A homesick student

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A 20-year-old, right-handed female student presented to a neurology clinic having developed depressive symptoms and become withdrawn. Her problems were initially attributed to homesickness. Over the next few months her condition gradually deteriorated. She developed drooling of saliva and retching and her speech became slurred. Her handwriting deteriorated and she was unsteady on her feet. There was urgency of micturition. These various symptoms had resulted in referral to ear, nose and throat and psychiatric services. A computed tomography (CT) scan of brain had been normal.

When first seen at the neurology clinic she was euphoric and mildly dysarthric with drooling. External appearances of the eyes were as shown in figure 1, funduscopy and eye movements being normal. There were dyskinetic movements of all four limbs with dystonic postures of the arms in flexion and adduction. There was normal power in all limbs with symmetrical reflexes. The left plantar response was extensor. She had mildly impaired concentration abilities but orientation and short-term recall appeared normal. There was a reduction in spontaneous speech output. Magnetic resonance imaging (MRI) of the brain was performed (figure 2). Full blood picture, renal function and liver function tests were all normal.

Figure 1 Corneal photograph of right eye

Questions

- 1 What does the corneal photograph show and what diagnosis does this suggest?
- 2 What biochemical tests would confirm the diagnosis?
- 3 What do the MRI scans show?
- 4 How would you treat this patient?
- 5 How should her family be managed?

Figure 2 MRI scans of brain, T2-weighted images (TR 4000 ms, TE 76 ms)

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Answers

QUESTION 1

The corneal photograph in figure 1 illustrates golden brown discolouration of the limbic region. This is a Kayser-Fleischer ring and is caused by copper deposition in Descemet's membrane. Given the history and clinical findings of a movement disorder, this suggests a diagnosis of Wilson's disease, although the rings themselves are not pathognomonic of the disorder, also being found in primary biliary cirrhosis, cryptogenic cirrhosis and chronic cholestasis.

QUESTION 2

Serum copper and caeruloplasmin should be measured, both of which would be expected to be low in value, whilst urinary copper excretion, which would be expected to be high, should be assessed by means of a 24-h collection. In this patient the following values were obtained: serum caeruloplasmin 0.03 g/l (normal range 0.21–0.58 g/l), serum copper 6.4 $\mu\text{mol/l}$ (12.6–26.7); urinary copper 5.0 $\mu\text{mol/24 h}$ (0.2–1.6).

QUESTION 3

The MRI scan of brain in figure 2 shows bilateral and symmetrical areas of abnormal increased signal intensity in the putamen and caudate nuclei (A), and midbrain (B).

QUESTION 4

Active management in cases of neurological Wilson's disease involves both dietary and pharmacological measures. Professional dietary advice and assessment is essential, the aim being to reduce dietary copper intake to < 1 mg/day. This involves avoidance of foods relatively rich in copper such as liver, mushrooms, cocoa, chocolate, nuts and shellfish.

D-Penicillamine has been a mainstay of treatment since its first use in 1956.¹ It is an effective copper-chelating agent which produces negative copper balance and subsequent detoxification of affected tissues. However, problems may arise with this compound in that sensitivity occurs in up to 20% of treated cases with the development of fever, leucopenia, rash and arthralgia. More seriously, it has been found that disastrous worsening can occur in as many as 50% of those with a neurological presentation treated with this drug, many of whom never recover.² A suggested mechanism for this is that the initial mobilisation and redistribution of hepatic copper causes higher levels of copper in critical areas of the brain. Another larger retrospective series has, however, shown that the initial deterioration with chelation therapy occurs less frequently (~21%) and may not be so crucial, with two-thirds of patients so affected eventually considered to have a good or very good outcome.³

Trientine dihydrochloride is another recently developed chelating drug. Although it has a similar mechanism of action to penicillamine and is therefore likely to share some of its toxicities, these may occur less frequently.

Because of these specific concerns regarding the use of chelating agents in neurological Wilson's disease, our patient was treated with a combination of zinc sulphate and a new agent, ammonium tetrathiomolybdate. Rather than causing a rapid mobilisation of copper, zinc acts by blockage of absorption of food copper and by blockage of reabsorption of endogenously secreted copper and puts the patient into a consistent negative copper balance in a way that does not suddenly cause an intense redistribution of copper.⁴ Ammonium tetrathiomolybdate forms a tripartite complex with copper and protein which renders the copper unavailable for uptake and removes it from toxic pools. There is evidence to suggest that this compound is more efficacious and better tolerated than penicillamine, with neurological deterioration being rare and recovery good to excellent in the majority of cases.⁵ As our patient regained independent mobility with resolution of her movement disorder and improvement in her speech, this report adds to the literature indicating the effectiveness of molybdate.

QUESTION 5

The early diagnosis of Wilson's disease is essential because many of the neurological features may not be fully reversible. As it has an autosomal recessive mode of inheritance, other siblings of the index case have a 25% chance of also being affected. Evidence of disease in as yet asymptomatic individuals should be sought by screening tests, including evaluation of urinary copper excretion and serum caeruloplasmin concentration.

Discussion

Wilson's disease is an autosomal recessive disorder characterised by a defect in copper metabolism; copper is unique among cations in that its balance is regulated by the liver. Although the exact nature of the defect is unclear, it causes a continual increase in tissue copper concentrations that become toxic to the liver, brain, kidney, eye and other organs. The responsible gene has been mapped to chromosome 13 and this has been cloned and found to encode for a cation-transporting P-type ATPase.⁶ Over 40 mutations in the gene have been found to be associated with the disease and there is some evidence to suggest that the extent of the genetic defect correlates with clinical severity, in that larger defects may result in the development of symptoms at an earlier age.

Hepatic presentation is the most common form in childhood, neurological presentation being most often observed, as in this case, in the late teenage years or adulthood. The mode of onset is very variable and often non-specific, making diagnosis initially difficult. Personality change is estimated to be the initial symptom in 32% of cases, other common symptoms at onset being speech disturbance, deterioration in school work, tremor, ataxia, drooling and dysphagia.⁷ The same large series of 136 patients found that the correct diagnosis was

Clinical features of advanced neurological Wilson's disease

- dysphagia and drooling
- rigidity
- bradykinesia
- flexed postures
- fixity of facial muscles with mouth agape
- virtual anarthria
- slow saccadic eye movements
- cerebellar ataxia

Box 1

made on first consultation with a doctor in less than one-third of cases. A diagnosis of psychiatric illness was made in almost 25% of cases, with a similar proportion given an organic diagnosis other than Wilson's disease. A classic misdiagnosis can arise from referral for a psychiatric opinion, where extrapyramidal features may be interpreted as being due to neuroleptic medication.

Apart from the common hepatic, neurological and psychiatric presentations, other organs may also be involved. Renal manifestations are many, with hypercalciuria and nephrocalcinosis being described. Proximal tubular dysfunction can result in Fanconi's syndrome with generalised aminoaciduria, glycosuria, hyperuricosuria and phosphaturia. Osteomalacia may result from phosphate wasting and chondrocalcinosis and osteoarthritis may arise from copper accumulation. Rapid uptake of copper into erythrocytes may produce an acute haemolytic anaemia. Myocardial involvement is reported and, in addition to Kayser-Fleischer rings, 'sunflower' cataracts may be seen in the eyes.

Previous MRI studies of the brain have indicated a predilection for copper deposition in certain areas, particularly the basal ganglia, cerebral white matter, midbrain, pons and cerebellum.⁸ Such a distribution has been demonstrated in this case and is borne out by the classic clinical syndrome manifest by patients with advanced disease (box 1). The onset can, however, be insidious and non-specific as illustrated here, with behavioural problems and intellectual decline preceding the onset of hard neurological signs and movement disorders.

One of the characteristic stigmata of Wilson's disease are Kayser-Fleischer rings, deposits of copper producing golden-brown discolouration in the peripheral cornea. Their earliest appearance consists of coloured crescents at the superior and inferior quadrants of the cornea that eventually become circumferential. Until recently they had been considered pathognomonic for Wilson's disease but several associations are now known (box 2). They had also been considered an invariable component in patients with neurological involvement but exceptions have recently been documented.⁹ As in this case, the rings may be readily

Diseases associated with Kayser-Fleischer rings

- Wilson's disease
- primary biliary cirrhosis
- chronic cholestasis
- cryptogenic cirrhosis

Box 2

Wilson's disease: learning points

- neurological presentation is more common in late adolescence and adulthood
- behavioural problems and cognitive decline may precede other neurological signs
- normal liver function tests do not preclude the diagnosis
- serum caeruloplasmin is normal in 5% of cases
- Kayser-Fleischer rings can only be excluded by slit-lamp examination
- penicillamine may cause irreversible deterioration in neurological manifestations
- ammonium tetrathiomolybdate should be considered as a first-line therapy
- potentially presymptomatic siblings must be identified by screening test

Box 3

detected by the naked eye. However, in other circumstances they may be easily missed unless sought by an experienced ophthalmologist using a slit-lamp.

In conclusion, this case illustrates the importance of contemplating the diagnosis of Wilson's disease in young patients presenting with behavioural disorders, extrapyramidal, or cerebellar signs since, although uncommon, it is so eminently treatable if recognised early and managed appropriately. Kayser-Fleischer rings are a characteristic feature but are neither pathognomonic for, nor an essential element in, those with neurological manifestations of the disease. Normal liver function tests do not preclude the diagnosis. Although the most appropriate initial treatment is not clearly established, caution should be exercised in the use of penicillamine and alternative therapy with zinc sulphate and/or ammonium tetrathiomolybdate should be considered. Finally, since prophylactic therapy in affected but presymptomatic patients can prevent the onset of symptomatic disease, the prompt diagnosis of affected presymptomatic siblings by means of screening tests should be a priority.

Final diagnosis

Wilson's disease.

Keywords: Wilson's disease; Kayser-Fleischer rings; copper; penicillamine; ammonium tetrathiomolybdate

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Images in medicine

Pneumatosis cystoides intestinalis

A 64-year-old woman was admitted to our hospital for a closer examination of occult blood in the stool. She appeared to be healthy, but physical examination revealed a soft elastic mass in her right lower abdomen. Laboratory examinations showed no abnormality of blood chemistry and that red and white blood cell counts were within the normal ranges. Abdominal X-ray revealed numerous round radiolucencies in the right side of the colon (figure

1), which were shown as honeycomb-like lesions by computed tomography. Total colonoscopy showed multiple submucosal cysts containing gas in the ascending and transverse colons (figure 2). She was therefore diagnosed as having pneumatosis cystoides intestinalis.

We should bear in mind that pneumatosis cystoides intestinalis can be easily diagnosed by the characteristic numerous round radiolucencies on abdominal X-ray, which can eliminate unnecessary invasive and expensive further examinations.

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Figure 1 Abdominal X-ray

Figure 2 Colonoscopic findings of the transverse colon