Case Report

Kayser-Fleischer Rings in Wilson's Disease

Hannan Masud, Tariq Bashir

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See end of article for authors affiliations

Correspondence to:
Hannan Masud
Classified Ophthalmologist
Combined Military Hospital
Pano Aqil, Sindh

Purpose: The Kayser Fleischer ring is the hallmark of Wilson's disease. We present a case of Wilson's disease with neurological manifestations and Kayser-Fleischer ring without chronic hepatic involvement.

Material and Methods: A male patient, 31 years of age, presented with two weeks history of difficulty in speaking and tremors of hands. He was married and had two healthy daughters. His parents were alive and healthy. He was conscious, well oriented and had stable vital signs. Neurological examination revealed mask like facies with a vacuous smile, dysarthria and bradykinesia. Kayser – Fleisher rings were seen on slit lamp examination. There was no clinical evidence of chronic liver disease.

The laboratory investigations showed haemoglobin 13.9 g/dl, platelet count $161x10^9$/l, WBC $6.5x10^9$/l, serum ALT 17 U/l (9-43 U/l), serum alkaline phosphatase 332 U/l (80-306 U/l), total bilirubin 23 umol/l (<19 umol/l), urea 4.4 mmol/l (3.2-6.7 mmol/l) and creatinine 105 umol/l (53-120 umol/l). Serum ceruloplasmin was 10 mg/dl (19-57 mg/dl). MRI brain showed hyperintense signals in caudate nuclei, lentiform nuclei, thalami and brainstem on T2W images and FLAIR.

Result: A diagnosis of Wilson's disease was made and Penicillamine (Vistamine) with oral Zinc was started. Follow up after 3 months showed improvement in clinical features and laboratory results. Follow up planned at 6 months and 12 months after treatment.

Conclusion: A high index of suspicion is required for early detection of Wilson's disease in adolescents and young adults with neurological disorders. Initiation of treatment at an early stage can prevent complications.

Wilson's disease (hepatolenticular degeneration) is an autosomal recessive disease of copper metabolism due to mutation in ATP7B gene[1,2]. The genetic defect causes excessive copper accumulation in the liver, brain and other body tissues.

The prevalence of Wilson's disease is one in 30,000 people worldwide and corresponding carrier frequency is one in 90[3]. Clinically, it presents as liver disease or neurological / neuropsychiatric disorder in different age groups (Table 1)[4]. It manifests as liver disease in children and young adults, typically between the ages of 6 and 45 years. Neurological and psychiatric symptoms are seen in adults in their twenties and older[5,6].

The identification of Kayser – Fleischer ring is helpful in the diagnosis of Wilson's disease. Patients suspected of this disease are referred to ophthalmologist for identification of Kayser – Fleischer ring by slit-lamp examination and gonioscopy. It is a rare disease and few ophthalmologists have ever seen a true Kayser – Fleischer ring. It is reported that often the Kayser – Fleischer rings of one patient are seen by multiple ophthalmologists in the department, so the total number of patients diagnosed is less than the total number of reported cases seen[7].

We present a case of Wilson's disease with neurological manifestations and Kayser – Fleischer ring without chronic hepatic involvement. This case has classic clinical features of the disease and typical

Kayser – Fleischer rings in the cornea. The ophthalmologist has an important role in identification of this disease in suspected cases but he is not directly involved in the treatment of such cases. It is considered appropriate to report this case and discuss clinical features, current status of management and prognosis of the disease so that they feel confident in management of this disease.

Fig. 1: A mask like facies with a vacuous smile, dysarthria and bradykinesia.

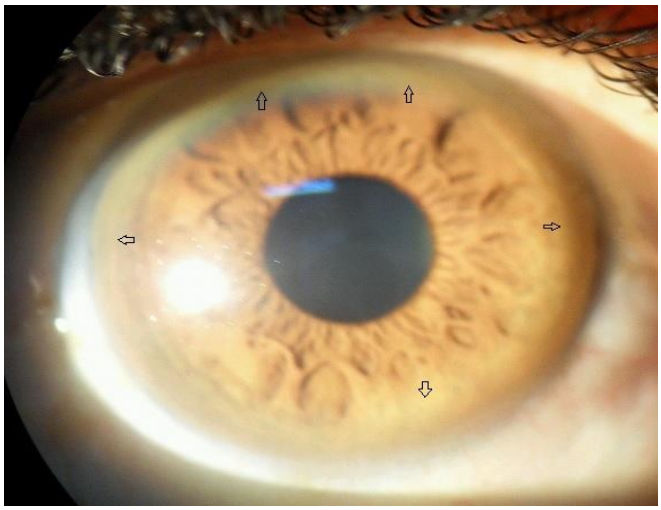

Fig. 2: Arrows indicate greenish - brown Kayser Fleisher Ring in descemet membrane of cornea.

CASE REPORT

A male patient, 31 years of age, presented with two weeks history of difficulty in speaking and tremors of hands. He was married and had two healthy daughters. His parents were alive and healthy. He was conscious, well oriented and had stable vital signs. Neurological examination revealed mask like facies with a vacuous smile, dysarthria and bradykinesia (Fig 1). Kayser - Fleisher rings were seen on slit lamp examination (Fig. 2). There was no clinical evidence of chronic liver disease.

The laboratory investigations showed haemoglobin 13.9 g/dl, platelet count 161 × 10^9/l, WBC 6.5 × 10^9/l, serum ALT 17 U/l (9 - 43 U/l), serum alkaline phosphatase 332 U/l (80 - 306 U/l), total bilirubin 23 umol/l (< 19 umol/l), urea 4.4 mmol/l (3.2 - 6.7 mmol/l) and creatinine 105 umol/l (53 - 120 umol/l). Serum ceruloplasmin was 10 mg/dl (19 - 57 mg/dl). MRI brain showed hyper intense signals in caudate nuclei, lentiform nuclei, thalami and brainstem on T2W images and FLAIR (Fig. 3). A diagnosis of Wilson's disease was made and Penicillamine (Vistamine) with oral Zinc was started. Follow up after 3 months showed improvement in clinical features, serum alkaline phosphatase 309 U/L (80 - 306 U/l), total bilirubin 21 (< 19 umol/l), urea 4.3 mmol/l (3.2 - 6.7 mmol/l) and creatinine 96 umol/l (53 - 120 umol/l) and serum ceruloplasmin was 11.9 mg/dl (19 - 57 mg/dl). Follow up planned at 6 months and 12 months after treatment.

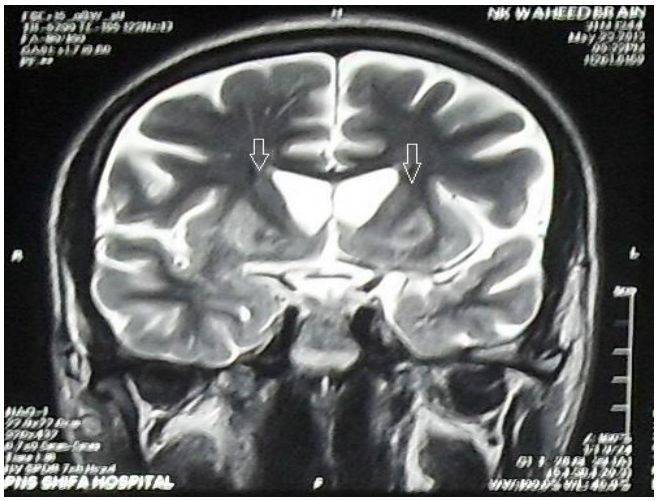

Fig. 3: MRI brain shows hyperintense signals in caudate nuclei, lentiform nuclei, thalami and brainstem on T2 W Images and FLAIR.

DISCUSSION

Samuel Alexander Kinnier Wilson (1878 - 1937) described this condition in 1912. The neurological form of Wilson's disease is also known as Westphal - Strumpell pseudosclerosis.

Table 1: Clinical features in Wilson's disease [3]

Hepatic
• Asymptomatic hepatomegaly
• Splenomegaly
• Persistently elevated serum aminotransferase activity (AST, ALT)
• Fatty liver
• Acute hepatitis / Resembling autoimmune hepatitis
• Cirrhosis: compensated or decompensated
• Acute liver failure
Neurological
• Movement disorders (tremor, involuntary movements)
• Drooling, Dysarthria
• Rigid dystonia
• Pseudobulbar palsy
• Dysautonomia
• Migraine headaches
• Seizures
Psychiatric
• Depression
• Neurotic behaviours / Psychosis
• Personality change
Other symptoms
• Ocular: Kayser Fleischer rings, sunflower cataracts
• Cutaneous: lunulae ceruleae
• Renal abnormalities: aminoaciduria & nephrolithiasis
• Skeletal abnormalities: premature osteoporosis and arthritis
• Pancreatitis
• Hypothyroidism
• Menstrual irregularities: infertility, repeated miscarriages

Wilson's disease manifests as neurological disease in adults[8]. It can present as movement disorders or rigid dystonias. Movement disorders appear earlier as tremors, poor coordination, loss of fine-motor control, micrographia, chorea and / or choreoathetosis. Spastic dystonia disorder manifests as mask-like facies, rigidity and gait disturbances[5]. Pseudobulbar involvement is more common in older individuals and presents as dysarthria, drooling and difficulty in swallowing.

Table 2: Diagnostic tests of Wilson's Disease [12]

• Kayser-Fleischer Rings
• Low Serum Ceruloplasmin levels (<0.20 g/l, normal is 0.20 to 0.40 g/l)
• 24 hour Urinary Copper Excretion (>100 µg/day or 1.0 mol/day)
• 24 hour Urinary Copper Excretion after D-penacillamine (>25 mol/day)
• Hepatic Copper Level on liver biopsy (>250 µg/g dry weight, normal is< 50 µg/g dry weight)
• Genetic mutation in ATP7B gene

The neurologic findings in patients with hepatic presentation may be subtle. Mood disturbance, depression and changes in school performance may be observed[5]. The psychiatric manifestations are variable. Pure psychotic disorders are uncommon.

The Kayser – Fleischer ring is the hall mark of Wilson's disease[9]. The copper deposition in Descemet's membrane of the cornea appears as Kayser-Fleischer ring and indicates a high level of copper in the body[10]. It appears as a golden brown ring in the peripheral cornea, extending from Schwalbe's line to less than 5 mm on to the cornea. It can be greenish yellow, ruby red or bright green in colour. It is almost always bilateral. Initially, it appears superiorly, then inferiorly, and later becomes circumferential. Gonioscopy is often required in early stages of disease but it can be seen in torch light in advanced disease. It is seen in about 85 – 100% patients with neurological and/or psychiatric manifestations, 33 – 86% patients with hepatic disease and up to 59% in asymptomatic patients[11]. With treatment, it disappears in 85 – 90% of patients[12,13]. Sunflower cataract appears as a late manifestation of neurological form of Wilson's disease. In torch light, it appears as greenish disc in the centre of the pupil and on slit – lamp examination, it appears as brown / green pigmentation of the anterior and posterior lens capsule[14].

The presence of Kayser-Fleischer rings, neurological symptoms and low serum ceruloplasmin are considered diagnostic of Wilson's disease[15]. Further tests are advised where indicated (Table 2)[7]. Wilson's disease is suspected in close relatives of the patient

and relevant clinical feature. In neurolocial symptoms, MRI brain shows hyperintensities in the basal ganglia in the T_2 setting. It may show the characteristic 'Face of the giant panda' sign[16].

Liver biopsy is the gold standard test and more than 250ug of copper per gram of dried liver tissue confirms Wilson's disease. Mutation analysis of the ATP7B gene may be performed[1,2]. If confirmed, family members can be screened as part of clinical genetic family counseling.

These patients are advised to take a diet low in copper – containing foods and avoid mushrooms, nuts, chocolates, dried fruits, liver and shell fish. They need a life-long treatment and it should not be discontinued. Symptomatic patients are treated with chelating agents[17,18]. Penicillamine is advised as tablet D-penicillamine by mouth 2 or 3 times a day[19]. Pyridoxine must be given with it. Full blood count and urinalysis is monitored regularly. 24 hours urinary copper values should be 5 – 10 times normal to confirm chelation and increased urinary excretion of copper. Lower values suggest non-compliance or body stores may have been adequately depleted. Serious side effects are seen in up to 30% patients and include severe thrombocytopenia, leucopenia, aplastic anemia, proteinuria, nephritic syndrome, polyserositis, Goodpasture syndrome and severe skin reactions. If side effects occur, tablet D-penicillamine is substituted with tablet trientine hydrochloride as an alternate treatment. If it is not available, these adverse events might be manageable with co-administration of steroids. Almost 50% patients with neurological disorder experience a paradoxical worsening in their symptoms with penicillamine.

Once laboratory investigations are within normal limits, zinc therapy is given to maintain stable copper levels[20]. Tablet Zinc acetate (Galzin) is advised at least 2 – 3 time daily before meals. It stimulates metallo-thionein which is a protein in gut cells that binds copper and prevents its absorption and transport to the liver.

The Kayser – Fleischer rings can be identified accurately by an ophthalmologist by using a slit lamp. The presence of Kayser-Fleischer rings, neurological symptoms and low serum ceruloplasmin are helpful in diagnosis of Wilson's disease. A high index of suspicion is required for early detection of Wilson's disease in adolescents and young adults with neurological disorders. Initiation of treatment at an early stage can prevent complications.

Author's Affiliation

Dr. Hannan Masud
Classified Ophthalmologist
CMH Pano Aqil
Sindh

Dr. Tariq Bashir
Classified Medical Specialist
CMH Pano Aqil
Sindh

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