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Extra Hepatic Manifestations of Liver Diseases



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INTRODUCTION

The liver is the largest organ in the body and conducts a myriad of vital metabolic and excretory functions. In addition, by virtue of its circulatory relationship to the absorptive surface of the gastrointestinal tract, the liver is the initial site where ingested materials entering via the gastrointestinal tract, such as drugs and bacterial metabolites are processed. Hepatocytes perform the function of homeostasis.¹ Dysregulation of the liver or hepatocytes thus produces clinical effects that are limited not only to the liver, but can also cause derangement in the internal milieu, thereby contributing significantly to mortality and morbidity in liver disease patients. The clinical syndrome produced by hepatic injury may include systemic manifestations and evidence of injury not limited only to the liver. It is therefore essential to recognize the various extrahepatic features of liver diseases for timely management

of these disorders. Patients with liver disease present with varying severity ranging from being asymptomatic with abnormal liver function tests to those patients with overt florid liver failure. This paper will review extrahepatic features of liver diseases.

Effects of Liver Diseases on the Heart

In patients with cirrhosis, there is increased arteriovenous (AV) shunting thereby increasing the resting cardiac output, left ventricular diastolic diameter, and mean velocity of the left ventricular wall. There is also decreased peripheral resistance and oxygen consumption related to AV shunting.² However, these effects are reversible after transplantation. Long-term estrogen and anabolic steroids use may aggravate preexisting vasculopathy, inducing sinusoidal dilation and subsequent peliosis hepatis and should be considered in the differential of high output failure in liver disease.³

The prevalence of myocardial infarctions is found to be lower in cirrhotic patients than in the general

(continued on page 38)

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(continued from page 36)

population. For mechanisms that remain unclear but are probably related to cholesterol metabolism, there is a protective effect on atherosclerosis in patients with cirrhosis, with exceptions being in patients with nonalcoholic steatohepatitis (NASH) and hepatitis C virus (HCV)-related cirrhosis.^{4,5} It has been found that HCV is an independent risk factor for accelerated atherosclerosis in cirrhotic patients. Similarly, it is reported that the prevalence of all coronary artery disease risk factors are significantly higher in NASH-related cirrhotic patients.⁶

There is paucity of data regarding the incidence of HCV infection in non-ischemic cardiomyopathy, although the association of dilated and hypertrophic cardiomyopathies with HCV have been reported widely. In some genetically predisposed individuals, HCV core protein may damage the myocardium through either direct or indirect immunological mechanisms.^{7,8} Fibrinous pericarditis, characterized by the presence of fibrinous exudates in the pericardial sac that are sometimes accompanied by a small amount of serous effusion, has also been described in patients with cirrhosis, although the underlying pathophysiology is poorly understood. It has been found that pericarditis can occur even in the absence of uremia as a result of decompensated liver disease.⁹

Effects of Liver Diseases on the Respiratory System

Patients with liver diseases may exhibit dyspnea due to a variety of cardiopulmonary alterations. Hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PPHTN) are two pulmonary vascular complications of liver disease manifesting as dyspnea. A careful evaluation of concomitant symptoms, physical examination, pulmonary function testing including an arterial blood gas analysis, echocardiographic imaging, and hemodynamic studies are useful for differentiating between these conditions and is crucial for selecting transplant candidates.¹⁰ HPS, occurring in 5%–32% of cirrhotic patients, is a triad of decompensated liver disease, arterial desaturation due to pulmonary gas exchange abnormalities, and evidence of intrapulmonary vascular dilatation (IPVD).¹¹ Arterial desaturation (a resting $P_{A-a,O_2} \geq 15 \text{ mmHg}$ and $\geq 20 \text{ mmHg}$ in patients 64 yrs) is due to increased intrapulmonary shunting (99Tc MAA shunting index $> 6\%$) without evidence of pulmonary arterial hypertension. Intrapulmonary

vascular dilatation can be diagnosed by transthoracic contrast enhanced echocardiography (CE TTE), technetium 99m labeled macroaggregated albumin (99Tc MAA) scan and pulmonary arteriography. Contrast enhanced transthoracic echocardiography is considered the gold standard for the diagnosis of HPS with detection of microbubbles within the left atrium considered to be a positive CEE.^{11,12} Orthotopic liver transplant can be considered in severe cases and is the most effective treatment.¹³

PPHTN is associated with portal hypertension without evidence of intrapulmonary shunting (99Tc MAA $< 6\%$) and intravascular pulmonary vascular dilation differentiating it from HPS. Although the mechanism of PPHTN remains unclear, it is thought to be due to accumulation of under-metabolized vasoactive substances in the pulmonary circulation. Orthotopic liver transplantation can worsen PPHTN and can lead to acute right ventricular failure. It is therefore contraindicated in patients with PPHTN, which makes distinguishing HPS from PPHTN critical prior to liver transplant.^{14,15}

Chronic HCV is associated with idiopathic pulmonary fibrosis and the cumulative rate of development is 0.9% at 20 years after HCV infection.¹⁶ This is evidenced by the higher frequency of HCV markers in IPF patients, an increase in lymphocyte and neutrophil numbers in bronchoalveolar lavage of HCV chronic infection patients.¹⁷

Effects of Liver Diseases on the Nervous System

The relationship between the functional status of the liver and that of the brain has been known for centuries.¹⁸ There are both central and peripheral neurological manifestations of liver diseases. For the purpose of understanding the central nervous system presentations, hepatic encephalopathy related and non hepatic encephalopathy-related changes will be reviewed.

Hepatic Encephalopathy Associated Central Nervous System Damage

Hepatic encephalopathy is a spectrum of neuropsychiatric damage ranging from inversion of sleep rhythm to deep coma. It can occur both in acute or chronic liver diseases. It is widely thought that the pathogenesis of hepatic encephalopathy is multifactorial. Currently,

(continued on page 40)

(continued from page 38)

the two factors considered to be most important in pathogenesis are raised brain concentration of ammonia and increased GABA mediated neurotransmission. Ammonia is normally metabolized by cerebral astrocytes by converting glutamate to glutamine. However in hepatic encephalopathy, due to excess ammonia, there is an excess production of glutamine that causes the astrocytes to swell resulting in the neuropsychiatric manifestations of hepatic encephalopathy.¹⁹ Potential mechanisms for increased inhibitory neurotransmitter GABA in hepatic encephalopathy include increased availability of GABA in synaptic clefts or increased blood to brain transfer of GABA and increased brain concentrations of natural benzodiazepine receptor agonist ligands.^{20,21} Hepatic encephalopathy has been classified into 4 stages based on the severity of the symptoms (Table 1). Stage I is the mildest form and includes symptoms such as mild confusion, and Stage IV is the most advanced and severe form, which includes coma.^{22,23}

Precipitating factors for hepatic encephalopathy include hypokalemia, hyponatremia, metabolic alkalosis, hypoglycemia, gastrointestinal bleeding, constipation, sedatives, tranquilizers, infection and portosystemic shunts (spontaneous, surgical, TIPS).²⁴

Asterixis or “liver flap” is often present in the early stages of hepatic encephalopathy. Asterixis consists of infrequent involuntary flexion-extension movements of the hand (one flap every one to two seconds), which may result in part from an impairment of the normal inflow of joint position sense to the brain stem reticular formation. Asterixis should be classified as a negative myoclonus rather than a tremor.²⁰

Recognizing and treating hepatic encephalopathy is important, because data from the Healthcare Cost and Utilization Project (HCUP) show that hepatic encephalopathy is associated with substantial healthcare utilization and costs.²⁵ Some management strategies include: 1) dietary protein restriction to reduce the ammonia load, 2) non absorbable disaccharides, 3) gut antibiotics like rifaximin, 4) branched chain AA, and 5) use of the GABA inhibitor, flumenazil. Non-absorbable disaccharides were shown to be inferior to antibiotics in reducing ammonia levels, but there was no significance in mortality between the two treatment groups.²⁶ Data suggest a significant improvement in cognitive function following liver transplantation, but patients do not return to normal.

Acquired (non-Wilsonian) hepatocerebral degeneration (AHCD) is a clinico-pathological syndrome of brain dysfunction resulting from repeated attacks of hepatic encephalopathy.²⁷

Non-Hepatic Encephalopathy Related Central Nervous System Damage

Under this entity, Wilson’s disease is the best known. Others include congenital diseases like Reye’s syndrome, congenital hyperammonemia, kernicterus, galactosemia, porphyrias, Zellweger syndrome.²⁰

Wilson’s disease is an autosomal recessive neuropsychiatric disorder that occurs due to excessive accumulation of copper in various organs, particularly the liver and brain. Psychiatric manifestations of Wilson’s disease are protean, but are predominantly personality changes. Four basic categories of disturbance have been described: behavioral/personality, affective, schizophrenia-like, and cognitive dysfunction. The neuropsychiatric manifestations such as dysarthria, dyspraxia, ataxia, a tremor-rigidity syndrome and psychoses, and progressive extrapyramidal neurological disorder are characteristic of Wilson’s disease.^{28,29} Hepatitis A infection can also result in encephalomyelitis.³⁰ It is also reported that chronic HCV infection results in neurocognitive damage secondary to the neuroinvasion of microglia by HCV.³¹ Hepatic myelopathy is characterized by spastic paraparesis with minimal sensory involvement. It is mainly due to symmetrical demyelination, predominantly of the lateral pyramidal tracts, sometimes associated with axonal loss from the cervical cord level. It is thought to be secondary to nitrogenous products bypassing the liver through the porto-caval shunt in advanced hepatic encephalopathy.³²

Gullian Barre syndrome is associated with HBV and rarely in HCV infection due to immune complex deposition in these infections.³³ The precise incidence, severity and characteristics of neuropathy, and the relationship of neuropathy to different etiologies of liver disease have not been defined. Peripheral neuropathy may be observed in patients with cryoglobulinemia in HCV infection, and usually is a moderate axonal sensory polyneuropathy. It is also seen in other conditions like porphyrias and alcoholic liver diseases. Sensory neuropathy is also a common manifestation of primary biliary cirrhosis. This contributes to hyperesthesia

(continued on page 42)

(continued from page 40)

leading to itching seen in primary biliary cirrhosis. In addition, autonomic dysfunction presenting as reduced 24-hour heart rate variability is also seen in primary biliary cirrhosis.^{13, 34}

Effects of Liver Diseases on the Skin

Understanding and recognizing skin changes that can occur in patients with liver failure is essential, as it often leads to prompt diagnosis and treatment of the underlying liver disease. For instance, jaundice, the cardinal sign of hyperbilirubinemia, is usually seen when serum bilirubin levels exceed 2.5 or 3.0 mg/dL.³⁵ The color of the skin typically reflects the severity of the bilirubin elevation. Another sign of an underlying liver disorder is evidence of xanthelasma, which is a painless yellow soft plaque that occurs due to localized deposition of cholesterol underneath the skin usually beneath the eyelids. another skin-related disorder occurring in patients with an underlying liver condition include hyper-pigmentation or a slate-gray discoloration of the skin, which occurs in cirrhosis, but more specifically in hemochromatosis. This is due to iron deposition in the skin and hence called as Bronze diabetes. Hyper-pigmentation should be contrasted with hypo-pigmented macules called Bier's spots, which can also occur in liver diseases, secondary to venous stasis from damage to the small vessels. These however disappear on pressure and limb elevation.^{35,36}

Pruritus

Until recently, it was thought that pruritus caused during liver disease was related to toxins deposited in the skin. However, studies now suggest that neural events originating from the CNS may cause pruritus. It has been observed that the central opioidergic tone is increased in cholestasis causing pruritus, and hence opiate antagonists ameliorate the pruritus of cholestasis.³⁷ In fact, studies have demonstrated a striking opioid withdrawal-like syndrome induced by the oral administration of a potent opiate antagonist, which further illustrates that increased central opioidergic tone is the cause of pruritus in patients with chronic cholestatic liver disease. Although pruritus is generally resistant to therapy, anion exchange resin cholestyramine, rifampicin, and opioid antagonist naltrexone have been used with varying success. Plasmapheresis has been used successfully in resistant cases, and liver transplantation has been shown to ameliorate pruritus completely.³⁸

Prurigo Nodularis

Another skin condition, prurigo nodularis, which are intensely pruritic, firm, crusty nodules, have been observed in patients with hepatitis C infection. These nodules lead to itching, excoriation and diffuse scarring. Corticosteroid cream, antihistamine, and low-dose thalidomide, and tumor necrosis factor (TNF) antagonist have been used to control symptoms.³⁵

Lichen Planus

Also seen in patients with hepatitis C infection are lichen planus, which are planar, polygonal, purplish pruritic papules occurring anywhere on the body, but are most prominent on the wrists and ankles. In approximately 85% of affected individuals, the papules usually resolve by 18 months. A subtype of this skin disorder, called lichen planopilaris, occurs on the scalp and results in permanent hair loss.³⁹

Vitiligo

Vitiligo is an autoimmune destruction of the melanocytes, and it manifests as depigmented, irregular, white patches. It occurs in primary biliary cirrhosis and also in patients with hepatitis C infection who are being treated with interferon. Interferon-induced vitiligo resolves after treatment cessation.³⁵ Porphria Cutanea Tarda results from a deficiency of the hepatic enzyme uroporphyrin decarboxylase. This causes a photochemical reaction that generates reactive oxygen species that activate uroporphyrinogen deposited in the skin, thus leading to the characteristic skin blistering. In 50% patients with hepatitis C in sun-exposed areas, as the blisters heal, keratin filled milial cysts develop in these areas of ulceration.^{13,40}

Dupuytren's Contracture

Dupuytren's contracture is the fibrotic thickening of the palmar fascia, resulting in painless stiffness, curling and loss of function of the involved fingers. Although the pathogenesis is unknown, it is usually observed in patients with alcoholic liver diseases. It is amenable to correction by surgery, radiation, simvastatin, or N acetyl cysteine. Facial lipodystrophy is also seen in alcoholic liver disease due to malnutrition.^{17,41}

Cutaneous Vascular Signs

The most common cutaneous vascular sign are echymoses, which occur due to easy bruising secondary to platelet function abnormalities in cirrhosis. Spider

Table 1. The West Haven Criteria of Altered Mental State in HE

Stage	Mental State
I	Mild confusion, euphoria or depression, decreased attention, slowing of ability to perform mental tasks, untidiness, slurred speech, irritability, reversal of sleep rhythm
II	Drowsiness, lethargy, gross deficits in ability to perform mental tasks, obvious personality changes, inappropriate behaviour, intermittent disorientation (usually for time), lack of sphincter control
III	Somnolent but rousable, unable to perform mental tasks, persistent disorientation with respect to time and/or place, amnesia, occasional fits of rage, speech present but incoherent, pronounced confusion
IV	Coma, with (IVA) or without (IVB) response to painful stimuli

nevi or Nevus areanus are dilation of a pre-existing vessel, usually in the area drained by the superior vena cava. It is due to an accumulation of free estradiol in patients with liver diseases causing these vessels to dilate and is associated with coexisting gastric and esophageal varices. Therefore, the presence of echymoses should prompt the clinician for endoscopic work up in liver disease.⁴² Papermoney skin, a random scattering of needle-thin thread-like capillaries in the upper trunk resembling American dollar bills, occurs in association with spider angiomas. Palmar erythema is a crimson discoloration of the palms and fingertips, more in the hypothenar eminence occurring in liver disease. It is thought to be secondary to localized increase in nitric oxide and prostacyclins resulting in vasodilation and erythema.³⁶ Advanced liver disease can cause thinning and loss of hair. Similarly, it can also cause thinning and damage of the nails. It can lead to clubbing, onycholysis and leuconychia. Terry's nails, which is a ground glass opacity of the proximal 2/3 of the nails can also occur in patients with cirrhosis.^{35,43}

Effects of Liver Diseases on the Renal System

Renal manifestations in liver diseases could be hepatitis-associated nephropathy or hepatorenal syndrome from cirrhosis, and it is essential to differentiate both.

Hepatorenal Syndrome(HRS)

The incidence of HRS is close to 40 % after 5 years of cirrhosis. Patients with ascites having dilutional hyponatremia secondary to renal retention of sodium are at an increased risk for HRS.^{44,45} Based on the rapidity of

progression of renal failure, they are classified as having Type 1 or type 2 failure. The predominant clinical feature of patients with type 1 HRS is severe renal failure, and that of patients with type 2 HRS is recurrent ascites. The mechanism is due to increased splanctic vasodilation in portal hypertension. This leads to arterial underfilling, triggering the vasoconstrictive compensatory mechanisms including the renal vasculature, thereby decreasing renal perfusion contributing to HRS.⁴⁶ The initial approach to these patients with renal failure, begins with urinalysis. The diagnosis of HRS is being made in the absence of parenchymal kidney disease, proteinuria <500 mg/d with elevated creatinine in a patient with cirrhosis with ascites in the absence of shock. Treatment includes volume expansion and vasoconstricting agents to improve the extremely dilated splanctic bed and to suppress the endogenous renal vasoconstriction for improved renal circulation. The survival expectancy is dependent on the type of HRS and the severity of liver disease. Even with liver transplant, the 3-year survival is lower in comparison with those patients with no HRS. In type 1, hospital survival is less than 10% and the expected median survival time only 2 weeks. By contrast, patients with type 2 have a much longer median survival time.^{44,45}

Hepatitis Associated Renal Disease

Hepatitis B is directly associated with membranous nephropathy and membranoproliferative glomerulonephritis (MPGN). HBV-related MPGN is due to immune complex deposition in the mesangium and subendothelial space. Antiviral treatment with lamivudine or interferon induces complete remission.^{47,48}

Nephrotic syndrome secondary to HBV-related membranous nephropathy resolves spontaneously in children unlike in adults, which does not respond to antiviral treatment either.¹³

The incidence of mixed cryoglobulinemia, MPGN and membranous nephropathy is more common with HCV than HBV. The pathogenesis of HCV related cryoglobulinemic MPGN is due to glomerular damage caused by immune complex deposition of HCV, IgG and IgM rheumatoid factors.⁴⁹ The combination treatment of peginterferon and ribavirin has been shown to effectively cause sustained virologic response, resolution of proteinuria along with improvement in creatinine levels. Rituximab has also been shown to be successful in improving glomerular nephritis.⁵⁰

Effects of Liver Diseases on the Blood

Platelet Abnormalities

Thrombocytopenia alone or in combination with other cytopenias is the most common cytopenia associated with liver disease and occurs in up to 77% of patients with cirrhosis.⁵¹

Multiple mechanisms involving decreased production and increased peripheral destruction contribute to this abnormality. Thrombopoietin is produced in the liver and it can be decreased in liver failure along with a decreased function of the synthesized platelets. Increased peripheral destruction could be related to splenic sequestration or antibody mediated as in HCV. High affinity binding of HCV to platelet membrane with subsequent binding of anti-HCV antibody with subsequent phagocytosis causes thrombocytopenia. They usually present as chronic ITP with anti-HCV antibodies positive in 10-30% of these patients.⁵² Moderate thrombocytopenia also develops following orthotopic liver transplantation in the first week with gradual resolution in the second week and requires only supportive care. However persisting or worsening thrombocytopenia may be due to sepsis, graft dysfunction, persistent portal hypertension or hypersplenism.^{53,54}

AST/ platelet ratio (APRI) is a predictor of liver failure in HBV infection and recurrent HCV after transplantation. APRI values of ≤ 0.3 and ≤ 0.5 rule out significant fibrosis and cirrhosis, and a value of ≥ 1.5 is indicative of significant fibrosis. In patients with NAFLD, APRI values tend to increase with the degree

of fibrosis, suggesting that it could be useful in this disease. APRI appears to be of no value in patients with autoimmune hepatitis.⁵⁵

Platelet count to spleen diameter (PC/SD) ratio less than 909 is one of several parameters proposed for the noninvasive prediction of esophageal varices.⁵⁶

Coagulopathy

Coagulation factors are synthesized in the liver and can cause abnormal coagulation in liver disease similar to DIC. A decreasing trend in factor VIII, fibrinogen and platelets is however more consistent with DIC as factor VIII is not produced in the liver. It also causes prolongation of PT, hyperfibrinolysis, dysfibrinogenemia all increasing the incidence of bleeding in liver diseases.⁵⁷ Budd Chiari syndrome is hepatic vein obstruction at various levels from either thrombosis or fibrosis. Patients should undergo a hypercoagulable workup for protein C, protein S deficiencies, factor V Leiden mutations, lupus anticoagulant, prothrombin gene mutation and antiphospholipid antibody syndrome.^{58,59} Paroxysmal nocturnal hemoglobinuria should be considered as a possibility when a patient presents with Budd Chiari syndrome -associated with pancytopenia.⁵³ Hepatocellular carcinoma is the most common cause of portal vein thrombosis but non-malignant PVT incidence is reported in 0.6 to 12% of patients with cirrhosis.⁵⁹ It can be asymptomatic or it may present with worsening of liver disease and complicates the procedure of liver transplantation. Decreased portal flow, previous abdominal surgery and sclerotherapy are identified as causes of portal vein thrombosis. If underlying inherited disorders are suspected, a thorough evaluation should be done prior to liver transplant, as it can increase the risk of post-operative venous thrombosis.⁵⁴

Erythrocyte Abnormalities

Anemia in liver diseases is multifactorial. Defective production of red blood cells could be due to nutritional deficiencies along with myelosuppression. It could also be due to acute blood loss in variceal hemorrhage. Hemolytic anemia occurs as spur cell anemia in NASH and alcohol liver disease, ribavirin induced hemolysis, autoimmune hemolytic anemia in autoimmune hepatitis. Sideroblastic anemia is seen in Wilson's disease secondary to treatment with trientine.^{13,60}

(continued on page 46)

(continued from page 44)

Leucocyte Abnormalities

Leucopenia occurs in cirrhosis secondary to splenic sequestration, due to circulating hematopoietic progenitor inhibitory factors, increased apoptosis or interferon related mechanisms. Decrease in lymphocytes is probably related to chronic malnutrition.^{13,60}

There is an increased risk of non Hodgkin's lymphoma in HCV due to increase monoclonal proliferation of B cells in HCV.⁶¹

Endocrine and the Liver

Endocrine disorders maybe coexistent with underlying liver diseases. We will highlight only the endocrine manifestations of liver diseases.

Thyroid Dysfunction in Liver Disease

Various liver diseases can have differing effect on thyroid hormone metabolism.

Cirrhosis usually produces sick euthyroid syndrome. As thyroxine-binding globulin is a positive acute phase reactant, total T4 levels are elevated with normal freeT4 levels in acute hepatitis. Primary biliary cirrhosis and autoimmune hepatitis also have associated autoimmune thyroid diseases. Primary sclerosing cholangitis is associated with Hashimoto's thyroiditis, Grave's disease and Reidel's thyroiditis. HCV can cause thyroid disorders including cancer, independent of interferon treatment.⁶²

Anti-thyroid antibodies are also seen in 14.7% of women with chronic HCV infection. Hence it is essential to screen these patients for thyroid diseases before treatment.⁶³

Hypothyroidism is also seen with transcatheter arterial chemoembolization and sorafenib used for hepatocellular carcinoma treatment. Severe diuretic resistant ascites can sometimes occur in uncontrolled hypothyroid cirrhosis. Thyroid hormone replacement therapy results in regression of the ascites over a few months. Hypothyroidism should be considered in patients with portal hypertension when they present with diuretic resistant ascites, and hormone replacement therapy often makes them diuretic sensitive.⁶²

Diabetes Mellitus, Lipids and the Liver

The development of diabetes mellitus, metabolic syndrome and NAFLD is interlinked. HCV infection is thought to produce diabetes by increasing the insulin resistance. This defective insulin signaling causes

increased free fatty acid oxidation and triglyceride accumulation within the liver causing steatosis. This triggers the inflammatory cascade causing stellate cell activation and the resultant hepatic fibrosis. This makes diabetes mellitus and concomitant HCV infection increase the development of hepatocellular carcinoma.^{62,64}

Screening for diabetes mellitus should be performed on all HCV patients and the use of hepatotoxic oral hypoglycemic agents should be used with caution in these patients. Biguanides, which improve insulin resistance, and alpha glucosidase inhibitors, which improve post prandial hypoglycemia, can be used in this population. that makes them susceptible for central obesity further aggravating the insulin resistance.⁶⁵ There is also a 2.3% risk associated hypopituitarism in patients with NAFLD.¹³

Adrenal Diseases and the Liver

There is 33 - 66% relative adrenal insufficiency (RAI) in liver failure and the degree of adrenal dysfunction correlates with the severity of liver diseases. It is seen even after orthotopic liver transplantation in the absence of sepsis. There are improved outcomes with corticosteroid supplementation.⁶² However they should be reserved only for patients with sepsis requiring vasopressors and at this point recommendations await further research.

Liver Diseases and Nutrition

The incidence of protein-energy malnutrition in liver disease is between 30 - 90% and is associated with adverse survival outcomes. Several studies have shown that the severe degree of malnutrition was associated with adverse outcomes even after transplantation.⁶⁶

Polyunsaturated fatty acid synthesis (PUFA) from essential fatty acid precursors occur in the liver. PUFA contributes to the fluidity of the cell membranes. PUFA deficiency occurs in cirrhosis and is an independent predictor of mortality of alcoholic cirrhosis. Hepatic glycogen stores are depleted in chronic liver diseases and produces severe catabolic state. Branched chain amino acids (BCAA) has shown to improve energy metabolism, reduce malnutrition, improve liver function tests and quality of life in cirrhosis.⁶⁷ However, as it may exacerbate glucose intolerance, the use of alpha glucosidase inhibitors with it is encouraged.

Hence it is important to diagnose these nutritional deficiencies early to improve mortality. The European

Society for Nutrition and metabolism guidelines state that subjective global assessment, anthropometry or hand grip strength are sufficient to identify undernutrition in this population.⁶⁸ An intake of 35–40 kcal/Kg/day (dry body weight) and 1.2–1.5 g/kg/day of protein, with low sodium content (<2g/day) combined with supplementation in small frequent meals is generally recommended in these patients.⁶⁹

Effects of Liver Diseases on Other Organ Systems

Advancing liver disease is associated with bone loss so improved disease progression may improve bone loss. The pathogenesis is similar to post menopausal and age related bone loss with estrogen deficiency. The other factors that either directly or indirectly alter bone mass such as insulin growth factor-1 (IGF-1) deficiency, hyperbilirubinemia, alcoholism, excess tissue iron deposition, subnormal vitamin D levels, vitamin D receptor genotype, osteoprotegerin deficiency, and immunosuppressive therapy preceding and following liver transplantation. High turnover osteoporosis has been described among 20% to 30% of patients with chronic cholestatic liver disease, primary biliary cholangitis, and primary sclerosing cholangitis.⁷⁰ Accelerated osteoporosis has also known to occur in chronic prednisone use in the setting of autoimmune hepatitis and post orthotopic liver transplantation for immunosuppression. Arthritis maybe the first manifestation of liver disease and it is also the most common extrahepatic manifestation in primary biliary cirrhosis, autoimmune hepatitis and hemochromatosis.⁷¹

Ophthalmic System

The early recognition of the eye signs can help in prompt diagnosis of the underlying liver diseases. Keratoconjunctivitis sicca is particularly common in 50% of patients with primary biliary cirrhosis and 35% of patients with active hepatitis.

Corneal clouding combined with hepatomegaly is a feature of several types of storage disorders. The Kayser Fleischer ring, which is a yellow, red, green or brown deposit in the peripheral cornea is pathognomic of Wilson's disease and resolves completely with treatment. Lens opacification is a feature of Wilson's disease, galactosaemia, Zellwegger's hepatocerebrorenal syndrome, neonatal adrenoleukodystrophy, and neonatal haemolytic jaundice syndrome. Prolonged use of systemic adrenocorticosteroids for immunosuppression

following orthotopic liver transplantation may also be complicated by cataract formation, opportunistic retinal and choroidal infections. Mucopolysaccharidoses are associated with pigmentary retinopathy and two of the sphingolipidoses manifest macular "cherry red spot". Primary biliary cirrhosis may be associated with treatable night blindness due to malabsorption of vitamin A. Parinaud's syndrome is seen in Niemann-Pick disease, kernicterus and Wilson's disease. Finally, there is a rare complication of acquiring hepatitis B following corneal transplantation, and should be considered prior to transplant.⁷²

Drug Induced Liver Diseases

Drug-induced liver disease (DILD) occurs in about 25% of patients of fulminant hepatic failure.⁷³ It accounts for 2-5% jaundice in hospitalized patients and about 10% of hepatitis in all adult patients.⁷⁴ The liver is the primary site of contact of ingested chemicals and the primary site of biotransformation, thereby making it especially vulnerable to chemical injury. The factors that affect vulnerability are related to the conversion of these ingested agents to a hepatotoxic metabolites.⁷⁴ It is multifaceted phenomenon and sometimes liver disease maybe the only clinical manifestation of the adverse drug effect with or without involvement of other organs. It may occur either as an idiosyncratic reaction to the drug (sulfonamides, dapsone, sulindac, etc.) or a consequence of intrinsic toxicity of the drug (acetaminophen, inorganic iron, anabolic steroids, tetracyclines, etc.).^{75,76} Clinical features most commonly include fever, eosinophilia and rash. Sometimes also have lymph node enlargement with atypical circulating lymphocytes (psuedomononucleosis).⁷⁶

CONCLUSION

Liver diseases represent an emerging health issue due to its increasing prevalence and complications worldwide. It is important for clinicians to be aware of the impact of liver diseases on the various organ systems to be able to identify the underlying liver disease early to prevent long term complications and improve the quality of life in these patients. ■

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(continued on page 50)

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