- The copper metabolism disorder Wilson’s disease was first defined in 1912 by Alexander Kinnier Wilson’s

- Early-onset presentations in infancy and late-onset

manifestations in adults older than 70 years of age are now well recognized

9month- 76y

Genetics

- Wilson’s disease is a monogenic, autosomal recessive
- condition. The causative gene, ATP7B, encodes a copper transporting P-type ATPase.
- More than 500 ATP7B mutations have now been identified.

- Mutations resulting in completely absent or non-functional ATP7B protein
- activity are associated with early-onset, typically hepatic,
- severe Wilson’s disease; these mutations are comparatively rare

Clinical manifestations

- Neurological symptoms in Wilson’s disease typically
- begin in the second or third decade of life.
- parkinsonism, dystonia
- wing-beating tremor or flapping
- tremor in all types
- dysarthria

- the youngest age of onset being 9 months.
- Although all children diagnosed in early

infancy with genetically confirmed Wilson’s disease

- present with hepatic symptoms,

The most common

- form of tremor in Wilson’s disease is an irregular, and
- somewhat jerky, dystonic tremor.
- Isolated cervical dystonia is nevertheless unlikely to be due to Wilson’s disease
- Dysarthria
- risus sardonicus,

involuntary grimacing with the mouth open and the upper lip contracted

- Pyramidal features, such as pathologically brisk deep
- tendon reflexes, can be present but paralysis is rare

- Seizures might also be
- the presenting symptom of Wilson’s disease; these can
- occur at any stage of the illness, but might be more common after treatment has been initiated.
- Abnormal vertical smooth pursuit has been reported in 85% of

patients

- 20% of people with Wilson’s disease

will have seen a psychiatrist before a formal diagnosis of Wilson’s disease was reached.

psychiatric features

- increased irritability or disinhibition,
- Personality changes, anxiety, and depression.
- Psychosis is much less common.

Cognitive impairment

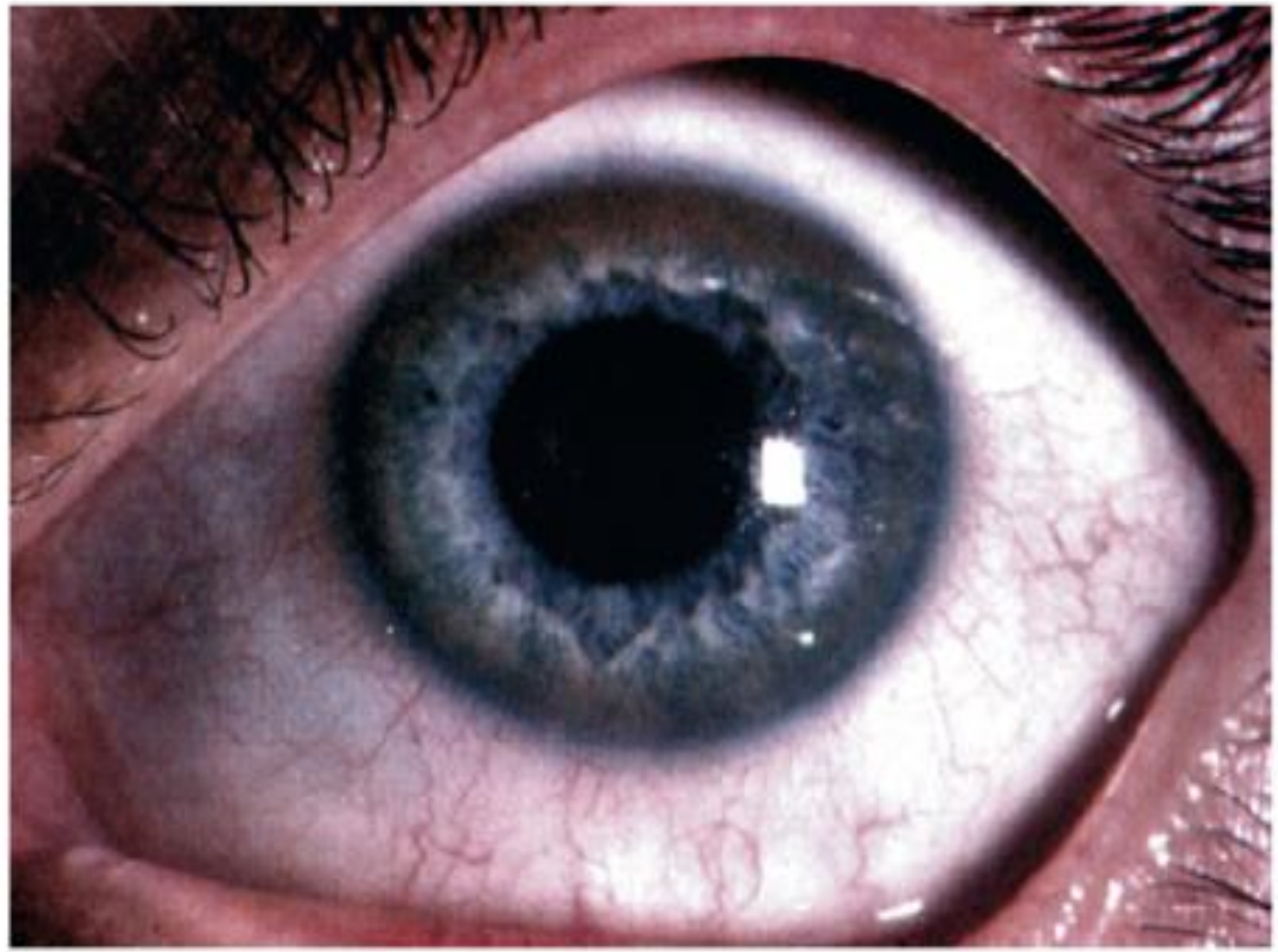
- might be global in patients with advanced,
- impaired executive function involving frontostriatal

circuits

Attention deficits

Ophtalmic involvement

- Kayser-Fleischer rings
- Sun flower catarct



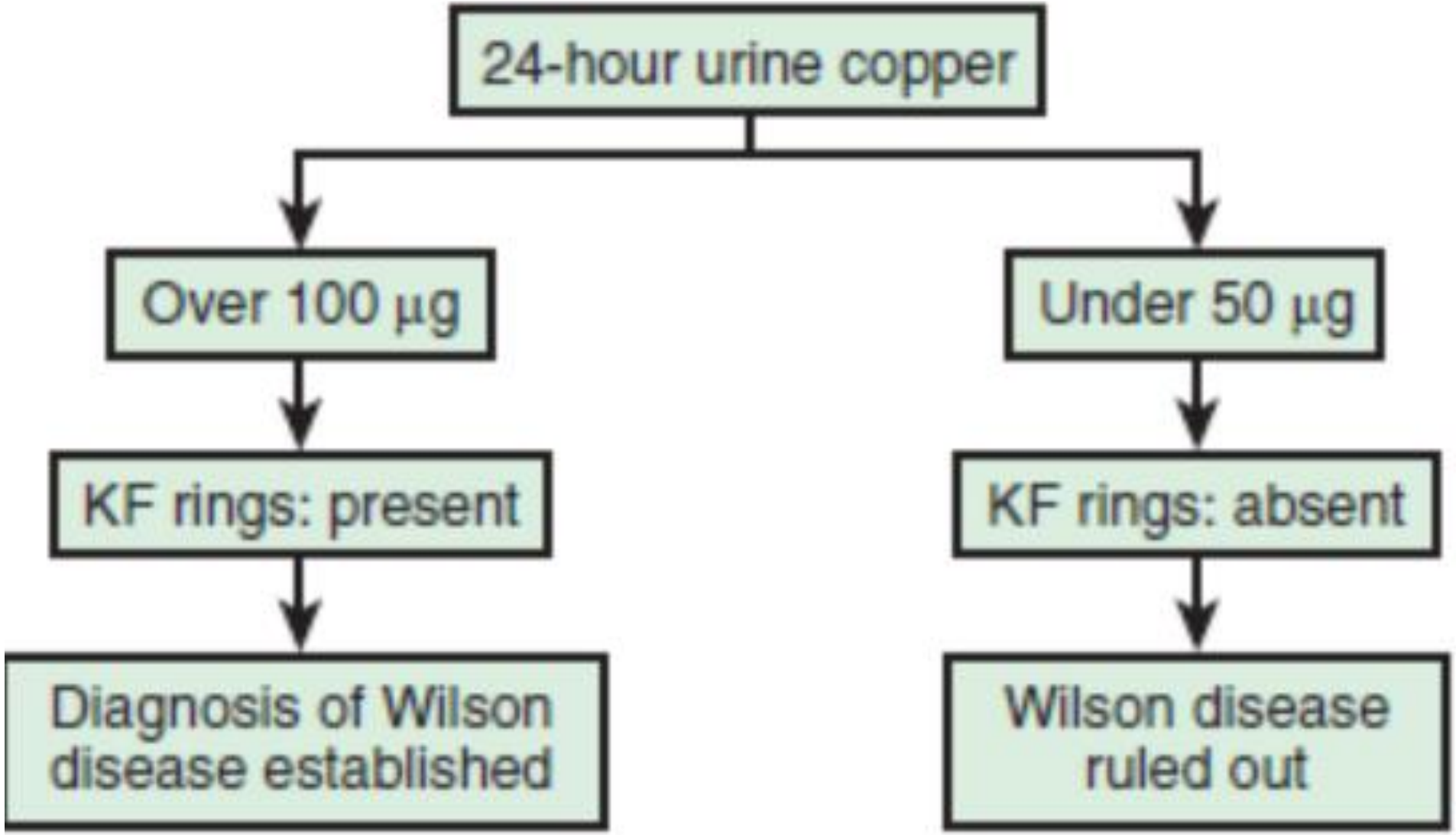
Diagnostic investigations

- Typically, the presence of Kayser-Fleischer rings and serum ceruloplasmin concentrations of less
- than 200 mg/L are sufficient to establish the diagnosis.

Table 24.3 The diagnosis of Wilson disease (WD)

1. Low serum ceruloplasmin (<20 mg/dL)
   False negatives in:
      5% of WD patients
      Pregnancy or birth control pills
   False positives in:
      Heterozygotes
      Severe protein loss
      Severe liver disease
      Menkes disease
2. Kayser–Fleischer ring
   False negatives in:
      Liver WD
      Local eye disease
   False positives in primary biliary cirrhosis
3. Raised 24-hour urinary copper excretion (>100 µg)
   False positives in cholestasis (NB: drugs)
4. Raised liver copper concentration (>250 µg/g dry weight)
   False positives in:
      Biliary cirrhosis
      Cholestasis
      (NB: histology is essential)
5. Genetic linkage studies to chromosome 13

SCREENING AND DIAGNOSIS IN PATIENTS WITH THE NEUROLOGIC/PSYCHIATRIC PRESENTATION



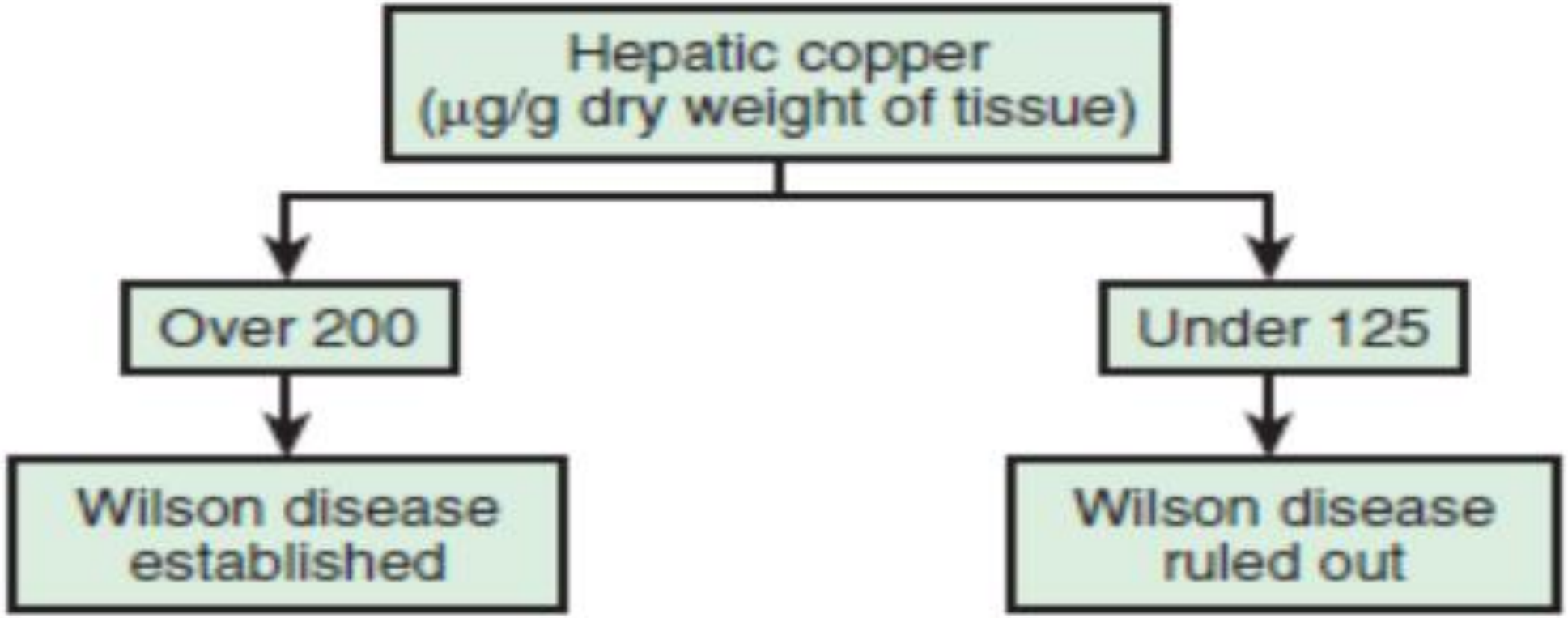
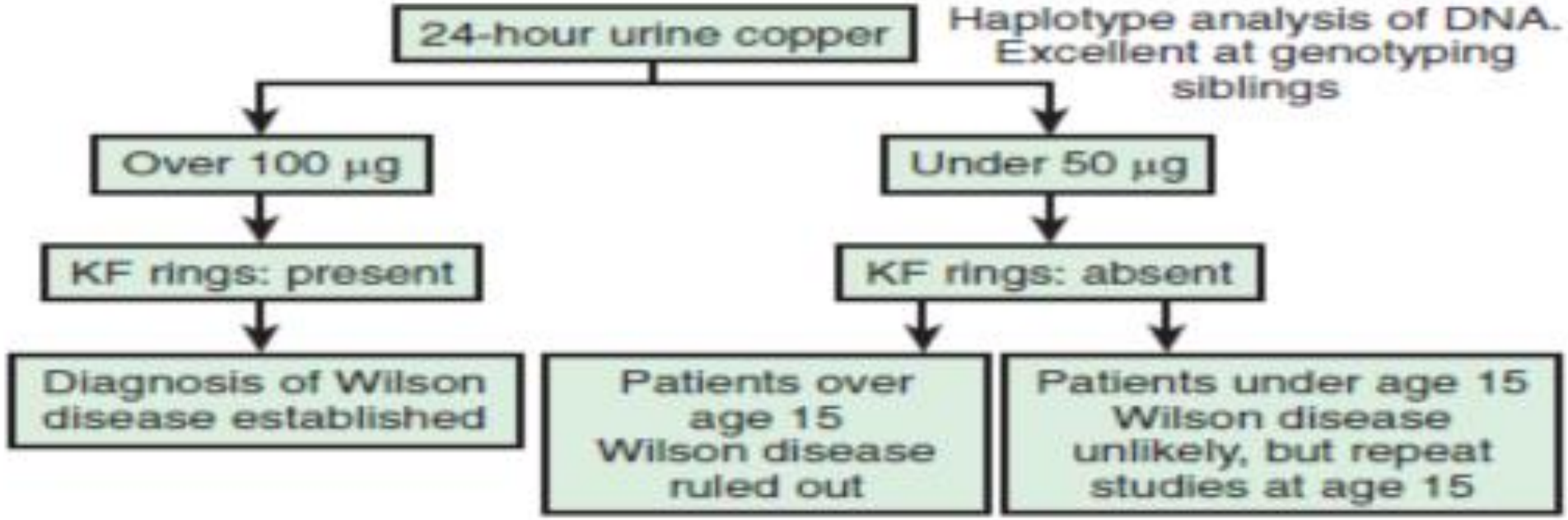
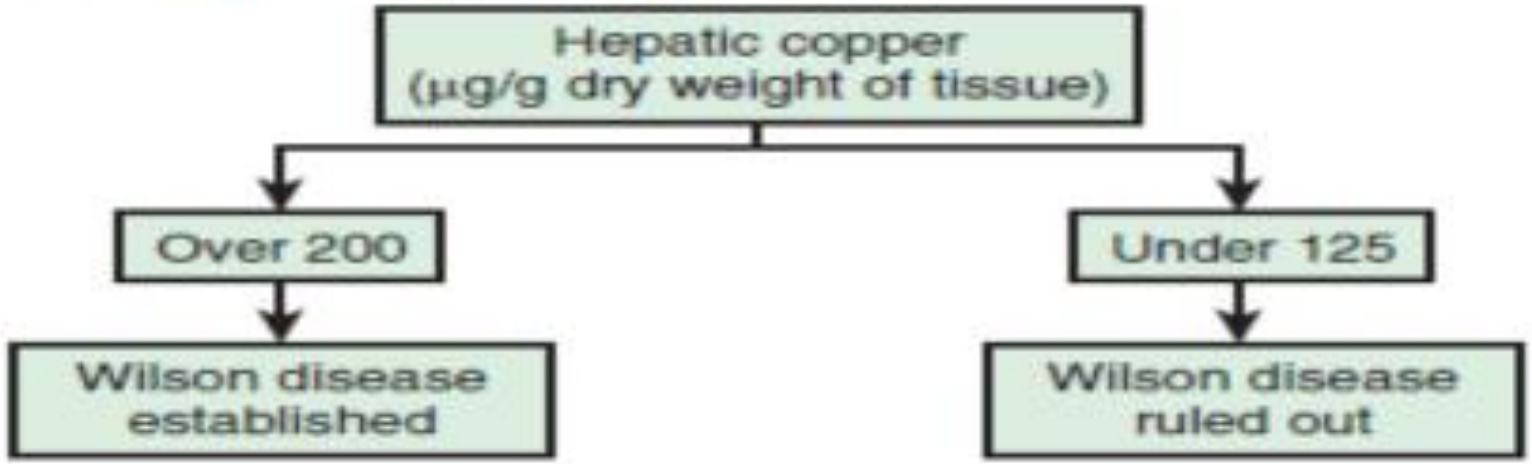


Figure 24.4 An algorithm for screening and definitive diagnosis in pa
with suspicion of Wilson disease. KF, Kayser–Fleischer. *From Brewer GJ. Wil*
disease. In: Hallett M, Poewe W (eds), Therapeutics of Parkinson's Disease and Other

SCREENING AND DIAGNOSIS OF PRESYMPTOMATIC SIBLINGS



If urine copper between 50 and 100 μg, liver biopsy with measure of copper required



- Hepatic copper values greater than 250 µg per
- gram of dry weight (normal 20–50 µg per gram)
- Intermediate values
- (50–200 µg per gram of dry weight liver tissue) suggest
- heterozygote ATP7B mutation carrier status.

screening of relatives

- clinical examination for Kayser-Fleischer rings,
- measurement of copper and ceruloplasmin concentrations.
- genetic testing should also be done

Imaging

- the so-called face of the giant panda sign was
- only detected in 14·3%.
- tegmental hyperintensity
- central pontine myelinolysis-like abnormalities
- signal changes putamen , thalamus, and brainstem
- diffiuse white matter

Treatment

- Medical therapy in Wilson’s disease must be lifelong
- treatment should have two phases:
- acute de-coppering therapy
- maintenance therapy

Table 24.4 Treatment of Wilson disease

1. D-Penicillamine
   - Low and slow: 1 g/day (0.5–2.0) before food
   - Pyridoxine 25 mg/day
   - Avoid copper-rich foods
   - Monitor blood count and liver function tests, serum and urinary copper, Kayser–Fleischer ring
   - Early side effects: allergy (20%) – fever, rash, glands; marrow depression; neurologic deterioration (20–40%)
   - Late problems: nephrotoxicity (proteinuria, nephrotic syndrome); systemic lupus erythematosus; thrombocytopenia; Goodpasture syndrome; dermatopathy; myasthenia
2. Trientine
   - 1–2 g/daily (250–500 mg four times per day)
   - Iron deficiency
3. Zinc (sulfate or acetate)
   - 50–200 mg three times a day
   - Gastrointestinal side effects
4. Tetrathiomolybdate
5. Liver transplant

- Chelating agents bind copper directly in blood and tissues and facilitate its excretion
- zinc interferes with the intestinal uptake of copper.

- The zinc interference mechanism
- includes induction of metallothionein synthesis in
- intestinal epithelial cells; increased metallothionein
- synthesis leads to preferential binding of dietary copper
- to metallothionein in these intestinal cells, which are
- subsequently shed.

- Paradoxical worsening of the clinical neurological
- presentation is reported in up to 20% of patients after
- initiation of chelation therapy with either penicillamine
- or trientine

- A different chelating compound, tetrathiomolybdate,
- might be a promising alternative because it is fast acting

and can restore copper balance within several weeks

- compared with the several months needed when treating

with copper chelators or zinc.

- With zinc, a comparatively long time
- (4–6 months) is needed to generate a negative copper
- balance when used in the initial stages of treatment,
- which might account for reports of non-response or
- worsening under zinc therapy

- A major concern in patients with
- Wilson’s disease on zinc monotherapy is control of the hepatic disease.
- insufficient hepatic treatment efficacy under zinc monotherapy,

Adverse effect

- nephrotoxicity, haematological abnormalities, and
- elastosis perforans serpiginosa (usually on the neck and axillae).
- Adverse events associated with trientine and
- tetrathiomolybdate use include bone marrow toxicity,
- whereas zinc therapy is often associated with
- gastrointestinal discomfort.

monitoring

- serum parameters of copper metabolism,
- urinary copper, and liver function tests.
- Very low urinary copper concentrations and pancytopenia might suggest overtreatment.
- ultrasound screening for hepatocellular carcinoma

Liver transplantation

- acute liver failure (fulminant Wilson’s disease) or decompensated (chronic) cirrhosis
- due to Wilson’s disease.
- Liver transplantation as a treatment option for patients presenting with severe neurological symptoms is controversial