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Case Report (Pages: 8697-8705)

# Creatinine Phosphokinase (CPK) Elevation in the Coexistence of Wilson's Disease and Autoimmune Hepatitis with Atypical Presentation: A Diagnostic Dilemma

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***Abstract***

***Background***: Wilson's disease (WD) is a genetic disorder with various clinical presentations due to excessive accumulation of copper in the liver and other organs. It can present as acute/chronic hepatitis, liver failure, extrahepatic and neuromuscular manifestations. Autoimmune hepatitis (AIH) is a necroinflammatory disease of the liver, which affects a lot of people particularly the children population. AIH has a broad clinical presentation that is similar to WD. Coexistence of WD with elevated creatinine phosphokinase (CPK) and AIH, may be a diagnostic dilemma.

***Case Report***: We presented a 6 years old boy with dysarthria, aggressive behavior, weak attention, concentration and weight loss with abnormal physical examination. Laboratory, histochemical, genomic studies, muscle/liver biopsy and atomic absorption test confirmed the diagnosis of both WD and AIH in the boy.

***Conclusion***

Although CPK and liver enzyme elevation is a rare presentation of chronic hepatitis with dominant feature of WD and AIH; however, simultaneous therapy with immunosuppressive drugs and Penicillamine may have superior benefit with a significant response.

***Key Words***: Autoimmune hepatitis, Atypical presentation, Children, Coexistence, Wilson disease.

*Please cite this article as: Dara N, Hosseini A, Tajalli S, Shahrbaf MA, Sayyari AA, Imanzadeh F, et al. Creatinine Phosphokinase (CPK) Elevation in the Coexistence of Wilson's Disease and Autoimmune Hepatitis with Atypical Presentation: A Diagnostic Dilemma. Int J Pediatr 2018; 6(12): 8697-8705. DOI: **10.22038/ijp.2018.33235.2932**

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Received date: Apr.14, 2018; Accepted date: Jul 22, 2018

## 1- INTRODUCTION

Wilson's disease (WD) and autoimmune hepatitis (AIH) are two prevalent causes of acute and/or chronic hepatitis in children. Coexistence of WD and AIH in one patient at the same time is rare (1, 2). Intracellular antigen exposure to the immune system is seen in WD secondary to hepatocyte necrosis which results in low titer of autoantibody production and may cause confusion, but higher titer is significant and suggestive for AIH; therefore, in patients with WD, a thorough screening for AIH is compulsory (1, 2). This finding is deceptive in differentiating AIH from WD. In these patients with WD, the serum levels of immunoglobulins are elevated and no evidence of dermatological and musculoskeletal manifestations of autoimmune disorders are present.

The creatine phosphokinase test measures creatine phosphokinase (CPK) level in the blood for specific enzymes that are found primarily in the skeletal muscle, heart and brain tissues. Measurement of creatine phosphokinase in a patient with high levels of liver enzymes aids diagnosis and differentiation of neurological and musculoskeletal disorders from liver disease. Review of literature shows that there is no literature, which has reported cases of coexistence of WD and AIH that presented with abnormal CPK prior to this study. In this study, we will present a case of chronic hepatitis with dominant features of both AIH and WD.

## 2- CASE REPORT

This study is a prospective review of a 6 years old boy that was evaluated for WD and AIH in our tertiary pediatric hospital (Mofid Children Hospital, Tehran, Iran). A 6 years old boy was admitted at our tertiary hospital with a history of frequent episodes of epistaxis, anorexia, weight loss (about 10 kg) since 3 years before the current presentation. Birth and admission weights were 4, 200 g and 21 kilograms, respectively. His mother complained of poor concentration and aggressive behavior in the boy. He was referred to our center due to elevation in liver enzymes. He had no history of any seizure disorder, spasticity, dystonia, weakness, excessive salivation, jaundice, tremor, nausea, vomiting, and fever in the past. He had no history of significant drugs or herbal medicine consumption that may affect liver enzymes. His first-degree and second-degree relatives had no history of similar liver disease condition.

The patient general condition was not bad. Clinical examination showed body temperature of 37$^{o}$C, blood pressure of 100/65 mmHg, heart rate of 72 beats/min and respiratory rate of 18/min. The spleen was not palpable and liver size and span was appropriate for the boy's age. Findings in favor of chronic liver disease, such as palmar and plantar erythema, spider hemangioma, caput medusa, jaundice and ascites were absent in abdominal investigation. Neurologic examination revealed difficulty in speaking (dysarthria), and weak attention. Gait, deep tendon reflex and motor power for both upper and lower extremities were normal. In the review of systems, other organs were in normal condition in the examination.

Laboratory investigations showed mild anemia, abnormal liver enzymes, very high creatinine phosphokinase (CPK) level and lactate dehydrogenase (LDH). The primary laboratory investigations are summarized in **Table.1** (*please see the table at the end of paper*). Advanced laboratory investigations, including ANA and other autoantibodies, serum ceruloplasmin, 24 hours urine copper and 24 hours urine copper with D-penicillamine challenge test were performed (**Table.2**) (*please see the table at the end of paper*). Serological tests for viral hepatitis A, B, C viruses, cytomegalovirus, herpes simplex virus,

and Epstein-Barr virus were negative. Therefore, we assessed him for WD and AIH in a primary investigation. Liver span was about 110 mm in ultrasonography with no space occupying lesion and homogenous echo pattern parenchyma. Spleen and gallbladder were normal in size as well as echogenicity. Echocardiography showed normal left ventricular function with ejection fraction of about 60%. The Kayser-Fleischer ring was not seen in slit-lamp examination by an ophthalmologist. Finally, liver biopsy was performed and histopathologic studies showed macro and microvesicular steatosis with mild ballooning change and feathery degeneration (**Figure A-D**) (*please see the figures at the end of paper*).

Few acinar formations, glycogenated nuclei, and focal sinusoidal collapsing were observed. (**Figure B**) (*please see the figure at the end of paper*). The portal spaces expanded due to mild fibrosis with focal reticulin condensation and revealed mild mixed inflammatory cell infiltration composed of mostly lymphocytes and eosinophils, which extended between the hepatocytes with mild interface hepatitis (**Figure D-E**) (*please see the figures at the end of paper*).

Specific staining of tissues did not show copper-rich cells. Histochemical analysis with rhodamine and orcein was negative. Atomic absorption of dry liver tissue for measurement of copper revealed excessive accumulation of 3000 mcg, which is more than 12 times the upper limit of normal. We confirmed Wilson's disease for him through our laboratory investigations and started treatment with D-penicillamine with an initial dose of 125 mg every 12 hours (10 mg/kg/day), 40 mg of oral pyridoxine daily and 400 mg of vitamin E daily with a gradual increase in D-penicillamine dose to a maximum of 250 mg dose divided into three course regimen, viz: morning, afternoon and evening. Liver function test, CPK and LDH did not show any improvement over 5 months of treatment with D-penicillamine alone in close follow-up. Therefore, in order to rule out any other differential diagnosis such as autoimmune hepatitis and musculoskeletal disease, mixed connective tissue advanced serological test, muscle biopsy with immune histochemical staining and genetic study for Wilson's disease were performed and their results are summarized in **Table.2** (*please see the table at the end of paper*). Genetic study for Wilson's disease revealed homozygote deletion in the ATP7B gene for a variant defined as c.1924G>C (P. Asp642His).

This result confirmed the diagnosis of WD in the boy. Muscle biopsy with immune histochemical staining revealed mild myopathic atrophy with a slight increase in lipid content of few fibers. No necrosis, regeneration, fibrosis and inflammation were observed. To examine autoimmune hepatitis, antinuclear antibody (ANA), anti-smooth muscle antibody (ASMA), and liver tissue were re-evaluated by a pathologist with vast and top-notch experience in pediatric liver disease.

Although there was no evidence of significant interface hepatitis in the hepatic sample, autoimmune hepatitis should be kept in mind. Based on the increase in ANA (1/640 speckled pattern) and ASMA (1/80), we added 40 mg prednisolone (2mg/kg/day) divided into three course regimen doses with reduction of the dose to 5 mg after 2 months. Liver enzymes, CPK and LDH decreased dramatically over three months. **Table.3** summarizes the liver function test carried out in the course of treatment. After a year of regular follow-up, all clinical symptoms such as poor concentration, aggressive behavior and dysarthria improved.

## 4- DISCUSSION

Autoimmune hepatitis and WD are considered as the leading causes of chronic and acute hepatitis, but their coexistence in

the same patient have been reported only in few cases (1, 4). However, the right diagnosis and selection of an appropriate therapy remain a clinical dilemma faced by pediatric gastroenterologists in their practice (5, 6). WD is an autosomal recessive hepatolenticular disease with various hepatic and extrahepatic presentations. Extrahepatic manifestations are neuropsychiatric (abnormalities of speech, mood/behavior change including depression, irritability, resting and intention tremor, dysarthria, dysphagia and mask-like face), musculoskeletal (rickets, Osteomalacia and arthropathy and muscle weakness) and cataract (5). AIH also is a chronic inflammatory liver disease, which may present with acute/chronic hepatitis, acute liver failure and extrahepatic manifestations (arthritis, autoantibody hemolytic anemia, myopathy and other endocrine abnormalities) (7).

Differentiation of these two diseases is imperative. In the early stage, hepatocellular antigen manifestation in the immune system due to hepatocyte necrosis can induce low titer of autoantibody production, which may cause confusion. However, the higher titer of autoantibody is significant and suggestive for AIH. Therefore, in patients with WD, a thorough screening for AIH is necessary, particularly when the response to chelating therapy is poor. Conversely, in patients with simultaneous WD superimposed feature of AIH, a combination of D-penicillamine and steroid may have beneficial effect (1-3, 8).

Several diagnostic modalities have been presented for the diagnosis of WD including serological test (Ceruloplasmin), 24 hours urine copper, D-penicillamine 24 hours copper challenge test and ophthalmic examination. Liver biopsy and histochemical staining with rhodamine provides qualitative evidence of increased liver copper (6). The creatinine phosphokinase test measures creatine phosphokinase (CPK) level in the serum, a specific enzyme that is found primarily in the skeletal muscle, heart and brain tissues. Measurement of creatinine phosphokinase in a patient with high levels of liver enzymes helps to diagnose and distinguish neurological and musculoskeletal disorders from liver disease. High levels of the CPK may occur due to inflammatory or non-inflammatory condition such as polymyositis, dermatomyositis, myocarditis, myopathy, rhabdomyolysis, muscular dystrophy, convulsions and several other conditions (9, 10). However, high creatinine phosphokinase level is an unusual manifestation of Wilson's disease or autoimmune hepatitis.

In the review of the literature, muscle weakness and other neuromuscular presentation have been reported in patients with Wilson disease; but elevated CPK, as well as high levels of transaminase and gamma-glutamyl-transferase (GTT) in coexistence with WD and AIH is very rare. Pfeifer N et al., reported two patients (a 5 years old girl and an 11 years old boy) with atypical finding recently. In their report, the girls' muscle biopsy showed myopathic changes with normal immunostaining and abnormal CPK (11). In our case, muscle biopsy with immune histochemical staining revealed mild myopathic atrophy with a slight increase in lipid content of few fibers, which may explain the elevation in CPK level as a non-inflammatory process.

## 5- CONCLUSIONS

This study highlights a combination of transaminase elevation with a significant increase in CPK level, which may lead to a neuromuscular disorder. In rare cases, an elevated CPK with musculoskeletal symptoms such as weakness could be the initial muscular manifestation of WD or AIH or their coexistence. Consequently, in the case of non-response of WD to chelators, high clinical awareness is

imperative for early diagnosis and initiation of treatment in patients with coexistence of Wilson's disease and autoimmune hepatitis, presenting with concomitant transaminase and elevation in CPK levels. Medical treatment for any of these diseases alone may result in poor response, but combination treatment with D-penicillamine and steroid may be more efficacious.

## 6- CONFLICT OF INTEREST: None.

## 7- ACKNOWLEDGMENT

Medical writing support was provided by Iranian Scientific Assosiation of Child Nutrition (ISACN).

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**Table-1**: Primary laboratory investigation

| | Serial liver function test | | | Cell blood count | | Chemistry and coagulation factor | | | |
|---|---|---|---|---|---|---|---|---|---|
| Marker | Value | Value | Value | Marker | Value | Marker | Value | Marker | Value |
| TP | 7.4 g/dl | 7.2 | 7 | WBC | 5700 $10^{*3}$ / mcL | Vit D25OH | 41 ng/Ml | TG | 88 mg/dl |
| Alb | 4.8 g/dl | 4.5 | 4.6 | RBC | 4.45 $10^{*6}$ / mcL | Ferritin | 125 ng/ml | Chols | 189 mg/dl |
| Golb | 2.6 g/dl | 2.7 | 2.4 | Hb | 11.9 g/dl | PT | 15 Sec | Uric acid | 3.2 mg/dl |
| AST | 475 U/L | 360 | 430 | MCV | 352 fL | INR | 1.5 IR | Ca | 9.3 mg/dl |
| ALT | 345 U/L | 290 | 485 | Plt | 352 $10^{*3}$ /mcL | PTT | 44 sec | P | 4.5 mg/dl |
| TB | 1.02 mg/dl | 0.2 | 0.6 | PMN | 29% | GGT | 43 Iu/L | BS | 83 mg/dl |
| DB | 0.10 mg/dl | 0.1 | 0.2 | Lymp | 64% | TSH | 2.67 mIU/ml | BUN | 13 mg/dl |
| AlKp | 1116 IU/L | 900 | 367 | ESR | 13 mm/h | T3 | 2.18 nmol/L | Cr | 0.66 mg/dl |
| LDH | 605 IU/L | 640 | 745 | CRP | 0.71 mg/L | T4 | 86.8 nmol/L | Na | 140 mEq/L |
| CPK | 5077 U/L | 2613 | 5600 | G6PD | Sufficient | Aldolase | 30 Iu/L high | K | 5 mEq/L |

Abbreviations: TP: total protein; Alb: albumin; Glob: globulin; ALT: alanine transaminase; AST: aspartate aminotransferase; TB: total bilirubin; DB: direct bilirubin; Alkp: alkaline phosphatase; LDH: lactate dehydrogenase; CPK: creatinine phosphokinase; BS: blood sugar BUN: blood urea nitrogen; Ca: calcium; Cr: creatinine; ESR: erythrocyte sedimentation sedimentation rate; Hb: hemoglobin; INR: international normalized ration; K: potassium; MCV: mean cell volume; Na: sodium; PT: prothrombin time; PTT: partial thromboplastin time; RBC: red blood cell; and WBC: white blood cell; GGT: gamma glutamyl transferase; G6PD: glucose-6-phosphate dehydrogenase; TSH: thyroid stimulation test; TG: riglyceride; Chols: cholestrole; P: phosphor.

**Table-2**: The specific laboratory investigation.

| Marker | Value | | Marker | Value |
|---|---|---|---|---|
| | 1st check | 2nd check | Ceroluplasmin | 4 mg/dl |
| ANA | 1/80 homogenous pattern | 1/640 speckled pattern | Urine 24 hr copper | 107 mcg/24hr |
| ASMA | 1/80 titer | 1/80 titer | Urine 24 hr copper challenge test | 954 mcg/24hr |
| AMA | <1/10 titer | Negative | HAV (IgM) | 0.4 COI |
| Anti LKM1 | 1 Ru/ml as negative | Negative | HCV (IgM) | 0.4 COI |
| Anti ds-DNA | 19.7 IU/ml as negative | | HBs Ag (ECL) | 0.2 IU/L |
| Anti histone | 11.6 IU/L as negative | | HBC Ab (ECL) | 0.7 COI |
| Anti LA(SS-B) | 1.6 RU/ml as negative | | HIV Ab (ELFA) | 0.6 COI |
| Anti RO (SS-A) | 2.4 RU/ml | | GP210 | +intensity |

Abbreviation: ANA: anti-nuclear antibody; AMA: anti-mitochondrial antibody; ASMA: anti-smooth muscle antibody; Anti-LKM1: anti-liver kidney microsome type 1 antibody; ECL: electrochemiluminescence; HAV Ab: hepatitis A virus antibody; HBs Ab: hepatitis B surface antibody; HBs Ag: hepatitis B surface antigen; HCV-Ab: hepatitis C virus antibody; and IgM: immunoglobulin M; GP210: integral protein of the nuclear membrane.

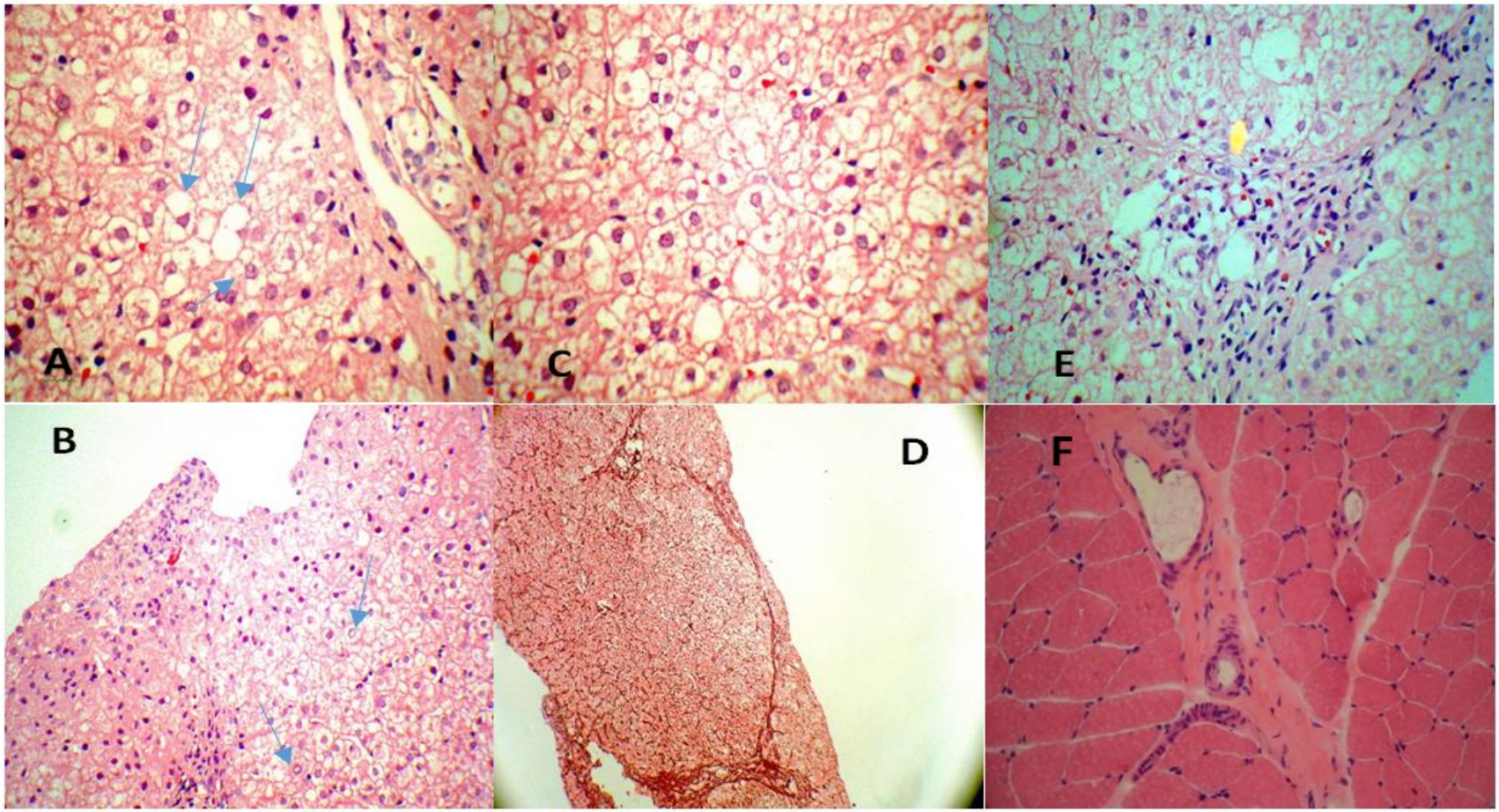


Fig (A): Ballooning changes with micro vesicular (short arrow) and macro vesicular (long arrow) fatty changes (H&E X 40). Fig (B): Feathery degeneration, glycogenated nuclei (arrow) with mild sinusoidal collapse (H&E X 20). Fig (C) Ballooning changes of hepatocytes with mild micro vesicular (short arrow) and macro vesicular (long arrow) steatosis (H&E X 40). Fig (D) Portal- Portal Bridging fibrosis (Reticulin x 10). Fig (E) Portal inflammation composed of lymphocytes and a few eosinophils with ballooning changes of hepatocytes (H&E x 40). Fig (F) Muscle biopsy: Mild fiber size variation with neither necrosis/regeneration nor inflammation, occasional internalized nuclei are seen (H&E x 100).

**Table-3**: Follow up serial liver function test with D-penicillamine and combination D-penicillamine plus prednisolone.

| Variables | D-penicillamine alone | | | | | D- penicillamine + prednisolone | |
|---|---|---|---|---|---|---|---|
| Time/ month | 1 Mo | 2 Mo | 3 Mo | 4 Mo | 5 Mo | 6 Mo | 8 Mo |
| TP | 6.99 g/dl | 6.8 | 6.9 | 7.6 | 7.4 | 6 | 7.2 |
| Alb | 4.69 g/dl | 4.42 | 4.5 | 4.9 | 4.9 | 4.4 | 5.1 |
| Glob | 2.30 g/dl | 2.4 | 2.4 | 2.7 | 2.5 | 1.6 | 2.1 |
| AST | 437 IU/L | 311 | 510 | 371 | 380 | 84 | 92 |
| ALT | 248 IU/L | 335 | 250 | 278 | 280 | 80 | 56 |
| TB | 0.53 mg/dl | 0.49 | 0.7 | 0.5 | 0.6 | 0.57 | 0.7 |
| DB | 0.11 mg/dl | 0.15 | 0.12 | 0.1 | 0.15 | 0.13 | 0.11 |
| Alkp | 827 U/L | 911 | 1100 | 1207 | 928 | 508 | 296 |
| CPK | 3986 U/L | 5487 | 9365 | 1515 | 3310 | 130 | 124 |
| LDH | 1045 U/L | 968 | 1020 | 864 | 653 | 518 | 422 |

Abbreviation: TP: total protein; Alb: albumin; Glob: globulin; AST: amino aspartate transferase; ALT: amino glutamate transferase; TB: total bilirubin; DB: direct bilirubin: Alkp: Alkaline phosphatase; CPK: creatinine phosphokinase; LDH: lactate dehydrogenase.