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Geriatric Hepatology: The Hepatic Diseases of the Elderly and Liver Transplant

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Abstract

Introduction: With the aging US population, chronic liver diseases are becoming more commonly diagnosed in the geriatric population. Advanced age leads to changes in liver blood flow, volume, morphology and normal physiology. This predisposes elderly patients to develop certain chronic liver diseases. Also, the clinical course and management differ in an older patient when compared to a younger patient. Some causes of chronic liver disease in the geriatric population include Hepatitis A, B, C, Non-Alcoholic Fatty liver disease, prolonged alcohol use and inflammation. Many chronic liver diseases are characterized by a slow, indolent course of progression with non-specific symptoms and thus may lead to diagnosis at a later age. The presence of an advanced liver disease, cirrhosis, and hepatocellular carcinoma are becoming more frequent in older patients and often the first clinical presentation.

Aim: The aim of this study is to highlight hepatic diseases in the geriatric population to better understand the scope of the clinical management including liver transplantation.

Method: PubMed, MEDLINE, EMBASE, and EMBASE classic were searched to research published articles, case reports, cross-sectional and case-control studies reporting regarding aging and the liver diseases.

Result: Decreases in the functioning of the liver and other organs, as well as, alterations in immune functions should be taken into consideration in the management of the liver diseases. Aging has been shown to not only enhance vulnerability to acute liver injury but also increase the susceptibility of the fibrotic response. Aging has a significant impact on the risk and poor prognosis of various liver diseases including NAFLD, ALD, HCV, and liver transplantation. The diagnosis of advanced liver disease is important to make in the elderly population since many of the condition's features are treatable and can lead to improved quality of life and, most importantly, decrease the likelihood of acute care hospitalization, which carries a high risk of nosocomial infections and therapeutic mishaps in the aged population.

Conclusion: Geriatric patients show various changes in the liver, which play a role in the clinical characteristics of liver diseases in these patients. Geriatric patients with risk factors for hepatitis should be screened for liver disease, along with those that have a family history of liver diseases, or a history of long-term or heavy alcohol consumption. Age cannot be a single exclusion criterion from the liver transplantation, and an individualization strategy, which takes into consideration all risk factors of a recipient, needs to be considered. We suggest geriatric patients should be a candidate for liver transplant, and the healthcare team treating our elderly generation to collaborate for these patients for them to have a smoother transition both in pre-transplant phase and post-transplant phase.

Keywords: Aging and Liver; Geriatric Hepatology; Liver Diseases in the Elderly; Transplant Hepatology

Introduction

Aging causes time-dependent, inevitable physiologic organ dysfunction that alters normal homeostasis and is a major risk factor for cancer development [1]. In the United States, as of 2009, there are 39.6 million people older than the age of 65, equating to 13% of the country's total population. This number is expected to increase to 72 million or 19% of the total US population by 2030 [2-4]. Aging has shown increase vulnerability to acute liver injury as well as progression to liver fibrosis. This is associated with associated with poor prognosis of various liver diseases including Nonalcoholic Fatty Liver Disease (NAFLD), Alcoholic Liver Disease (ALD), Hepatitis C (HCV), Hepatocellular Carcinoma (HCC) and Liver Transplantation (LT). Studies have compared changes in the liver due to liver diseases with the process of aging [5]. Approximately, 8 million Americans suffer from chronic hepatic diseases, of which, more than half a million people have cirrhosis and nearly, 31 thousand Americans die each year from cirrhosis [6-8]. Old age seems to favor NAFLD, NASH, and ultimately HCC, in agreement with the inflammatory aging theory, according to which aging accrues inflammation [5]. The higher vulnerability to environmental factors (Especially oxidative stress), the reduction in the rate of hepatic blood flow, the reduced mitochondrial capacity and the impaired immunity are all mechanisms possibly involved in a faster progression of liver damage [9].

Aging and Liver Volume, Blood Flow, And Function

Both liver volume and blood flow decrease significantly with age. Hepatic blood flow is estimated to be decreased by 35%-50% in the elderly and may be responsible for age-related reductions in liver volume [10]. The neural fat and cholesterol volumes in the liver gradually expand as one gets older, and therefore causes an increase in total serum cholesterol and high-density lipoprotein cholesterol. Meanwhile, the metabolism of the low-density lipoprotein cholesterol decreases by 35%. The serum γ-glutamyltransferase and alkaline phosphatase levels increase with aging, while Alanine Aminotransferase (ALT) concentrations and serum bilirubin are gradually reduced with age, independent of components of the metabolic syndrome, the serum aminotransferase maintains normal level and albumin remains within normal limits or is slightly decreased due to aging [11]. Humans show a slight decrease in the serum albumin concentration or maintain the normal level in the natural aging process [11].

Alanine Aminotransferase (ALT) concentrations have been reported to decrease with age, independent of components of the metabolic syndrome. These findings suggest the need to identify an optimal cut-off point for normal ALT in Geriatric patients [12]. Hepatic Encephalopathy (HE) also can occur because of portal hypertension. Resistance to blood flow leads to shunting of blood around the liver, allowing blood from the gut containing ammonia and other byproducts of bacterial metabolism to bypass the liver and reach the systemic circulation [7]. Exposing the brain to these chemicals can result interfere with the normal synaptic transmission of electrical and chemical signaling. As a result, cognition and memory are affected, leading to memory loss, impaired thinking, and an inability to perform fine motor tasks [13,14].

Aging-Related Changes in Liver Cells

Aging-related changes in liver cells include volume changes, polyploidy, accumulation of dense bodies (Lipofuscin) inside liver cells, a decreased area of the smooth endoplasmic reticulum, and a declining number and dysfunction of mitochondria [15]. Compared with the studies on liver cells, relatively little is known about what kind of effect aging has on liver sinusoidal endothelial cells, Kupffer cells, and hepatic stellate cells [16]. The functionality of Kupffer cells is to remove antigen–antibody complexes or nanoparticles such as senescent cell fragments in the liver sinusoidal vascular system and is important to point out that aging increases the number and activation level of Kupffer cells [17]. A study by Sotaniemi, et al [18], suggested that drug metabolism is reduced by up to 30% after 70 years of age, and that a reduction in liver cytochrome P450 may also contribute to decreased drug metabolism. Cytochrome P450 activity was shown to be 32% lower in subjects > 70 years than in subjects aged 20-29 years [18].

First-pass hepatic uptake (Phase I) of drugs has been reported to be decreased in the elderly, possibly due to reduced liver volume and hepatic blood flow, leading to a decline in hepatic drug metabolism [19]. Metabolism of drugs with low phaseI hepatic metabolism is likely to be impaired mainly by liver volume reduction [19]. Volume and blood flow changes coupled with decreased cytochrome P450 activity can affect drug metabolism, increasing susceptibility to drug-induced liver injury [20]. Immune responses against pathogens or neoplastic cells are decreased in the elderly, although individuals may also be predisposed to autoimmunity through impairment of dendritic cell maturation and reduction of regulatory T cells [21]. Such changes in immune functions could alter the pathogenesis of viral hepatitis and autoimmune liver diseases and development of hepatocellular carcinoma [22,23]. Geriatric patients have significantly decreased reserve functions of various other organs as well, reducing their tolerability to treatments for liver diseases [24].

Hepatic Diseases of Elderly

NAFLD

Non-alcoholic fatty liver disease is a clinical syndrome predicted to be the next global epidemic affecting millions of people worldwide, especially the geriatric population [25,26]. The

natural course of this disease including its subtype, Non-Alcoholic Steatohepatitis (NASH), is not clearly defined especially in the elderly segment of the US population [26]. NAFLD affects mainly the middle-aged and the elderly and previously was reported be benign, however more recent studies suggest an increased mortality in the patients older than 60-year [27]. With advancing age come more risk factors for its development. Aging increases risk factors which predispose progression to NAFLD. Older patients have more severe biochemical, hematological, and histological changes [28]. The pivotal role of inflammation in the pathogenesis of liver steatosis has been emphasized in the literature; the link between insulin resistance and inflammation and the possible role of C‐Jun N‐Terminal Kinases (JNKs) in the progression of this condition has been clearly defined, along with the involvement of endoplasmic reticulum stress and of the unfolded protein response [29]. Aging-related alterations of the pro-inflammatory vs anti-inflammatory balance, described as the inflammatory aging theory may represent the biological background of these findings [30]. Current guidelines for treatments for NAFLD are to control body weight and treatment of metabolic disorders by changing lifestyle and improve insulin resistance [31,32].

Metformin and thiazolidinedione's are insulin sensitizers, which metformin is known to be effective in reducing body weight and improving insulin resistance [33], but its histological effect of improving necrotic inflammation in the NASH has not been proven [34,35]. In very rare cases, it can cause lactic acidosis in the elderly [36,37]. Another treatment option would be bariatric surgery, but is important to note that bariatric surgery causes an upsurge in the morbidity rate among geriatric patients compared with younger patients, and is no significant difference in the mortality rate except for those with patients with cardiovascular diseases [38,39]. Liver transplantation can be an option for patients with decompensated liver cirrhosis due to NASH and, it is also worthy to not that, in the geriatric patients, careful consideration should be paid in consideration of common age-related comorbidities, which has a significant influence on their survival and hospitalization period after liver transplantation, due to cardiovascular complications which they will have [40,41]. More accurate understanding of the molecular pathways, gut microbiome analysis, and precise investigation of the mechanisms of geriatric NAFLD will help in identifying the most appropriate diagnostic and therapeutic approach for individual geriatric patients [42-46]. With aging, the liver undergoes substantial changes in structure and function that are associated with significant impairment of detoxification activities and many hepatic metabolic dysfunctions [47-49].

Acute Liver Failure

Acute Liver Failure (ALF), is an uncommon condition with potentially devastating consequences, including an increased rate of short-term morbidity and mortality [50-52]. Common causes for ALF in elderly is excessive alcohol consumption and in some rare cases which physicians should pay close attention for is overly excessive use of acetaminophen [53,54]. The primary treatment for alcoholic liver disease is abstinence from drinking and provide sufficient nutrients and vitamins, but in geriatric patients, this is a major problem due to prolonged use of alcohol and late diagnosis of ALF [55]. Half of the elderly patients who develop cirrhosis die within 1 year of diagnosis [56]. Glucocorticoid treatment can be helpful for some patients with mild to moderate alcohol hepatitis whose Maddrey's discriminant function scores are higher than 32 [57]. However current research has described glucocorticoids-induced hyperglycemia elderly patients and physicians should be aware of this complication [58]. For patients who have a contraindication for steroids, pentoxifylline, a TNF-α Inhibitor (TNFI), can be considered as an alternative treatment which the retention rate of TNFI in the elderly is comparable with that in younger patients [59]. It is imperative to identify geriatric patients with ALF as soon as possible to transfer them to a liver transplant center for an evaluation and life style modification. Emergent liver transplant in the geriatric patient with ALF may place the patient at risk for severe complications in the postoperative period [60], but in the long run, may help to prevent mortality.

Hepatitis A

Although Acute Hepatitis A (HAV) infection is usually self-limiting in general population. However, elderly patients with acute HAV infection can experience hepatocellular dysfunction with frequent jaundice and coagulopathy, as well as an increased incidence of complications, such as prolonged pancreatitis, cholestasis, and ascites [61]. During 1994 and 1995, Memphis and Shelby County, Tennessee, experienced an epidemic of HAV, which 42% of patients aged 70 years or older required hospitalization compared with 3%-20% of adults aged 40-49 years [62]. Vaccination for HAV should be offered for those who plan to travel to endemic areas, especially patients living in nursing homes.

Hepatitis B

Acute Hepatitis B Virus (HBV) infection is very uncommon in the geriatric patients because the opportunities for acquiring HBV infection are estimated to be low in this population. However, HBV infections have been reported in residents of nursing homes [63]. The rate of progression to chronic hepatitis B is higher in the elderly vs younger patients [64]. A report of an outbreak in a nursing home showed that 59% of patients older than 65 years of age developed chronic HBV infection [64]. Regarding the lab results of elderly patients with HBV infection, older age and male, in addition to serum HBV DNA levels, are regarded as risk factors not only for progression to cirrhosis [65], but the development of HCC [66]. Nucleoside analogs are effective in treating HBV infected patients, with similar efficacy in the elderly as in younger patients [67]. Interferon-based therapy may also be effective for

the treatment of chronic HBV infection, however, its therapeutic effects are inferior in elderly patients [68]. Vaccinations should be considered if patients have not been vaccinated.

Hepatitis C

The population infected with HCV is aging as most in the US acquired the infection during World War II [69]. A total of 320,000 deaths, 157,000 cases of HCC, and 203,000 cases of cirrhosis are predicted in the US for the upcoming 35 years, despite the highly effective and readily available treatment regimens [70]. An increased number of Americans with advanced liver diseases in part can be attributed to the 3.3% prevalence of HCV in the geriatric population [71]. According to a research by Poynard, et al. [9], age itself is more important than duration of infection for predicting the occurrence of cirrhosis. This will create a tremendous burden on the healthcare system, including skilled nursing and long-term care facilities [72-75]. In the US, most patients with HCV infection were born between 1945 and 1965, who acquired the infection during the 1970s and 1980s from exposure to blood or blood products [76-78]. Evidence shows that treatment of HCV can prevent the progression of end-stage liver disease in geriatric patients [79]. Since the first introduction of the interferon-alone treatment, the antiviral treatments for chronic hepatitis C have developed dramatically through the combination therapy of peg-interferon-α and ribavirin to direct-acting antiviral agents such as protease inhibitors and polymerase inhibitors.

When the elderly people aged more than 65 years are treated with a combination therapy of peg-interferon-α and ribavirin, their Sustained Virological Response (SVR) is lower than those under 65 years old (Genotype 1: 22.9 vs. 47.3%; genotype 2: 65.6 vs. 82.9%), whereas their treatment termination rate is higher due to side-effects (genotype 1: 42.9 vs. 24.1%; genotype 2: 24.4 vs. 10.8%) [80-82]. The combination of three agents such as peg-interferon-α., telaprevir, and ribavirin is given to genotype 1 patients showed no significant difference in their SVR between the young and elderly [83]. Also, this treatment regime was discontinued due to complications such as severe malaise [84-86]. According to a research by Pawlotsky [87], it is important to state that, all-oral, interferon-free combinations of drugs are expected to cure more than 90% of infections, but this has not been tested in elderly patients [87]. Current research supports that the supplementation of vitamin D and vitamin B12 increases the SVR, and as elderly people have a lack of these vitamins, they should be taking these supplements [88-92].

SVR has been shown to improve biochemical characteristics and portal hypertension in some patients diagnosed with HCV, it is unclear in which specific patients may benefit from treatment with a history of decompensated liver disease [93]. It is thoroughly documented that HCV infection has a negative impact on the quality of life of elderly patients, until this date, the complexity of treatment and the lack of supportive data in elderly patients have significantly limited the treatment options [84]. Now that the era of baby boomers and populations is rapidly changing, and that new IFN-free treatment options are becoming widely available, the limited but available evidence concerning the benefit of viral eradication in the elderly population should be carefully considered [69]. The faster the health care system changes their policy with respect to an a priori obstacle for anti-HCV treatment in the elderly, the sooner we will begin to help many geriatric patients diagnosed with HCV [69]. HCV infection is the most common indication for Orthotopic Liver Transplantation (OLT) in the United States [94]. Recent studies from selected centers have suggested that older donor age is associated with worse outcomes after transplantation for HCV [95].

According to a research by Dultz, et al. [96] both older donor age and older recipient age plus markers of severity of disease, including requirement for mechanical ventilation and renal insufficiency, are negatively associated with survival after liver transplantation [94]. According to a research by Pyrsopoulos, et al. [97] the combination of LED/SOF with RBV for 12 weeks or ledipasvir/sofosbuvir for 24 weeks is very effective and safe in treating OLT recipients with recurrent HCV [97]. These factors should be considered when assessing OLT recipient and donor candidacy in patients with HCV. Concerted efforts are necessary to increase diagnosis and treatment rates, optimize care of patients with cirrhosis and HCC and provide care to liver transplant recipients to reduce the overall HCV-related disease burden in the United States [96].

Cholestatic Liver Disease

Primary Sclerosing Cholangitis (PSC) and Primary Biliary Cirrhosis (PBC) are chronic diseases which can manifest in adult patients [98]. In a recent study by Tanaka, et al. [98] they reported that conclude that PSC in the young resembles those in Europe and the USA in terms of the onset age and prevalence of IBD, while PSC in the elderly is really unique in Japan. Presenting complications of elderly patients with PSC is no different than those of the younger patients [99], but there is certain degree of cholangiocarcinoma presentation in older patients [100-102]. Eventually all patients with PSC will require LT, and is better for the elderly patient to receive the LT before the age of 60 [99]. According to a research by Newton, et al. [103] they reported that 35% of patients out of 1000 examined had PBC. Symptoms of clinical presentation was no different for young patients versus the elderly [103]. Although there has been reported that a 92 year-old men with PBC after under undergoing Computed Tomography (CT) and ultrasound scans of his abdomen revealed a large hepatic tumor, which was confirmed on liver biopsy to be HCC [104]. Furthermore, biomarkers reflecting disease activity and prognosis in Primary Sclerosing Cholangitis (PSC) have not been firmly established and

due to complex interplay which exists between IBD, PSC, and LT which requires explanation with further research.

Hepatocellular Carcinoma

With age the risk of HCC increases significantly, and this is independent of prolonged HCV infection as a shorter interval between acquiring HCV infection and the diagnosis of HCC has been demonstrated in elderly patients [105]. Many elderly HCC patients with intermediate to terminal stage at their initial diagnosis will have more compromised liver regeneration and comorbidities compared with those of younger age [106]. Elderly patients require long-term follow-up even after viral eradication and especially male patients with liver cirrhosis since research has shown that they are prone to developing HCC [107]. Hepatic resection for HCC can be performed safely and effectively in elderly patients [108-110]. A recent report by Borzio, et al. [111] showed that age did not predict short-mid-term survival within 24 months, while it was a significant independent predictor of long-term survival. Also age had a substantial long-term survival effect mainly on early HCC stages (Barcelona Clinic for Liver Cancer [BCLC] 0-A), its influence on BCLC B stage was shown to be lower, while it was negligible for advanced terminal stages Age should not impact on short-mid-term prognosis of elderly patients with HCC and should not represent a restriction to the management [112]. The pool of elderly patients with the history of HCC receiving a liver transplantation is increasing [113]. This can be attributed to the improvement of HCC surveillance approaches and diagnostic techniques leading to earlier diagnoses of HCC in the elderly population.

Geriatric Liver Transplant

Liver Transplant (LT) is a standard treatment for End-Stage Liver Disease (ESLD). At present, 1-year survival rate is approximately 90% and 10-year survival rate may exceed 70% in many indications [114,115]. Patients with ESLD will require liver transplantation to prevent morbidity and mortality associated with end-stage-liver disease [116]. The proportion of adult liver transplantation recipients in the United States older than 60 years of age increased from 10% in 1990 to more than 20% by 1999 [117]. The era when an ideal liver donor was younger than the age of 40 years seems to have be gone out of current practice management [118]. Many transplant programs have expanded eligibility to include patients previously ineligible because of advanced age [119]. Several studies showed that outcomes after LT with livers of patients older than 70-years are comparable, and sometimes even better compared to younger donors, with 1-year and 3-year patient and graft survival ranging 66-95% and 58-91%, respectively [120].

According to a research by Adani, et al. [121], clinical outcomes after liver transplantation in the elderly are nearly similar to young people, considering if individual surgery risks are equivalent [121]. United Network for Organ Sharing Database conducted a study which revealed prognostic factors: they found that diabetes mellitus, the ventilator status, history of HCV, creatinine at least 1.6 mg/dl, and combined donor age and the recipient age are the most prevailing prognostic indicators among the recipients of LT older than 60-years old [122]. If the numbers of positive indicators among them are 0, 1, and 2, their 5-year survival rates are recorded at 75, 69, and 58%, respectively. If the number of positive indicators is more than three, the elderly patients 5-year survival rate was below 50% [123].

Although it is important to note that geriatric patients may have multiple risk factors, including artery disease or malignancy, coronary disease and face age-related quality of life impairments, such as incontinence, gate instability, immobility, dementia, and many are on regimen of polypharmacy [124]. It is important for the healthcare team to also take in account these parameters when considering the patient for LT. A successful LT depends on the liver's structure and hepatic function, but as research indicate these parameters decline with the process of aging [125]. Considering that there is a rise in elderly patients the aging population is increasingly suffering from cerebrovascular disease [126-131], the use of chronologically old, but biologically young liver donors would expand the donor pool and, hopefully, reduce waitlist mortality. Advanced age alone should not be considered a contraindication for LT due to potentially poor quality of life outcomes [132]. Further research is necessary to confirm whether and which geriatric-like measures can be used to select livers of older donors for LT.

Conclusion

Geriatric patients show various changes in the liver, which play a role in the clinical characteristics of liver diseases in these patients. Decreases in the functioning of the liver and other organs, as well as, alterations in immune functions should be taken into consideration in the management of the liver diseases. Aging has been shown to not only enhance vulnerability to acute liver injury but also increase the susceptibility of the fibrotic response. Aging has a significant impact on the risk and poor prognosis of various liver diseases including NAFLD, ALD, HCV, and liver transplantation. The diagnosis of advanced liver disease is important to make in the elderly population since many of the condition's features are treatable and can lead to improved quality of life and, most importantly, decrease the likelihood of acute care hospitalization, which carries a high risk of nosocomial infections and therapeutic mishaps in the aged population. Geriatric patients with risk factors for hepatitis should be screened for liver disease, along with those that have a family history of liver diseases, or a history of long-term or heavy alcohol consumption. Age cannot be a single exclusion criterion from the liver transplantation, and

an individualization strategy, which takes into consideration all risk factors of a recipient, needs to be considered. We suggest geriatric patients should be a candidate for liver transplant, and the healthcare team treating our elderly generation to collaborate for these patients for them to have a smoother transition both in pre-transplant phase and post-transplant phase.

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