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Case Report

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Acute Deep Vein Thrombosis Presenting as an Early Complication of Wilson Disease: A Case Report

Aseel Faroun[1*], Roua Faroun[2], Rania Mashal[2], Mutaz Sultan[2,3]

[1]Faculty of Medicine, Al-Quds University, Jerusalem, Palestine.

[2]Faculty of Medicine, Al-Quds University, Jerusalem, Palestine.

[3]Department of Pediatrics, Faculty of Medicine, Makassed Hospital, Al-Quds University, Jerusalem, Palestine.

Abstract

Background

Wilson disease is a rare autosomal recessive disease characterized by defective copper metabolism due to ATP7B gene mutation on chromosome 13. Mutation in this gene that encodes for a membrane-bound copper-transporting ATPase leads to decreased serum ceruloplasmin and decreased biliary copper excretion. Free serum copper can be accumulated in different body organs, such as the liver, enterocytes, cornea, basal ganglia, brainstem, and kidneys. Neuropsychiatric and hepatic manifestations can represent a wide spectrum in the early stages of Wilson's disease. However, thrombotic events such as deep vein thrombosis are uncommon presentations of the disease, exclusively in pediatric patients.

Case Presentation

An 11-year-old female patient presented with a deep vein thrombosis clinical picture after 2 months of Wilson disease diagnosis. The patient presented with pain, warmth, and swelling in her left arm, besides jaundice, ascites, and lower limb pitting edema. Wilson disease was confirmed as an initial diagnosis associated with acute liver failure and acute deep vein thrombosis. Subsequently, the investigation results showed the cause beyond acute liver failure is Wilson disease. Factor V Leiden mutation & heterozygosity of MTHFR predispose to thrombotic events with Wilson disease.

Conclusion

Careful monitoring of Wilson's disease should be prioritized, and appropriate treatment plans should be established during diagnosis to achieve satisfactory outcomes and prevent thrombotic sequences. This case highlights the importance of considering coagulopathy management and administering vitamin K in unexplained thrombotic events in Wilson disease patients.

Keywords: Wilson Disease; Deep Vein Thrombosis; Pediatric Thrombosis; Hepatic Coagulopathy; Rare Presentation.

[*]**Corresponding author:** Aseel Faroun, Faculty of Medicine, Al-Quds University, Jerusalem, Palestine.

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Introduction

Background

Wilson disease is one of the rare diseases worldwide, exhibited in one to three cases in a population of 100,000 people. The ATP7B gene mutation plays a crucial role in copper metabolism and its accumulation in the liver, brain, corneas, and other tissues, which results in Wilson disease (WD) or hepatolenticular degeneration [1, 2, 3, 4, 5]. Wilson's Patients' ages vary from 3 to 74 years, and males and females are equally affected. The presentation of the disease presentation also varies from Kayser-Fleischer rings to neuropsychiatric symptoms, liver dysfunction, ascites, itching, yellow skin, and muscle stiffness [1]. Moreover, males are more likely to present with neurological symptoms (60% vs. 39%), but females are more likely to present with hepatic dysfunction clinical presentation (58% vs. 41%) [6]. Systemic manifestations may occur due to hepatic dysfunction-related coagulopathy. However, this case report highlights a unique presentation of Wilson's disease with acute deep-vein thrombosis, demonstrating the importance of considering Wilson's disease in children with unexplained thrombotic events [7]. Though the concurrence of deep vein thrombosis and Wilson disease is considered rare, they can be managed with copper chelation therapy, such as penicillamine and trientine, coagulopathy management, and vitamin K administration [4, 5, 8].

Case Presentation

We state a case of an 11-year-old white Middle Eastern female, who is a known patient of Wilson disease and was diagnosed 2 months before presenting to the hospital with the symptoms of acute deep vein thrombosis. The patient complained of left arm pain and swelling that started five days before admission to the hospital, associated with a feeling of warmth in it, a feeling of heaviness, and visible veins in the left arm and forearm but with normal regular pulses and normal vital signs. She has no family history of Wilson disease or thrombotic events, and she denied any history of recent trauma, prolonged immobilization, or infection. It is worth mentioning that since the diagnosis date, the patient was compliant with a high penicillamine dose (250 mg*4) and a low-copper diet.

On examination, she had yellowish skin, petechial rash on the ankle area bilaterally, not Blanche, mildly visible dilated chest vein, and lower limb pitting edema bilaterally (+3) with no deformities, distended abdomen (abdomen circumference = 70 cm), dull on percussion, and no shifting dullness; liver and spleen edges couldn't be palpated; neurological exams and other systems exams demonstrated normal findings. Patient hospital admission was done for her symptom management to do further investigations and to look forward to any early Wilson complications. First of all, the patient remained hemodynamically stable, as her ABGs on admission were: pH (7.28), CO2 (41), HCO3 (19.7), temp (36.9 C), heart rate (111), respiratory rate (27), blood pressure (120/67), and O2 sat (98%).

During her admission to ensure her Wilson disease diagnosis, physicians repeated her blood ceruloplasmin, which showed decreased levels (0.03 mg/dl; reference range > 20 mg/dl) and increased 24-hour urine copper excretion (it was 200 mcg/day, and then after penicillamine administration, it became 340 mcg/day). Routine laboratory studies, such as CBC & liver studies, showed increased transaminases (AST = 162.8 IU/L, ALT = 56 IU/L), low serum albumin (2.7 g/dl), hemolytic anemia, and thrombocytopenia as shown in (Table 1) and (Table 2). Also, slit lamp exam reports were requested from the ophthalmic hospital where she performed the exam 2 months ago, and the results were as shown in (Table 3) and (Table 4). However, an MRI of the brain was performed, as shown in (Figure 1). It revealed symmetric T2 and FLAIR hyperintense signals of the caudate nucleus and putamen and a small retention cyst in the floor of the right maxillary sinus. The other paranasal sinuses and mastoid air cells are clear, there is no midline shift, and the ventricular systems and CSF spaces are within normal limits. Thus, the imaging findings are highly suggestive of CNS involvement. Overall, these patient findings correspond to the Wilson disease diagnosis criteria [2, 5, 9].

Test Name	Normal Range (children)	Results
Bilirubin (direct)	0.0-0.3 mg/dl	3.36
Bilirubin (total)	0.3-1.2 mg/dl	4.94
Lactate dehydrogenase total (LDH)	100-300 IU/L	331
Ammonia	< 50 mmol/L	16.45
Aspartate Aminotransferase (AST)	10-40 U/L	162.8
Alanine Aminotransferase (ALT)	10-40 U/L	56
Alkaline Phosphatase (ALP)	130-560 U/L	259.1
Albumin	3.5-5.0 g/dl	2.7
Total Protein	6-8.3 g/dl	6
C-Reactive Protein (CRP)	8-10 mg/L	8.2
Lactic Acid (Venous Blood)	0.5-2.2 mmol/L	1.56
Prothrombin Time (PT)	11-15 sec	30.6 sec
International Normalized Ratio (INR)	0.9-1.1	2.44
Activated Partial Thromboplastin Time (aPTT)	24-40 sec	47.4
D-Dimer	< 250 ng/dl	681

Table 1: Liver Function Tests Laboratory Results upon Admission Day

Test Name	Reference Range (for Children)	Results
WBC	4.5-11 *10^9/L	2.99*10^9/L
NEU	2.5-7.0/L	0.877
LYM	3.0-9.5 /L	1.873
PLT	150-450 *10^9/L	123*10^9/L
Hgb	12.1 – 15.1 g/dl	9.53
Reticulocytes %	0.5 – 2.5%	3.20%
Direct Coombs Test (DCT)		Positive 2058 (IgG)/64 (C3)/ 7 (C4)
Indirect Coombs Test (ICT)		Negative
Ferritin	13 – 150 ng/mL	p = 0.008
TIBC	50 – 170 mcg/dl	148
Blood Film		Slight Anisocytosis, few ovalocytes
Na	135 – 145 mEq/L	129
K	3.6 –5.2 mmol/L	4.02
Cl	96 – 106 mEq/L	101
Calcium (Ca), serum	8.6 – 10.3 mg/dl	8.33
Phosphate	2.8 – 4.5 mg/dl	2.07
Mg	1.7 – 2.2 mg/dl	1.9

Table 2: Hematological, Metabolic & Serum Electrolytes Laboratory Results upon Admission Day

Abbreviations: NEU: Neutrophils, LYMP: Lymphocytes, PLT: Platelets, Hgb: Hemoglobin, TIBC: Total Iron Binding Capacity.

R. Note	Label	L. Note
Normal	LIDS	Normal
Patent	LACRIMAL System	Patent
Normal	CONJUNCTIVA	Normal
Normal	Sclera	Normal
Typical Kaysar Fleischer ring with endothelium deposition	Cornea	Typical Kaysar Fleischer ring with endothelium deposition
Quiet and Deep	Anterior Chamber	Quiet and Deep
Normal	IRIS	Normal
Round Regular Reactive	Pupil	Round Regular Reactive
Clear	Lens	Clear
Healthy Average Size	Optic Disc	Healthy Average Size
Clear	Vitreous	Clear
Flat with healthy	Retina	Flat with healthy

Table 3: Eye Examination

Vision Actually Test	Right Without Corr.	Left Without Corr.	Both Without Corr.
LogMAR	0.1 (6/7.5)	0.1 (6/7.5)	0.1 (6/7.5)

Table 4: Eye Vision

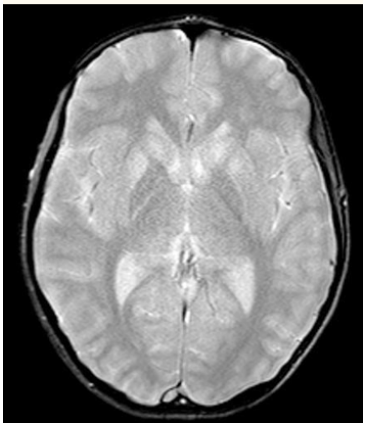

Figure 1: Brain MRI showing symmetric T2 and flair hyperintense signals of the caudate nuclear and putamen.

For further investigations to see the kidney involvement in her Wilson disease, urine analysis was also done as shown in (Table 5). Urine analysis and serum electrolytes demonstrate that there is normal functioning of the renal system and kidney damage or involvement due to Wilson disease except for hyponatremia, revealed in (Table 2), which was corrected easily after administrating hypertonic saline (HTS 20%) 10 cc*3, adjusting the penicillamine dose to 250 mg*2, and starting zinc sulfate 50 mg*2. Hyponatremia was explained by the hospital physicians as a possible complication of high penicillamine dose as we mentioned above. However, this patient has no Wilson disease kidney involvement yet, and hyponatremia can be caused by high penicillamine doses or liver dysfunction [22]

Urine Color	Orange
Specific gravity	1.03
Protein	Negative
RBC	0-2
WBC	05-Aug
Casts	Negative

Table 5: Urine Analysis Results during the patient's hospitalization

According to the patient's presenting symptoms, such as fatigue, jaundice, lower limb pitting edema, and ascites, there is acute liver failure secondary to Wilson's disease. Also, her previous lab tests, as shown in Table (1) and Table (2), align with the symptoms and the diagnosis, such as the elevated liver chemistries (AST=162.8 U/L, ALT=56 U/L), coagulopathy (INR equals 2.44), low platelet count, and hypoalbuminemia (2.7 g/dl). It is worth mentioning that she had a normal lipid profile: triglycerides (131 mg/dl; normal is < 150 mg/dl), HDL (24.1 mg/dl; normal is < 50 mg/dl), LDL (98 mg/dl; normal is < 100 mg/dl), total cholesterol (158.5 mg/dl; normal is < 200 mg/dl), and random blood sugar (95). However, a viral hepatitis panel was performed and showed negative results in (Table 6). Thus, viral hepatitis was ruled out as a cause of acute liver failure.

EBV IgG	46
EBV IgM	0.1
EBNA-1 IgG	26.28; CUT OFF POINT IS < 25 U/mL
HAV IgM	Negative
HAV IgA	Negative
HBsAg	Non-Reactive
CMV IgM	0.14
CMV IgG	111(then avidity test was ordered and results were negative)

Table 6: Viral Hepatitis Panel

During the patient's hospitalization, the management included monitoring serum electrolytes, administering Ursolit, anticoagulants, penicillamine, zinc sulfate, and hypertonic saline (HTS) 20% PO 10 cc * 3, and improving thrombocytopenia. Also, she showed significant improvement in her symptoms and laboratory tests on the discharge day, as albumin (3.1 g/dl), AST (76.9 U/L), ALT (46.8 U/L), INR (1.82), PT (23.4 sec), total protein (6.4 g/dl), total bilirubin (1.34 mg/dl), and direct bilirubin (1.01 mg/dl) compared to the results that were mentioned in (Table 1).

The patient's prescribed medication on discharge day was Vitamin K 4 mg*1, slow K 2 tabs q 8 hr, Ursolit 300 mg*2, Vitamin E 400 IU *1, Aldactone 50 mg*2, Penicillamine 250 mg q 12 h, Adol 10 drops *1, Zinc Sulfate 50 mg*2, and Hypertonic Saline (HTS) 20% PO 10 cc *3. During her last visit to the clinic after this hospital admission, the patient showed significant improvement in her symptoms, including the pain, and the swelling in her left arm was completely relieved. It is worth mentioning that specific genetic tests were requested, which may help in understanding the uncertain cause of the thrombotic event that occurred in this young patient. Lately, the genetic test reports were provided and established results as shown in (Table 7) and confirmed her Wilson disease diagnosis in (Table 8).

Genetic Factor*	**Results**
FII Prothrombin (Ala20210Gly)	Normal
MTHFR (Ala1298Cys)	**Heterozygous**
FXIII (Val34Leu)	**Heterozygous**
FV (Tyr1702Cys)	Normal
Factor V Leiden (FV Arg506Gln)	**Heterozygous**
FV (His1299Arg)	Normal
Factor V Cambridge (FV Arg306Thr)	Normal
MTR (Ala2756…	Normal
MTHFR (C677T)	Normal
PAI-1 5G/4G	**Homozygous**
B-Fibrinogen (Gly544Ala)	**Heterozygous**
MTRR (Ala66Gly)	Normal

Table 7: Thrombophilia Panel (CVD)

Test Methodology: Test was performed using real time PCR machine according to the manufacturer Thrombophilia Multipex real time PCR kit B (Cat.No:10R-20-12B) from SNP Biotechnology.

Gene	Transcript	Position	Nucleotide	dbSNP	Zygosity	ACMG Classification
ATP7B	NM_0000S3.4	13:52534477	c.1947- 19T>A	Rs1593733949	HOM	Likely Pathogenic

Table 8: SNV Results Details

Her coagulation studies upon admission showed increased initial D-dimer (681 ng/mL) as shown in (Table 1). According to the hospital physicians, the patient's clinical picture, including the pitting edema, localized tenderness, and swelling of her arm, can establish a +3 score in the modified Wells criteria for DVT [10, 11]. Furthermore, a Doppler ultrasonography report lately demonstrated an acute venous thrombosis in the patient's left arm.

Discussion

We present a case of an 11-year-old female patient with Wilson disease manifesting as an acute deep vein thrombosis. The patient presented with pain, warmth, and swelling in her left arm, besides jaundice, ascites, and lower limb pitting edema. Wilson disease was confirmed as an initial diagnosis associated with acute liver failure and acute deep vein thrombosis. Subsequently, the investigations resulted in showing the cause beyond acute liver failure; hemolytic anemia and thrombocytopenia are Wilson disease, and viral hepatitis was ruled out due to the negative viral hepatitis panel results [12, 13]. Hepatic dysfunction in Wilson disease is caused by copper accumulation, as its pathogenesis involves the failure of copper excretion into bile due to a defect in the ATP7B enzyme-encoding gene, which leads to copper dynamic balance disorder. Liver damage that is induced by copper oxidative stress can vary in the clinical picture as it ranges from acute liver failure to liver cirrhosis or neuropsychiatric disorder [1, 14]. However, the cause of acute deep vein thrombosis (DVT) wasn't fully understood. This case establishes a rare presentation of Wilson's disease with DVT, which seemed like an early complication, and the genetic tests helped to further understand the cause beyond the thrombotic event.

As it is known, chronic liver dysfunction can lead to reduced synthesis of coagulation factors II, VII, IX, and X, and fibrinogen, which increases the risk of bleeding. Advanced liver damage leads to reduced anticoagulant levels such as protein C, S, and anti-thrombin, which predispose the patient to thrombotic events. Thus, coagulopathy is commonly seen in advanced Wilson disease [15]. While our patient has a classical early presentation of Wilson disease and met all the diagnostic criteria: Kayser-Fleischer rings, low plasma ceruloplasmin and albumin, and high 24-hour urinary collection [2, 5], she showed early thrombotic events during her disease course, through her Wilson disease is not advanced. DVT clinical presentation is unusual to be seen with Wilson disease [9]. According to the genetic reports results as shown in (Table 8), the patient is at risk of developing thrombotic events due to the heterozygous change in the FV (FV Leiden) gene, and the heterozygosity of MTHFR (A1298Cys) associated with a 30% reduction of the MTHFR enzymatic activity [16]. Moreover, the homozygosity of the PAI-15G/5G gene has been described to increase the risk of thrombosis, but its role in recurrent abortion is still unclear [17,18].

This young patient is worth reporting due to the rarity of Wilson's disease to be early presented with DVT. A similar case had been reported in a 32-year-old male [19], who presented with right leg DVT as an initial presentation of Wilson disease. He exhibited significantly prolonged prothrombin time, reduced platelet counts, and increased levels of factor VIII and von Willebrand factor; those abnormal results were due to acute liver failure complicated by Wilson's disease [19]. In patients with liver disease and abnormal laboratory tests of coagulation factors, vitamin K is recommended to be routinely administered to aid in the synthesis of coagulation factors [17, 19]. Deep vein thrombosis in Wilson disease patients should be carefully monitored to prevent further complications [20, 21].

Conclusion

Despite the limited presentation of deep vein thrombosis in patients with Wilson disease, careful monitoring should be prioritized, and appropriate treatment plans should be established at the time of diagnosis to achieve favorable outcomes. Overall, while thrombosis is a rare early complication or presentation in Wilson's disease, this case highlights the importance of considering coagulopathy management and administering vitamin K in unexplained thrombotic events in Wilson's disease patients. In our case, the absence of a family history of Wilson's disease highlights the sporadic nature of the disease and reinforces the need for clinical observance.

Availability of data and materials

Information related to the case is available from the corresponding author upon reasonable request.

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Authors Contribution

AF contributed to the design of the study, data collection, data entry, data interpretation, and drafting of the manuscript. RF and RM contributed to the design of the study, data collection, and drafting of the manuscript.

MS contributed to the supervision of the work. All authors have read and approved the final manuscript. Each author has participated sufficiently in the work to take public responsibility for the content.

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Declarations

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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