PICTURE QUIZ

Eye sign in an 18 year old man with psychosis

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An 18 year old man presented after developing progressive dysarthria and abnormal limb postures. From the age of 15 he had been increasingly irritable, belligerent, and difficult to discipline. He played truant from school, wandered aimlessly around the city claiming to be a dynamic entrepreneur, and heard voices plotting against him. Examination revealed psychosis, severe dysarthria, and generalised dystonia with prominent oromandibular involvement. A diagnostic eye sign was noted (fig 1). Treatment for 18 months led to considerable clinical improvement and regression of the abnormality in the eye.

Fig 1 Diagnostic eye sign

Questions

1 What is the eye sign shown?
2 What clinical features and investigations can support the diagnosis?
3 How can it be treated and what is the prognosis?

Answers

Short answers

1 The eye sign shown is Kayser-Fleischer rings—greenish discoloration at the outer corneal circumference (fig 2). This abnormality was named after ophthalmologists Bernhard Kayser and Bruno Fleischer, who described the sign independently in the early 1900s. The rings were later recognised to be copper deposits and diagnostic of Wilson’s disease.

Fig 2 Kayser-Fleischer rings, visible as a greenish ring at the outer corneal surface (arrow)

2 The combination of psychosis, extrapyramidal features (dystonia), and Kayser-Fleischer rings is classic for Wilson’s disease. A positive family history, low serum ceruloplasmin, high 24 hour urinary copper excretion, high liver copper, and the results of brain magnetic resonance imaging will support the diagnosis.

3 Untreated Wilson’s disease is fatal. Early diagnosis and lifelong copper chelation, with close clinical monitoring, are essential. The chance of neurological recovery is high.

Long answers

1 Eye sign

Wilson’s disease (hepatolenticular degeneration) is an autosomal recessive disorder of copper metabolism, named after Samuel AK Wilson, a British neurologist, who described the disease in 1912 as progressive lenticular degeneration with liver cirrhosis.¹² It is caused by mutation of the ATP7B gene, which results in impaired hepatic copper excretion and excessive...
copper deposition, mainly in the liver, brain (basal ganglion), and cornea. The disease manifests itself in children and young adults with liver, extrapyramidal, neuropsychiatric, or osseomuscular symptoms and is progressive and fatal without copper chelation.2 3

Kayser-Fleischer rings are formed from copper deposits in the corneal Descemet’s membrane; they are visible as greenish discoloration at the outer corneal circumference. They first appear in the upper corneal limbus, followed by the lower limbus, and then form a complete ring that expands centripetally. Kayser-Fleisher rings can be seen using a torchlight directed tangentially at the cornea; however, early rings require slit lamp examination (fig 3).1 4 The rings do not impair vision, and after copper chelation they clear in the opposite sequence to which they were deposited. Up to 95% of patients with Wilson’s disease who have neurological symptoms and 44-62% of those with liver symptoms have Kayser-Fleischer rings.2 They are a crucial diagnostic sign of Wilson’s disease and aid in monitoring treatment.2 3 Absence of these rings does not rule out Wilson’s disease, and rarely the rings are seen in other chronic cholestatic liver diseases of childhood.2 3

Fig 3 Kayser-Fleischer rings have recently been graded as part of the global assessment scale for Wilson’s disease. Grade 0: absent (A); grade 1: visible only with a slit lamp (not shown); grade 2: incomplete ring (B); grade 3: complete thin ring (C); and grade 4: complete thick ring (D). Grade 2-4 rings can be seen using a torchlight directed tangentially at the cornea.

2 Diagnosis of Wilson’s disease

Wilson’s disease is treatable, but because of its rarity and varied clinical presentation the diagnosis is often missed, resulting in preventable morbidity and mortality.1 6

Genetic diagnosis is expensive and remains impractical because common Wilson’s disease mutations have been identified in only select populations, and a negative genetic test does not rule out the disease.2 Currently, Wilson’s disease is diagnosed on the basis of a combination of family history of the disease, characteristic multisystemic involvement, Kayser-Fleischer rings, and laboratory markers such as low serum ceruloplasmin, high 24 hour urinary copper excretion, and high liver copper content on biopsy.2 3 What looks like the face of a giant panda on magnetic resonance imaging of the brain, plus striatal T2 weighted hyperintensities (representing tissue damage from copper deposition), and pallidal T1 weighted hyperintensities (representing manganese deposition secondary to liver failure) support the diagnosis.1 3 However, each diagnostic feature and test has many confounding factors, and none is entirely sensitive or specific for the disease, which makes test selection and interpretation of test results challenging.2 3 8 Although the combination of neuropsychiatric features and Kayser-Fleisher rings is diagnostic of Wilson’s disease, presymptomatic patients and those with pure liver disease often pose a diagnostic dilemma.2 3 8 Ferenci’s scoring system and available algorithms aid diagnosis.2 3 9

3 Management and prognosis of Wilson’s disease

It is crucial to screen siblings of patients diagnosed with Wilson’s disease for the disorder.1 7 8 Symptomatic and asymptomatic patients with the disease must avoid food and water rich in copper and require lifelong copper chelation.2 9 10 Penicillamine was the first oral chelator used for Wilson’s disease and remains the most widely used drug.7 9 11 Trientine and tetrathiomolybdate were introduced more recently and probably have a better safety profile, especially in patients with neurological symptoms.2 9 In general, drug doses are titrated slowly because of concerns about neurological deterioration after rapid mobilisation of copper from the liver to the brain.2 7 Zinc blocks intestinal copper absorption, is well tolerated, and has been used as first line treatment in asymptomatic patients, during pregnancy, and as maintenance treatment.2 12 Liver transplantation is an option in patients with end stage liver disease or those who do not tolerate medical treatment.2

With timely diagnosis and judicious copper chelation, patients can lead a normal life, and good pregnancy outcomes can be expected.2 7 Even patients with severe neurological disabilities improve.2 9 Disease progression, treatment efficacy, and compliance are monitored by objective clinical assessments.2 4 11 Periodic liver function tests can detect subclinical liver dysfunction, whereas urinary copper excretion and indices like non-ceruloplasmin copper estimation can help check compliance and indicate the pace of copper chelation.2 The rate of disease progression and recovery can vary across different systems, and patients are best managed by multi-specialist teams with an interest in the disease.2 3

Patient outcome

Wilson’s disease was diagnosed in our patient on the basis of psychosy, extrapyramidal features, Kayser-Fleisher rings (fig 4), a silent cirrhosis on abdominal ultrasound, low serum ceruloplasmin, and high 24 hour urinary copper excretion. The family had no history of consanguinity or Wilson’s disease. Treatment with penicillamine for 18 months led to considerable clinical recovery, and he resumed school. Over this time, the Kayser-Fleisher rings decreased from grade 3 to grade 2 (figs 4 and 5).
At the time of diagnosis of Wilson’s disease, Kayser-Fleischer rings were seen as complete thin rings (grade 3 Kayser-Fleischer rings).

After 18 months of copper chelation, the Kayser-Fleischer rings reduced to crescents at the upper corneal pole (grade 2 Kayser-Fleischer rings).

Competing interests: None declared.

Provenance and peer review: Not commissioned; externally peer reviewed.

Patient consent obtained.

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Cite this as: BMJ 2009;339:b3494

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