

diagnosis before referral in half of the patients in this study. Indirect immunofluorescence or solid phase immunoassays to detect antibodies to the cytoplasm of neutrophils are becoming more widely available and have greatly helped in diagnosis.

We suggest that patients who present to their general practitioners with persistent non-specific symptoms should have a urine dipstick test followed by blood tests and urgent referral to hospital if necessary; figure 2 shows an algorithm to illustrate this. Hospital doctors should be aware of the speed and accuracy with which current assays can confirm a diagnosis of rapidly progressive glomerulonephritis. This approach should

reduce the morbidity and mortality associated with this group of diseases.

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Lesson of the Week

Wilson's disease in adults with cirrhosis but no neurological abnormalities

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Adults with Wilson's disease may present with liver disease without neurological symptoms

The classic description of Wilson's disease is a progressive dystonic neurological disorder in young adults who have a chronic liver disease determined by examination, investigation, or at necropsy. A progressive accumulation of copper in the liver and spillover to the brain is well established. The cause of the hepatic copper retention remains unknown, although defective incorporation of copper into caeruloplasmin and decreased biliary excretion of copper have been suggested.^{1,2} It is well accepted that patients with Wilson's disease often present with liver disease alone in childhood and early adult life, and it is generally agreed that Wilson's disease is the most common definable cause of chronic liver disease in later childhood.^{1,3} The fallibility of the standard diagnostic tests for Wilson's disease in this age group is also well recognised: Kayser-Fleischer rings may be absent and serum copper and caeruloplasmin concentrations may be normal or near normal.^{1,3} The copper content of the liver and profile of clearance of copper-64 from the blood⁴ must be estimated in these cases.

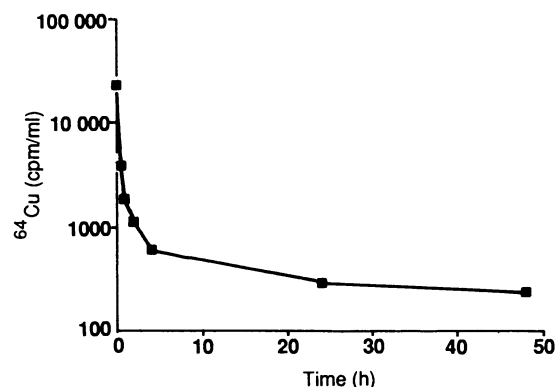
Wilson's disease is not generally considered in patients aged over 30 presenting with liver disease without neurological signs, and the fallibility of standard tests in such patients is not well recognised. Indeed, most reports of large series of patients with Wilson's disease include no such case. Scheinberg and Sternlieb mention two patients aged 30 to 35,² and another study briefly mentions four patients with onset at 37, 37, 47, and 55 years of age but gives no clinical details or results of tests.⁵ The man aged 55 was probably the same one described in another report⁶: he had Kayser-Fleischer rings, low serum caeruloplasmin and copper concentrations, and an abnormal rate of copper clearance.

We report on four adults with Wilson's disease aged 43-58 who presented within 12 months with chronic or acute on chronic liver disease without neurological symptoms in whom assay of hepatic copper content or clearance of ⁶⁴Cu from the blood, or both, were required to diagnose their condition.

Case reports

Case 1—A man aged 43 presented with general malaise, loss of energy, and mild jaundice. He had a history of pulmonary sarcoidosis, which had

been diagnosed when he was 34 and treated with corticosteroids; vitiligo for 10 years; and steatorrhoea due to pancreatic insufficiency, which had been diagnosed when he was 40 and treated with pancreatic enzyme replacement. None of the known hepatitis viruses could be identified, autoantibody tests yielded negative results, and his alcohol intake was minimal. Kayser-Fleischer rings were not visible with a slit lamp, and his serum copper concentration was normal (24 µmol/l). A liver biopsy showed cirrhosis with no features of cholestasis or primary biliary cirrhosis, but the copper content had not been measured. His rate of clearance of ⁶⁴Cu was measured by injecting the isotope intravenously and taking serum samples at 0, 5, and 30 minutes and 1, 2, 4, 24, and 48 hours. The results were typical of Wilson's disease (figure). After six



Clearance of intravenously injected ⁶⁴Cu in patient with Wilson's disease

months of treatment with penicillamine (500 mg twice daily) and zinc sulphate (220 mg (50 mg zinc) three times daily) his liver function improved. Wilson's disease was excluded in his younger sister by testing her clearance of ⁶⁴Cu.

Case 2—A 48 year old man was diagnosed as suffering from cirrhosis after hepatomegaly was noted as an incidental finding. He had no relevant symptoms or history. He had never drunk alcohol, none of the known hepatitis viruses could be identified, and no autoantibodies were detected. He had no Kayser-Fleischer rings, and his serum copper and caeruloplasmin concentrations were normal (22 µmol/l

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and 430 mg/l respectively). A liver biopsy showed no evidence of cholestasis or primary biliary cirrhosis. Wilson's disease was diagnosed by measuring clearance of ^{64}Cu and further confirmed by finding a copper content of 1164 $\mu\text{g/g}$ dry weight in a sample of liver obtained by needle biopsy. Penicillamine (1 g twice daily) increased his copper excretion to an adequate rate ($>25 \mu\text{mol/day}$) even while zinc sulphate (220 mg three times daily) was given, and his liver function improved.

Case 3—A 44 year old woman presented with acute hepatorenal failure with bleeding, coma, and anuria and died within 24 hours despite intensive care and haemofiltration. She had suffered jaundice and general ill health for two months and had developed ascites some days before referral. Her very rapid deterioration was associated with *Escherichia coli* septicaemia. A serum copper concentration of 28 $\mu\text{mol/l}$ and caeruloplasmin concentration of only 140 mg/l (copper content 7 $\mu\text{mol/l}$) suggested Wilson's disease, but no Kayser-Fleischer rings were seen. Her high plasma concentration of free copper persisted after haemofiltration (43 $\mu\text{mol/l}$), and at necropsy her liver and kidney copper concentrations were 717 and 749 $\mu\text{g/g}$ dry weight respectively. Her liver showed chronic hepatitis with Mallory's bodies and infiltration of fat but not primary biliary cirrhosis or chronic cholestasis. No autoantibodies or hepatitis viruses were detected. One of her brothers had died in his 20s of unknown cause.

Case 4—A 58 year old woman presented with acute hepatorenal failure and died 36 hours later despite intensive resuscitation. She had been unwell with jaundice and anorexia for one week and vomiting for two days. Her serum copper concentration was 11.4 $\mu\text{mol/l}$ and caeruloplasmin concentration 120 mg/l. Her eyes were not examined for Kayser-Fleischer rings. Necropsy showed massive subacute hepatic necrosis but no evidence of primary biliary cirrhosis or any other cholestatic liver disease. Positive staining for copper led to analysis of the hepatic copper content, which was 1199 $\mu\text{g/g}$ dry weight. Her sister had died of cirrhosis and liver failure aged 28.

Discussion

Wilson's disease is diagnosed if the profile of clearance of ^{64}Cu from plasma is typical of the disease or there is a great increase in the concentration of copper in the liver. None of our patients had antimitochondrial antibodies or histological evidence of primary biliary cirrhosis or other conditions that might be confused with Wilson's disease. All four patients were unusual as they had only liver disease and no neurological symptoms or signs at ages of 43, 44, 48, and 58 years. Two presented with rapidly progressive liver failure. Three were examined for Kayser-Fleischer rings with negative findings. Only one woman (case 3) had diagnostic abnormalities of serum copper and caeruloplasmin concentrations.

Our observations suggest that there may be other adults with liver disease due to undiagnosed Wilson's disease, and we believe that a more aggressive approach to diagnosis is needed. As is now accepted in childhood, perhaps all adults with persistent or severe liver disease without clearly defined cause should be regarded as having Wilson's disease until this diagnosis is firmly dismissed. This attitude is justified because Wilson's disease is one of the few treatable causes of severe liver disease.

Although other tests can often be used to diagnose Wilson's disease, the most reliable method of ruling out this diagnosis in a patient with cirrhosis is to show a

normal concentration of copper in the liver. Most patients with persistent liver disease require liver biopsy for histological assessment, but histological staining for copper is not sufficiently reliable for this purpose. Clearance of ^{64}Cu from the blood can be a valuable diagnostic indicator as it detects one of the fundamental disturbances in Wilson's disease, the defective incorporation of copper into caeruloplasmin. A large pool of copper in the liver of patients with other liver diseases may dilute the isotope and slow the normal rise in serum radioactivity but does not usually produce the continued fall in radioactivity seen in patients with Wilson's disease.

We recommend the following protocol:

If a liver biopsy is performed the copper content of the sample should be measured. Concentrations below 150 $\mu\text{g/g}$ dry weight exclude Wilson's disease, and those above 500 $\mu\text{g/g}$ dry weight (in the absence of histological and other features of primary biliary cirrhosis or other chronic cholestatic processes) are strongly suggestive of Wilson's disease. Patients with intermediate concentrations should be investigated further.

If a liver biopsy is not performed or further investigations of copper concentration are required serum copper and caeruloplasmin concentrations should be assayed. A low caeruloplasmin concentration ($<200 \text{ mg/l}$) with a less severely reduced serum copper concentration ($<12 \mu\text{mol/l}$) and increased free copper concentration ($>6 \mu\text{mol/l}$) supports a diagnosis of Wilson's disease. A 24 hour urinary excretion of copper greater than 3 μmol a day or the presence of Kayser-Fleischer rings on examination of the eyes with a slit lamp also strongly supports diagnosis.

If the diagnosis is still in doubt the clearance of copper from the blood should be measured with ^{64}Cu .² A continued fall in radioactivity in the plasma throughout 48 hours strongly supports the diagnosis; a doubling of plasma radioactivity between two hours and 48 hours is normal; and a subnormal increase between two hours and 48 hours is seen in hepatic accumulation of copper secondary to other forms of liver disease.

In acute fulminant liver disease the hazard of liver biopsy may be considered unacceptable and results of studies with copper radioisotopes may be difficult to interpret. Fortunately, the results of assays for copper and caeruloplasmin in plasma and urine are often diagnostic if correctly interpreted. The concentration of free (non-caeruloplasmin) copper is generally very high ($>15 \mu\text{mol/l}$) as is the rate of urinary copper excretion ($>5 \mu\text{mol/day}$). Anuria, however, may prevent the urinary copper excretion from being assessed. The free copper concentration (normal range 2-5 $\mu\text{mol/l}$) can be estimated by subtracting the calculated caeruloplasmin copper concentration (caeruloplasmin concentration in $\text{mg/l} \times 3 \div 63.5 \mu\text{mol/l}$) from the measured plasma copper concentration.

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