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ORIGINAL RESEARCH ARTICLE

KAYSER-FLEISCHER RING EVALUATION IN WILSON'S DISEASE IN A TERTIARY EYE CARE CENTRE OF NEPAL

AK Sharma [1] *, S Sitaula [1], M Thapa [1], GS Shrestha[1], BP Gajurel[2] , KK Oli[2]

[1] Department of Ophthalmology, B.P Koirala Lion's Centre for Ophthalmic Studies

[2] Department of Neurology, Tribhuvan University Teaching Hospital, Institute of Medicine, Maharajgunj, Kathmandu, Nepal

***Correspondence to:** Dr. Ananda Kumar Sharma, Department of Ophthalmology, B.P. Koirala Lions Center for Ophthalmic Studies, Maharajgunj, Nepal.
E-mail: dr.anandasharma@gmail.com*

ABSTRACT

Wilson's disease is a hereditary disorder of copper metabolism which is characterized by neuropsychiatric and hepatic manifestations as well as appearance of Kayser-Fleischer ring. This is a retrospective review of the records of the patients of Wilson's disease who attended Neuro-ophthalmic clinic for the identification of Kayser-Fleischer (K-F) ring from January 2010 to June 2012. Detailed eye examination included visual acuity assessment, slit lamp biomicroscopy and intra-ocular pressure measurement. Data regarding clinical features, laboratory investigations and the status of K-F ring was recorded. Seven cases of Wilson's disease with age range of 9-15 years were included in the study. Among them four (57.1%) had neuropsychiatric symptoms, two (28.5%) had hepatic disease and one (14.3%) was asymptomatic, diagnosed by positive family history and laboratory tests. Among four subjects having K-F ring, three (75%) subjects had neuropsychiatric symptoms and one subject had hepato-billiary disease. Besides K-F rings, other ophthalmic findings were sunflower cataract (14.3%) and vernal keratoconjuctivitis (14.3%). The identification of K-F ring is a simple and cost effective screening test for the diagnosis of Wilson's disease. K-F is present in majority of the patients with neurological manifestations.

Key Words: *D-Penicillamine, Kayser-Fleischer ring, Serum Ceruloplasmin, Wilson's Disease.*

INTRODUCTION

Wilson's disease (WD) is an autosomal recessive disorder of copper metabolism that results in the deposition of copper in a variety of tissues throughout the body. The disease is characterized primarily by cirrhosis of the liver, progressive degeneration of the central nervous system, and appearance of Kayser-Fleischer (K-F) ring in the cornea.[1-3] The K-F ring which is the ocular hallmark of WD is characterized by deposition of copper on the descemet's membrane of the cornea at the periphery.[1,2,4] In this study, we have described the clinical presentations, finding of laboratory tests and identification of K-F ring among subjects with WD.

METHODS

This is a retrospective review of the medical records of the patients with WD who attended Neuro-ophthalmic clinic of B. P. Koirala Lions center for Ophthalmic Studies (BPKLCOS) for evaluation of Kayser-Fleischer ring from January 2010 to June 2012. After taking a clinical and a family history, detailed neurological and systemic examination was carried out in all the study subjects. Anterior and posterior segment examination of eye was performed by using slit lamp biomicroscopy. Detailed examination of the cornea for the identification of Kayser-Fleischer ring was performed by slit lamp biomicroscopy and gonioscopy.

Relevant laboratory investigations included estimation of 24-hour urine for copper, serum copper levels, level of serum ceruloplasmin and liver function tests. Ultrasound of abdomen was also performed in all subjects to rule out hepato-billiary manifestations. The diagnosis of Wilson's disease was based on clinical presentation, positive results of the key laboratory tests such as low level serum ceruloplasmin and increased urinary copper excretion, and presence of K-F rings. Photographic documentation of the cornea and anterior segment of the eyes were performed after taking informed consent from the subjects. Then the patient were prescribed medications from the neurology clinic of Tribhuvan University, Teaching Hospital (TUTH) and asked for follow up examinations in Neuro-ophthalmology clinic at BPKLCOS.

RESULTS

The patient's particulars, presenting clinical features, laboratory findings and the result of K-F ring evaluation is presented in table 1. Seven cases of WD were diagnosed and had received treatment during the study period, were included in this study. All the patients belonged to the paediatric age group. Male and female ratio was 4:3. On presentation to the hospital, four subjects (57.1%) had neurological features, two subjects (28.5%) had features of hepatic disease and a subject had no symptoms but positive family history and decreased serum ceruloplasmin levels on laboratory investigations.

Table 1: Distribution of subjects based on clinical features, the K-F ring finding, Laboratory investigations in Wilson's disease

Description		Case one	Case two	Case three	Case four	Case Five	Case six	Case seven
Age/Sex		13/F	13/M	9/M	15/M	14/F	10/M	8/F
Neurological finding		Dysphasia, dysarthria, fine tremor, cranial nerves 7, 9 & 10 palsy	Abnormal movement of head and body	Quadriparesis	Generalized slowness, cranial nerves 7, 9 & 10 palsy	-	-	-
Hepatic finding		-	-	-	-	Cirrhosis	Acute hepatitis	-
Psychiatric symptom		Deterioration of school performance	-	-	-	-	-	-
Ocular findings	**K-F ring**	Present	Present	-	Present	-	Present	-
	Others	Sunflower cataract	-	-	-	-	VKC	-
Lab findings	24 hour urinary copper (<60µg/day)	283	600	655	384	410	479	214
	Serum copper (80-155µg/dl)	54	185	55	57	61	65	54
	Serum ceruloplasmin (25-46mg/dl)	8	12	15	58	20	43	18
	LFT	Abn	N	Abn	N	N	N	Abn
USG abdomen		CLD	N	CLD	N	N	N	Abn

Abn= abnormal, N= Normal, VKC= vernal keratoconjunctivitis, LFT- liver function test, CLD= chronic liver disease, Lab= laboratory

Among four subjects (57.1%) with Kayser-Fleischer (K-F) ring (Figures 1, 2 & 4), three of them (75%) had neurological disorders and one of them (25%) had hepatic involvement as well as vernal Keratoconjunctivitis (Figure 3). One subject with WD having K-F ring was also noted to have sunflower cataract (figure 4). There was a complete resolution of K-F ring after treatment with D-Penicillamine in two subjects (figure 5) after one year of the therapy. However, K-F ring was noted to be decreased in severity and width without complete resolution following the treatment in other two cases. Laboratory investigations of 24 hour urine for copper estimation were elevated in all subjects.

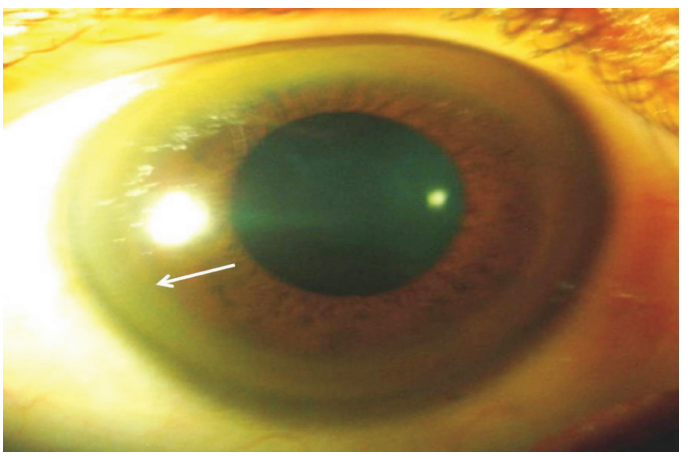

Figure 1: A 13 year male with prominent KF ring

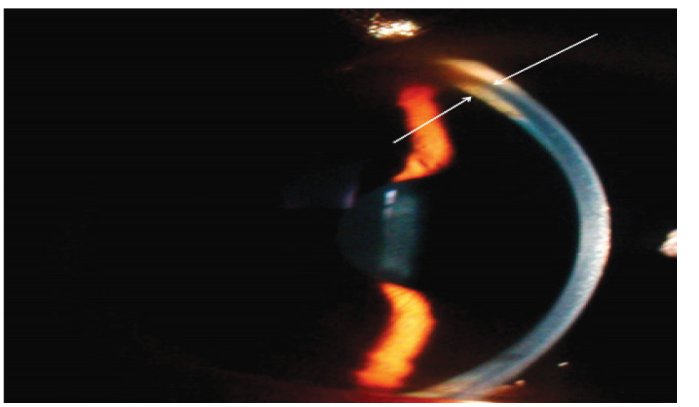

Figure 2: A slit view of K-F ring in Wilson's diseases (as indicated by arrow)

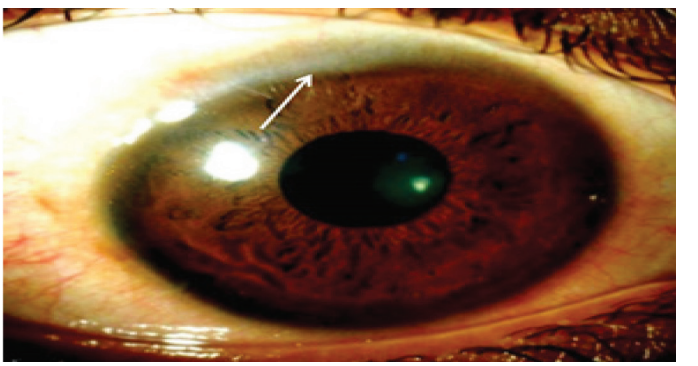

Figure 3: VKC in a case of Wilson's disease

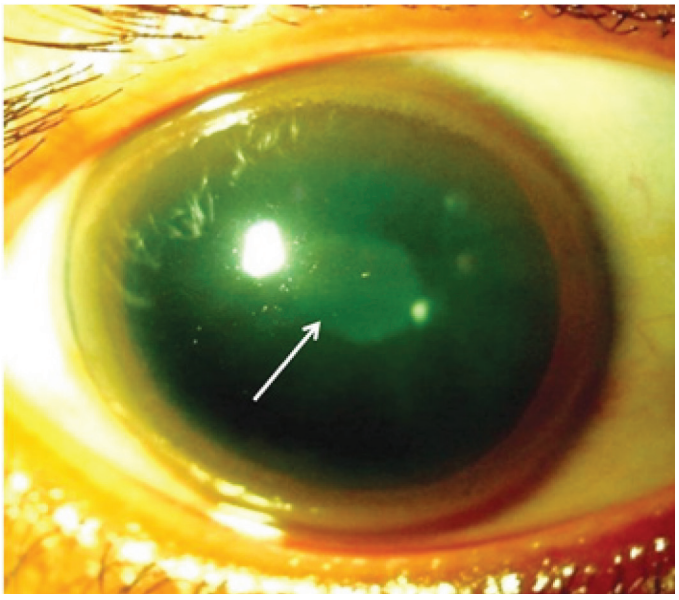

Figure 4: A 13 year old female with K-F ring and Sunflower Cataract

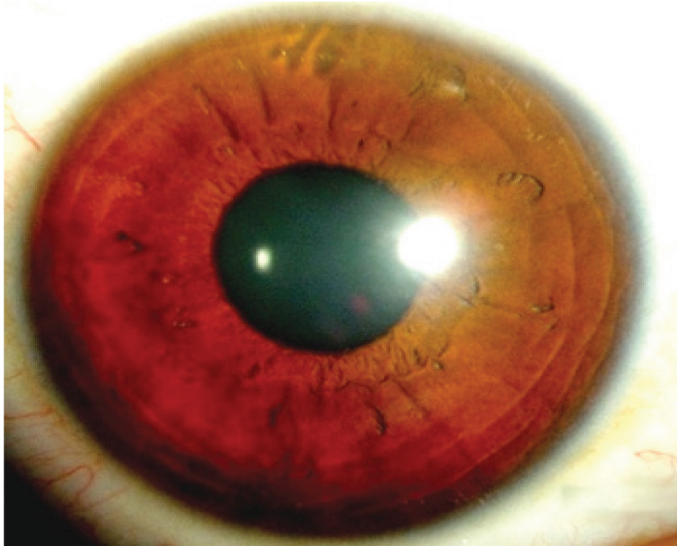

Figure 5: Disappearance of KF ring after treatment

DISCUSSION

We have described the clinical features, finding of laboratory investigations apart from Kayser-Fleischer (K-F) ring evaluation in diagnosed cases of WD. A wide spectrum of clinical manifestation of WD has been reported in literatures. A high level of clinical suspicion is necessary along with the laboratory investigation for proper diagnosis. However, a single test may not establish a diagnosis of WD. There must be a combination of clinical features, laboratory findings, and the results of mutation analysis to make proper diagnosis.[1] A cost effective and simple way of screening a patient of suspected WD is to perform a detailed ophthalmic evaluation for the presence of K-F ring.K-F ring was first described by the German ophthalmologists Bernhard Kayser (1902) and Bruno Fleischer (1903) independently in a patient with multiple sclerosis.[5] Later in 1912, Fleischer recognized it as a part of Wilson's disease. Later, Harry et al (1970) described the electron microscopic appearance of the K-F ring as electron-dense deposits of copper of varying sizes lying mainly in the Descemet's membrane. The site of earliest pigment deposition is an arc in the superior periphery of the cornea from the 10- to 2-O'clock meridian. The arc spreads slowly toward the horizontal plane and gradually broadens. Later on the progression of the ring formation, a band appears inferiorly as a crescent stretching from the 5- to 7-o'clock positions then these two arcs meet with each other.[6] With treatment, the sequence of events is reversed, the copper gets reabsorbed, and a pitted or beaten silver pattern may become apparent at the previous site of the ring. This is an indication that treatment has produced a negative copper balance.[7] In most patients, the neurologic and hepatic lesions remit. However, K-F ring regression does not correlate with neuropsychiatric improvement.[8]

In our study K-F ring was found in 57.1% of the patients as similar to other studies. [1,9-11] The presence of K-F ring and low serum ceruloplasmin levels are considered sufficient to establish the diagnosis of Wilson's disease.[4,12] However K-F rings are rarely seen in pediatric population.[1] In the Indian subcontinent, the early age of onset of symptoms, prolonged persistence of K-F rings and progression of symptoms among siblings despite proper therapy is of great interest that can be correlated to the copper intake by the practice of using brass or copper utensils for cooking.[13] The absence of K-F rings does not necessarily exclude the possibility of Wilson's disease. Patients with predominantly neurological symptoms, K-F rings are absent in only less than 2% of cases. In our study, among four children having neurological symptoms, three of them had K-F ring. Moreover the diagnosis of Wilson's disease can be more difficult in patients with liver disease.[14] Many times the presence of K-F ring may be the only initial finding in the cases of Wilson's disease. Besides it also serves as a useful test to monitor the patient's compliance and the response to treatment.[15]

Another important ocular finding in Wilson's disease is the sunflower type of cataract which is present in one patient having neurological manifestations. Sunflower cataract is brilliantly multicolored deposits of copper in the lens. The other uncommon ophthalmic findings are strabismus, optic neuritis or pallor of the optic disc, and night blindness.[16] Abnormal ocular movements such as slow horizontal saccades, upward gaze restriction and impaired convergence are also reported in Wilson' disease.[17]

In our paediatric case series, four children (57.1%) presented with neurological symptoms, two children (28.5%) presented with hepatic features and one case (14.2%) was asymptomatic sibling diagnosed on the basis of positive family history and laboratory findings. This result is similar to the report of Shakya (2004)[18] study and different from the study of Manolaki et al (2009) among paediatric population in which hepatic manifestation was more common.[1]

All 7 patients in our series had high urinary copper excretion, whereas, serum ceruloplasmin level was found lower than 25

mg/dl in 6 patients (85.7%). These findings are similar to other previous reports. [18, 19]

In 50% cases there was complete resolution of KF ring after treatment with D-Penicillamine during follow up of two years. In two cases there was evidence of decrease in width of KF ring after 6 months however complete resolution was not observed on the last follow. This is similar to the results observed in the Indian study where a large number of patients showed prolonged persistence of KF ring.[13]

CONCLUSION

The identification of Kayser-Fleischer ring is a simple and cost effective screening test for the diagnosis of Wilson's disease. Kayser-Fleischer ring is present in majority of the patients with neurological manifestations. The ring may disappear in variable time following D-Penicillamine therapy.

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