, especially in individuals younger than 40 years. The condition may also manifest as acute hepatitis. Hepatic dysfunction is the presenting feature in more than half of patients. The 3 major patterns of hepatic involvement are (1) chronic active hepatitis, (2) cirrhosis, and (3) fulminant hepatic failure. The most common initial presentation is cirrhosis.

  - **Neuropsychiatric**

    - Most patients who present with neuropsychiatric manifestations have cirrhosis. The most common presenting neurologic feature is asymmetric tremor, occurring in approximately half of individuals with Wilson disease. The character of the tremor is variable and may be predominantly resting, postural, or kinetic.

    - Frequent early symptoms include difficulty speaking, excessive salivation, ataxia, masklike facies, clumsiness with the hands, and personality changes.

    - Late manifestations (now rare because of earlier diagnosis and treatment) include dystonia, spasticity, grand mal seizures, rigidity, and flexion contractures.
One study describes 4 distinct diagnostic categories based on patients' major neurologic findings (Walshe, 1984).

- The parkinsonian patients (45%) were distinguished by paucity of expression and movement.
- The pseudosclerotic patients (24%) had tremor resembling multiple sclerosis.
- The patients in the dystonic group (15%) were characterized by hypertonicity associated with abnormal limb movements.
- The patients in the choreic group (11%) were predominantly characterized by choreoathetoid abnormal movements associated with dystonia.

Psychiatric features include emotional lability, impulsiveness, disinhibition, and self-injurious behavior. The reported percentage of patients with psychiatric symptoms as the presenting clinical feature is 10-20%. The range of psychiatric abnormalities associated with Wilson disease has been divided into 4 basic categories, as follows:

- Behavioral
- Affective
- Schizophreniclike
- Cognitive
  - Ophthalmologic

Kayser-Fleischer rings are formed by the deposition of copper in Descemet membrane in the limbus of the cornea. The color may range from greenish gold to brown; when well developed, rings may be readily visible to the naked eye or with an ophthalmoscope set at +40. When not visible to the unaided eye, the rings may be identified using slit-lamp examination or gonioscopy.

Figure 4. Kayser-Fleischer rings

Kayser-Fleischer rings are observed in up to 90% of individuals with symptomatic Wilson disease and are almost invariably present in those with neurologic manifestations.

Although Kayser-Fleischer rings are a useful diagnostic sign, they are no longer considered pathognomonic of Wilson disease unless accompanied by neurologic manifestations. They may also be observed in patients with chronic cholestatic disorders.
such as partial biliary atresia, primary biliary cirrhosis, primary sclerosing cholangitis, and cryptogenic cirrhosis.

- Kayser-Fleischer rings consist of electron-dense granules rich in copper and sulfur. The rings form bilaterally, initially appearing at the superior pole of the cornea, then the inferior pole, and, ultimately, circumferentially.

  o Musculoskeletal

  - Skeletal involvement is a common feature of Wilson disease, with more than half of patients exhibiting osteopenia on conventional radiologic examination.

  - The arthropathy of Wilson disease is a degenerative process that resembles premature osteoarthritis. Symptomatic joint disease, which occurs in 20-50% of patients, usually arises late in the course of the disease, frequently after age 20 years. The arthropathy generally involves the spine and large appendicular joints such as knees, wrists, and hips. Osteochondritis dissecans, chondromalacia patellae, and chondrocalcinosis have also been described.

  o Hematologic

  - Hemolytic anemia is a recognized but rare (10-15%) complication of the disease.

  - Coombs-negative acute intravascular hemolysis most often occurs as a consequence of oxidative damage to the erythrocytes by the higher copper concentration.

  o Renal

  - The Wilson disease gene is expressed in kidney tissue; therefore, any renal manifestations may be primary or secondary to release of copper from the liver.

  - Clinically, patients may resemble those with Fanconi syndrome, demonstrating defective renal acidification and excess renal losses of amino acids, glucose, fructose, galactose, pentose, uric acid, phosphate, and calcium. The frequency of renal manifestations is variable.

  - Urolithiasis, found in up to 16% of patients with Wilson disease, may be the result of hypercalciumia or poor acidification.

  - Hematuria and nephrocalcinosis are reported, and proteinuria and peptiduria can occur both before treatment as part of the disease process and after therapy as adverse effects of D-penicillamine.

Physical: Physical findings are consistent with liver disease, to include jaundice, varices, spider angiomas, and palmar erythema.

Causes: Initially, Wilson postulated that the familial incidence of hepatolenticular degeneration was attributable to environmental rather than genetic factors. Nearly a decade later, Hall reported that Wilson disease was more frequent in siblings. In 1953, Bearn discovered an autosomal recessive mode of inheritance confirmed by extended genetic analysis of 30 families. Frydman et al localized the Wilson disease (WD) gene to chromosome 13.

The WD gene product is a 1411 amino acid protein with highest levels of expression in the liver, kidneys, and placenta. The WD gene codes for P-type copper-transporting ATPase, now characterized as ATP7B. Many of the gene defects for ATP7B are small deletions, insertions, or missense mutations. Most patients carry different mutations on each of their 2 chromosomes. More than 40 different mutations have been identified, the most common of which is a change from a histidine to a glutamine (H1069Q).
Figure 5. The Wilson disease protein is a copper-transporting CPx-type ATPase. The transporter consists of transmembrane, phosphorylation, nucleotide-binding, and actuator domains common to other P-type ATPases. Features unique to CPx-type ATPases include a large cytoplasmic metal-binding domain containing between one and six metal-binding motifs, a pair of N-terminal transmembrane helices, CPC, and the SEHPL motifs.

WORKUP

- **Lab Studies:**
  - The presence of Kayser-Fleischer rings and ceruloplasmin levels of less than 20 mg/dL in a patient with neurologic signs or symptoms suggest the diagnosis of Wilson disease. If a patient is asymptomatic, exhibits isolated liver disease, and lacks corneal rings, the coexistence of a hepatic copper concentration of more than 250 mg/g of dry weight and a low serum ceruloplasmin level is sufficient to establish a diagnosis.
  
  - **Serum ceruloplasmin**
    - Serum ceruloplasmin levels are low in newborns and gradually rise within the first 2 years of life. Approximately 90% of all patients with Wilson disease have ceruloplasmin levels of less than 20 mg/dL (reference range, 20-40 mg/dL).
    - Ceruloplasmin is an acute phase reactant and may be increased in response to hepatic inflammation, pregnancy, estrogen use, or infection.
    - Falsely low ceruloplasmin levels may be observed in any protein deficiency state, including nephrotic syndrome, malabsorption, protein-losing enteropathy, and malnutrition. Ceruloplasmin levels may also be decreased in 10-20% of WD gene heterozygotes, who do not develop Wilson disease and do not require treatment.
  
  - **Urinary copper excretion**
    - The urinary copper excretion rate is greater than 100 mg/d (reference range, <40 mg/d) in most patients with symptomatic Wilson disease. The rate may also be elevated in other cholestatic liver diseases.
    - Both the sensitivity and specificity of this test are suboptimal for use as a screening test; however, it may be useful to confirm the diagnosis and to evaluate the response to chelation therapy.
  
  - **Hepatic copper concentration**
    - This test is regarded as the criterion standard for diagnosis of Wilson disease.
A liver biopsy with sufficient tissue reveals levels of more than 250 mcg/g of dry weight even in asymptomatic patients. Special collection vials are available to help avoid contamination.

A normal hepatic copper concentration (reference range, 15-55 mcg/g) effectively excludes the diagnosis of untreated Wilson disease. An elevated hepatic copper concentration may be found in other chronic hepatic (mostly cholestatic) disorders.

Figure 6. The liver in Wilson disease with advanced cirrhosis

- Radiolabeled copper

  - Radiolabeled copper testing directly assays hepatic copper metabolism. Blood is collected at 1, 2, 4, 24, and 48 hours after oral ingestion of radiolabeled copper (\(^{64}\)Cu or \(^{67}\)Cu) for radioactivity in serum. In all individuals, radioactivity promptly appears after absorption, followed by hepatic clearance. In healthy people, reappearance of the radioactivity in serum occurs as the labeled copper is incorporated into newly synthesized ceruloplasmin and released into the circulation.

  - Heterozygotes exhibit a slow lower-level reappearance of radioactivity rather than the continued fall in radioactivity in those with Wilson disease, but there may be considerable overlap between the two. Patients with Wilson disease, even those with normal ceruloplasmin levels, do not exhibit the secondary rise in radioactivity.

  - Genetic diagnosis: Linkage analysis has been used in family studies for presymptomatic testing. The multiplicity of mutations that require screening in individuals without affected family members is large and not currently feasible. Therefore, the use of molecular testing is currently limited to screening of family members for an identified mutation detected in the index patient.

- Imaging Studies:

  - Cranial CT scan

    - The cranial lesions observed on CT scan are typically bilateral and are classified into 2 general categories, ie, (1) well-defined, slitlike, low-attenuation foci involving the basal ganglia, particularly the putamen and (2) larger regions of low attenuation in the basal ganglia, thalamus, or dentate nucleus.

    - Widening of the frontal horns of the lateral ventricles and diffuse cerebral and cerebellar atrophy, which correlate histologically with widespread neuronal loss, have also been described.
Figure 7. CT scan in Wilson disease demonstrates a well-defined, slitlike, low-attenuation foci involving the basal ganglia, particularly the putamen (yellow arrows)

- Brain MRI
  - MRI of the brain appears to be more sensitive than CT scanning in detecting early lesions of Wilson disease.

  - MRI studies have identified focal abnormalities in the white matter, pons, and deep cerebellar nuclei. These lesions, measuring 3-15 mm in diameter, are typically bilateral, appearing with low signal intensity on T1-weighted images and with high signal intensity on T2-weighted images, representing cell loss and gliosis. Other studies describe decreased signal intensity in the putamen and other parts of the basal ganglia, which may represent either copper or iron ferritin deposition.

  - A characteristic "face of the giant panda" sign has been described, formed by high signal intensity in the tegmentum (except for the red nucleus), preserved signal intensity of the lateral portion of the pars reticulata of the substantia nigra, and hypointensity of the superior colliculus.

Figure 8. MRI T2 images of Wilson disease cases showing hypointensity involving the thalamus and corpus striatum (left image), the dentate nucleus (middle image) and the caudate nucleus (right image)

- Positron emission tomography scan
  - Positron emission tomography (PET) scan reveals a significantly reduced regional cerebral metabolic rate of glucose consumption in the cerebellum, striatum, and, to a lesser extent, in the cortex and thalamus.

  - PET analyses of patients with Wilson disease have also demonstrated a marked reduction in the activity of dopa-decarboxylase, indicative of impaired function of the nigrostriatal dopaminergic pathway.

  - These abnormalities improve with chelation therapy, indicating a reversible component of
striatal neuron injury.

Figure 9. PET images at the level of the basal ganglia, before and after treatment with the copper chelator D-penicillamine in a patient with Wilson’s disease. Prominent hypometabolism was found in both putamina in the first PET examination (left image) whereas the second study (after treatment) showed a marked but incomplete improvement of glucose utilization in the basal ganglia. In this case, the predominant residual deficits were observed in the right putamen while clinical symptoms of striatal dysfunction persisted on the left side. Regions of interest have been drawn on caudate nuclei and putamina and the right side of the brain is at the left of the images as indicated.

- **Abdominal imaging**
  - CT scan, MRI, ultrasound, and nuclear medicine studies of the liver have been uninformative, with findings neither specific nor sensitive for Wilson disease.

- **Electron microscopy**
  - Electron microscopic studies on ultrathin sections reveal numerous electron-dense lysosomes and residual bodies.
  - The elemental analysis in transmission electron microscopy with electron energy loss spectroscopy, and in scanning electron microscopy with energy dispersive x-ray analysis, shows copper-specific signals of electron-dense accumulations inside these dark lysosomes and residual bodies.
  - The electron microscopic detection of copper-containing hepatocytic lysosomes is helpful for the diagnosis of early stages of Wilson disease in addition to the quantification of hepatic copper by atomic absorption spectrophotometry.
In Wilson disease, the following are observed in the basal ganglia in a bilateral, fairly symmetrical fashion:

- T2 hyperintense zones are primarily due to cavitations, astrogliosis and spongy degeneration.
- T2 hypointense zones are primarily due to excessive iron deposition in the same areas of copper deposition. This occurs due to low to low-normal levels of plasma iron-binding globulin. Ceruloplasmin directly affects the transfer of iron from tissue cells to plasma transferrin.

**Other Tests:**
- Resting ECG abnormalities include left ventricular or biventricular hypertrophy, early repolarization, ST segment depression, T-wave inversion, and various arrhythmias.

**Procedures:**
- In the absence of Kayser-Fleischer rings or neurologic abnormalities, a liver biopsy for quantitative copper determination is essential to establish the diagnosis of Wilson disease (see Lab Studies for description of hepatic copper measurement).

**Histologic Findings:**
- Hepatic
  - The earliest changes detectable with light microscopy include glycogen deposition in the nuclei of periportal hepatocytes and moderate fatty infiltration. The lipid droplets, which are composed of triglycerides, progressively increase in number and size, sometimes resembling the steatosis induced by ethanol. Hepatocyte mitochondria typically exhibit heterogeneity in size and shape, with increased matrix density, separation of the normally apposed inner and outer mitochondrial membranes, widened intercristal spaces, and an array of vacuolated and crystalline inclusions within the matrix. With progression of disease, copper protein is sequestered in lysosomes and is visible as electron-dense pericanalicular granules.
  - Despite consistently elevated hepatic copper levels in patients with Wilson disease, histochemical staining of liver biopsy specimens for copper is of little diagnostic value. Early in the disease, copper distribution is primarily cytoplasmic and is not readily apparent with rhodamine or rubeanic acid staining.

In the MRI T2 images a mixture of T2 hypointensities and hyperintensities are observed mainly in the basal ganglia and less commonly in the dentate nucleus.
The rate of progression of the liver histology from fatty infiltration to cirrhosis is variable, although it tends to occur by one of two general processes, either with or without hepatic inflammation. The histologic picture may be histologically indistinguishable from that of chronic active hepatitis. Pathologic features include mononuclear cell infiltrates, which consist mainly of lymphocytes and plasma cells, piecemeal necrosis extending beyond the limiting plate, parenchymal collapse, bridging hepatic necrosis, and fibrosis. The histologic pattern is one of a macronodular or mixed micro-macronodular cirrhosis, with fibrous septa (containing predominantly types I and III collagen), bile ductule proliferation, and variable septal round cell infiltration. Hepatocytes at the periphery of the nodules frequently contain Mallory hyalin.

One proposed mechanism implicates copper as the inducer of fibrogenesis. Interestingly, hepatocellular carcinoma is exceedingly rare in patients with Wilson disease compared to patients with hemochromatosis. This may be attributable to the significantly shortened life expectancy in untreated patients, which does not allow time for carcinoma to develop. An increasing number of case reports suggest that the incidence will likely increase with improved survival. It has been proposed that the diminished cancer risk is due to the relatively low inflammatory component in the pathogenesis of Wilson disease.

Neurologic

Observed gross anatomic changes include degeneration and cavitation, primarily involving the putamen, globus pallidus, caudate nucleus, and thalamus.

Little correlation has been observed between the degree of neurologic impairment and the neuropathologic findings. The affected areas of the brain do not possess higher copper concentrations than the unaffected portions.

Figure 11. A case of Wilson disease showing degeneration of the caudate nucleus and parts of the corpus striatum. The lesions are symmetrically and bilaterally distributed, presumably representing chronic gliotic and edematous changes. Mild degree of central atrophy is present.

Staging: The natural history of the disease may be considered in 4 stages, as follows:

- Stage I - The initial period of accumulation of copper by hepatic binding sites
- Stage II - The acute redistribution of copper within the liver and its release into the circulation
Stage III - The chronic accumulation of copper in the brain and other extrahepatic tissue, with progressive and eventually fatal disease

Stage IV - The achievement of copper balance with chronic chelation therapy

Figure 12. A case of Wilson disease showing degeneration of the caudate nucleus and parts of the putamen. The lesions are symmetrically and bilaterally distributed, presumably representing chronic gliotic and edematous changes. Notice central atrophy.

Table 1. Differences between brain neuroimaging findings in Wilson disease and non-Wilsonian chronic liver disease

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Wilson disease</th>
<th>Non Wilsonian chronic liver disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomical site of cranial involvement</td>
<td>Putamen and caudate nuclei</td>
<td>Globus pallidus, pituitary gland</td>
</tr>
<tr>
<td>MRI signal changes</td>
<td>T1 No significant changes or T1 hypointensities</td>
<td>T1 Precontrast T1 hyperintensity</td>
</tr>
<tr>
<td></td>
<td>T2 A mixture of hyper and hypointensities</td>
<td>T2 No significant changes</td>
</tr>
<tr>
<td>Aetiology of MRI signal changes</td>
<td>Spongy degeneration, cavitations, astrogliosis, and iron deposition</td>
<td>Manganese accumulation</td>
</tr>
<tr>
<td>Association with clinical symptoms and signs</td>
<td>Symptomatic and correlates with pseudoparkinsonian signs</td>
<td>Asymptomatic</td>
</tr>
</tbody>
</table>
Figure 13. A, MRI T2 image of a patient with Wilson disease, B, Precontrast MRI T1 image of a patient with hepatic encephalopathy due to causes other than Wilson disease. Notice the T2 mixture of hyper and hypointensities (in the putamen and head of caudate nuclei) in Wilson disease (A) which is always symptomatic and correlates with pseudoparkinsonian signs, while in hepatic encephalopathy there is asymptomatic precontrast hyperintensity in the globus pallidus.

MANAGEMENT

Medical Care: The mainstay of therapy for Wilson disease is pharmacologic treatment with chelating agents.

- **Surgical Care:**
  - The use of surgical decompression or transjugular intrahepatic shunting (TIPS) in the treatment of portal hypertension is reserved for individuals with recurrent or uncontrolled variceal bleeding that is unresponsive to standard conservative measures.
  - Orthotopic liver transplantation is a potentially curative treatment of Wilson disease.
    - Transplantation is primarily reserved for treatment of patients with fulminant liver failure or end-stage liver cirrhosis, which progresses despite chelation therapy.
    - The selection of patients for transplantation may be facilitated by determination of a prognostic index, which is based on the degree of abnormality of serum aspartate aminotransferase, bilirubin, and prothrombin time and appears to accurately predict a fatal or nonfatal outcome.
    - In the absence of severe hepatic disease, liver transplantation is generally not recommended for treatment of refractory extrahepatic manifestations.

- **Consultations**
  - Consider consultation with gastroenterologists with specialty training in hepatology for any patient with Wilson disease, especially when evidence of hepatic insufficiency is present.
  - Consultation with surgeons may be sought for liver transplantation when deemed necessary.

- **Diet**
Patients should generally avoid eating foods with a high copper content such as liver, chocolate, nuts, mushrooms, legumes, and shellfish (especially lobster). Drinking water from atypical sources (e.g., well water) should be analyzed for copper content and replaced with purified water if the copper content is greater than 0.2 parts per million.

**MEDICATION**

The mainstay of therapy for Wilson disease is the use of chelating agents and medications that block copper absorption from the GI tract.

**Drug Category: Chelating agents** -- Bind excess copper. Tetrathiomolybdate is being used under the investigational new drug approval of the US Food and Drug Administration at the University of Michigan as an initial treatment for those who present with neurologic or psychiatric manifestations. This drug works as both a chelating agent and as an inhibitor of copper absorption from the GI tract.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Penicillamine (Cuprimine, Depen) -- Forms soluble complexes with metals excreted in urine. DOC before newer regimens were available. Because of extensive toxicities, alternative agents are used. Must be administered with pyridoxine 25 mg PO qd.</th>
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<tbody>
<tr>
<td>Adult Dose</td>
<td>Initial: 1.5-2 g PO qd Maintenance: 750 mg to 1 g/d PO qid 30 min ac</td>
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<tr>
<td>Pediatric Dose</td>
<td>25 mg/kg PO qd</td>
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<td>Contraindications</td>
<td>Documented hypersensitivity; renal insufficiency; previous penicillamine-related aplastic anemia</td>
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<td>Interactions</td>
<td>Increases effects of immunosuppressants, phenylbutazone, and antimalarials; decreases digoxin effects; effects may decrease with coadministration of zinc salts, sucrafate, antacids, and iron; probenecid may increase adverse effects</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>D - Unsafe in pregnancy</td>
</tr>
<tr>
<td>Precautions</td>
<td>Thrombocytopenia, agranulocytosis, and aplastic anemia may occur</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Trientine (Syprine) -- Effective oral chelator used to induce cupriuresis. Useful for patients who cannot tolerate penicillamine. Indicated in Wilson disease if initial presentation is hepatic. Should be administered with zinc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Dose</td>
<td>250-500 mg PO tid ac</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Not established</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity; biliary cirrhosis; rheumatoid arthritis; cystinuria</td>
</tr>
<tr>
<td>Interactions</td>
<td>Effects decrease with iron or other mineral supplements</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>C - Safety for use during pregnancy has not been established.</td>
</tr>
<tr>
<td>Precautions</td>
<td>Can cause bone marrow suppression and proteinuria; perform weekly CBC counts at initiation of therapy</td>
</tr>
</tbody>
</table>

**Drug Category: Nutrients** -- Essential to normal growth and development. Play a role in many metabolic processes.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Zinc (Verazinc, Orazinc, Zincate) -- Cofactor for &gt;70 types of enzymes. Approved for patients initially treated with a chelating agent. Should be used for maintenance after initial therapy. DOC in presymptomatic, pregnant, and pediatric populations. Second DOC if initial</th>
</tr>
</thead>
</table>
**Follow-Up**

- **Further Outpatient Care:**
  - Perform a physical examination, 24-hour urinary copper excretion assay, CBC count, urinalysis, serum free copper measurement, and renal and liver function tests on a weekly basis for the first 4-6 weeks following initiation of chelation therapy.
  - Bimonthly evaluations are recommended through the first year, followed by yearly examinations thereafter.
  - In patients with Kayser-Fleischer rings, a yearly slit-lamp examination should document fading or disappearance if patients are being adequately "decoppered."
  - Lifelong, uninterrupted chelation therapy is necessary in all patients with Wilson disease.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Pyridoxine (Nestrex) -- Involved in synthesis of GABA within the CNS.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Dose</td>
<td>25 mg PO qd</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Not established</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity</td>
</tr>
<tr>
<td>Interactions</td>
<td>May decrease levodopa, phenytoin, and phenobarbital serum levels</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>C - Safety for use during pregnancy has not been established.</td>
</tr>
<tr>
<td>Precautions</td>
<td>&gt;200 mg/d may precipitate withdrawal effects when medication is discontinued</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dimercaprol (BAL in Oil) -- For refractory cases of Wilson disease not responding to first- or second-line treatment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Dose</td>
<td>3-5 mg/kg IM q4h</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Administer as in adults</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity; G-6-PD deficiency; concurrent iron supplementation therapy</td>
</tr>
<tr>
<td>Interactions</td>
<td>Toxicity may increase when coadministered with selenium, uranium, iron, or cadmium</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>C - Safety for use during pregnancy has not been established.</td>
</tr>
<tr>
<td>Precautions</td>
<td>May be nephrotoxic and may cause hypertension; caution when administering to patients with oliguria or G-6-PD deficiency; may induce hemolysis in patients with G-6-PD deficiency</td>
</tr>
</tbody>
</table>
Frequent follow-up with patients is necessary, secondary to patient decompensation due to noncompliance. This is one of the major causes of fulminant liver failure.

Patients must avoid most alcohol consumption and potential hepatotoxic drug therapy.

- **In/Out Patient Meds:**
  - Zinc and penicillamine are lifelong medications for patients with Wilson disease. Dosages vary with severity of disease.

- **Complications:**
  - The major complications in patients with untreated Wilson disease are those associated with liver failure and a chronic, relentless course to cirrhosis, which is characterized by a progressive lassitude, fatigue, anorexia, jaundice, spider angiomas, splenomegaly, and ascites. Bleeding from varices, hepatic encephalopathy, hepatorenal syndrome, and coagulation abnormalities occur as liver failure ensues.

- **Prognosis:**
  - **Prognostic Index in Fulminant Wilsonian Hepatitis**

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum bilirubin (reference range, 3-20 mmol/L)</td>
<td>&lt;100</td>
<td>100-150</td>
<td>151-200</td>
<td>201-300</td>
<td>&gt;300</td>
</tr>
<tr>
<td>Serum aspartate transaminase (reference range, 7-40 IU/L)</td>
<td>&lt;100</td>
<td>100-150</td>
<td>151-200</td>
<td>201-300</td>
<td>&gt;300</td>
</tr>
<tr>
<td>Prothrombin time prolongation (seconds)</td>
<td>&lt;4</td>
<td>4-8</td>
<td>9-12</td>
<td>13-20</td>
<td>&gt;30</td>
</tr>
</tbody>
</table>

- Patients with a prognostic index (ie, score) of 7 or greater should be considered for liver transplantation. All patients who exceeded this score died within 2 months of diagnosis despite the institution of appropriate medical therapy.

- Prognosis after liver transplantation is relatively good. In a study involving 55 patients with Wilson disease who underwent hepatic transplantation, the 1-year survival rate was 79% and the overall survival rate was 72% at 3 months to 20 years.

- **Medical/Legal Pitfalls:**
  - Failure to consider Wilson disease in the differential diagnosis of any unexplained chronic liver disease, or an abnormal liver enzyme profile, especially in individuals younger than 40 years is a potential medicolegal pitfall. The typical age for hepatic presentation is 10-13 years, whereas that for neuropsychiatric presentation is 20 years.

  - In female patients with Wilson disease, it should be explained that very few women can become pregnant once cirrhosis develops.

- **Special Concerns:**
  - **Pregnancy**
    - Excessive intrauterine copper concentrations may be responsible for the high rate of spontaneous abortions in patients with Wilson disease. D-penicillamine (0.75-1.5 g/d) appears to pose no major risk to the fetus and should be continued throughout the pregnancy.

    - While pregnancy per se does not appear to have a deleterious effect on the course of
treated patients, the risk of ascites or bleeding from gastroesophageal varices in pregnancy is increased for any individual with cirrhosis, regardless of the underlying etiology.

- **Pediatric**
  - Pediatricians should consider Wilson disease in any child with hepatic abnormalities.
  - The initial tests should be performed, and further workup by a pediatric gastroenterologist may be necessary if suspicion remains high.

- **Geriatric**
  - Almost all patients have significant hepatic and neuropsychiatric symptoms before reaching the geriatric age group.
  - Patients with Wilson disease who are untreated will most likely present with fulminant hepatic failure or with signs and symptoms of cirrhosis in the geriatric population. Consideration for liver transplantation is less likely with advancing age.

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**SUMMARY**

- **The clinical picture of Wilson disease**

Neurological manifestations are the presenting symptoms in the older age group. The neurologic manifestations are so varied that it is impossible to describe a clinical picture that is characteristic. In the past, texts have distinguished between pseudosclerotic and dystonic forms of the disease: the former dominated by tremor, the latter by rigidity and contractures. In actuality, most patients, if untreated, ultimately develop both types of symptoms. In essence, Wilson disease is a disorder of motor function; despite often widespread cerebral atrophy, there are no sensory symptoms or reflex alterations. Symptoms at onset are shown in Table 2. Symptoms of basal ganglia damage usually predominate, but cerebellar symptoms may occasionally be in the foreground. Tremors and rigidity are the most common early signs. The tremor may be of the intention type, or it may be the alternating tremor of Parkinson disease. More commonly, however, it is a bizarre tremor, localized to the arms and best described by the term "wing-beating". This tremor is usually absent when the arms are at rest; it develops after a short latent period when the arms are extended. The beating movements may be confined to the muscles of the wrist, but it is more common for the arm to be thrown up and down in a wide arc. The movements increase in severity and may become so violent that the patient is thrown off balance. Changing the posture of the outstretched arms may alter the severity of the tremor. The tremor may affect both arms, but is usually more severe in one. The tremor may occasionally be present even when the arm is at rest. Many patients have a fixed, open-mouth smile.

Rigidity and spasms of the muscles are often present. In some cases, a typical parkinsonian rigidity may involve all muscles. Torticollis, tortipelvis, and other dystonic movements are not uncommon. Spasticity of the laryngeal and pharyngeal muscles may lead to dysarthria and dysphagia. Drooping of the lower jaw and excessive salivation are common. Other symptoms include convulsions, transient Periods of coma, and mental changes. Mental symptoms may dominate the clinical course for varying periods and simulate an affective disorder of functional psychosis.
Tendon reflexes are increased, but extensor plantar responses are exceptional. Somatosensory evoked potentials are abnormal in most patients with neurologic symptoms. The intracorneal, ring-shaped pigmentation first noted by Kayser and Fleischer may be evident to the naked eye or may be seen only by slit-lamp examination. The ring may be complete or incomplete and is present in 75% of patients who present with hepatic symptoms and in all patients with cerebral symptoms alone or both cerebral and hepatic symptoms. The Kayser-Fleischer ring may antedate overt symptoms and has been detected even with normal liver functions.

CT/MRI usually reveals ventricular dilatation and diffuse atrophy of the cortex, cerebellum, and brain stem. In about half the patients, there are hypodense areas in the thalamus and basal ganglia on CT scan. Increased density due to copper deposition is not observed. As a rule, magnetic resonance (MR) scans correlate better with the clinical symptoms than CT, demonstrating abnormal signals in the lenticular, caudate, and dentate nuclei and thalamus and, in a few subjects, focal white matter lesions.

Table 2. Clinical Manifestations at Onset of Wilson Disease

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic or hematologic abnormalities</td>
<td>35%</td>
</tr>
<tr>
<td>Behavior abnormalities</td>
<td>25%</td>
</tr>
<tr>
<td>Neurologic symptoms</td>
<td>40%</td>
</tr>
<tr>
<td>• Pseudosclerotic form one or more of the following:</td>
<td>40%</td>
</tr>
<tr>
<td>o Tremor at rest or purposive</td>
<td></td>
</tr>
<tr>
<td>o Dysarthria or scanning speech</td>
<td></td>
</tr>
<tr>
<td>o Diminished dexterity or mild clumsiness</td>
<td></td>
</tr>
<tr>
<td>o Unsteady gait</td>
<td></td>
</tr>
<tr>
<td>• Tremor, alone</td>
<td>33%</td>
</tr>
<tr>
<td>• Dysarthria, alone</td>
<td>5%</td>
</tr>
<tr>
<td>• Dystonic form one or more of the following:</td>
<td>60%</td>
</tr>
<tr>
<td>o Hypophonic speech or mutism</td>
<td></td>
</tr>
<tr>
<td>o Drooling</td>
<td></td>
</tr>
<tr>
<td>o Rigid mouth, arms, or legs</td>
<td></td>
</tr>
<tr>
<td>• Seizures</td>
<td>1%</td>
</tr>
<tr>
<td>• Chorea or small-amplitude twitches</td>
<td>&gt;1%</td>
</tr>
</tbody>
</table>

- **Management of Wilson disease**

The clinical picture of Wilson disease is fairly clear-cut when the disease is advanced. The important features are the family history of hepatic or neurologic disease, progressive extra-pyramidal symptoms commencing during the first or second decade of life, abnormal liver function, aminoaciduria, cupriuria, and absent or decreased ceruloplasmin. The Kayser-Fleischer ring is the most important diagnostic feature; absence of corneal pigmentation in untreated patients with neurologic symptoms rules out the diagnosis. The ring is not seen in most presymptomatic patients or in some children with hepatic symptoms. Although 96% of patients with Wilson disease have low or absent serum ceruloplasmin, some cases have been reported with normal ceruloplasmin levels. In affected families, the differential diagnosis between
heterozygotes ad presymptomatic homozygotes is of utmost importance because homozygotes should be treated preventively.

Low ceruloplasmin levels in an asymptomatic patient are indicative of the presymptomatic stage of the disease. However, because 6% of heterozygotes also have low ceruloplasmin levels, which is a phenomenon that tends to be familial, the ceruloplasmin levels of the affected patient's parents should be determined. Whenever the diagnosis remains unresolved, a liver biopsy must be performed to measure hepatic copper content. The relatively close linkage to esterase D should facilitate diagnosis in families with a previously affected member.

A variant of Wilson disease begins in adolescence and is marked by progressive tremor, dysarthria, disturbed eye movements, and dementia. Biochemically, it is characterized by low serum levels of copper and ceruloplasmin. Kayser-Fleischer rings are absent and liver copper concentrations are low. Metabolic studies using labelled copper suggest a failure in copper absorption from the lower gut. Another variant, in which there is a familial aceruloplasmin deficiency but no neurologic symptoms other than blepharospasm, confirms that ceruloplasmin plays only a secondary role in the pathogenesis of Wilson disease.

○ Treatment

The aim of treatment is to prevent tissue accumulation of copper by restricting the intake of the metal, and by removing excessive amounts already deposited. A copper-poor diet and potassium sulfide, 20 mg with each meal, are recommended to minimize copper absorption. Penicillamine, 1 to 3 daily in divided doses, on an empty stomach, is given to promote urinary excretion of copper. Improvement of neurologic symptoms and signs and fading of the Kayser-Fleischer rings result from this therapy. As a rule, patients with the predominantly pseudosclerotic form of the disease fare better than those with dystonia as the main manifestation. In some dystonic patients, addition of L-dopa to the Penicillamine regimen has been beneficial. Serial CT demonstrates progressive reduction of the hypodense areas in the basal ganglia. Survival for many years with complete or almost complete remission of symptoms has been reported.

• Addendum

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