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ORIGINAL ARTICLE

Biochemical markers in the Wilson's disease patients in adolescents presenting at tertiary care hospital.

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ABSTRACT… Objective: Estimating biochemical markers in Wilsons disease (WD) patients in adolescents group presenting at tertiary care hospital. **Study Design:** Cross Sectional study. **Setting:** Outpatients and Medical Wards, Isra University Hospital. **Period:** January 2024 to March 2025. **Methods:** One hundred diagnosed cases of WD were enrolled for estimating the biochemical markers of copper metabolism in adolescents. Cases were diagnosed and reconfirmed by a consultant physician. Blood sample were taken. Sonography was ordered. Biochemical parameters were estimated by Roche Cobas Chemistry Analyser and Atomic spectrophotometry. Variable were analyzed on SPSS 21.0 ver. P – value is taken at (USA) at 95% CI ($P \leq 0.05$). **Results:** Age was 17.31±7.97 years. Male - female ratio was 3:1. Icteric sclera was noted in 57 cases, hepatomegaly in 69 cases, splenomegaly in 71 cases, and KF rings noted in 21 cases. 24 hour urinary copper measured as 2913.5± 711.6 (409 – 3901) mg/dl serum ceruloplasmin measured as 17.01±54.87 mg/day. **Conclusion:** We observed low ceruloplasmin and high urinary copper in WD patients. Penicillamine challenge show high 24 – hour urinary copper excretion.

Key words: Ceruloplasmin, Copper Excretion, Wilson`s Disease.

INTRODUCTION

Copper is an essential element required for enzyme activity in the living cells. Absorption of copper occurs in the small intestine and circulates in blood capillaries bound to plasma proteins. There is one known disorder of copper metabolism called the Wilson's disease (WD), mentioned after its inventor – Samuel Alexander Kinnier Wilson (1912). It is an autosomal-recessive genetic disorder of copper metabolisms. WD patients have a predisposition of depositing copper excessively in the hepatocytes, cornea, and basal nuclei.[1,2] Excessive copper induces free radical formation and toxicity. Chronic liver disease, eye, and basal nuclei of brain are the mainstay of the WD. Other body organs are also affected included are the pancreas, heart, kidneys, skin, etc. Clinical presentation occurs in young childhood and adolescents. Global prevalence of this disease is about 1/10000 and 1/30000 by WHO.[2] A frequency of 0.58% gene mutation is reported. Carrier frequency of WD 1 out of 90 has been reported Worldwide.[1,2] WD is caused by a ATP7B gene mutation. Gene product translates a transport – protein of ATPase function. The protein amalgamates copper to apo – ceruloplasmin that excretes copper into bile. Mutation of ATP7B creates fallacy in free copper being released into the blood capillaries for excretion through feces and urine.[2,3] Biliary canaliculi receive excreted copper with the help of ATP7B transporter in the bile to excrete into feces through gut. Copper binding protein – ceruloplasmin, a plasma protein, carries 95% of it. Liver hepatocytes synthesize and secrete apo ceruloplasmin into capillaries, where it binds with copper and becomes holoceruloplasmin. Ceruloplasmin carries 6 copper).[3,4] Low blood ceruloplasmin is a hallmark of WD causing copper deposition in various organ systems and consequent injury to vital organ and pathological sequelae. Neurological symptoms are observed when the ceruloplasmin levels are below 0.2 mg/dL. Serum ceruloplasmin concentrations

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fluctuates form very low to 50% in WD patients.[2]

Clinical conditions such as protein – losing enteropathies, chronic liver disease, chronic kidney disease often show low ceruloplasmin levels.[5,6] Heterozygous carriers often reveal 20% activity of ceruloplasmin. Acute inflammation and infections are found with normal levels of serum ceruloplasmin similar to acute-phase protein.[6] In WD, the neurological features are observed in 2nd decade and liver disease in 1st decade. 95% of WD with neurological features exhibit deposits of copper in Descemet's membrane of cornea forming a ring like structure. It appears as a brownish discoloration ring called the Kayser–Fleisher (KF) ring. It is a pathognomic sign of WD. Patients without neurological symptoms exhibit KF ring in 50%–60% cases.[6,7]

In Pakistan there is disastrous deficiency of community based prevalence studies, hence data is seriously lacking. A search of published medical literature shows few studies with insufficient samples. There is a much research gap and WD needs further research and clinical studies. The present study is conducted to study the biochemical markers in the Wilsons disease patients in young adolescents presenting at tertiary care hospital.

METHODS

A cross – sectional study was conducted according to research guidelines of institute after approval from ethical committee (ERC-No/: 176/2024/14/0075-01/24). Study setting was the Outpatient and medial wards of the Isra University hospital, Hyderabad campus. A sample of 73 diagnosed WD cases was studied from January 2024 to March 2025. Patients of adolescent ages; 10-20 years were included. Diagnosed cases of WD were included aided by a consultant physician. Clinical criteria were hepatic and neurological symptoms, Kayser-Fleischer rings by slit lamp examination, serum ceruloplasmin <0.20 g/l and 24 – hour urinary copper excretion >1600 mg/24 h.[6,7] Clinical symptoms of jaundice, organomegaly, liver function tests, KF rings by slit lamp examined by ophthalmological examination were employed before patient induction. A written informed consent was necessary for volunteers to be included in the study protocol. Data of patient, clinical examination, Sonography and biochemical tests were saved in a pre – structured proforma. Clinical history was enquired in broad way including family history. Enquiry of icteric sclera, abdominal ache & distension, consanguineous marriage, and family history was made and noted. Each participant was asked for physical examination, and slit lamp ophthalmological examination of KF rings by a consultant Ophthalmologist. Volunteers were informed about the purpose of study protocol and blood samples. Five ml of blood sample was drawn from an ante – cubital veins using tourniquet in a test tube. Blood was centrifuged at 2000g rev. to get sera for biochemical analysis. Serum bilirubin, serum alanine transaminase (ALT), serum albumin and serum ceruloplasmin were estimated. 24 hour urinary copper excretion was quantified after penicillamine (250mg x2 tablets) orally.[1,6] Penicillamine challenge protocol was followed. Urinary copper samples were collected for "Atomic absorption spectrophotometer" detection. Chemistry of samples was estimated by Roche Cobas Chemistry Auto – analyzer. Variables were analyzed on SPSS 21.0 ver. Student's t test and Chi square test for continuous and categorical variables respectively. P value is taken at (USA) at 95% CI ($P \leq 0.05$).

RESULTS

Age was 17.31±7.97 years. Male - female ratio was 3:1. Icteric sclera was noted in 57 cases, hepatomegaly in 69 cases, splenomegaly in 71 cases, and KF rings noted in 21 cases (Table-I). 24 hour urinary copper measured as 2902.5± 709.09 (407 – 3909) mg/dl serum ceruloplasmin measured as 15.21±4.87 (13.7 – 24.91) mg/ day. Table-II shows summary of biochemical parameters.

	No.	%
Icteric Sclera	57	78.0
Hepatomegaly	69	94.5
Splenomegaly	71	97.2
Kayser Fleischer (KF) ring	21	28.7

Table-I. Clinical signs of Wilson`s Disease cases (n=73)

	Mean	SD	Range
Bilirubin (mg/dl)	3.23	1.79	1.81 – 5.11
ALT (U/L)	163.3	27.2	57 – 309
Albumin (g/dl)	3.71	1.82	2.09 – 4.31
Ceruloplasmin (mg/dl)	15.21	4.87	13.7 – 24.91
Copper excretion (µg/day) (24 hours Urinary)	2902.5	709.09	407 – 3909

ALT- alanine transaminase,

Table-II. Laboratory findings of Wilson`s Disease (n=73)

DISCUSSION

The present prospective study analyzed biochemical findings of copper and ceruloplasmin levels in diagnosed cases of Wilsons Disease presenting at a tertiary care hospital. WD shows varied clinical presentation making it challenging differential diagnosis. A senior consultant physician made a diagnosis of WD. We could collect a sample of 73 patients over more than a year of duration. Male - female ratio was 3:1. Serum ceruloplasmin was found as 17.01±54.87 mg/day (Table-II). Previous studies have shown low serum ceruloplasmin in observed in 45% cases.[8,9] We found 24 hour urinary copper measured as 2913.5± 711.6 (409 – 3901) mg/dl and this is in agreement with previous studies.[10] Elevated urinary copper following penicillamine challenge is very important step in WD diagnosis combined with low serum ceruloplasmin. It is mentioned the penicillamine challenge is reliable test in diagnosing WD.[8,9]

In current study, WD was diagnosed by a consultant physician, followed by ophthalmologist slit lamp examination showing KF rings and finally by serum ceruloplasmin (<20 mg/dl) and 24 – hour urinary copper excretion (>1600 mg /24 hours) in response to penicillamine therapy.[6,7] Age of study subjects was 17.31±7.97 years as adolescent population was study this particular age group, the findings are in agreement with previous studies.[10,11] Most of the adolescents were above the age of ten. WD least age noted was 9.3 years. This is consistent with previous studies.[12] Male - female ratio was 3:1, this is in agreement with previous studies[13,14] showed male predominance. In present study, male counted 75% of adolescents similar to 71% mentioned by a previous study.[15] In present study, the clinical and Sonography examination reveals hepatomegaly, splenomegaly and both hepatosplenomegaly similar to previous studies.[15,16] Icteric sclera was noted in 78%, and KF rings in 28.7% cases (Table-I). Serum bilirubin and serum alanine transaminase were raised while serum albumin was found low indicating liver injury. These biochemical results are in agreement with studies.[17,18]

In present study, serum albumin was noted 3.78±1.83 g/dl, this is in keeping with previous study.[19] In current study ceruloplasmin was 17.01±3.97 mg/dl that is very low and supported by past studies.[19,20] Low ceruloplasmin levels, termed hypo–ceruloplasminemia, are observed in hereditary conditions, chronic kidney and liver diseases, hepatitis, enteropathies, nephrotic syndrome, etc.[21-23] Adolescents presenting clinically with hepato – splenomegaly should be screened for WD through biochemical testing and clinical examination is required for timely intervention of disease and its sequelae. This will improve the future complication of WD in adolescents. It is advised the hospital and community based screening testing be performed at national level to estimate the true burden of WD disease and making future guidelines for proper management of this population. The findings of present study are worth to report for a neglected health issue existing in the young populations.

CONCLUSION

We observed low serum ceruloplasmin and high urinary copper excretion. Yellow sclera, hepato–splenomegaly and Kayser Fleischer rings are were present prominently. 24 – hour urinary copper excretion was increased following penicillamine load.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Haji Khan Khoharo:** Study design, concept.
2	**Fatima Qureshi:** Literature review, results.
3	**Farheen Malik:** Analysis.
4	**Salahuddin Shaikh:** Data collection, paper writing, discussion.