Wilson's Disease: Gastrointestinal Features

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Wilson's disease is an autosomal recessive disorder that causes copper to accumulate in various tissues throughout the body. Carriers occur at a rate of approximately one in 100, but the disease occurs in 1–4 per 100,000. Disease found early can be treated, but advanced disease may require a liver transplant [1].

Gastrointestinal symptoms associated with the disease are [1, 2]:

- Combination of liver disease with neuropsychiatric disturbances
- Symptoms related to end-stage liver disease or acute liver failure

Clinical signs and findings include [1, 2]:

- Elevated aminotransferases
- Acute or chronic hepatitis
- Fulminant hepatic failure
- Cirrhosis/end-stage liver disease with portal hypertension
  - Ascites/fluid retention
  - Esophageal/rectal varices
  - Portal hypertensive gastropathy
  - Hemorrhagic diathesis
  - Hepatic encephalopathy
- Kayser–Fleischer rings
- Sunflower cataracts
- Skin manifestations of chronic liver disease
  - Spider telangiectasias
  - Gynecomastia
  - Jaundice/icterus
  - Muehrcke's lines, Terry's nails
  - Palmar erythema
- Osteoarthritis
- Cardiac findings
- Nephrocalcinosis
- Chondrocalcinosis
- Hypercalciuria
- Depression
- Mood lability
- Psychosis
- Cognitive decline
- Tremor
- Dysarthria/aphasia
- Ataxia/bradykinesia
- Infertility/increased risk of miscarriage
- Hypoparathyroidism

The pathogenesis is based on a genetic defect in the excretion of copper [3]:

- Autosomal recessive
- Mutations in the *ATP7B* gene on chromosome 13
  - Reduction in the *ATP7B* function results in decreased biliary copper excretion
  - Increased copper accumulation in hepatic and extrahepatic tissues
  - Excess copper released into circulation and taken up by central nervous system

Typical liver pathology shows [3]:

- Liver biopsy dry weight 75 μg/g copper
- Liver biopsy histology varies with stage (see Fig. 69.1)
  - Early: hepatic steatosis, mitochondria with crystalline deposits and dilated cristae with advancing fibrosis
  - Later: lysosomal deposits of copper and copper metallothionein
  - Late stage: hepatocellular disruption with advanced cirrhosis and fibrosis
  - Acute liver failure: apoptosis and necrosis on the background of advanced fibrosis
- Copper staining of liver biopsy

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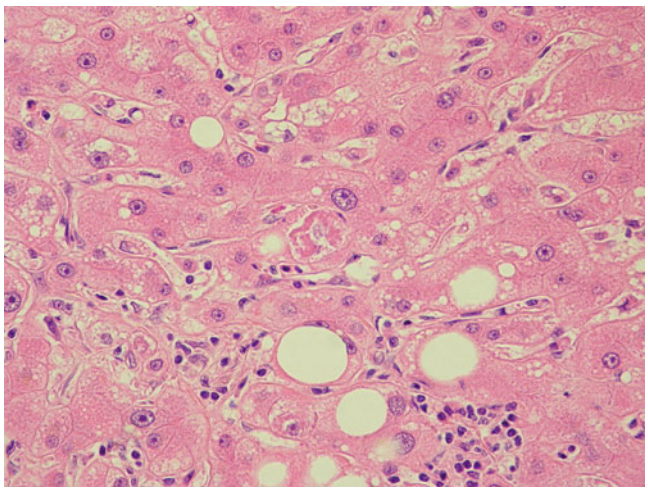

Fig. 69.1 Photomicrograph of liver biopsy specimen from a patient with Wilson's disease showing periportal region with spotty necrosis (focal inflammatory cell infiltration and hepatocellular pleomorphism indicating focal hepatocellular necrosis). There is also fatty change and a large Mallory body in the center. Hematoxylin and eosin, ×400

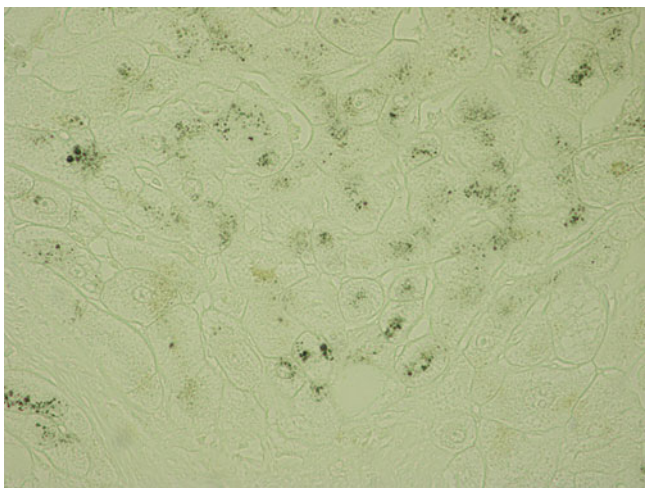

Fig. 69.2 Photomicrograph of liver biopsy specimen a periportal region showing copper deposition (*black granules*) in the hepatocytes. Copper stain ×400

  - Copper staining positive nodules with nearby areas absent for copper staining (regenerative areas)(see Fig. 69.2)

The diagnosis is made by considering [3]:

- Family history
- Genetic testing with two mutations of *ATP7B*
- Physical examination
  - Kayser–Fleischer rings
  - Neuropsychiatric disturbances
- Imaging
  - MRI/CT brain detects changes in the basal ganglia or pons or thalamus
- Laboratory testing
  - Depressed levels of serum alkaline phosphatase for the degree of jaundice
  - Alkaline phosphatase:bilirubin level ratio <4
  - Aspartate aminotransferase/alanine aminotransferase (AST:ALT) >2.2
  - Serum copper >200 μg/dL
  - Serum free copper >20 μg/dL
  - Low ceruloplasmin <20 mg/dL
  - 24 h urinary copper
    - o One hundred micro grams per 24 h (in the presence of Kayser–Fleischer rings)
    - o Forty micro grams per 24 h (in the presence of liver biopsy consistent with Wilson's disease)
- Liver biopsy with hepatic copper >75 μg/g dry weight

The differential diagnosis of Wilson's disease should include [2, 3]:

- Nonalcoholic fatty liver disease
- Acute or chronic hepatitis
  - Viral hepatitis
  - Autoimmune hepatitis/overlap syndromes
- Fatty acid oxidation metabolism disorder
- Mitochondrial disorder

The treatment involves [2, 3]:

- Penicillamine 20 mg/kg/day by mouth to a maximum of 2 g/day
- Trientine 750–1,500 mg by mouth three to four times a day (adults)
- Zinc salts 150 mg by mouth three times a day (adults)
- Liver transplant

References

1. Ferenci P. Pathophysiology and clinical features of Wilson disease. Metab Brain Dis. 2004;19:229–39.
2. Schilsky M. Wilson disease: current status and the future. Biochimie. 2009;91:1278–81.
3. Rosencrantz R, Schilsky M. Wilson disease: pathogenesis and clinical considerations in diagnosis and treatment. Sem Liver Dis. 2011;31:245–59.