Wilson's disease

1. Wilson's disease

Wilson's disease is a genetic condition which causes intracellular accumulation of copper, resulting in liver disease, neurological symptoms and psychiatric symptoms (NEJM 2023;389:922).

What do we need to know about it in primary care? It is very unlikely we will ever make a diagnosis of Wilson's disease ourselves! However, we may suspect it and refer, or have a patient on our list with known Wilson's disease.

This article was updated in December 2023.

1.1. How common is Wilson's disease?

Not very! It affects 30 people in every million (NEJM 2023;389:922).

1.2. What causes Wilson's disease?

- Wilson's disease is an autosomal recessive condition (Handb Clin Neurol 2017;142:19).
- It is due to a number of different mutations in the gene for ATP7B on chromosome 13 (NEJM 2023;389:922).
- The different mutations (deletions, insertions, etc.) all cause a decrease or absence of ATP7B, which results in copper accumulation (NEJM 2023;389:922).

1.3. When should I suspect it?

Wilson's disease can present at any age, but is more likely to present before 50y (NEJM 2023;389:922).

Copper accumulation initially causes hepatocellular injury. As the disease progresses, neuropsychiatric symptoms are also seen (NEJM 2023;389:922). It is a multisystem condition; suspect if a combination of the following (NEJM 2023;389:922, Cochrane Database Syst Rev. 2017 Sep; 2017(9): CD009739):

System affected	Systems
Liver	Steatosis, hepatitis, acute liver failure or cirrhosis.
Neurological (often affects basal ganglia and so causes movement problems)	Dysarthria: may have drooling or difficulty swallowing. Dystonia or athetosis. Decreased movement, similar to Parkinson's rigidity. There may be poor coordination or loss of fine motor control. This may present as clumsiness, loss of coordination when playing sports or decreased school performance. Tremor: may be a fine tremor (+/- head involvement) or a wing-beating tremor. Cognition is usually maintained.
Psychiatric	Depression, bipolar disorder, psychosis, anxiety, phobias, aggression or antisocial behaviours.
Eyes	Kayser-Fleischer rings (only present about 50% of the time, and less if younger). Sunflower cataracts (central lens opacities, multicoloured and radiating).
Other	Bones: osteopenia or osteoporosis. MSK: arthritis, rhabdomyolysis, muscle weakness. Endocrine: panhypopituitarism, hypoparathyroidism, pancreatitis. Renal: renal tubular dysfunction. Reproductive: amenorrhoea, infertility, testicular dysfunction. Cardiac: arrhythmias, cardiomyopathy. Haematological: haemolysis.

1.4. Tests for Wilson's disease

When we think about Wilson's disease, we think about high copper – but it is intracellular levels that are high; bound serum copper is low (NEJM 2023;389:922):

- When ATP7B functions normally, copper from the portal circulation is processed inside the hepatocyte by ATP7B and packaged up as holo-ceruloplasmin, which circulates extracellularly (i.e. in the blood).
- In Wilson's disease, ATP7B function is decreased or absent so copper accumulates inside the hepatocyte; extracellular holo-ceruloplasmin levels are then reduced.

Because of this, we do not measure serum copper. **Serum ceruloplasmin (the bound form) should be measured, and is usually low in Wilson's disease** (NEJM 2023;389:922).

Test findings (NEJM 2023;389:922, PLoS One 2021;7:e38327):

- Serum ceruloplasmin levels are usually low (although may be normal).
    - A level of <5mg/dL is strongly suggestive of Wilson's disease.
- Liver biochemistry should be measured to assess for hepatocellular injury and synthetic liver function.
- Basal 24h urinary copper excretion is usually >40mcg (why urinary copper is raised is not well understood).

1.5. Referral

If suspected, refer. The diagnosis will be confirmed in secondary care with a liver biopsy and/or genetic testing (NEJM 2023;389:922).

Secondary care may also arrange imaging of other systems, e.g. in those with neurological symptoms, MRI brain often shows basal ganglia abnormalities (NEJM 2023;389:922).

Screening for relatives

If Wilson's disease is confirmed, all first-degree relatives should be offered screening. Screening may involve clinical/biochemical assessment, genetic screening or both (NEJM 2023;389:922).

1.6. Treatment

Without treatment, Wilson's disease is progressive and fatal. With treatment, life expectancy is similar to the general population (NEJM 2023;389:922).

Copper-rich foods should be avoided (dietician input can be helpful), but Wilson's disease cannot be treated by diet alone (NEJM 2023;389:922).

The mainstay of treatment is with copper chelation, e.g. with penicillamine or trientine, which result in urinary excretion of copper (NEJM 2023;389:922, Cochrane Database Syst Rev. 2017 Sep; 2017(9): CD009739, BNF accessed December 2023). Secondary care will advise regarding chelation, but, as a rule of thumb, chelation is advised if (NEJM 2023;389:922):

- Symptomatic disease.

- Asymptomatic disease with signs of organ damage on histology, biochemistry or imaging.

If no signs of organ damage, lower-dose chelation or zinc is usually advised (NEJM 2023;389:922).

Compliance with medication can be a challenge; treatment is usually at least twice daily and needs to be lifelong (NEJM 2023;389:922).

Liver transplant will be considered if (NEJM 2023;389:922):

- Acute liver failure.
- Decompensated cirrhosis that has not responded to medical therapy.

As Wilson's disease is a multisystem disease, many different teams may be involved in care, e.g. hepatology, neurology, psychiatry, genetics, GP, dietician, physiotherapy, occupational therapy and speech and language therapy (NEJM 2023;389:922).

Screening for hepatocellular cancer and oesophageal varices

There is an increased risk of hepatocellular carcinoma and cholangiocarcinoma, but the risk appears to be less than with other chronic liver diseases (NEJM 2023;389:922).

If cirrhosis is present, secondary care should arrange screening for hepatocellular cancer and assessment for portal hypertension and its complications (NEJM 2023;389:922).

See the article *Liver disease and cirrhosis* for more information on the management of cirrhosis.

Wilson's disease

- A rare, autosomal recessive condition.
- Causes abnormal intracellular processing of copper, resulting in intracellular copper accumulation and decreased circulating ceruloplasmin.
- If suspected, refer.
- The mainstay of treatment is with MDT care and lifelong copper chelation.
- Appropriate treatment and compliance results in a life expectancy similar to the general population.

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