ORIGINAL RESEARCH PAPER
Volume - 11 | Issue - 03 | March - 2022 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

WILSON'S DISEASE PRESENTING AS COOMB'S TEST NEGATIVE HEMOLYTIC ANEMIA

Medical Science

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ABSTRACT

Wilson's Disease (WD) is an autosomal recessive genetic disorder associated with excess storage of copper in liver, brain and other organs. Wilson 's disease could be fatal if not diagnosed early and not treated. We report a 10year old female case presenting with discoloration of eyes, dark urine, generalized itching with loss of appetite and nausea turned out to be Wilson's disease presenting as Coomb's test negative Hemolytic Anemia and comorbid Rickettsial fever. Slit lamp examination revealed Kayser-Fleischer ring around the cornea, and 24-hour urinary copper and serum ceruloplasmin confirmed the diagnosis. Treatment aimed at preventing accumulation of copper in tissues and reducing already accumulated copper in the body. A combination of copper chelators like D-penicillamine and zinc therapy is used to prevent progress of WD. She was started on D-Penicillamine with Zinc supplements and Tablet Doxycycline for Rickettsial fever. Prognosis and possibility of requirement of Liver transplantation at later stage of life explained to the attenders.

KEYWORDS

Wilson's disease; hemolytic anemia; rickettsial fever; genetics

INTRODUCTION

Wilson's disease (WD) is an autosomal recessive genetic disorder associated with excess storage of copper in liver, brain and other organs. It takes two altered gene copies, one inherited from each parent, to cause the disorder [2]. WD is distributed throughout the world. The prevalence is 3-20 per 1, 00,000 and may vary by population. Higher prevalence of WD in Japanese population is linked to consanguineous marriage. [1] WD could be fatal if left untreated. Early diagnosis and treatment may prevent long-term disability and further complications.

WD is generally not considered as a differential diagnosis for hemolytic anemia.[3] Here we present a case of Wilson's disease presenting as Coombs negative hemolytic anemia.

Case Summary:

A 10yr female child initially well, developed yellow discoloration of eyes, dark urine, generalized itching, loss of appetite, nausea since 7 days. She was diagnosed to have viral hepatitis from a private clinician, and was started on Hepatoprotective drugs. She became symptomatically better by 10 days of treatment, after that she again developed yellow discoloration of eyes, dark urine, generalized itching, loss of appetite with darkening of skin in a duration of 5 days of completion of treatment. She came to our OPD after 10 days of presenting complaints. Her past medical and surgical history was not contributory. She was a product of 3rd degree consanguineous marriage.

On examination, she weighed 30kgs. Other vital signs were within normal limits. There was pallor and a darkening of skin. Significant findings on systemic examination was the presence of hepatomegaly: non tender, firm to hard consistency of liver with span of 12 cm and sharp margins. Spleen tip was also palpable.

She was advised investigations to check for infective hepatitis cause, obstructive hepatitis cause, defects in copper storage. Hepatitis A IgM, Hepatitis B Ag to rule out infective cause. Liver function test, Blood routine to check for Hemoglobin, Blood picture, Reticulocyte counts, ANA & Direct Coomb's Test, Cold Agglutinin Test to rule out auto immune hemolysis.

Her investigations revealed Liver function tests suggestive of early hepatic failure. (PT 30.3, INR 2.3, SGOT & SGPT ratio was 2.12) Serum Copper was normal, Serum ceruloplasmin levels (<9.18mg/dl) were low, 24hour Urine Copper was elevated (346.32microgms/Day) contributing to diagnosis of WD. The investigations are depicted in Table 1. A slit lamp examination of eyes was performed and revealed the presence of Kayser Fleischer (KF) rings on both eyes confirming the diagnosis as shown in Figure 1.

Blood picture showed a moderate macrocytic & microcytic hypochromic anemia with anisocytosis. Significantly, many polychromatophilic erythrocytes were seen. Immature or atypical cells were not found. Her platelet count was normal. This prompted a workup for hemolytic anemia. Her LDH was elevated (376.61IU/L) which is suggestive of hemolysis. A cold agglutinin test was positive, but the Direct Coombs test was negative and ANA levels were normal. Hence Coomb's negative hemolytic anemia was considered.

Table 1: Investigations conducted and the results.

Investigation	25th Nov 2019	Results	Investigation	25th Nov 2019	Result
Hb%		6.7gm%	SGOT		62.9U/L
RBC's		2.3mill.cell	SGPT		29.6U/L
WBC		15100 cells	Alkaline Phosphatase		109.9U/L
DC		N-53%, L-29%, M-3%, E-5%	Total Bilirubin		5.57mg/dl
ESR		12mm/hr	Direct Bilirubin		1.09mg/dl
CRP		Negative	Albumin		2.7g/dl
HIV,HBSAg		Negative	Globulin		3.93g/dl
Hep A IgM		Negative	A/G Ratio		0.69:1
HCT		21.3	PT		30.3
ANA		Negative	INR		2.3
DCT		Negative	Total proteins		6.63g/dl
Cold Agglutinin Test		Positive	LDH		376.6IU/L
Weil Felix	24th Dec 2019	OX:K 1:640, OX:2 1: 1280, OX:19 1: 640 Positive			
Serum Ceruloplasmin levels	26th Nov 2019	<9.18mg/dl (20 – 60 mg/dl)			
24 hr urine copper	30th Nov 2019	346.32 microgm/day (Ref.range: 2 – 80 microgm/day)			

Blood picture	**25th Nov 2019**	Moderate macrocytic & microcytic hypochromic anemia with anisocytosis seen. Many polychromatophilic erythrocytes are seen, mild leukocytosis seen. Neutrophils showed mild toxic granulation. Immature or atypical cells not found. Platelets are adequate.
Upper GI Endoscopy	**28th Nov 2019**	Normal
Slit lamp examination of eyes	**27th Nov 2019**	Kayser Fleischer (KF) rings present

Patient started on D-Penicillamine 250mg twice daily and Zinc supplements. She started spiking fever with bilateral cervical lymphadenopathy after 20 days of treatment giving rise to the suspicion of drug fever, Lupus like reaction to drug or an infection. A Weil Felix test was sent because Mysore is endemic for rickettsial infections. Her titres were significantly high. She was then started her on Tab. Doxycycline 100mg twice daily after checking interactions with D-Penicillamine and Zinc. The patient became afebrile and cervical nodes started regressing in 2 days of initiation of treatment with Doxycycline.

Our case did not have clinically established neurological or psychological deficits. Hence MRI Brain was not performed. Liver biopsy was not done as it would not much to the diagnosis and the distribution of copper in the liver tends to be uneven. Molecular Genetic testing for ATP7B

gene to diagnose and identify the mutations and carriers in the family were not performed due to cost constraints and lack of genetic testing facility in Mysore.

Her diagnosis at discharge was Wilson's Disease with Coomb's negative hemolytic anemia and Rickettsial fever.

Figure 1: Kayser Fleischer (KF) rings (deposits of Copper in Cornea)

DISCUSSION

Mageed SA et al, had reported a patient first presented with unexplained acute severe hemolytic anemia at 16 years old. The diagnosis of WD had not yet been reached at this stage, and the patient had typical features of SLE, so the anemia was attributed to SLE.[3] Occurrence of hemolytic anemia was reported before detecting WD by Ye et al. [4] reported a 15-year-old girl who had acute hemolytic anemia as the first presentation of WD. However, the diagnosis was not reached until recurrence of the hemolytic attack with hepatic and neurological deterioration. Similarly, Santra et al. [5] reported two cases of acute hemolytic anemia of unclear etiology as an initial presentation of WD.

Hepatic involvement is the most common presenting feature of WD followed by neurological and psychiatric manifestations [6]. The temporal presentation of our case is consistent with the above cases. However, our case was complicated by Hepatitis A at the time of initial presentation and Rickettsial fever at the beginning of treatment. In the tropics where concurrent infections are not rare, one must have a high index of suspicion for underlying non-infectious diseases when things don't add up.

Therapy for WD is aimed at preventing accumulation of copper in tissues and reducing already accumulated copper in the body. A combination of copper chelators like D-penicillamine and zinc therapy is used to prevent progress of WD. Patients are advised to avoid certain high copper foods such as chocolate, mushroom, nuts etc. Liver transplantation becomes lifesaving for subjects in advanced stage of WD [1].

Our patient's family was counseled regarding the course and prognosis of the disease. The possibility of liver transplantation at the later stages of life was also made known. She is currently on regular follow up with a hepatologist.

CONCLUSION

Hemolytic anemia is a rare presentation of Wilson's disease. Uncommon presentations of common diseases have to be considered in differential diagnosis, since Rickettsial fever as in this case.

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