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Case Report
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Undiagnosed Wilson's Disease, Mimicking HELLP Syndrome during Puerperium

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Abstract

Inthisreport, the case of a young Greek primigravida who showed the clinical features of hemolysis, elevated liver enzymes and HELLP syndrome after an elective caesarian section is discussed. Further diagnostic tests confirmed first manifestation of undiagnosed Wilson's disease. Are views of the literature revealed only one more similar case of Wilson's disease first presenting during pregnancy mimicking HELLP syndrome, rendering the current report very important. Although Wilson's disease is recognized early in adulthood, mainly due its complications, perhaps it should be included in an obstetrician's differential diagnosis when investigating a woman antenatally or during the puerperium who presents with symptoms of pre-eclampsia or HELLP syndrome. The diagnosis of such a disease during pregnancy demands a particularly high index of suspicion on behalf of the clinical doctor and demands the valuable collaboration of an experienced hematologist.

Keywords: HELLP syndrome; Pregnancy; Wilson's disease; Acute liver failure; Hemolytic anemia; *ATP7B*

Introduction

Wilson's disease or WD, is an autosomal recessive disease, characterized by impaired function of a copper transporting protein (ATP7B), resulting in the toxic accumulation of copper in tissues, particularly in brain and liver [1]. The disease phenotype varies greatly and includes mainly hepatic and neuropsychiatric symptoms [2-4]. Over 80% of patients present the first symptoms of the disease within the first three decades of life. 40% to 70% of the first clinical symptoms of WD involve the liver [5]. The hepatic manifestations of WD include from the asymptomatic liver function abnormalities and chronic hepatitis, to cirrhosis or acute liver failure [1]. The biochemical parameters that are usually affected in patients with WD complicated with acute liver failure are mild elevations of transaminase, highly increased concentration of total bilirubin and decreased hemoglobulin and serum alkaline phosphatase, in combination with elevated copper levels in serum, urine and liver tissue [6,7]. The characteristic Wilsonian acute liver failure coexists with a cute Coombs negative intravascular hemolytic anemia, which in some patients may be the first clinical manifestation of the disease [8,9]. Liver cell necrosis can release amount of free copper ions in the circulation giving rise to hemolysis due to oxidant stress, damage of red cells' cellular membrane and inhibition their metabolism [9].

The diagnosis of acute liver failure due to WD is challenging, as similar signs and symptoms can be found in a variety of other clinical situations. In pregnant women with undiagnosed WD, acute liver failure concomitant with hemolysis can be misinterpreted as HELLP syndrome.

HELLP syndrome is a serious complication in pregnancy characterized by hemolysis, elevated liver enzymes and low platelet count. The syndrome occurs in about 0.5% to 0.9% of all pregnancies and in 10% to 20% of cases with severe preeclampsia [10]. Although HELLP syndrome used to be regarded as an entity separated from severe preeclampsia, currently it is considered to be a variant of severe preeclampsia or a complication [11]. Diagnosis of the complete form of the HELLP syndrome requires the presence of all 3 major components, while partial or incomplete HELLP syndrome consists of only 1or 2 elements of the triad (H or EL or LP) [11]. HELLP syndrome is a multisystem disease characterized by a broad spectrum of clinical manifestations-from asymptomatic disease to fatal failure-as well as laboratory findings [7]. In about 70% of the cases, the HELLP syndrome develops before delivery [12] with a peak frequency between the 27th and 37th gestational weeks; 10% occur before the 27th week, and 20% beyond the 37th gestational week [11,13]. Approximately

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30% of cases occur after delivery [14]. Two classification systems have been suggested to categorize patients with possible HELLP syndrome by researchers in the university of Mississippi and Tennessee. The Tennessee system categorizes patients in "complete" and in "partial" syndrome according to the presence of the following criteria: thrombocytopenia, liver dysfunction, haemolysis (complete HELLP syndrome: all of the three parameters, partial HELLP syndrome: only one or two parameters) [15]. The Mississippi Triple-class HELLP System further classifies the disorder by the nadir platelet counts [11] (Table 1).

Although the pathophysiology of the disease remains partially unknown, activation of endothelial cells may lead to release of von Willebrand factor multimers, which are highly reactive with platelets [15]. Independently of triggering mechanism, an important step-in the pathogenesis of the HELLP syndrome seems be endothelial damage and/or dysfunction followed by thrombosis in hepatic capillaries [7]. The risk factors for the presentation of HELLP syndrome include nulliparity, advanced maternal age, previous pregnancy with preeclampsia, and family history, which are the same also for pre-eclampsia [16]. The patients may present initially with nonspecific symptoms such as nausea or vomiting, headaches, blurred vision and right upper quadrant pain, all of which are similar to those in patients with pre-eclampsia. However, the presence of HELLP syndrome is associated with significant maternal mortality and morbidity including acute renal and liver failure, Disseminated Intravascular Coagulopathy (DIC), pulmonary edema, cerebrovascular accident, and sepsis [17]. Additionally, perinatal morbidity and mortality are also markedly high and are related primarily to the complications of prematurity and growth restriction [17]. Approximately 70% of pregnancies complicated by HELLP syndrome require preterm delivery, with 15% occurring at extremely preterm gestational age (before 27 completed weeks' gestation) [17,18].

Table 1: Main diagnostic criteria of HELLP syndrome.

HELLP class	Tennessee classification	Mississippi classification
1	PLTs ≤ 100 ×10^9/l	PLTs ≤ 50 × 10^9/l
	AST ≥ 70 IU/l	AST or ALT ≥ 70 IU/l
	LDH ≥ 600 IU/l	LDH ≥ 600 IU/l
2		PLTs ≤ 100 × 10^9/l and ≥ 50 × 10^9/l
		AST or ALT ≥ 70 IU/l
		LDH ≥ 600 IU/l
3		PLTs ≤ 150 × 10^9/l and ≥ 100 × 10^9/l
		AST or ALT ≥ 40 IU/l
		LDH ≥ 600 IU/l

Table 2: Mild elevation of liver function tests and moderately prolonged coagulation times.

SGOT	67 IU/l	(5-40 IU/l)
γGT	333 U/l	(8-61 U/l)
Total serum protein	5.6 g/dl	(6.4-8.3 g/dl)
Hgb	13.3 g/dl	(11.6-16.4 g/dl)
Hct	39.9%	(36%-48 %)
INR	1.82	(0.85-1.15)
aPTT	44.8 sec	(21-31sec)

Table 3: Increase in bilirubin levels and marginal rise in blood pressure.

Fibrinogen	109 mg/dl	(180-350 mg/dl)
Hct	27%	(36%-48%)
Hgb	9.1 g/dl	(11.6-16.4 g/dl)
INR	1.87	(0.85-1.15)
aPTT	57.1 sec	(21-31 sec)
tbil	11.6 mg/dl	(0.1-1.2 mg/dl)
dbil	8 mg/dl	(0-1 mg/dl)

Case Presentation

A 17-year old woman in her early puerperium, G1P1, was urgently referred to Ioannina University Hospital from General Hospital of Ioannina "Chatzikosta". She was subjected to an elective caesarian section in 38+6 weeks of singleton gestation in Corfu General Hospital, two days ago. The patient was reported to have exhibited elevated blood pressure, hemorrhagic mood with prolonged coagulation times and progressively worsening signs of acute hepatic insufficiency post operatively. From her personal medical history, hypothyroidism under T4 (88 μg and 75 μg) was reported and toxoplasmosis during the first trimester of her pregnancy. The patient also reported an unclear medical history of coagulation disorders, with "easy bleeding" after injuries and various episodes of epitasis before her pregnancy.

Acute toxoplasmosis in pregnancy

It has to be reported that positive IgG and IgM antibodies against toxoplasma gondii were found, during 6+4 weeks of gestation, a find that insisted two weeks later with a low antibody avidity of 38.8%. Furthermore, during this first biochemical test other results included AST 79 IU/l, ALT 188 IU/l, γGT 180 IU/l, LDH 243 U/l and normal values of total and direct bilirubin. The couple opted to carry on with the pregnancy and an amniocentesis was performed to detect possible toxoplasmosis infection of the amniotic fluid, in 16+4 weeks of gestation, which was came back as negative. The pregnancy continued without other complications up to GA of 38+6 weeks when a planned caesarian section was performed in Corfu General Hospital, on maternal request. Preoperative laboratory testing showed a mild elevation of liver function tests and moderately prolonged coagulation times (Table 2).

Immediately post-operatively, the patient showed bleeding diathesis, with postpartum vaginal bleeding and formation of an extensive subcutaneous hematoma in the anterior abdominal wall, with progressive fall in fibrinogen, HCT and Hgb levels, red blood cells without morphological defects microscopically, prolongation of coagulation times, increase in bilirubin levels and marginal rise in blood pressure (140 mmHg/90 mmHg) (Table 3).

Initially, the patient was treated conservatively with transfusion of 3 units RBC and 5 units FFP, stabilizing her hemodynamically. Due to the patient's gradual deterioration of liver functional tests, the onset of signs of microangiopathic hemolytic anemia during the direct microscopy of peripheral blood smear (microspherocytes/schistocytes) and drop in platelet count (PLT 95,000/μl) during the first postoperative day, her immediate transfer to a tertiary hospital, in order to deal with the situation, was decided.

Upon arrival in "Chatzikosta" General Hospital, the patient was hemodynamically stable and the PPH from the genital tract had been controlled. She was further transfused with another unit of RBC and 3 more units of FFP in total. An abdominal ultrasound and a CT were ordered which showed: "small pleural effusion, a mild enlargement of

Table 4: The deterioration of the patient's laboratory tests.

Wbc	25.83 k/μl	(4.5-10 × 10^3/mm^3)
Fibrinogen	109 mg/dl	(180-350 mg/dl)
Hct	26.90%	(36-48%)
Hgb	8.9 g/dl	(11.6-16,4 g/dl)
Plt	112 × 10^3/μl	(150-400 × 10^3/μl)
Tbil	24.54 mg/dl	(0.1-1.3 mg/dl)
Dbil	20.05 mg/dl	(0-0.25 mg/dl)
UA	1.4 mg/dl	(2.3-6.1 mg/dl)
INR	1.77	(1-1.3)
aPTT	48.43 sec	(26-36 sec)

Table 5: New biochemical results.

Wbc	21.92 k/μl	(4.5-10 ×10^3/mm^3)
Fibrinogen	109 mg/dl	(180-350 mg/dl)
Hct	21.50%	(36%-48%)
Hgb	7.1 g/dl	(11.6-16.4 g/dl)
Plt	111 × 10^3/μl	(150-400 × 10^3/μl)
tbil	38 mg/dl	(0.1-1 mg/dl)
dbil	17.6 mg/dl	(0.01-0.2 mg/dl)
UA	1.4 mg/dl	(2.4-6.1 mg/dl)
AST	65 IU/l	(10-35 IU/l)
INR	2.14	(0.8-1.2)
aPTT	40.5 sec	(25-35 sec)
Alb	2 g/dl	(3.5-5.1 g/dl)
TPR	3.6 g/dl	(6.2-8.4 g/dl)

the liver's and spleen's dimensions, without obvious focal lesions of the parenchyma as well as the presence of gallstones with associated mild thickening of the gall bladder's wall". The deterioration of the patient's laboratory tests continued (Table 4), while the direct and indirect Coombs tests were negative and severe proteinuria (+++) was detected in the urinalysis.

Due to the severity of the patient's condition, her further transfer to the Obstetrics and Gynecology department of Ioannina University Hospital was ordered in the second post-operative day.

After consultation with the gastroenterologists, hematologists and nephrologists on duty, the patient was put on ursodeoxycholic acid 250 mg × 3, prednisolone 25 mg × 2, ciprofloxacin 500 mg × 2, Human albumin 50 mg × 2, inj. furosemide 20 mg × 2 and Vit K. A new abdominal CT and a triplex examination of the liver portal system were also performed showing: "A significant increase of the bilateral pleural effusion, dilation of renal urinary tract (mostly right), ascites, increased liver diameter (~17 cm) with normal shape and echogenicity, without dilatation of the intrahepatic bile ducts, increased spleen size (13.6 cm × 4.5 cm) with normal echogenicity and a non-specific increase of gallbladder's wall thickness (~1.5 cm) with the presence of biliary sludge in gallbladder".

The differential diagnosis included HELLP syndrome, acute fatty liver of pregnancy, D.I.C., cholestasis of pregnancy, autoimmune hepatitis, viral hepatitis/hepatotropic viral infection.

The patient's clinical condition further deteriorated in the afternoon of the 2nd postoperative day, developing generalized edema, skin and mucosal jaundice, decreased breath sounds noted towards the lung bases, oliguria (~20 ml/h) and tachycardia (~100 bpm), without any signs of hepatic encephalopathy. New biochemical results (Table 5).

During the microscopic examination of peripheral blood smear, echinocytes, acanthocytes, spherocytes, polychromatophils, target cells and schistocytes were observed. It was decided that the patient should be admitted in the ICU, due to acute liver failure. During the patient's first day in the ICU, an assessment by the General surgeon on duty was carried out to exclude acute cholecystitis, due to the relevant findings of imaging tests.

On the 3rd postoperative day, immunological, as well as hepatotropic viral infections tests were ordered that came back as negative. Furthermore, the patient's plasma ceruloplasmin levels were reduced, 16 mg/dl (normal range 22 to 58 mg/dl). The patient's hemodynamic condition was stable, maintaining an excellent level of consciousness and acceptable diuresis, while on low-fat, hydric, per Os diet. A mild decrease of bilirubin levels was also noted (tbil 41.5 mg/dl and dbil 27.5 mg/dl). Furthermore, a 24-h urine sample was tested for copper levels and a slit lamp exam was performed by an ophthalmologist, without detecting any Kayser-Fleischer rings.

New laboratory results on the 4th postoperative day, revealed a drop in hematocrit (19.6% with Hgb 6.4 g/dl), which was dealt with a new transfusion of 1 unit RBC, while the urine culture developed *Candida* spp 100.000 cfu/ml. Patient's alimentation halted in the afternoon of same day, due to the onset of vomiting. Further blood tests revealed an alarming deterioration (Table 6).

The diagnosis of acute liver failure due to Wilson's disease was made and the patient's transfer to "Δ" Internal Medicine ward of Thessaloniki's General Hospital "Hippocrateio" was ordered for the specialized management of her condition.

The patient underwent a new series of laboratory and imaging tests, including an abdominal CT and a brain MRI, without any remarkable changes, compared to the previous tests, while the MRI did not confirm any copper deposits in the basal ganglia of the brain. Moreover, a new, negative for Kayser-Fleischer rings slit lamp examination was performed by an ophthalmologist. Finally, a new 24-h urine sample testing for discarded copper levels was carried out, measuring 2080 μg/24 h (normal range <100 μg/24 h). Genetic testing for Wilson's disease was sent to "Choremion" Research Laboratory of Medical Genetics of "St. Sophia's" Children's Hospital, which returned as "positive" for two pathological mutations of the *ATP7B* gene (genotype p.[His1069Gln]+p.[His1069Gln]).

Table 6: Laboratory results on the 4th postoperative day.

Wbc	27.09 k/μl	(4.5-10 × 10^3/mm^3)
Hct	25%	(36%-48%)
Hgb	8.5 g/dl	(11.6-16.4 g/dl)
tbil	45 mg/dl	(0.1-1 mg/dl)
dbil	25.4 mg/dl	(0.01-0.2 mg/dl)
AST	99 IU/l	(10-35 IU/l)
ALT	46 IU/l	(10-35 IU/l)
INR	1.99	(0.8-1.2)
aPTT	39.4 sec	(25-35 sec)
LDH	730 U/l	(115-230 U/l)

Table 7: Biochemical test results prior to discharge.

Wbc	5.4 k/μl	(4.5-10 × 10^3/mm^3)
Hct	40%	(36%-48%)
Hgb	13.4 g/dl	(11.6-16.4 g/dl)
tbil	7.85 mg/dl	(0.1-1 mg/dl)
dbil	3.43 mg/dl	(0.01-0.2 mg/dl)
AST	122 IU/l	(10-35 IU/l)
ALT	196 IU/l	(10-35 IU/l)
INR	1.45	(0.8-1.2)
γGT	262 IU/l	(6-32 IU/l)
ALP	174 IU/l	(30-125 IU/l)

Therapeutically, the patient was put under antibiotics (ampicillin/sulbactam), hydration with Dextrose 5% IV and the per OS prednisolone was converted to IV. She was also treated with penicillamine per OS and diuretics (furosemide and spironolactone) as well as lactulose, even without any signs of hepatic encephalopathy. The patient was also urgently put on the waiting list for a possible liver transplant.

A gradual improvement in the patient's daily liver function test results was noted, as early as on the 3rd day after her transfer (9th postoperative day). A progressive improvement in ascites and generalized edema was also observed and finally led to hematocrit being restored to normal range and to patient's discharge, on the 21st postoperative day. Biochemical test results prior to discharge are available in Table 7.

Discussion

The present case was deal initially as HELLP syndrome, due to the similarity in clinical presentation. Further diagnostic tests confirmed first presentation of undiagnosed Wilson's disease. Therefore, the question was raised whether the clinical signs and symptoms as well as laboratory findings were indeed clinical manifestations of HELLP syndrome, or rather a form of acute liver disease due to Wilson's disease.

The clinical symptoms and laboratory findings in our case were arterial hypertension, profound thrombocytopenia, raised liver function tests and raised levels of LDH. All the above characteristics were interpreted as manifestations of HELLP syndrome. However, similar laboratory findings are also observed in patients suffering from acute liver failure due to WD. The levels of serum LDH are usually being elevated in case of liver cell necrosis, regardless of the etiology. There are five LDH isoenzymes, with LDH1 and LDH2 found mainly in red blood cells and being increased in hemolytic anemias. Neither the distinct LDH isoenzymes nor serum haptoglobin were not tested in our patient. Moreover, a profound increase in bilirubin serum level, is uncommon in HELLP syndrome (usually normal or mildly increased), but often occurs in the context of acute liver failure due to WD. This observation, although was made early in the diagnostic process, was not capable of leading to the diagnosis of HELLP syndrome being rejected, due to the patient's clinical picture. Besides, severe proteinuria observed in urinalysis, was clearly in favor of a diagnosis near the spectrum of preeclampsia/HELLP syndrome, as the presence of protein in urine, was considered a pathognomonic feature of HELLP syndrome for several years, although eclampsia as well as HELLP syndrome, can also occur up to 20% in the absence of hypertension and/or proteinuria [19].

In acute hepatitis due to WD, the low levels of serum ALP can aid establishing the correct diagnosis. Specifically, a serum ALP to serum total bilirubin level ratio below 2 has 100% sensitivity and specificity for acute liver failure due to WD. Unfortunately, in our case the level of serum ALP was tested, not until the diagnosis had been confirmed.

Finally, imaging tests, such as abdominal ultrasound and CT, did not seem to provide sufficient evidence to rule out or confirm any definite diagnosis, while liver biopsy was not performed in our case.

Of course, the diagnosis of WD is definite when high serum and urine copper concentrations, as well as low serum ceruloplasmin levels (<200 mg/l) are found. However, these laboratory tests require a high level of suspicion to be performed in a previously asymptomatic woman, during her early puerperium.

Administration of d-penicillamine is considered first-line treatment for WD. It has the ability to bind copper molecules forming non-toxic compounds which then can easily be excreted in urine. If d-penicillamine is not well tolerated, trientine can be used instead, whereas zinc supplementation appears to have favorable long-term results, as it competes copper molecules, leading to their reduced absorption by the gastrointestinal tract.

By studying the existing literature, it becomes apparent that WD treatment should also be continued antenatally, as no treatment for WD or its discontinuation, appears to be related with an increased risk of serious morbidity, similarly to our case. D-penicillamine treatment is preferred during pregnancy as well, as it is usually well tolerated and relatively safe, both for the mother and fetus. Nevertheless, the use of the lowest possible effective dose is recommended.

Conclusion

After reviewing the literature, it seems that both asymptomatic and symptomatic WD patients undergoing treatment can achieve uncomplicated, full term pregnancies, whereas infertility and/or recurrent miscarriages are common in undiagnosed patients or in those not receiving treatment. Treatment for Wilson's should also be continued throughout pregnancy, while increased alertness and close monitoring is required for early identification of liver and neurological symptoms. The authors of this report have the opinion that Wilson's disease should be included in the differential diagnosis, in cases that the clinical picture indicates HELLP syndrome, due to the possibility of the first manifestation of WD appearing during pregnancy or the puerperium. Maintaining a high level of suspicion, as well as treatment administration as soon as possible after diagnosis, are necessary to prevent the risk of disease progression and the onset of serious hepatic and neurological complications.

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