Clinical and Experimental HEPATOLOGY

Clinical and Experimental HEPATOLOGY 2015; 3: 117–119
DOI: 10.5114/ceh.2015.55569
Received: 02.10.2015, **Accepted:** 21.10.2015, **Published:** 12.11.2015

Review article

Liver involvement in children with collagen vascular diseases

Joanna Pawłowska[1], Magdalena Naorniakowska[1], Anna Liber[2]

[1]Department of Gastroenterology, Hepatology, Nutritional Disorders and Pediatrics, The Children's Memorial Health Institute (CMHI), Warsaw
[2]Individual Specialist Medical Practice, Warsaw

Abstract

Liver injury such as hepatomegaly, splenomegaly and various degrees of biochemical abnormalities are quite common in children with collagen vascular diseases. They may be primary or secondary, particularly due to drug therapy (drug toxicity, fatty infiltration), superadded infections, diabetes or overlap with autoimmune hepatitis.

Key words: liver diseases, systemic lupus erythematosus, juvenile rheumatoid arthritis, Kawasaki disease, children.

Address for correspondence

Joanna Pawłowska, Department of Gastroenterology, Hepatology, Nutritional Disorders and Pediatrics, The Children's Memorial Health Institute (CMHI), Al. Dzieci Polskich 20, 04-730 Warsaw, phone: +48 22 815 73 80, e-mail: j.pawlowska@ipczd.pl

Introduction

Liver injury such as hepatomegaly, splenomegaly and various degrees of biochemical abnormalities are quite common in children with collagen vascular diseases. They may be primary (vascular infiltration or thrombosis) or secondary, particularly due to drug therapy (drug toxicity, fatty infiltration), superadded infections, diabetes or overlap with autoimmune hepatitis.

Systemic lupus erythematosus

Lupus erythematosus is a systemic, autoimmune disease classically involving the skin, kidneys, cardiovascular system and central nervous system. Hepatic disease is not a significant cause of morbidity or mortality, but liver involvement in systemic lupus erythematosus (SLE) is now considered to have greater clinical significance. In adult patients elevated liver enzymes are observed in up to 25-50% and palpable liver in 33% [1, 2]. The liver is not a major target in patients with SLE, and despite its frequent involvement, abnormality of liver function is not included in the diagnostic criteria.

Liver dysfunction is seen in neonatal lupus erythematosus (NLE), which is an acquired autoimmune disease of the developing fetus and neonate that is caused by transplacental passage of maternal anti-SSA/Ro autoantibodies (anti-Sjögren's-syndrome-related antigen A). The most significant site of involvement in NLE is the heart, causing conduction abnormalities, especially complete heart block. Other less common manifestations are skin, hematologic or neurologic problems. Hepatitis may be the only manifestation of NLE. Initially the liver disease was considered to be secondary to heart failure, but recent reports have described a cholestatic syndrome that may resemble extrahepatic biliary atresia. The histology shows large duct obstruction, portal fibrosis and inflammation. Cholestasis mostly resolves spontaneously, although death secondary to liver disorders was reported before 6 months of age [3, 4].

A wide spectrum of liver disorders is associated with SLE in teenagers and adult patients. They may be classified as:

- existence of some kind of liver parenchymal injury associated with SLE usually referred to as "lupus hepatitis",

- overlap syndromes with another autoimmune liver disease,
- non-autoimmune hepatopathy such as toxic liver damage, viral hepatitis, fatty liver, or thrombotic liver disease.

There are some prospective and retrospective studies of frequency of liver abnormalities, but none of them is dedicated to children [5, 6]. The recent data published by Takahashi *et al.* reported liver dysfunction in 59.7% of adult patients (123 out of 206) [7]. The most common is toxic injury (30.9%), than caused by SLR itself (lupus hepatitis – 28.5%), fatty liver (17.9%), autoimmune hepatitis (AIH) (4.9%), primary biliary cirrhosis (PBC) (2.5%) and cholangitis (1.6%). Luckily, in the majority of patients the liver dysfunction tends to be mild, except when caused by AIH.

Systemic lupus erythematosus and autoimmune hepatitis – overlap syndrome

The existence of overlap syndromes linking SLE with other autoimmune liver diseases is controversial. It is still discussed whether AIH and SLE-associated hepatitis are two distinct entities. Some authors suggest that SLE and AIH are different diseases. However, clinical, biochemical and serological characteristics may show an overlapping syndrome with polyarthralgia, hypergammaglobulinemia and positive ANA (anti-nuclear antibodies), ASMA (anti-smooth muscle antibodies) and anti-ribonucleoprotein [8, 9]. It is important to distinguish AIH from SLE, since therapy and complications are different. Autoimmune hepatitis may lead to end stage liver disease, while SLE may result in end stage renal disease. Histopathology differentiating features are severe portal and periportal lymphoid inflammation, hepatocyte pseudorosette, dominant portal tract plasma cell infiltration in AIH and presence of lobular inflammation and occasionally portal inflammation with paucity of lymphoid infiltrates in SLE [10].

In SLE-AIH overlap syndrome a mixed histological picture is expected. Hepatitis with severe inflammatory activity with focal necrosis, periportal hepatitis, infiltration of lymphocytes and plasma cells, presence of fibrosis and later on eventually cirrhosis are observed [9].

In patients with SLE-AIH overlap syndrome treatment with ursodeoxycholic acid, prednisone, immunosuppressive thiopurine analogs or a combination is usually successful [9, 11].

Juvenile rheumatoid arthritis

Juvenile rheumatoid arthritis (JRA) rarely presents with systemic features, and that is why liver involvement is less common than in SLE. In adult patients liver diseases is documented in nearly 6% of patients with rheumatoid arthritis.

In children the most common clinical feature is hepatomegaly, which tends to decrease as the disease is treated. It may be accompanied by a mild increase in serum aminotransferases. Elevated liver enzymes in patients with rheumatoid arthritis may have various causes. These include the rheumatic disease itself and the anti-rheumatic medication, or they may be the manifestation of an associated autoimmune disease [12].

Liver histology mainly reveals nonspecific periportal collections of inflammatory cells and Kupffer cell hyperplasia. When progressive hepatomegaly is seen, it may suggest secondary amyloidosis [13].

Methotrexate (MTX) is a cornerstone in the treatment of JRA. Although associated with many mild adverse effects, the short- and long-term safety of MTX in JRA has been excellent. While many JRA children treated with MTX develop liver enzyme abnormalities, no cases of irreversible liver damage or of severe non-infectious hepatitis with Reye-like features have been reported in non-systemic disease [14].

Aspirin hepatotoxicity is usually asymptomatic but serum aminotransferases are elevated in nearly 60% of children receiving long-term salicylate therapy. They also have a higher incidence of Reye syndrome than in the general population.

Nowadays nonsteroidal anti-inflammatory drugs (NSAIDs) have replaced aspirin and hepatotoxicity occurs less often.

Kawasaki disease

Kawasaki disease (KD) is a systematic vasculitis of children that affects small- and medium-sized arteries with a predilection for the coronary arteries. The diagnostic criteria for KD are fever lasting at least five days and four of the five following conditions: cervical lymphadenopathy, polymorphous exanthema, nonpurulent conjunctivitis, changes in the lips or oral mucosa, changes in extremities. Although gastrointestinal (GI) involvement does not belong to the classic diagnostic criteria, abdominal pain, liver function impairment or gallbladder abnormality is observed in some patients with KD [15].

Patients with KD may have a hepatobiliary manifestation ranging from asymptomatic increase in liver enzymes to severe cholestatic hepatitis and acute acalculous cholecystitis (AAC) or hydrops of the gallbladder [16].

Eladawy in a retrospective study of 240 patients with KD found that 45.4% had at least one abnormali-

ty in the liver function test (LFT) at presentation [17]. Although most patients had only mild elevated transaminases, less than twice the upper limit of normal, a few had elevations of more than 10-fold and presented with a picture of clinical hepatitis with jaundice.

The definite mechanism of abnormalities of LFTs in Kawasaki patients has not been established jet. Postulated mechanisms include generalized inflammation, vasculitis of small and medium sized vessels, congestive heart failure secondary to myocarditis, nonsteroidal anti-inflammatory antipyretics, toxic injury, and a combination of the above.

Hepatomegaly, but not splenomegaly, was detected in children with KD in physical examination. In laboratory findings elevated alanine aminotransferase and gamma-glutamyl transpeptidase were noted in almost all patients with abdominal pain and in a few cases was associated with conjugated hyperbilirubinemia.

Gall bladder abnormalities are observed in up to 15% of patients during the first few weeks of illness, and their prevalence is expected to increase with the development of ultrasound examination. It is postulated that they are secondary to a vasculitic process in the gallbladder wall. Some studies suggest that obstruction of the cystic duct caused by enlarged lymph nodes or inflammatory infiltrates with polymorphs, lymphocytes and eosinophils may play a role [18]. Gallbladder abnormality can be associated with resistance to intravenous immunoglobulin – typical treatment for KD [19]. The prognosis in KD depends mainly on cardiac complications. In almost all cases the resolution of GI symptoms and laboratory abnormalities is observed. Gastrointestinal symptoms can be the initial presentation masking typical symptoms of KD. The difficulty in diagnosing KD with atypical manifestation can lead to delay in appropriate treatment, increasing the risk of complications, especially coronary artery abnormalities.

Disclosure

Authors report no conflict of interest.

References

1. Vaiphei K, Bhatia A, Sinha SK. Liver pathology in collagen vascular disorders highlighting the vascular changes within portal tracts. Indian J Pathol Microbiol 2011; 54: 25-31.
2. Gibson T, Myers AR. Subclinical liver disease in systemic lupus erythematosus. J Rheumatol 1981; 8: 752-759.
3. Assari R, Ziaee V, Moradinejad MH, Mirmohammadsadeghi A. Neonatal lupus erythematosus following rheumatoid arthritis: case report and literature review. Iran J Pediatr 2014; 24: 445-448.
4. Cimaz R, Spence DL, Hornberger L, Silverman ED. Incidence and spectrum of neonatal lupus erythematosus: a prospective study of infants born to mothers with anti-Ro autoantibodies. J Pediatr 2003; 142: 678-683.
5. Miller MH, Urowitz MB, Gladman DD, Blendis LM. The liver in systemic lupus erythematosus. Q J Med 1984; 53: 401-409.
6. Fox RA, Riechlin MW, Isenberg DA. Liver function test abnormalities in systemic lupus erythematosus. Rheumatol 1997; 36 (Suppl): S10.
7. Takahashi A, Abe K, Saito R, et al. Liver dysfunction in patients with systemic lupus erythematosus. Intern Med 2013; 52: 1461-1465.
8. Leggett BA. The liver in systemic lupus erythematosus. J Gastroenterol Hepatol 1993; 8: 84-88.
9. Bessone F, Poles N, Roma MG. Challenge of liver disease in systemic lupus erythematosus: clues for diagnosis and hints for pathogenesis. World J Hepatol 2014; 6: 394-409.
10. Kaw R, Gota C, Bennett A, et al. Lupus related hepatitis: complication of lupus or autoimmune association? Case report and review of the literature. Dig Dis Sci 2006; 51: 813-818.
11. Usta Y, Gurakan F, Akcoren Z, Ozen S. An overlap syndrome involving autoimmune hepatitis and systemic lupus erythematosus in childhood. World J Gastroenterol 2007; 13: 2764-2767.
12. Hartmann U, Schmitt S, Reuss-Borst M. Elevated liver enzymes in rheumatoid arthritis: differential diagnostic considerations based on a case report. Z Rheumatol 2008; 67: 440-444.
13. David J, Vouyiouka O, Ansell BM. Amyloidosis in juvenile rheumatoid arthritis: a morbidity and mortality study. Clin Exp Rheumatol 1993; 11: 85-94.
14. Ting TV, Hashkes PJ. Methotrexate/naproxen-associated severe hepatitis in a child with juvenile idiopathic arthritis. Clin Exp Rheumatol 2007; 25: 928-929.
15. Eladawy M, Dominquez SR, Anderson MS, et al. Kawasaki disease and the pediatric gastroenterologist: a diagnostic challenge. JPGN 2013; 56: 297-299.
16. Yi DY, Kim JY, Choi JY, et al. Hepatobiliary risk factors for clinical outcome of Kawasaki disease in children. BMC Pediatrics 2014; 14: 51-59.
17. Eladawy M, Dominguez SR, Anderson MS, Glode MP. Abnormal liver panel in acute Kawasaki disease. Pediatr Infect Dis J 2011; 30: 141-144.
18. Mofenson HC, Greensher J, Molavi M. Gallbladder hydrops: complication of Kawasaki disease. NY State J Med 1980; 80: 249-251.
19. Chen CJ, Huang FC, Tiao MM, et al. Sonographic gallbladder abnormality is associated with intravenous immunoglobulin resistance in Kawasaki disease. Sci World J 2012 (2012): Article ID 485758.