Original article

Value of Kayser-Fleischer ring as a diagnostic tool for Wilson's disease in children

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Abstract

The Kayser-Fleischer(K-F) ring is the hallmark of Wilson's disease (WD). In most adults or older children, the diagnosis of Wilson's disease may be made easily when K-Frings and low ceruloplasmin levels are present. In this study presence of K-F ring has been evaluated among children with liver disease in Bangladesh to improve the management of Chronic liver disease due to WD and reduce complications. This cross-sectional study was carried out at the Department of Paediatric Gastroenterology and Nutrition, BSMMU, Dhaka on 60 children presented with liver disease. Thirty children over three years of age considered as cases (Group-I) and thirty children with non-Wilsonian liver disease as control (Group-II). Slit lamp examination for K-F ring and twenty-four hour urinary copper excretion after giving one gram d-penicillamine 12-hour apart were done in each patient. The efficacy of K-F ring was studied. Mean age of WD patients was 8.9± 2.78 years, with a male female ratio of 1.3: 1. There was significant low level of serum ceruloplasmin in 93.33% of cases (p<.001). After penicillamine challenge, 24-hour urinary copper excretion was found significantly higher in patients with WD (median 3626.5±1698 µg/24h, range 1262- 195000) than non-Wilsonian liver disease (median 450±278.09 µg/24-h, range 47- 2062 µg/24h), (p<.001). K-F ring was found in 15 (50%) patients, absent in all patients of non-Wilsonian liver disease group and the difference was statistically significant (p<.001). Evaluation of Kayser-Fleischer ring is still a very essential diagnostic tool and is a non-invasive, affordable way to assist in the diagnosis of a potentially fatal disease.

Keywords: Chronic liver disease, Urinary copper, Wilson's disease, Kayser-Fleischer ring.

Introduction

Wilson's disease (WD) is an autosomal recessive disorder of copper metabolism caused by mutations within the ATP7B gene. This causes impaired biliary copper excretion, resulting in hepatic copper toxicity and subsequent multisystem disease involving the liver, brain, cornea, skeletal system etc. It affects 1 in 30,000 people with fatal outcome if untreated.[1] The K-F ring is the hallmark of Wilson's disease and its detection may be critical for diagnosis.[2] There are reports where it has been the first detectable manifestation of Wilson's disease, which led to early diagnosis and treatment for the disease. [3] The presence of K-F rings in combination with low serum ceruloplasmin is considered diagnostic of Wilson's disease based on Sternlieb's criteria.[3] In the cornea, the excess circulating copper is deposited in Descemet's membrane and is usually seen as a golden brown ring located in the peripheral cornea, beginning at Schwalbe's line and extending less than 5 mm onto the cornea. The ring may also appear as greenish yellow, ruby red, bright green, or ultramarine blue. It is almost always bilateral and appears superiorly first, then inferiorly, and then later becomes circumferential. In the earlier stages of disease, gonioscopy is often needed to detect this subtle finding, but in advanced disease it can be seen with the naked eye.[2,3]

K-F rings may be absent in up to 50% of patients with Wilsonian liver disease and in an even higher proportion with fulminant Wilsonian liver disease.[4] There are a number of conditions that have also been linked to colored rings in the cornea, including other liver diseases such as primary biliary cirrhosis, neonatal hepatitis, and cryptogenic cirrhosis, or elevated copper for other reasons such as in multiple myeloma, pulmonary carcinoma, benign monoclonal gammopathies, chronic lymphocytic leukemia, or even oral contraceptive use. [2,3,4] After the initiation of treatment, the Kayser-Fleischer ring disappears in 85-90% of cases.[4] In most adults or older children with clinical evidence of liver involvement only, the diagnosis of WD may be made easily when K-F rings and low ceruloplasmin levels are present. However, in a number of cases, particularly in

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the younger pediatric population in whom K-F rings are frequently absent, the diagnosis of WD is most challenging. After the age of twenty, 75% of cases present with neurological manifestation and 25% with hepatic and neuropsychiatric manifestations.[3- 5]

Therefore the present study has been undertaken to observe the presence of K-F ring for the diagnosis of Wilson disease in children attending in a tertiary care hospital in Bangladesh.

Materials and methods

This Cross-sectional study was conducted in the Department of Paediatric Gastroenterology and Nutrition, BSMMU from January 2015 to January 2016 on the paediatric patients with liver disease admitted during the study period. Thirty WD positive children and thirty children with non-Wilsonian liver diseases were studied. Children more than three years of age with any form of liver disease attended were screened for Wilson's disease. After case selection informed written consent was taken from legal guardians of individual patients. Then the patient's particulars were recorded in the case record file. Initial evaluation of the patients by history and clinical examination were collected by researcher herself and recorded in the preformed data collection sheet. Slit-lamp eye examination was done in each patient (both case and control) at ophthalmology department of BSMMU by a single expert ophthalmologist and results were recorded in case record file. All the cases were numbered chronologically. Children with any form of non-wilsonian liver disease after three year of age attending in the Paediatric Gastroenterology and Nutrition Department who did not fulfill the inclusion criteria for the diagnosis of WD, were considered as control.

Children who presented with any form of liver disease after three years of age having the diagnosis of WD which was made upon the basis of presence of elevated 24-hour urinary copper excretion (≥1200µgm/24-hour after D-penicillamine challenge) plus at least one of the following three criteria in a child who presented with liver disease, Positive family history of liver disease, History of parental consanguinity, Low ceruloplasmin level and Presence of Kayser Fleiscer (KF) ring by slit lamp eye examination. Age <3 yrs and >18yrs, Unwilling to give consent were excluded.

Prior to the commencement of this study, the research protocol was approved by the Institutional Review Board of BSMMU,Dhaka. Data were collected by investigator herself with a structured data sheet which included all the variables of interest. Penicillamine challenge test (PCT) was carried out in all children with liver disease (both Wilson"s disease and non-Wilsonian liver disease). For performing PCT five hundred milligrams of D-Penicillamine was given to each patient independent of body weight at the beginning of urine collection (zero hour) and five hundred milligram after twelve hours (total 1 gram of penicillamine) and then urine was collected for 24-hour from zero hour,the last voided sample urine was collected in a metal-free dispensable plastic tube, supplied by atomic energy centre, for copper estimation. Result was calculated with 24-hour total urinary volume.

24-hour urinary copper excretion ≥ 1200 µgm was regarded as compulsory diagnostic parameter for WD. The remaining 3 ml of blood was taken into the test tube from the haematology laboratory containing 0.2 ml 3.8% trisodium citrate and sent to the Haematology Department of BSMMU for estimation of CBC with PBF and the prothrombin time (PT).Then serum bilirubin, was measured by auto analyzer (Back man coulter auto analyzer, USA, model-5x) and result was expressed as µmol/l. Serum ALT & Serum albumin was also measured by same method and the result of serum ALT & Serum albumin were expressed subsequently as U/L & gm/L. 2 ml of venous blood was collected for determination of serum ceruloplasmin. The test is done at BSMMU so the blood sample was sent to a biochemistry department for estimation of serum ceruloplasmin. Data were analyzed statisticaly by SPSS analysis.

Results

A total of 60 cases were included in the study and their age range was 3 - 15 years. The mean age of group-I (WD) patient was 8.9±2.78 years and that of group-II (Non-WD) 9.2±2.62 years. Most of the patients in both groups (66.67% in group-I and 66.67% in group-II), were in the age ranges of 5–10 years. The age difference between two groups was not statistically significant (Table-I)

Among the 30 WD patients (group-I), 17 (56.6%) were male and 13 (43.3%) female (ratio 1.3:1). In non-Wilsonian liver disease group (group-(II), 16 (53.3%) were male and 14 (46.61%) female (ratio 1.1:1).

Regarding presentation of WD 79.3% patients presented only with hepatic manifestation, 3% only with neurological features and 15% manifested with others. Among hepatic presentation 16(53.3%) patients presented with chronic liver disease, Acute hepatitis 3(10%) and Acute liver failure 3(10%). Two patients (6%) were diagnosed on family screening & one patient (3%) was HBsAg positive. Other (15%) patients presented with WD with Acute glomerulonephritis (1), WD with betta Thalassemia (1), WD with Acute pancreatitis (1) respectively. Out of 30 WD positive cases, 26.67% had normal ALT level, 36.67% had mildly elevated ALT level, 26.67% and 10% had moderate and severely raised ALT levels respectively. Fifty Six percent of WD cases had serum bilirubin level within 2-10 mg/dL, 23% had <2 mg/dL and 20% had >10 mg/dL. Coagulopathy and hypoalbuminaemia was found in 60% and 86.64% of cases respectively. Among these 30 WD cases 10% were severely pale, while 36.67% had moderate palor and 60% cases had hemoglobin level >9 gm/dL (Table-III).

Among the 30 patients with non-Wilsonian liver diseases, cryptogenic CLD 50%was the commonest presentation. Next to that, chronic HBV infection was 16.67%. Three (10%) controls were asymptomatic siblings of WD patients& three controls (10%) were Celiac disease. Among the rest 4 patients 2 (6.67%) were diagnosed as autoimmune hepatitis and 2 (6.67%) as Acute hepatitis.

Parental consanguinity and positive family history were present in 9 (30%) and 5 (16.67%) of cases respectively. At the time of diagnosis of WD patients, K-F ring was found in 15 (50%) patients. It was absent in all patients of non-Wilsonian liver disease group and the difference was statistically significant, p<.001 (Table-II). Twenty eight (93.33%) cases in group-I and 5(16.6%) case in group-II, had serum ceruloplasmin level of <20 mg/dl. This level was significantly lower in children with WD (group-1) in comparison to non-Wilsonian liver disease group (p<.001).

Tables & figures

Table-I: Age distribution of the studied patients (N=60)

Age range (year)	Group I (n=30) No. (%)	Group II (n=30) No. (%)	p value
<5	2 (6.66)	1(3.33)	
5-10	20 (66.67)	20(66.67)	
11-15	8 (26.67)	9(30)	0.82^{NS}
>15	0	0	
Mean ±SD	8.9 ±2.78	9.2 ±2.62	

n=No of patients, NS = Not significant

Chi-Square Tests

Table-II: K-F ring distribution of the studied patients (N=60)

K-F ring	Group I (n=300 No (%)	Group II (n=30) No (%)	X2value	p value
Absent	5(16)	30(100)	42.857	0.00^{S}
Present	25(83)	0		

Chisquare test, n=No of patient, S=significant

Table-III: Biochemical parameters of the patients with Wilson's disease (N=60)

Investigation	Frequency	Percent
Serum ALT		
Normal (Upto 65U/l)	8	26.67
66-100	11	36.61
101-400	8	26.67
>400	3	10
Serum Bilirubin(mg/dl)		
<2	7	23
2-10	17	56.67
>10	6	20
Prothombin Time		
Normal	12	40
Prolonged	18	60
Serum Albumin(35-55g/l)		
Normal	4	13.34
Reduced	26	86.64
Haemoglobin		
<6	1	10
6-9	2	36.67
>9	18	60

Studied patients (n=60)

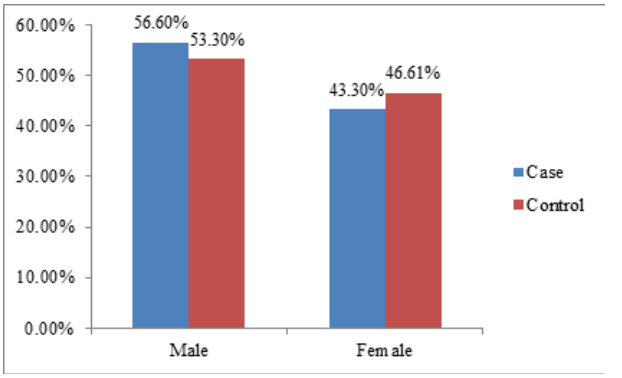

Figure 1: Sex distribution of the studied patients (n=60)

Discussion

In Bangladesh liver disease is a common medical problem. In case of children with Wilson's disease hepatic manifestations are more common than in older patients.[4] Early diagnosis of WD is essential for better patient management. But diagnosis of this disease may be a challenge as there is no single ideal diagnostic test that can exclude or confirm the disease with certainty. Twenty four hour urinary copper excretion after penicillamine challenge is a useful test for the diagnosis of WD in children, but it is time consuming and difficult to collect. The present study was carried out with an aim to observe the presence of K-F ring in children with chronic liver disease for the diagnosis of WD.

Most (93.3%) of the patients in the present study were in the age ranges from 5–15 years. The mean (±SD) age of WD patients was 9 ± 2.68 years. Similar result was also observed in another study done in Bangladesh. [6]

Wilsons disease is an autosomal-recessive disorder. In autosomal-recessive disorder both male and female may affect equally. Male female ratio of this study was 1.3: 1. Seventeen (53.3%) of 30 WD patients were male and 13 (43.3%) female. A male predominance (Mawas 2:1)also found in another study in Bangladesh,[7] In the present study we found 79.3% patients presented only with hepatic

manifestation, 3% only with neurological features and 15% manifested with others. In the present study chronic liver disease 16(53.3%) was the commonest presentation. Similar observation was made earlier another three studies of three different countries.[6,7,8] They found chronic liver disease as the most common presentation. Taly et al. in Bangalore, India, demonstrated parental consanguinity in 54% of cases and positive family history of liver disease in 47% of cases. In the present study parental consanguinity was found in 9 (30%) cases and positive family history of liver disease in 5 (16.67%) cases. In another study done in Bangladesh by Karim et al. parental consanguinity was found in 12.5 % cases, which is consistent with the present study.In the present study, among the 30 WD cases, Most common symptom was jaundice (61.6%), followed by as hepatosplenomegaly (40%), ascites (35%), Splenomegaly(28.4% hepatomegaly (16.67%). In another study Jaundice & Ascitis was found to be the most common clinical presentation which is consistent with the present study.[6,8]

In the present study abnormal liver function test was observed in 70-80% of cases. A similar observation had also been made by Zhang where abnormal liver function was found in 100% of cases.[10]

Kayser-Fleischer ring, the cardinal sign of WD is formed by deposition of copper within Descemet's membrane. In hepatic presentations it is seen in 33%-86% of patients. In the present study, K-F ring was found in 83.3% of WD cases by slit lamp eye examination. A similar observation had also been made by Muller, de Bem and Rukonuzzaman. They found K-F ring in their studies in 47%, 55.6% and 76% cases respectively.[7,11]

The presence of KF ring and low serum ceruloplasmin are considered to be sufficient to establish the diagnosis of WD.[12-14] The present study shows that K-F ring is highly significant & more common for the diagnosis of WD in children.

Conclusion

Wilson"s disease in children is frequently missed and requires a high index of suspicion. Diagnostic difficulty arises in paediatric cases where K-F rings are absent, serum ceruloplasmin level is normal, baseline urinary copper excretion only minimally elevated. Although 24-hour urinary copper excretion is a useful test for the diagnosis of WD in children, but it is relatively cumbersome and time consuming. On the other hand, based on a survey of hepatologists, an ophthalmologic evaluation to look for Kayser-Fleischer rings is still a very essential diagnostic tool and is a non-invasive, affordable way to assist in the diagnosis of a potentially fatal disease. When a patient presents with advanced disease or neurological and/or psychiatric manifestations of Wilson's disease, a Kayser-Fleischer ring is present in almost all cases and can non-invasively help to solidify the diagnosis. When a patient presents with less advanced disease or hepatic disease only, the diagnosis is much more difficult and the critical evaluation of all available tests is often needed to confirm the diagnosis. Because many laboratory tests are inconclusive in patients with less advanced disease, and because the gold standard liver biopsy is an invasive and high cost procedure, the non-invasive evaluation for a Kayser-Fleischer ring is still an essential part of the diagnostic work up for Wilson's disease.

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