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A CASE REPORT ON COMPLICATIONS OF WILSON'S DISEASE

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Abstract : Wilson disease is a hereditary condition marked by an excess of copper buildup in the body, which can cause a variety of clinical symptoms. It is a major contributor to young people's chronic liver disease (CLD), which can manifest as anything from neurological and behavioral disorders to hepatic dysfunction. An important consequence of chronic liver disease (CLD) is portal hypertension, which is caused by an accumulation of copper in the liver. Wilson disease patients frequently have hypothyroidism at diagnosis, which can make managing the condition more difficult. A 40 years old male patient was brought to casualty with chief complaints of hematemesis in the form of clots massive 500 ml since 1 day 3 episodes, loose stools since 1 day 6 episodes, melena, generalized weakness; Patient he is a known case of chronic liver disease, portal hypertension splenomegaly since past 8 years, not on medication. Patient is not addictive to alcohol or smoking. On examination the patient was afebrile and conscious coherent with Pallor ++. On laboratory examination CBP reveals Decreases Hb, Platelet Count, Total WBC, Serum albumin and Serum Ceruloplasmin confirming the diagnosis as chronic liver disease with portal hypertension; decompensated cirrhosis of liver disease; severe anemia; secondary to Wilson's disease. The Patient was treated Inj .octreotide, Tab. Udiliv, Inj Human Albumin, Tab Zinc, Tab. Rifaximine, Tab Thyroxine Sodium. The patient was recovering UGI bleed and hematological report shown improvement in blood levels, anemia is resolving and patient was discharged.

Keywords: *Wilson Disease, Chronic Liver Disease, Portal Hypertension, Hypothyroidism,Complication of CLD, Increased Copper*.

I. INTRODUCTION

Wilson disease is a autosomal recessive disorder caused due to impairment in the activity of ATPase 7B gene which is found on chromosome 13 long arm ,which is encoded by ATP7B,an enzyme that is mostly present in liver cells is in charge of cellular copper transport which is declined in Wilson's disease ,its half-life shortens and it experiences localization in the cell due to its inability to collaborate with antioxidant protein 1 (ATOX1), which is required for the appropriate transport of copper in the cell.[1]

Copper miss binds to apoceryloplasmin due to ATPase 7B malfunction, impairing the elimination of excess copper in bile and causing copper retention in cells, especially hepatocytes. After liver cells are damaged due to exceeding their capacity threshold, copper is released into the bloodstream. Unbound with ceruloplasmin (CPN) this form of copper is extremely toxic and readily accumulates in other organs such as the intestines, brain, kidneys and cornea.[2]

An estimated 1:30,000 people are believed to be affected by WD, which affects 6-12% of patients under 40 who are hospitalized for acute liver failure (ALF). [3]

Higher levels of IgG and IgM, as well as a higher titer of antibodies against Kunin's CA antigen, indicate an increased humoral immune response. Conversely, lower levels of cellular immunity, such as a response against E. coli and 2,4-dinitrochlorobenene (DNCB), lower lymphocyte transformation following concanavalin stimulation A (Con A), lower levels of purified tuberculin protein derivative (PPD), lower levels of Candida albicans, and lower production of macrophage migration inhibitory factor were observed. They also discovered that copper ions inhibited several cellular immunity tests and that leukocytes from WD patients had lower bactericidal activity. Although they postulated that liver cirrhosis causes immunological problems in WD, it is impossible to rule out the possibility that copper ions have an inhibitory influence on leukocyte metabolism and the immune response.[4]

The accumulation of copper in the Descemet corneal membrane causes a Kayser–Fleischer (KF) ring, which is seen in nearly all patients suffering from neurological disorders.

There are three different clinical manifestations of WD that can be identified based on the predominant symptoms: hepatic (affecting about 45% of patients), neurological (affecting about 35% of patients), and psychological (affecting about 10% of patients). Non-specific symptoms such irregular menstruation, kidney failure, bone and joint pain, and spontaneous miscarriages are also experienced by 5% of patients. Hemolytic anemia, Fanconi syndrome, pancreatitis, hypothyroidism, parathyroidism, or cardiomyopathy are uncommonly the initial signs of the illness.[5]

Physiological role of copper in human

Copper has diverse roles in redox homeostasis, biomolecule synthesis, mitochondrial energy production and maintenance, general signaling, extracellular matrix modeling, and biosynthesis, copper is an essential trace metal element for humans. In physiological concentrations, copper is involved in the production of hemoglobin, the metabolism of drugs and other xenobiotics, the metabolism of carbohydrates, the manufacture of catecholamines, the cross-linking of collagen, elastin, and hair keratin, and antioxidant defense systems.[7]Numerous illnesses, such as Menkes disease, cancer, cardiovascular disease, and neurological diseases are brought on by copper deficiency and sideroblastic anemia. On the other hand, Wilson disease is characterized by an excess of copper accumulation, and certain patients have iron deposits found in their livers.[8]

Clinical Presentation

Table 1:Clinical presentation of Wilson's disease

S.No	Clinical Presentation	S.No	Clinical Presentation
1	Fulminant Liver Failure	7	Disturbances in Muscle Tone
2	Hemolytic Anemia	8	Bradykinesia
3	Hepatosplenomegaly	9	Kayser-Fleischer Ring
4	Thrombocytopenia	10	Fanconi Syndrome
5	Coagulopathy	11	Cardiomyopathy
6	Encephalopathy	12	Hypothyroidism

Diagnostic Criteria for Wilson Disease

1. **Serum Ceruloplasmin:**Ceruloplasmin in serum One possible sign of WD is a low blood level of ceruloplasmin, typically less than 0.2 g/L (normal range: 0.2–0.5 g/L) or less than 50% of the lower limit of the normal range.[9] Evaluation for the presence of ocular symptoms, such as Kayser-Fleischer rings, and measurement of the blood level of ceruloplasmin (levels lower than 10 mg/dL in the normal range of 20–50 mg/dL) should be carried out in patients with neurologic and/or hepatic diseases suggesting the disease. Liver biopsy and measurement of the blood level of ceruloplasmin are necessary in clinically asymptomatic patients without Kayser-Fleischer rings who exhibit isolated abnormalities in liver tests (copper content in the liver tissue above 250 mg/g of dry weight confirms the diagnosis).[10,11]
2. **Urinary Copper:** High urine copper excretion over a 24-hour period, often greater than 100 µg/24 hrs in adults and 40 µg/24 hrs in children with WD, is generally indicative of the illness. The test is still the most accurate one-time screening method for WD diagnosis.[10,11]
3. **Blood Liver Test:**Liver tests in blood the most common characteristic of WD, observed in over 50% of patients, is hepatic impairment. Acute liver failure, chronic hepatitis, liver cirrhosis, and asymptomatic abnormal liver tests are only a few of the possible laboratory changes. Increased levels

of bilirubin and the liver enzymes aspartate transaminase (AST) and alanine transaminase (ALT) can indicate hepatocellular injury caused by liver chemistry. When end-stage liver disease manifests, decreased albumin concentration, coagulopathy with prothrombin time extension, or thrombocytopenia (caused by hypersplenism and portal hypertension) typically happen.[10,11]

Drug Therapy for Wilson Disease

1. **Copper Chelator: D-Penicillamine:** First-line treatment for Wilson disease patients involves the use of copper chelators such as D-penicillamine, which aid in the removal of circulating copper linked to albumin and enables the kidneys to excrete copper through the urine. D-penicillamine is initially given at a daily dose of 300 mg and is increased weekly from 300 mg up to 1500 mg/d.[12]
2. **Using Trientinein Drug Therapy:** Trientine therapy has long been advised as a second-line treatment for Wilson disease patients, despite the lack of head-to-head studies for the initial course of treatment.[13]
3. **Zinc Therapy:** With the exception of severe gastrointestinal discomfort that may force drug withdrawal, the use of zinc as zinc salts, or the more palatable zinc–amino–acid–bound medicines, is linked to less adverse drug reactions (ADRs). Adults should take 3 × 50 mg daily, while children and adolescents should take 3 × 25 mg. In terms of reducing liver damage, it was judged to be less effective than chelators. Intestinal metallothionein, which zinc promotes, increases excretion in the feces and inhibits copper absorption, improving symptoms.[14]

Dietary Recommendations

High-content foods that contain copper include cocoa made from Owena cocoa (Theobroma cacao L.), which has been contaminated by copper-containing fungicides; dark chocolate made from contaminated cocoa; nuts; raisins; shellfish; oysters; and butchery items made from the liver and kidneys of cattle that were grazing on grounds where plants may have been contaminated with copper [164,165]. Products like dark chocolate and cocoa that contain significant levels of copper are crucial in the clinical nutritional context of Wilson disease and should not be ingested by people with the condition.[15]

II.CASE REPORT

A 40 years old male patient was brought to casualty with chief complaints of hematemesis in the form of clots massive 500 ml since 1 day 3 episodes, loose stools since 1 day 6 episodes, melena, generalized weakness; Patient has the same past medical history 8 years ago ;he is a known case of chronic liver disease, portal hypertension splenomegaly since past 8 years, secondary to variceal bleeding in hypovolemic shock with severe anemia with splenic lymphoma ; denovo hypothyroidism, celiac disease and is not on medication. Patient is not addictive to alcohol or smoking.

On general examination the patient was afebrile and conscious coherent. On Physical Examination his vitals observed as PR- 82bpm, SPO2 -99%, BP- 120/80 mmHg. On systemic examination, CVS-S1 S2-+, CVS-S1S2+, CNS- B/L NAD, Pupil -NSRL, BAE+, GRBS-235 mg/dl, Pallor ++.

On laboratory examination the blood profile reveals the following data to be abnormal: Complete Blood Picture reveals Decreases Hemoglobin 6.2 g/dl, Platelet Count 93 thousand/$mm^3$and Total WBC 2.50 thousand/mm^+. Biochemistry reveals increased Direct bilirubin 0.26mg% and decreased Serum albumin 2.77g/dl. Serum Ceruloplasmin was found to be decreased 19.46 Mg/dl.

On radiological examination of upper GI endoscopy reveals small esophageal varices, Ultrasound scan of abdomen shows altered echo texture of liver with mild ascites and splenomegaly with peri splenic collaterals noted. And Ecg observed as sinus tachycardia, widespread st-t abnormality may be due to myocardial ischemia. Based on all the above examinations the patient was diagnosed as chronic liver disease with portal hypertension; decompensated cirrhosis of liver disease; severe anemia; secondary to Wilson's disease.

The following are the details of lab investigation of the patient

Table 2:HematologicalReports

Test Name	Values	Normal Range
Hemoglobin	**6.2** g/dl	12.0-17 g/dl
Total RBC count	2.59mln/cmm	3.8-4.8 mln/cmm
Platelet count	**93** thousand/cmm	150-400 thousand/cmm
Total WBC count	**2.50** thousand cell/cmm	4-11 thousand cell/cmm
Eosinophils	10.0 %	01-06 %
Monocytes	8.8%	02-10 %
Basophils	0.4%	00-01 %
Lymphocytes	20.8%	20-40%
Neutrophils	60.0%	50-70 %
MCV	85.3fl	80-100 fl
MCH	23.9pg	27-34 pg
MCHC	28.1g/dl	320-360 g/dl

Table 3:Biochemistry Report

Test Name	Values	Normal Range
Blood urea	18.0 mg/dl	15-40mg/dl
Serum creatinine	1.12 mg/dl	
Total serum bilirubin	0.99 mg %	0.2-1.0mg %
Direct bilirubin	**0.26 mg %**	0.0-0.2mg %
Serum albumin	**2.77 gm/dl**	3.5-5.5 gm/dl
SGOT	21.02 U/L	0 -35U/L
ALP	85.67 U/L	35-129U/L
Albumin	**1.82 gm/dl**	3.5 – 5.5 gm/dl
Total Proteins	**5.92 gm/dl**	6 – 8gm/dl
Na+	**131.5 mEq/L**	136-145mEq/L
Cl-	99.3 mEq/L	98-107mEq/L
K+	4.10 mEq/L	3.5-5.5mEq/L
T3	**0.33µg/dl**	4.5 – 9.8 µg/dl
T4	1.5ng/ml	0.8 – 2 ng/ml
TSH	1.15µIU/ml	0.4 – 5.5 µIU/ml
Ceruloplasmin, Serum Method : immunoturbidimetric	**19.46 mg/dl**	20-60 mg/dl

Treatment

On admission patient was treated Inj .octreotide 100µg Stat followed by 50 mg/hr IV infusion, Inj. Pantoprazole 40mg IV OD ,Inj. Ondensetron 4 mg IV OD , Syrup lactulose 10 ml H/S , Tab. Udiliv 300 mg PO OD, IV NS, DNS 50 cc/min, Inj Human Albumin 20% 100ml, Tab Zinc 20mg PO OD . During the stay at hospital the medications were prescribed i.e Tab. Rifaximine 550 mg PO BD, Tab. Glutathione 500 mg PO TID, Inj. Vitamin K 1amp IV OD, Tab S-Adenosyl Methionine 400 mg PO TID, Tab. Thyronom 25 ug PO BD , Tab. Levocetrizine 5 mg PO BD, Tab. Carvedilol 325 mg PO OD, Tab. Lasix 20 mg PO BD, Albucare powder 2 scoops in milk(protein powder). On day 4 the patient complained with itching which was treated with the ointment Clotrimazole 1%, still by the use of ointment itching was not controlled, the on Day 7 Patient was prescribed with T Levocetrizine them the itching was subsided and Levocetrizine was continued. Hypovolemic Shock was treated with Nor Adrenaline 5µg/min infusion until MAP >65mmHg. On next following days the patient was recovering, Hypovolemic shock; UGI bleed recovered and hematological report shown improvement in blood levels, anemia is resolving and patient was discharged.

Table No 4 : List of Drugs prescribed to the patient

S.No	Drug	Dose	ROA	Freq	D1	D2	D3	D4	D5	D6	D7	D8	D9
1	Inj Octeoride	100µg Stat Followed by 50µg/hr infusion	IV	OD	✓	✓	✓	✓	✓	✓	✓	✓	✓
2	Inj Pantoprozole	40mg	IV	OD	✓	✓	✓	✓	✓	✓	✓	✓	✓
3	Inj Ondensetrone	4mg	IV	OD	✓	✓	✓	✓	✓	✓	✓	✓	✓
4	Syp Lactulose	10ml	PO	HS	✓								
5	Tab Udiliv	300mg	PO	OD	✓	✓	✓	✓	✓	✓	✓	✓	✓
6	Tab. Rifaximine	550mg	PO	OD		✓	✓	✓	✓	✓	✓	✓	✓
7	Tab. Zinc	20mg	PO	OD	✓	-	-	-	-	-	-	-	-
8	Inj Ceftriaxone	100mg	IV	BD	✓	-	-	-	-	-	-	-	-
9	Inj Human Albumin	20% 100ml	IV	OD	✓	✓	✓	✓	✓	✓	-	-	-
10	T Glutathione	500mg	PO	TID	-	✓	✓	-	-	-	-	-	-
11	Inj Vitamin K	5 amp	IV	OD	-	✓		-	-	-	-	-	-
12	Tab Nusan	300 mg	PO	BD	-	✓		✓	✓	✓	✓	✓	✓
13	Tab Thyroid Sodium	25µ	PO	OD	-	-	-	✓	✓	✓	✓	✓	✓
14	Tab Levocetrizine	5mg	PO	HS	-	-	-	-	-	-	✓	✓	✓
15	Tab Furosemide	40mg	PO	BD	-	-	-	-	-	-	✓	✓	✓

III. DISCUSSION

As the patient is suffering from hematemesis, the patient is treated with IV fluids, immediate blood transfusion, the use of NSAIDS should be monitored as it may induce the effect. The main cause for hematemesis includes esophageal varices, peptic ulcer, Mallory –Weiss tears. Esophageal varices usually develop when blood flow to the liver is blocked in patients with advanced liver disease. Portal hypertension, is another serious complication of advanced liver disease in this the blood pressure is elevated in portal vein which is mainly due to portal venous system drains blood from the stomach, intestine, pancreas, and spleen into liver. The potential complication of portal hypertension includes ascites, GI bleed, hypersplenism, low blood oxygen, hepatic encephalopathy.

The hemolysis in Wilson's disease is due to the deficiency of ceruloplasmin , the copper transport protein which results in excessive inorganic copper in the blood circulation much of which accumulates in red blood cell, although the exact mechanism is not known. Glucocorticoids can help patients to get through hemolytic crisis. In Wilson's disease Kayser-Fleischer rings are formed which are green to brownish colored rings that appears around the colored part of the eye in people with Wilson's disease which develops bilaterally , it can be visible with slit lamp examination. It's caused by copper deposits in the cornea's Descemet membrane.

There is no completely reliable test for Wilson's disease but a liver biopsy is the gold standard . S-Adenosyl L-Methionine is most helpful in treating liver diseases including serving as a precursor for cysteine, 1 of 3 amino acids of glutathione the major physiologic defense mechanism against oxidative stress. SAMe also acts as the main methylating agent in liver. The precursor of SAMe is methionine, one of the essential amino acids , which is activated by SAMe-synthetase in mitochondria. Ursodeoxycholic acid (UDCA) is widely used for the treatment of cholestatic liver diseases it helps in protection of injured cholangiocytes, Inhibition of apoptosis of hepatocytes.

IV. CONCLUSION

Wilson's disease is a genetic disorder that leads to excessive copper accumulation in the body, primarily affecting the liver, brain, and other organs. Early diagnosis and treatment are crucial to prevent serious complications such as liver failure and neurological damage. Symptoms can vary widely including hepatic dysfunction, ocular manifestations, neurological issues. The mainstay of the treatment is chelation therapy, using agents like penicillamine or trientine to promote copper excretion. Zinc therapy used to inhibit copper absorption from the gastrointestinal tract. Lifelong monitoring and adherence to treatment plans are essential for optimal outcomes. Regular follow up with healthcare providers can help mitigate complications and improve quality of life.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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