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Published in:
Age and Ageing

DOI:
10.1093/ageing/afy170

Publication date:
2019

Document Version
Peer reviewed version

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Abstract

Hepatitis C and Hepatitis B, are common blood borne viruses that can cause acute hepatitis but are more clinically relevant because of the chronic infection that is associated with fibrosis the development of cirrhosis and Hepatocellular carcinoma. Both these viruses are becoming more common in the older population, due to the aging of generations exposed to the risk factors associated with infection; intra venous drug use, multiple sexual partners and men who have sex with men. This review will cover the natural history and epidemiology of these infections as well as the revolution in drug therapy that now allows cure of HCV infection and complete control of HBV infection.

Introduction

According to the World Health Organisation (WHO) Global Hepatitis report in 2017, approximately 257 million individuals have chronic hepatitis B Virus (HBV) infection. Additionally, there are 71 million persons with chronic hepatitis C virus (HCV) seropositivity [1]. In those who remain untreated; HBV and HCV may sequentially lead to chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC); which carry enormous morbidity and mortality. These complications account for 96% of deaths relating to viral hepatitis [1].

As the aging population continues to grow the baby boomers of 1940-60 are now approaching their 70th birthday. An updated overview of the UK population as of July 2017 from the office of national statistics showed the population to be becoming progressively older with 18% aged 65; and over 2.8% aged 85 and over.[2] With this in mind the number of patients with viral hepatitis presenting to the medicine for the elderly services is ever increasing. There have been enormous advances in the understanding and management of the chronic infectious hepatitides (Hepatitis B (HBV) and Hepatitis C (HCV)) in recent years. Within this review we will focus on hepatitis B and C; specifically focussing on presentation, treatments and some of the associated morbidity within an aging populace.

This is a pre-copyedited, author-produced version of an article accepted for publication in *Age and Ageing* following peer review. The version of record Kemp, L., et al. "New horizons in hepatitis B and C in the older adult", *Age and Ageing* (2018) is available online at: https://doi.org/10.1093/ageing/afy170.

The first report of the virus was by Nobel Prize winner Baruch Blumberg in 1963; with the discovery of a new antigen termed Australian antigen (AuAg, now known as surface antigen) being reported publically.[3] In the years to come AuAg became the first marker for viral hepatitis and following this Hepatitis B became a driving force for modern development of virus diagnostics and vaccines. Epidemiological studies estimate that one third of the world's population has evidence of past or present infection.[4]

Hepatitis B belongs to the hepadnavirus family. It is a composed of partially double-stranded viral DNA capable of reverse transcriptase.[5] The complex viron is composed of a double stranded- DNA, nucleocapsid (HBcAg) and the outer surface of the viron, the hepatitis B surface antigen (HBsAg). Another nucleocapsid antigen is hepatitis B-e antigen (HBeAg).[6] It is transmitted when blood, semen or another contaminated bodily fluid from a person infected with the virus comes into contact with mucus membranes or an open wound of someone who is virus naive. Transmission may be though sharing of needles, syringes or other drug injecting paraphrenalia, via sexual contact[7] or by vertical transmission (from mother to child) at birth.[8]

The natural history of the disease can vary from acute infection, inactive carrier state to progressive chronic hepatitis B even leading to cirrhosis and potentially hepatocellular carcinoma.

The WHO recognises Hepatitis B as a major global health problem. The prevalence varies and is an estimated 1.6% in the WHO European Region and 0.7% in the WHO Region of the Americas.[41] The UK falls into the lowest category of Hepatitis B prevalence, as determined by the WHO (0.1-0.5% of the population).[9] Although acute HBV infection rates have fallen rapidly, the data from the Health Protection Agency indicated the frequency of chronic infection is increasing. Therefore it is likely that with increasing emigration patterns, particularly from those countries where Hepatitis B is more prevalent, with these persons also often bring additional affected family members. Not surprisingly, there is an increased prevalence in previously low predominance countries. In North America and Europe (including the UK) the main risk factors are birth in an endemic country, intravenous drug use and men who have sex with men. All of these risk populations are increasing in age, the teenagers of the "swinging 60's" and the citizens from the decades of mass migration are now pensioners. Though these patients are poorly representative of the elderly population as a whole. [6] There are scattered reports of HBV outbreaks in nursing home residents in the literature; however, these are relatively historical; occurring in the 1970s. [10]

Clinical Manifestations

Acute hepatitis B in older adults is usually mild and self-limiting. Infected elderly individuals often develop a subclinical or oligo-symptomatic hepatitis with a low rate of HBV clearance.[11] In many cases the pattern of liver function derangement can be cholestatic in nature; which can lead to the performance of unnecessary tests and be miss leading in diagnosis of the condition as extrahepatic diagnosis such as pancreatic tumours or gall stones are considered first. Therefore, in every older patient presenting with elevated liver enzymes, it is suggested serological tests for hepatitis should be determined before proceeding to further investigation.[12] The natural course of chronic HBV is influenced by a multitude of variables including age.[13] The risk of progression to chronic hepatitis B is inversely related to age at the time of infection. In infants progression to chronic hepatitis B has been reported in >90% of those infected, 25-50% of children aged 1-5 years old and progression from acute to chronic hepatitis B occurs in less than 5% of young adults, but is observed more frequently in the elderly.[13] In Japan an outbreak in a nursing home lead to almost 60% of the infected becoming HbsAg carriers.[12] There are however some conflicting reports with regard to seroclearance with more than one study suggesting thatage >60 years has been shown to be an independent predictor for HbsAg clearance, but this has principally been demonstrated in Asian populations [14,15].

The virus stages of chronic HBV infection are classified in EASL[4] documents, this is illustrated in table 1. The 5 phases are presented as a linear progression but it is important to note that patients can move back and forth between the phases.

- Phase 1-The Immune tolerant phase is characterised by HBeAg positivity, high levels of HBV replication, normal or low levels of aminotransferases, no liver necrosis and no or slow progression to fibrosis, but is highly contagious and is the situation most commonly seen in children and young adults.
- Phase 2-The Immune reactive phase again has HBeAg positivity, but lower replication rates, increased or fluctuant levels of aminotransferase, on liver biopsy moderate to severe necro-inflammation and more rapid progression to fibrosis. It is the most dangerous phase of chronic HCV infection, with patients progressing to cirrhosis and liver failure. This is the disease state targeted by current treatments, with the aim of suppressing viral replication.
- Phase 3- Inactive HB carrier state is defined by seroconversion of HBeAg to anti-HBe antibody and low or undetectable levels of HBV DNA. Usually aminotransferases are normal. There is a low risk of cirrhosis and HCC and this usually depends on the degree of damage before this phase is reached. This phase can reactivate to immune reactive, especially with inter-current illness, immunosuppressive therapy and some of the new biological agents.
- Phase 4- HBeAg negative CHB occurs in the presence of a HBV mutant virus that is not supressed or only partially suppressed by the seroconversion from HBeAg to anti HBe-antibodies. This may be apparent immediately on leaving the immune-reactive phase or may become apparent after many years or decades of the inactive carrier state. It is characterised by fluctuating HBV DNA and aminotransferase with an active hepatitis. There is active liver disease with risk of progression to advanced fibrosis, cirrhosis and the complications related to this, progression is usually slower than in the immune-reactive phase
- Phase 5-HBsAg-negative phase is characterised by serum negative HBsAg and positive antibodies to HBcAg (anti-HBc), with or without detectable antibodies to HBsAg (anti-HBs). This phase is also known as ‘‘occult HBV infection”. Key to understanding this phase is the recognition that these patient shad early phase of chronic infection and are different to the resolved/cured acute infection, despite the fact they have the same immunological profile. Most of these patients were previously regarded as cured and that is still indeed the case for the majority, especially if they have minimal liver damage by the time they reach this stage. The true occults still have cccDNA in their livers, which can lead to reactivation of infection usually with inter-current illness, immunosuppressive therapy and some of the new biological agents. Currently there are no reliable assays that can exclude the presence of cccDNA in the liver

Table 1. Stages of chronic HBV infection

Phase of chronic HBV	Previous Name	HBeAg	Anti- HBe antibody	HBV replication	Aminotransferase level	Necrosis fibrosis
1	Immune tolerant	Positive	Negative	High	Normal or low	None slow progression
2	Immune reactive	Positive	Negative	Lower	Increased or fluctuant	Mod/severe necrosis Rapid progression
3	Inactive HB carrier	Negative	Positive	Low	Normal	Low risk Low Risk
4	HBeAg negative CHB	Negative	Positive	Periodic re-activation	Fluctuant	Active liver disease Risk of progression
5	Occult HBV	Negative	Negative	may persist in liver	Normal	dependent on duration of previous phases

Vaccinations

Childhood vaccinations are recommended routinely in many countries including the UK as of August 2017 and also for those with increased risk of infection primary vaccination of adults.[16] Studies into the response of elderly patients to the hepatitis B vaccination have found that when compared to a younger cohort, antibody response to primary vaccination was delayed.[17] Within this specific study; no antibodies were detected after the first vaccination, and only 30% of the elderly participants showed an increase in their antibody levels after subsequent inoculation. By contrast, all but one of the younger participants in this, albeit small study, had mounted protective antibody levels 4 weeks after their second dose. This age- associated delay in primary immune response has also been described in yellow fever vaccination.[18] Thought to be implicated in this decline in immune function in the elderly is T-cell dysfunction. Supporting this, in vitro studies have demonstrated normal production of antibodies to HBsAg when T cells from young individuals is added to the serum of elderly adults.[19] Therefore, it is always worth ensuring appropriate antibody titres are achieved; with judicious use of booster courses as needed in this cohort of patients, the corollary of this is that patients with existing HBV vaccination my need boost vaccination.

Treatments

Treatments of chronic HBV have improved significantly. Nucleoside analogues (NAs), now form the backbone of the armamentarium against chronic HBV, with Interferon alpha still making a contribution. The aim of treatment is to supress the level of viral replication as this is strongly associated with cirrhosis and HCC. This can be achieve immunologically or pharmacologically.

Interferon therapy stimulates an immunological response that can lead to virological cure in up to 30% of cases, but with a formidable side-effect profile, success rates are lower in older patients. Pharmacological therapy is NAs that suppress viral replication by direct interference in the replication mechanism, these are highly effective, achieving complete suppression in most patients. However they have to be taken long term, as the suppression last only as long as the half-life of the drug. Overall, NAs have a reasonable side effect profile and require infrequent monitoring. They are better tolerated and are the preferred treatment for those with significant fibrosis, cirrhosis or undergoing transplant. The need for treatment is determined by overall evidence of viral activity, seroconversion of Hepatitis e-Ag, evidence of necroinflammation and presence or absence of established liver disease, and should be co-ordinated by a specialist in infectious hepatitis.[20]

With regards to specific treatment strategies for elderly patients with chronic HBV; those with deteriorating renal function or osteoporosis, treatment with Tenofovir Alafenamide and Entacavir has been shown to have less systemic effects and is preferred. It is therefore suggested that patients at risk of deteriorating renal function especially those over 60 if already on Tenofovir Disoproxil are considered for a switch. [4]

Hepatitis C (HCV)

The hepatitis C virus (HCV) is a blood borne, hepatotropic RNA virus which can cause both acute and chronic infection. Acute HCV infection is rarely symptomatic; with one large meta-analysis study suggesting spontaneous clearance rates of the virus of 26%.[21] Those who have been unable to spontaneously clear the virus go on to develop chronic hepatitis C which, similar to the acute phase, is usually asymptomatic [22] Chronic hepatitis C is defined as the persistence of HCV RNA in an individual's blood for at least 6 months after the onset of acute infection. This can therefore cause significant intrahepatic damage before it is clinically recognized. Chronic HCV infection predisposes the individual to liver fibrosis, cirrhosis and hepatocellular carcinoma (HCC), conditions associated with significant morbidity and mortality[22]. As well as this, 1-2% of chronically infected individuals will develop extrahepatic manifestations of the disease commonly cryoglobulinemia, membranoproliferative glomerulonephritis and vitiligo. Data also suggests an association between chronic HCV infection and the development of both Hodgkins and non-Hodgkins lymphoma[23]. HCV infection is diagnosis on the combination of a positive HCV antibody in a patient serum, which indicates current or previous infection (the antibody is not protective against further infection) and the detection of HCV RNA in a patients serum which indicates active infection requiring treatment. The combination of positive antibody and negative HCV RNA indicates spontaneous or treatment induced cure.

The rate of chronic HCV infection has been shown to be reliant on many factors including gender, ethnicity, age at the time of infection and the presence of jaundice during the acute infection[23]. Of those with chronic HCV infection; it is estimated that between 5 and 20% of individuals will go on to develop liver cirrhosis. In these cirrhotic patients, there is a 25% risk of progressing to end-stage liver disease and 3-5% annual risk of developing HCC[25,26]. It is therefore unsurprising; that the Centres for Disease Control and Prevention (CDC) have reported that worldwide, chronic HCV infection is the leading cause for requiring a liver transplant[27].

The virus is transmitted by percutaneous exposure to infected blood. The leading mode of transmission since the 1970's has been injection drug use however other modalities of transmission include the reuse or inadequate sterilisation of medical equipment, haemodialysis (typically unscreened blood products before 1992), healthcare work and military service[13]. Although uncommon; HCV can be transmitted through sexual activity, tattoos and vertically from mother to baby. Injection drug use remains the leading mode of transmission in the developed world whilst unsafe healthcare practice accounts for the majority of new infections in the East Mediterranean

countries[1]. With regards to HCV testing, the WHO recommend screening for individuals at an increased risk of infection.

Hepatitis C appears to be endemic in most areas of the world. With an estimated global prevalence of over 71 million people (1% of the global population) and an annual incidence of between 3 and 4 million cases[1], chronic HCV infection is one of the leading causes of chronic liver disease worldwide. There are considerable variations in the age and geographic prevalence of HCV infection and genotype; rates of disease differ across and within each country. According to statistics published by the WHO in 2017, the highest prevalence of HCV infection was found in the Eastern Mediterranean region (2.3%) followed by the European region (1.5%)[1]. Data has shown that countries in the eastern and southern parts of Europe have a higher HCV prevalence than countries in the northern or western regions. The reported prevalence of HCV infection in the general population ranges from 0.1% in the Netherlands, Ireland and Belgium to 5.9% in Italy. Other counties with reasonably high rates of HCV include Romania (3.2%), Latvia (2.4%) and Greece (2.2%)[29].

With regards to the incidence of HCV in the USA, there has been a disproportionate birth-related cohort of infection. It has been recognised that up to 80% of individuals infected with HCV were born during the 'baby boom' between 1946 and 1964[30]. This generation constitute the largest birth cohort in US history and reflects a marked increase in births following World War II. Data suggests that individuals born during this period are five times more likely to have chronic HCV infection than other adults[31]. The reasons for this are not entirely understood however it is believed that the baby boomers became infected with HCV between the 1960's and 1980's when transmission of this virus was highest. It is thought that in this generation, the introduction of new pathways of HCV transfer coupled with a lack of knowledge on the prevention of spreading blood-borne viruses has created a higher disease prevalence. To this day, the majority of people with chronic HCV infection are unaware of their condition. Even in those with a diagnosis, many do not know how or when they became infected[31].

The US Census Bureau have projected that in 2030, the elderly population will comprise approximately 20% of the total US population[32]. Given the natural history of chronic HCV infection and its high prevalence amongst this cohort, it is no surprise that the incidence of HCC in the USA has tripled over the past decade[33]. The high seroprevalence amongst this age group coupled with the discovery of highly effective anti-viral therapy prompted the CDC to change HCV screening recommendations in the US. In 2012; the CDC recommended a universal 'one-time testing', without ascertaining previous HCV risk, for individuals born between 1945-1965[24]. Despite this new recommendation, the 2015 National Health Interview survey revealed that only 13.8% of this cohort had been tested for HCV. This slow uptake in screening is likely to be due to a lack of awareness amongst both patients and physicians to these new recommendations. Other influences may include the patient's unapparent symptoms and barriers to preventative medicine[34].

Considering it is estimated that less than 15% of patients with chronic HCV infection are aware of their status, it is important to have a low threshold to investigate patients presenting with signs and symptoms of liver failure[35]. In comparison with younger individuals, adults aged over 65 are more likely to present with complications of liver cirrhosis namely hepatic failure and HCC as an initial manifestation of HCV infection[36]. Features of decompensated liver cirrhosis include upper gastrointestinal bleeding secondary to oesophageal varices or portal hypertensive gastropathy, development of abdominal ascites, hepato-renal syndrome and hepatic encephalopathy[23]. The overall morbidity and mortality rates associated with the complications of acute and chronic liver disease are much higher in the elderly population. This is partly due to a higher prevalence of co-morbid conditions but also because physiological changes related to aging make compensation and recovery difficult[13]. The treatment options available for advanced liver cirrhosis and HCC in elderly patients who do survive, are limited. In light of the new antiviral therapies, HCV infection is now recognised as curable. Emphasis should be placed on screening the at risk 'baby boomer' population as initiation of HCV eradication treatment may halt progression to advanced cirrhosis and its associated complications.

Treatments

Pharmacological treatment of HCV infection has been revolutionised over the past decade. The new direct acting antiviral regimens offer a sustained virological response (SVR) of 90-95% in patients with HCV-related liver cirrhosis including those with decompensated disease[26]. The efficacy and safety of treating HCV infection in elderly patients has previously been debated due to issues with compliance, co-morbid conditions and the side effect profiles of the medications. However, the introduction of the newer, safer agents with lesser contraindications, provide highly effective therapeutic options for these patients who have previously been deemed unsuitable for treatment. Observational studies have revealed that in patients aged over 65, the first generation protease inhibitor-based regimens has a similar efficacy to that of younger patients, albeit with more frequent adverse effects[37]. Therefore the decision of whether to commence an elderly patient on HCV treatment should be guided by an assessment of liver-disease dependant and comorbidities dependant life expectancy and drug-drug interactions rather than their biological age. There is no licensed vaccine for HCV presently.

Cirrhosis and Hepatocellular Carcinoma

The liver is formed by parenchymal cells (hepatocytes) and other non-parenchymal cells; liver sinusoidal endothelial cells (LSECs), Kupffer cells (KC) and hepatic stellate cells (HSC). These cells line the walls of hepatic sinusoids. Both parenchymal and non parenchymal cells are involved in the initiation and progression of liver fibrosis and cirrhosis.[42] While the cause of liver disease is often multifactorial liver cirrhosis, in both chronic HBV and HCV infection, alcohol consumption can accelerate disease progression as can the metabolic syndrome, there is the final pathological result and there are common pathological characteristics in all cases of cirrhosis. The cycles of viral assault on the liver and immunological response results in degeneration and necrosis of hepatocytes, replacement of liver parenchyma by fibrotic tissue and regenerative nodules and loss of liver function and ultimately cirrhosis[42], the cumulative effect of this at the time of viral cure or suppression determines the long prognosis and risk of development of the complications of cirrhosis and HCC.

Liver cirrhosis is the major risk factor for the development of Hepatocellular carcinoma.[43] Hepatocellular carcinoma is the fifth most common cancer worldwide and the second most common cause of cancer-related death.[38] Although HCC is more common in cirrhotic patients it can also develop in non-cirrhotic patients, this is well recognised in HBV patients, and there are now case reports of HCC in non-cirrhotic HCV patients. HCC arises in a cirrhotic background in 90% of cases.[44] It is therefore recommended by NICE that patients with cirrhosis should undergo 6 monthy screening which entails and ultrasound scan with or without alpha-fetoprotein checking. For those with cirrhosis and HBV surveillance should include alpha-fetoprotein testing. The aim of surveillance is to achieve a reduction in the overall mortality and should be cost effective.[45] The risk of developing HCC is known to be age dependant and with the prospect of an aging population invariably implying that rates of HCC will invariably increase.

Male-to-female preponderance is greater than 2:1 with liver cancer, and approximately 83% of the estimated 782,000 new HCC cases in 2012 occurred in less developed regions of the world. East and South Asia plus sub-Saharan Africa were the regions of highest incidence, Southern Europe and North America being of intermediate incidence, and Northern Europe and South Central Asia being the regions of lowest incidence.[39]

Treatment for HCC has advanced significantly in the last few decades with there being many treatment options now available. Treatments can include surgical resection or liver transplantation, TransArterial catheter ChemoEmbolisation (TACE), percutaneous radiofrequency ablation, percutaneous ethanol injection, percutaneous microwave coagulation therapy and molecular targeted therapy. Current guidelines for the management of HCC do not stratify for age.[40] Irrespective of these advances however, the overall mortality associated with Non-transplanted HCC is significant.

Conclusion

Although in this day and age, both HBV and HCV infection are generally associated with intravenous drug use, non-sterile healthcare practice and unsafe sexual practice, it is important to remember, particularly in the US, the data has shown that one of the highest risk groups for infection is those aged over 65. It is therefore imperative that healthcare workers test elderly patients presenting with signs or symptoms of chronic or decompensated liver disease.

With the introduction of the new and effective antivirals, the long-term sequelae of HCV induced liver disease and subsequently high morbidity and mortality rates in the elderly could become a problem of the past. Whilst therapies for HBV lag behind somewhat; there are increasing efforts to identify affected individuals early, prior to the development of chronic liver disease and its associated sequelae in an attempt to improve outcomes. Emphasis should also be toward effective vaccination programmes for HBV given the presently incurable nature of the virus.

It is imperative that we appreciate the burden of undiagnosed HBV and HCV that exists within our cohort of elderly patients; and ensure appropriate screening is undertaken at opportune times.

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