

HEPATITIS A, A POTENTIAL LIFE-THREATENING CONDITION IN SMALL CHILDREN WITH WILSON DISEASE – A CASE REPORT

Stud. Cristian Dan Marginean¹, Nicoleta Tomsa², MD, Bianca Aron², MD, Daniela Ciobanu², MD, Lecturer Lorena Elena Melit^{1,2}, MD, PhD

¹ „G.E. Palade” University of Medicine, Pharmacy, Sciences and Tehnology, Tg. Mures, Romania

² Pediatrics Clinic, Emergency Clinical County Hospital, Tg. Mures, Romania

ABSTRACT

Introduction. Hepatitis A is the most common cause of acute hepatitis in children. Wilson disease (WD) is a rare autosomal recessive condition that can result in chronic liver disease. Hepatitis A may be a trigger in the onset of WD.

Case presentation. We report the case of a previously healthy 7-year-old girl, admitted in our clinic for upper digestive hemorrhage, jaundice and increased abdomen in volume. The onset of the disease was 1 month before when she was diagnosed with hepatitis A. The laboratory tests at the time of admission pointed out anemia, increased inflammatory biomarkers, conjugated hyperbilirubinemia, hypoalbuminemia, hepatic cytolysis, elevated alkaline phosphatase levels, hyponatremia, and severe coagulopathy. The abdominal ultrasound showed hepatomegaly, inhomogeneous structure, granular echogenicity, with micronodules, diameter of the portal vein 9 mm, altered portal vein pulsatility, splenomegaly and ascites. The upper digestive endoscopy revealed hyperemia and edema of the gastric mucosa, adherent gastric clots, incipient varices of the gastric fornix. The echocardiography showed mild pleural and pericardial effusion. We ruled out hepatitis B, hepatitis C, toxoplasma, rubella, herpes virus, Epstein Barr virus, cytomegalovirus, but also autoimmune hepatitis. Based on the low levels of ceruloplasmin and serum copper, and the positive D-penicilamine test associated to gastric varices and portal hypertension, we established the diagnosis of WD. The ophthalmology and neurological consults found no pathological changes. The patient's clinical and biochemical evolution was favorable after the initiation of chelation therapy.

Conclusion. Though rare, the association between hepatitis A and WD can result in acute liver failure and death, especially in previously healthy children.

Keywords: hepatitis A, Wilson disease, hepatic cirrhosis, child, acute liver failure

Abbreviations

Alb – albumin	Hb – hemoglobin
ALT – alanine aminotransferase	Htc – hematocrit
Aph – alkaline phosphatase	INR – international normalized ration
AST – aspartate aminotransferase	Na – sodium
CRP – C-reactive protein	TBi – total bilirubin
DBi – direct bilirubin	WD – Wilson disease
ESR – erythrocyte sedimentation rate	

INTRODUCTION

Hepatitis A is a worldwide spread condition, being the most common cause of acute hepatitis in children [1]. Hepatitis A virus is a RNA picornavirus and it does not result in chronic liver disease, being trans-

mitted through a fecal-oral route [2]. Even though the incidence varies among different geographic areas being related to the sanitary conditions, socio-economic level, prevailing hygiene, and vaccination, approximately 10 million individuals are diagnosed each year

Corresponding author:
Lecturer Lorena Elena Melit, MD, PhD
E-mail: lory_chimista89@yahoo.com

with hepatitis A [3,4]. Thus, in endemic areas, the incidence can reach 150 cases per 100,000 every year [5]. Despite its self-limiting clinical course, the morbidity and mortality rates related to hepatitis A infection remain important, accounting for a mortality rate of 0.2% [6]. The clinical course varies from asymptomatic to fulminant liver failure depending on age, and most the cases in pediatric ages remain unrecognized due to the lack of symptoms or the presence of unspecific ones [7]. Initial symptoms comprise nausea, vomiting, anorexia, low grade fevers, weight loss, fatigue, arthralgia and myalgia defining the anicteric phase that can last up to 7 days [8]. This phase is followed by the icteric one expressed by dark urine and pale stools. During this phase, only 10% of children below the age of 6 years will present jaundice, 40% of those between 6 and 14 years of age, and 70% above the age of 14 years in comparison to adults where it can occur in up to 85% of the cases [8]. In case of typical hepatitis A, the previously mentioned symptoms can last several weeks, with a mean of 4 weeks, and usually, the infection resolves spontaneously with minimal sequelae [9]. The diagnosis is established on the detection of IgM anti-hepatitis A virus antibodies, elevated transaminases, total bilirubin (TBi), direct bilirubin (DBi), albumin, total protein, complete blood count and coagulation tests [9]. Nevertheless, atypical symptoms of hepatitis A have also been reported when the IgM anti-bodies may persist for as long as 6-12 months, and they have been related to other conditions, such as autoimmune hepatitis, immune complex disorders, cholestatic hepatitis, relapsing hepatitis, and others [8,9]. Moreover, hepatitis A may be a trigger for the onset of both autoimmune hepatitis and Wilson disease [8,10]. Uncomplicated cases of hepatitis require only supportive treatment, liver transplantation being necessary only in 3-8% of the cases when fulminant hepatic failure occurs [9]. National vaccination programs are essential for decreasing the morbidity and mortality rates related to hepatitis A.

Wilson disease (WD) or hepatolenticular degeneration was described for the first time in 1912 by Samuel Alexander Kinnier-Wilson as a neurological disorder defined by progressive lenticular degeneration of the brain associated with liver cirrhosis [11]. It is an autosomal-recessive disease with a low frequency accounting for approximately 1 in 30,000 individuals [12]. The common onset of WD is during early child-

hood into early adulthood, with a peak around 17 years of age [13]. The patients that express primarily liver symptoms usually manifest earlier in life than those with primarily neurological ones [14]. The neurological presentation is defined by dysarthria, dystonia, abnormal gait, tremor, Parkinsonism, chorea, athetosis and seizures [13]. On the other hand, the hepatic features associated to WD comprise acute hepatitis, acute fulminant hepatic failure, chronic active hepatitis and cirrhosis [13]. Kayser-Fleischer rings occur in case of copper deposits in the limbic area of the cornea, and are pathognomonic for WD [13]. Other signs and symptoms may appear in patients with WD, such as renal impairment, gallstones, osteoporosis, osteomalacia, arthritis, arthralgia, oligomenorrhea or amenorrhea, myocarditis, electrocardiographic abnormalities orthostatic hypertension, pancreatic impairment, skin manifestations or parathyroidism [13]. The biochemical diagnosis of WD includes a low plasma ceruloplasmin, elevated basal urine copper per 24 hours, a raised liver copper concentration, but serum copper may also be useful in diagnosing these patients [15]. Genetic testing for detection of ATP7B gene is usually performed only in cases of diagnosis uncertainties. The treatment for WD must be lifelong and is targeted to treat the copper overload, including the following drugs: D-penicillamine, triethylenetetramine hydrochloride, zinc, tetrathiomolybdate and dimercaprol. Physician's communication skills are essential for the proper monitoring of these patients [16].

The aim of this case report is to underline that hepatitis may trigger the onset of liver cirrhosis due to WD in a child without any family or personal history of WD.

The informed consent was obtained from the patient's mother prior to the publication of this case report.

CASE REPORT

Presenting concerns

We describe the case of a 7-year-old girl, without any previously known conditions, admitted in our clinic for upper digestive hemorrhage, jaundice and increased abdomen in volume. The onset of the disease was approximately 1 month before the admission in our clinic when she was diagnosed with hepatitis A. She was referred to our clinic for jaundice persistence

and upper digestive hemorrhage for approximately 1 week.

Clinical findings

The clinical exam at the time of admission revealed influenced general status, intense jaundice of the skin and mucosa, palpebral and lower limb edema, distended abdomen, abdominal tenderness, hepatomegaly (the liver at 2 cm under the right costal rib) and splenomegaly (the spleen at 3 cm under the left costal rib). The patient weighed 23 kg.

Diagnostic focus and assessment

The laboratory tests at the time of admission pointed out anemia (Hb 7.6 g/dl, Htc 23.2%), increased inflammatory biomarkers (CRP 13.61 mg/l, ESR 30 mm/h), conjugated hyperbilirubinemia (T_{Bi} 11.959 mg/dl, D_{Bi} 10.131 mg/dl), hypoalbuminemia (Alb 2.5 g/dl), hepatic cytolysis (AST 204.1 U/l, ALT 103.7 U/l), elevated alkaline phosphatase (APh 660 U/l), and hyponatremia (Na 134 mmol/l). She also associated severe coagulopathy (INR 4.1). The abdominal ultrasound showed hepatomegaly, inhomogeneous structure, granular echogenicity, with micronodules, diameter of the portal vein 9 mm, altered portal vein pulsatility, splenomegaly and ascites. The upper digestive endoscopy revealed hyperemia and edema of the gastric mucosa, adherent gastric clots, incipient varices of the gastric fornix GOV I. The echocardiography showed mild pleural and pericardial effusion. We ruled out viral infections, such as hepatitis B, hepatitis C, toxoplasma, rubella, herpes virus, Epstein Barr virus, cytomegalovirus, but also autoimmune hepatitis. We identified low levels of ceruloplasmin (0.135 g/l) and serum cooper (55.58 µg/dl), but urinary cooper was within normal ranges (22.47 µg/24h). The ophthalmology and neurological consults found no pathological changes. Based on all these findings we raised the suspicion of WD associated with acute liver failure, portal hypertension and varices of the gastric fornix.

Therapeutic focus and assessment

We administered substitution with human albumin and blood transfusion, diuretic (Furosemide), amino acids by vein, vitamin K, antibiotics, and we initiated the treatment with nonselective beta-blocker (Propranolol) and d-penicillamine.

Follow-up and outcome

The patient's evolution was favorable after the initiation of the above mentioned treatment, without any signs of upper digestive bleeding, the remission of ascites, pleural and pericardial effusions after approximately 1 month, and normalization of the portal vein velocity. Moreover, the coagulation test improved considerably (INR 1.49) as well as the bilirubin levels (T_{Bi} 4.438 mg/dl, D_{Bi} 3.366 mg/dl). After approximately 24 hours, we repeated the ceruloplasmin in order to rule out a possible false positive value due to hypoproteinemia and the urinary cooper. Thus, the level of ceruloplasmin remained low (0.197 g/l), and the value of the urinary cooper doubled (42.15 µg/24 h) strengthening once more our diagnosis of Wilson disease triggered by hepatitis A.

DISCUSSIONS

Hepatitis community-wide outbreaks are common in endemic areas such as underdeveloped and developing countries due to the improper sanitary and hygiene conditions. Nevertheless, in Romania, especially in Mureş county, we noticed an outbreak of hepatitis A from september 2018 to January 2019. Our patient was diagnosed with hepatitis A based on positive serology during this outbreak period. It is well-known that hepatitis A is a self-limiting condition and more than 70% of children under the age of 6 years are asymptomatic [17]. Also, up to 20% of those above this age do express any symptoms [17]. Our patient presented gastrointestinal symptoms, but after their remission, she started to express signs of cirrhosis.

Acute liver failure is a rare condition in children that carries a high rate of mortality. The definition of acute liver failure according to The Pediatric Acute Liver Failure Group involves the following conditions: no evidence of previously known chronic liver disease, biochemical proof of acute liver injury, and hepatic-related coagulopathy expressed by a prolonged prothrombin time ≥ 15 seconds or INR ≥ 1.5 not corrected by vitamin K supplementation associated to clinical signs of hepatic encephalopathy, or prothrombin time ≥ 20 seconds or INR ≥ 2.0 independent of the presence or absence of encephalopathy [18]. A recent study performed on children with acute liver disease underlined that clinical hepatic encephalopathy is uncommon in pediatric ages in comparison to

adults [19]. Moreover, the same study showed that WD was the second most frequent cause of acute liver failure in children, 16 patients, followed by hepatitis A, 14 patients [19]. Our patient fulfilled the criteria previously mentioned for acute liver failure since she did not have any previously known chronic liver condition, she was found with biochemical evidence of acute liver disease, and even though she did not express any clinical signs of hepatic encephalopathy, her INR at the time of initial presentation in our clinic was 4.1. Fortunately, the coagulopathy responded very good to vitamin K therapy. Most likely, both hepatitis A and WD contributed to the development of acute liver failure in our patient, but the detection of gastric varices and micronodular ultrasound liver aspect sustain the undetectable underlying chronic period, commonly encountered in WD before the diagnosis. The same study mentioned before, established a classification of patients into three risk groups as it follows: group I comprising patients with total bilirubin level < 5.35 mg/dl and INR < 3.66 (or PT < 23.5 seconds), group II for total bilirubin level > 5.35 mg/dl or INR > 3.66 (or PT > 23.5 seconds), and group III in case of patients with total bilirubin level > 5.35 mg/dl and INR > 3.66 (or PT > 23.5 seconds) [19]. The authors showed that 37 of the 38 patients included in group III died [19]. According to the classification mentioned above, our patient can be classified as high risk, belonging to group III. Nevertheless, her evolution was outstandingly favorable after the initiation of supportive and vitamin K supplementation therapy. Moreover, after the initiation of D-penicillamine, the bilirubin level decreased < 5 mg/dl, and the INR < 1.5.

Acute insults, such as acute viral hepatitis A or intake of certain drugs and toxins are well-known triggers in the decompensation of a patient with chronic

liver disease. The literature regarding this association is scarce, especially in children. Thus, the study of Jagadisan et al. proved that superinfection with hepatitis viruses A, B, and E in children previously known or unknown with chronic liver disease can result in acute liver failure [20]. Moreover, the authors showed that Wilson disease and autoimmune hepatitis were the most frequent causes of chronic liver disease that manifested clinically for the first time with liver failure [20]. Among the 10 patients diagnosed with WD in their study, only 3 survived [20]. The patients who recover after the acute insult are considered to have a good-long term survival [20]. Despite, the initial predicted poor prognosis, our patient recovered from the acute insult produced by the hepatitis A superinfection, presenting a favorable clinical and biochemical evolution. Moreover, due to the initiation of chelation therapy, most-likely her long-term outcome will improve considerably. Özçay et al. reported a similar case of hepatitis A as a trigger for acute liver injury in a 7-year old girl unknown with WD, but their patient died on the 12th day of admission [21]. Fortunately, our patient presented a favorable evolution after the recovery from acute hepatitis A. Though rare, WD may also be associated with autoimmune hepatitis [22]. In our case, the serology for autoimmune hepatitis was negative.

CONCLUSIONS

Acute liver failure is not common in children, but it is associated with high rates of mortality. The onset of symptoms in children unknown with WD can be triggered by hepatitis A infection. Thus, our case emphasizes the acute need of a national vaccination program in order to prevent acute liver failure-related death in this group of patients.

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