Case 47

A 20-year-old woman presented with a 3-day history of jaundice, nausea, and abdominal discomfort. She had noticed dark urine, but had normal stool and no itch. She was born in Poland and had been for a 2-week holiday to Thailand, returning 2 weeks ago. She had previously been fit and well, and was on no medication. She drank <10 units/week. Examination was normal apart from jaundice.

Investigations showed:

- Hb 9.5g/dL, WCC 14 x 10^9/L (10.5 neutrophils), platelets 171 x 10^9/L
- Na 133mmol/L, K 3.7mmol/L, urea 4.2mmol/L, creatinine 98μmol/L
- Bilirubin 377μmol/l, AST 43 IU/L, ALT 69 IU/L, ALP 130 IU/L, albumin 28g/L
- CRP normal
- Prothrombin time 26 sec.

On examination the following day, she looked well, apart from deep jaundice. There was no encephalopathy. Urine output was <30ml/hour.

Further investigations:

- Hb 7.0g/dL, WCC 21.8 x 10^9/L, platelets 144 x 10^9/L
- Blood film: polychromasia, burr cells, microspherocytes; no fragmented cells
- Reticulocytes 6.7% (normal range <2%)
- Prothrombin time 30 sec
- Na 134mmol/L; K 4.8mmol/L; creatinine 164μmol/L
- Bilirubin 489μmol/L; AST 59 IU/L, ALT 42 IU/L, ALP 69 IU/L, albumin 23g/L
- Abdominal ultrasound: no comment on liver texture, splenomegaly (14cm).

Questions

47a) What is the diagnosis?

47b) How is the condition usually diagnosed?

47c) What is the treatment?

47d) What other symptoms can this disorder present with?

47e) Should siblings be screened and if so how?

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Answers

47a) **What is the diagnosis?**

The diagnosis is acute liver failure due to **Wilson's disease**. All other causes of acute liver failure should be considered (see Case 1) and a full liver screen should be carried out, but the haemolysis is characteristic of Wilson's disease. Wilson's disease is a rare autosomal recessive disorder of copper metabolism. The major physiological aberration is excessive absorption of copper from the small intestine and decreased excretion of copper by the liver. The **genetic defect**, localized to chromosome 13q, affects the copper-transporting adenosine triphosphatase gene (ATP7B) in the liver. The process of incorporating copper into caeruloplasmin and excretion of excess copper into bile is impaired in Wilson's disease. As liver copper levels increase, copper is released into the circulation and deposited in other organs.

Symptoms generally present from 6 years to 40 years of age. Hepatic dysfunction is the presenting feature in more than half of patients. The three major patterns of hepatic involvement are:

- Chronic hepatitis (elevated transaminases)
- Cirrhosis (the most common initial presentation)
- Acute hepatic failure.

This case presented with acute hepatic failure and severe coagulopathy; encephalopathy can occur. Acute intravascular haemolysis and early renal failure are clues to the diagnosis. **Haemolysis** is due to rapid release of copper into the circulation, which also causes acute renal tubular dysfunction. Acute viral hepatitis is usually the working diagnosis, because the patient is not suspected of having underlying liver disease. An important clue to Wilson's disease is the **disproportionately low serum AST** (usually much less than 1500 IU/L), which would be exceptional in acute viral hepatitis. The ALP is usually in the normal range or even low for age, and the serum **bilirubin is disproportionately elevated** because of haemolysis. However, biochemical indices are not specific. The acute presentation of Wilson's disease is more common in women than in men (4:1 ratio).

47b) **How is the condition usually diagnosed?**

The diagnosis is confirmed by measurement of serum caeruloplasmin, urinary copper excretion, hepatic copper content, and the detection of Kayser–Fleischer rings. A patient with the classic combination of chronic

liver disease, tremor or dystonia, and Kayser–Fleischer rings is readily diagnosed, but such patients are exceptional. There are two major disturbances of copper deposition in Wilson's disease: a reduction in the rate of incorporation of copper into caeruloplasmin, and a decrease in the biliary excretion of copper. Table 47.1 shows typical levels in a patient with Wilson's disease compared with the normal reference ranges.

Serum caeruloplasmin: many patients with Wilson's disease have a caeruloplasmin within the normal range. Caeruloplasmin is an acute phase protein, and increases in response to inflammation, pregnancy, oestrogen use, or any infection. Falsely low caeruloplasmin concentrations may occur in any protein deficiency state, including nephrotic syndrome, malabsorption and protein-losing enteropathy. Caeruloplasmin levels may also be low in 10–20% of heterozygotes for the Wilson's disease gene, but who do not develop the disease and do not require treatment.

Serum copper concentration is low, in parallel with the low serum caeruloplasmin, in most patients with Wilson's disease. Very high levels are detected in acute liver failure, because of rapid release of copper from the liver.

Urinary copper excretion rate is >100μg/d (reference range, <40μg/d) in most patients with symptomatic Wilson's disease. The rate may also be elevated in other cholestatic liver diseases. Both the sensitivity and the specificity of this test are insufficient for it to be used as a screening test, but it usefully confirms the diagnosis and helps to evaluate response to chelation therapy. A provocative test of urinary copper excretion in which penicillamine (500mg orally every 12 hours) is given while a 24-hour urinary collection is obtained sometimes provides useful information: a normal person excretes as much as 20 times the baseline level

Table 47.1 Copper measurements in Wilson's disease and normal individuals

Measurement	Wilson's disease	Normal adults
Serum caeruloplasmin	0–200	200–350
Serum copper (μg/L)	190–640	700–1520
(μmol/L)	3–10	11–24
Urinary copper (μg/day)	100–1000	<40
(μmol/day)	>1.6	<0.6
Liver copper (μg/g dry weight)	>200	20–50

after penicillamine, but a urinary excretion of >25μmol of copper 24 hours after penicillamine is diagnostic of Wilson's disease.

Hepatic copper concentration is the gold standard for diagnosis of Wilson's disease. A liver biopsy with sufficient tissue reveals levels >250μg/g of dry weight, even in asymptomatic patients. This assumes the absence of cholestatic liver disease, which leads to reduced biliary secretion and copper accumulation in the liver. A normal hepatic copper concentration (reference range 15–55μg/g) effectively excludes the diagnosis of untreated Wilson's disease.

Kayser–Fleischer rings: slit-lamp examination may reveal Kayser–Fleischer rings. These are found at the limbus and are caused by copper deposition in Descemet's membrane in the cornea. A careful slit-lamp examination is mandatory and can be the most rapid way of making the diagnosis: it is only visible on direct inspection when iris pigmentation is light and copper deposition is heavy. Kayser–Fleischer rings are observed in up to 90% of individuals with symptomatic Wilson's disease, and are almost invariably present in patients with neurological manifestations. Kayser–Flesicher rings may be absent in 10–50% of patients with exclusively hepatic involvement, and in presymptomatic patients. Consequently, the absence of Kayser–Flesicher rings does not exclude the diagnosis, and are no longer considered pathognomonic of Wilson's disease unless accompanied by neurological manifestations. They have been observed in patients with chronic cholestatic disorders, such as partial biliary atresia, primary biliary cirrhosis, and primary sclerosing cholangitis.

47c) **What is the treatment of this condition?**

Patients with **fulminant hepatic failure** from Wilson's disease need immediate referral for **liver transplantation**, because such patients do not respond well to chelation treatment.

Patients with a prognostic index (Table 47.2) of >7 should be considered for liver transplantation. Our patient had a score of 8. Most patients who exceed a score of 7 die within 2 months of diagnosis unless they have a liver transplant. Prognosis after liver transplantation is good. In a study of 55 patients with Wilson's disease who underwent transplantation, the 1-year survival rate was 79%, and overall survival rate was 72% 20 years after transplantation.

The mainstay of therapy for Wilson's disease is the use of **chelating agents** and medications that block copper absorption from the gastrointestinal tract (Table 47.3). There are three recognized treatments:

Table 47.2 Prognostic index in fulminant Wilson's disease

Score	0	1	2	3	4
Serum bilirubin (mmol/L)	<100	100–150	151–200	201–300	>300
Serum AST (IU/L)	<100	100–150	151–200	201–300	>300
Prolongation of prothrombin time (seconds)	<4	4–8	9–12	13–20	>30

- Penicillamine
- Trien (trientine)
- Zinc.

With effective chelation therapy, most patients live normal, healthy lives. Early treatment is critical, and outcome is best for patients in whom the disease is diagnosed and treatment initiated before the disease causes symptoms. There is a potential role for gene transfer therapy in the future.

47d) **What other symptoms can this disorder present with?**

Neuropsychiatric: most patients who have neuropsychiatric manifestations also have cirrhosis. The most common neurological feature

Table 47.3 Medical treatment of Wilson's disease

Drug	Mechanism	Dose	Monitoring for efficacy	Monitoring for side effects
Penicillamine	Increases urinary excretion of copper	Initially 1–1.5g/d, Maintenance: 1g/day	Urinary copper excretion 500–800μg/d Estimated non-caeruloplasmin-bound copper <100μg/L	Full blood count (thrombocytopenia, leucopenia, aplastic anemia) Urinalysis (proteinuria) Examine skin for rashes
Trientene	Increases urinary excretion of copper May impair intestinal absorption of copper	1–1.2g/day	As with penicillamine	Full blood count Iron studies
Zinc	Interferes with copper absorption, increases copper excretion in stools	Initially 50mg three times/day Maintenance: titrate against efficacy	24-hour urinary copper 200–400μg/day Estimated non-caeruloplasmin bound copper <100μg/L	Serum Zn

is **asymmetric tremor**, occurring in half of individuals with Wilson's 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, mask-like facies, clumsiness, and personality changes. Late manifestations (now rare because of earlier diagnosis and treatment) include dystonia, spasticity, grand mal seizures, rigidity, and flexion contractures. Psychiatric features include emotional lability, impulsiveness, disinhibition, and self-injurious behaviour. About 10–20% of patients present with psychiatric symptoms and the cause may be overlooked.

Musculoskeletal: osteopenia is common in Wilson's disease. An **arthropathy** resembling premature osteoarthritis generally involves the spine and large appendicular joints, such as knees, wrists, and hips. Symptomatic joint disease occurs in 20–50%, usually late in the course of the disease and frequently > 20 years of age. Osteochondritis dissecans, chondromalacia patellae, and chondrocalcinosis have also been described.

Haematological: haemolytic anaemia is a rare (10–15%) but characteristic complication of the disease, usually in conjunction with acute hepatic presentations.

Renal: the gene is expressed in kidney tissue, so any renal manifestations may be primary or secondary to release of copper from the liver. Patients resemble those with Fanconi's syndrome, with defective renal acidification and excess **renal losses of amino acids**, glucose, fructose, galactose, pentose, uric acid, phosphate, and calcium. Urolithiasis, found in up to 16% of patients, may result from hypercalciuria or poor acidification. Haematuria and nephrocalcinosis are reported, as are proteinuria and peptiduria. Both can occur as part of the disease process or after therapy as an adverse effects of penicillamine.

47e) **Should siblings be screened and if so how?**

More than 300 mutations in the ATP7B gene for Wilson's disease have been detected. Genetic markers that closely flank the gene are used for pre-symptomatic diagnosis of siblings of a known patient, when the patient and parents are available for testing. Overt symptoms of Wilson's disease have not been reported in heterozygotes. In the absence of marker analysis, screening should include a physical examination, liver biochemical tests, serum copper and caeruloplasmin levels, 24-hour urinary copper measurement, and careful slit-lamp examination.

Further reading

Perri RE, Hahn SH, Ferber MJ (2005). Wilson Disease – keeping the bar for diagnosis raised. *Hepatology*; **42**: 974.

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