Chronic liver disease in an ageing population

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Abstract

The prevalence of chronic liver disease is increasing in the elderly population. With a mostly asymptomatic or non-specific presentation, these diseases may easily go undiagnosed. Abnormal liver function tests of unknown cause are a common reason for referral to secondary care. Investigating the older person with abnormal liver function is important; even with mild abnormalities, the same vigilance should be applied to an older person as in a young person. Liver biopsy is safe but often overlooked in this age group and may provide useful information to diagnose, direct therapy and prognosticate. Treatment options are similar for all age groups, with a few subtle differences, although further evidence is frequently required for the older population. Morbidity and age-adjusted mortality are often more severe in older people, and therefore early diagnosis and intervention is important. Presented here are the most common chronic liver diseases that geriatricians are likely to encounter in clinical practice. Their epidemiology, clinical features, investigation, treatment and mortality are described with a particular focus on the elderly population.

Keywords: chronic, liver disease, elderly

Introduction

No liver disease is specific to old age; however, as the population ages geriatricians are frequently managing older patients with chronic liver diseases. Presented here are some of the more common chronic diseases that affect the liver and how their clinical features, investigations, treatment and mortality are affected by advancing age. The epidemiological characteristics of each disease are presented in Table 1.

Please see Appendix 1 in the supplementary data available at Age and Ageing online for search strategy and selection criteria.

Basic science

The liver has a remarkable ability to regenerate and maintain function during the ageing process. There are, however, changes on a cellular and physiological level which reduce the overall function of the liver.

Despite compensatory cell hypertrophy, in response to the decreased number of hepatocytes seen with ageing, liver size reduces by 25% between the age of 20 and 70, with a 33% reduction of hepatic blood flow in over 65 year olds [1].

The aged liver takes on a dark, macroscopic appearance, resulting from the accumulation of intracellular debris that may arise from defective protein synthesis and degradation [1].

Activity in hepatic cytochrome P450 oxidation is reduced with age, as is the protective enzyme superoxide dismutase, both of which may contribute to increased sensitivity of hepatocytes to xenobiotics [2]. A reduction in protective enzymes, a decline in response to growth factors and a theoretical risk of increased pathogen load from the gut all put the aged liver at increased risk of disease [3].

Investigations

Laboratory markers of liver disease [liver function tests (LFTs): bilirubin, transaminases, hepatic alkaline phosphatase (AP)] do not change with advancing age. Hepatic alcohol dehydrogenase also has no age-related reduction in function; it is worth noting, however, that gastric alcohol dehydrogenase is found in lower levels in the elderly [4, 5].

Liver biopsy is safe in the elderly, with 6% of liver biopsies in England and Wales being performed in over 80 year olds. The mortality in this age group having liver biopsy is
mon in the elderly is controversial; some studies noted an increase in mortality seen with advancing age [6]. A summary of investigations and how they guide management is presented in Figure 1.

### General management principles in advanced liver disease

Ascites is a feature of advanced liver disease related to cirrhosis. In addition to sodium and water restriction, which patients often find unpalatable and tolerate poorly, the 2003 Consensus recommends the use of anti-mineralocorticoids [7]. There are no age-related absolute contraindications to diuretics; however, some adverse effects may be more severe with advancing age. Elderly patients with cirrhosis are more likely to suffer from disturbed fluid balance homeostasis, leading to orthostatic hypotension as a result of low intravascular volume, exacerbated by diuretic use. Furthermore, older patients prescribed diuretics are at increased risk of incontinence.

Paracentesis is recommended for ascites unresponsive to medical therapy. There are no age-related contraindications; however, most trials have not included patients beyond the age of 65 years [8, 9].

Transjugular intrahepatic portosystemic shunt (TIPS) is effective for refractory ascites and for uncontrolled variceal bleeding. It should be considered if paracentesis is required more than three times per month [7]. TIPS is more effective at improving sodium excretion in those who are aged <60 years. Whether or not complications are more common in the elderly is controversial; some studies noted an increased incidence of post-TIPS hepatic encephalopathy in subjects over 60 years, but this has not been confirmed in further studies [10, 11, 12].

The use of lactulose is recommended in minimal hepatic encephalopathy as it improves cognition and quality of life. It has not, however, been shown to prevent the progression of hepatic encephalopathy or improve survival [13]. Care should be taken when treating the elderly with laxatives; malabsorption, dehydration, electrolyte imbalance and faecal incontinence are all more likely to occur [14].

### Liver transplantation

The mean age of liver transplantation in 1985 was 29 years, increasing to 41 years by 1995 [15]. The proportion of over 60 year olds who received liver transplants during 1990–91 was 10%, doubling to 21% during 1997–99 [16].

In a study following 478 liver transplant recipients over 13 years, comparing over and under 60 year olds, there were no significant differences in length of hospital stay, repeat admissions, infections, rejection or repeat transplantation [17].

Five and 10 year survival in over 60-year-old recipients was significantly reduced (52%, 35%) when compared to an under 60-year-old group (75%, 35%) in one study. Conversely, other studies demonstrate that there are no significant survival differences between older and younger patients if they are classified as low-risk pre-treatment. Factors which contribute to significantly worse mortality in the elderly include being in hospital pre-transplant, low albumin,
Chronic liver disease in an ageing population

**Alcoholic liver disease (ALD)**

Clinical features

The very old are more likely to have signs of severe liver disease on presentation than the young. The commonest presentations in the older patient are non-specific and include general malaise, anorexia and abdominal pain. In those aged over 70, dizziness is one of the most common presentations. Jaundice, oedema and ascites are more common in the older than in the young, suggesting a more severe stage of ALD at presentation [19, 20].

Investigations

Older patients have histologically more advanced liver disease compared to younger patients; however, this may not be apparent on routine laboratory tests which show no significant differences between older and younger patients. The most common abnormalities found in those over 60 are elevated serum aspartate aminotransferase (AST) and bilirubin, increased mean corpuscular volume and raised AP [19, 20]. Importantly, one study which biopsied 96% of its subjects identified that 100% (n = 7) of men aged over 70 years presenting with ALD had cirrhosis on biopsy, compared to 55% (n = 112) in men aged 20–59 years [20].

Treatment

There are no specific differences in the treatment of the older patients. However, blood alcohol levels may be higher in the elderly per unit consumed because of the lower body water content in which it is distributed. Acute withdrawal can easily be missed in the elderly patient and may require treatment with sedatives. Benzodiazepines are commonly used to treat or prevent withdrawal symptoms but their distribution can be affected in the elderly who have a higher proportion of fat; the resulting prolonged half-life could result in prolonged sedation. Adverse effects associated with benzodiazepines are more common in the elderly; drowsiness, fatigue, confusion, ataxia, falls and incontinence are significantly more common with increasing age [21].

Mortality

One-year mortality following diagnosis of cirrhotic ALD is 34% in the over 60s, significantly greater than those below...
60 (5%). Of those over 60 who die, 87% have liver-related
deaths, the commonest causes being hepatorenal failure, gas-
trointestinal bleeding and cardiomyopathy. The commonest
cause of death in men under 60 is myocardial infarction [19,
20].

Non-alcoholic fatty liver disease (NAFLD)

Clinical features
The natural history and pathogenesis of NAFLD is increas-
ingly being understood, with insulin resistance being a central
factor. Known risk factors are obesity, hypertriglyceridaemia,
hypertension and type 2 diabetes. Raised serum fasting insulin
and c-peptide indicate insulin resistance and may contribute
to the diagnosis in non-diabetics.

Treatment
In order to prevent progression from steatosis to fibrosis, risk
factors should be addressed as early as possible. A reduction
in total daily energy intake with a 10% weight reduction does
improve metabolic and histological abnormalities; this
benefit is augmented with exercise (burning 400 calories, 3–4
times per week) [22]. However, it is not yet clear whether
the elderly will benefit to the same extent as the young from
this intervention.

Mortality
Age is an independent risk factor for severe fibrosis in
NAFLD (odds ratio 5.6 in those aged >45 years) [23, 24];
whether this is due to impaired regeneration and recovery
of the liver to inflammatory insults, or whether it is
because the older have had NAFLD for longer, is not known.
Increased risk of death is also significantly linked to advanc-
ing age ($P < 0.0001$) [25]. In a population-based study of 435
patients with NAFLD (mean age 49 ± 15 years), survival
over 10-year follow-up was significantly less than the general
population (standardised mortality ratio 1.34, $P = 0.03$) [25].

Autoimmune hepatitis (AIH)

Clinical features
There are no differences in clinical presentation between
younger and older patients with AIH, with both more likely
to have an insidious rather than an acute onset. Retrospective
review of 54 patients over 65 years found that 20% were
asymptomatic on presentation, ∼50% had non-specific
symptoms (lethargy, pruritus, abdominal pain) and ∼25%
were jaundiced or showed signs of hepatic failure [26].
A larger systematic, retrospective analysis of AIH patients
found that patients aged over 65 years were significantly more
likely to have ascites on presentation than younger patients
(30% vs. 9%, $P < 0.001$), suggesting a more severe stage of
the disease [27, 28].

Autoimmune disease associations are similar in the old
compared to the young, but younger subjects have a more diver-
se ‘catalogue’ of disease associations (Table 2) [28, 29, 30].

Table 2. Disease associations seen in autoimmune hepatitis

<table>
<thead>
<tr>
<th>Conditions seen in younger AIH</th>
<th>Conditions seen in the over 65 year old</th>
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<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>Rheumatoid arthritis</td>
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<td>Autoimmune thyroid disease</td>
<td>Autoimmune thyroid disease</td>
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<td>Ulcerative colitis</td>
<td>Ulcerative colitis</td>
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<td>Hyperparathyroidism</td>
<td>Hyperparathyroidism</td>
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<td>Vasculitis</td>
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<td>Vitiligo</td>
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<td>Polymyalgia rheumatica</td>
<td>Pernicious anaemia</td>
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<td>Idiopathic thrombocytopenia purpura</td>
<td>Temporal arteritis</td>
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<td>Type 1 diabetes mellitus</td>
<td>&gt;2 autoimmune diseases</td>
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<td>Systemic lupus erythematosus</td>
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<td>Erythema nodosum</td>
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<td>Sjögren’s syndrome</td>
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<td>Myasthenia gravis</td>
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<td>Multiple sclerosis</td>
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Investigations
No significant differences exist with advancing age in labo-
atory tests, including AP, serum transaminases, gammaglutamyl
transpeptidase, bilirubin, serum immuno-
globulins (raised IgG), anti-nuclear antibodies, smooth muscle
antibodies and type 1 liver–kidney microsomal antibodies
[28, 29, 31]. It is unknown whether older patients with AIH
are less likely to have a liver biopsy as clinical trials and reviews
focus on patients with confirmed histological diagnosis.

Treatment
Treatment strategies are identical for all adult ages. Pred-
nisolone alone or prednisolone with azathioprine prescribed
as initial therapy has been used at equal rates with equal out-
comes in the elderly and the young [29, 31]. The same is
true for maintenance therapy with prednisolone alone, pred-
nisolone with azathioprine or azathioprine alone [29].

Responses to immunosuppression are generally excellent
in AIH irrespective of the presence of cirrhosis [32, 33]. The
significance of relapses between the two groups is not clear,
with contradicting results [28, 29]. No difference has been
seen in rates of liver transplant between older and younger
patients nor in their mortality [28].

Measurements of baseline bone density are of use in all age
groups, and treatment/prevention directed as appropriate.

Mortality
Most patients with AIH die of non-liver-related disease. One
study has noted that in over 65 year olds, no deaths were
related to liver disease, but in the under 65-year-old group, 7%
died as a result of complications of chronic liver disease [26].

Primary biliary cirrhosis (PBC)

Clinical features
The majority of patients are asymptomatic on presentation;
however, younger patients are significantly more likely to
have non-specific symptoms compared to those over 65 years (Sjogren’s syndrome, pruritus, weight loss, xanthelasma, fatigue, abdominal discomfort) [34].

Investigations

No differences in laboratory data occur between older and younger PBC patients. AP is likely to be the most deranged LFT, followed by alanine aminotransferase (ALT), bilirubin and albumin. Anti-mitochondrial antibody is present in 95% of patients [35], and a raised IgM may also be present. Older patients are significantly less likely to have a liver biopsy for histological confirmation/diagnosis but have significantly more advanced histological staging when they do undergo biopsy [34].

Treatment

Ursodeoxycholic acid may have some benefit in PBC patients; however, further studies are required to explore the long-term outcome. Transplantation is the only curative option, but rarely undertaken in the very old.

Mortality

Liver-related deaths are significantly more frequent in the over 65 year olds when compared to under 65 year olds, but overall non-liver-related deaths are more common [34]. Patients aged over 65 years with fatigue have significantly greater mortality than those over 65 without fatigue; the fatigued over 65 year olds also have higher mortality compared to those aged less than 65 with fatigue (9.3% vs. 1.4% per year of follow-up) [36].

Primary sclerosing cholangitis (PSC)

Increasing age is an independent risk factor for a poor outcome [37]. However, very little data exist on PSC in the elderly, perhaps because the median age of diagnosis is 40 years with a median survival of 11.9 years, and because it is itself a rare disease. However, with a second peak in the incidence of inflammatory bowel disease in the 7th–8th decade [38], and survival of IBD patients similar to that of the general population, we may expect to see more PSC in the elderly [39].

Viral hepatitis—hepatitis B

Clinical features

Clinical features of HBV infection in the elderly were noted during one outbreak in a nursing facility. Symptoms (anorexia, vomiting and jaundice), as expected, were present in only a few cases and are typical of HBV in any age [40].

Investigations

In the aforementioned outbreak, ALT was transiently raised in those with transient HBV, was fluctuant initially in those with persistent infection and returned to normal in all patients. Nine of the 31 patients who were initially positive for HBsAg were negative at 6 months and therefore infected only transiently. In 13 of the 22 cases followed up at 6 months, HBsAg persisted with a resultant carrier rate of 59%. Although these numbers are very small, no association was seen between age and carrier rate [40]. Residents of nursing homes may be at increased risk of contracting HBV, and with relatively high transmission rates, this group of people should be considered for vaccination [41].

Clinically HBsAg, anti-HBsAg, HBeAg, anti-HBeAg and HBV-DNA are the most useful investigations guiding treatment and prognosis, by providing details of active viral replication and staging. However, HBV DNA and HBeAg are generally low or absent in the elderly, resulting in fewer elderly patients being treated [42].

Treatment

Treatments include interferon or pegylated interferon, and the antivirals lamivudine, adefovir, entecavir and telbivudine, or a combination of these. In general, interferon (given as three subcutaneous injections per week) and pegylated interferon (one subcutaneous injection per week) are given for a fixed period, usually 6–12 months, and offer sustained 'off-therapy' responses. Antiviral agents have fewer side-effects and better tolerability and can be given for longer periods. Lamivudine is the most widely used agent, but the emergence of resistant strains is higher than that with the other antivirals. Adefovir has better long-term outcomes and is also indicated in lamivudine-resistant HBV. Resistance to entecavir is rare and it is more potent than the other antivirals at reducing HBV DNA at end of therapy. The use of telbivudine is unclear at present because of its unfavourable resistance profile [43].

The efficacy of some treatments has not been assessed specifically in the elderly; however, some trials do include elderly subjects, including a meta-analysis of randomised controlled trials assessing the efficacy of combination interferon with lamivudine versus interferon alone—equally effective in younger and older groups [44]. Assessment of lamivudine in the elderly has shown that it is as effective in both over and under 60 year olds at reducing ALT and HBV DNA, with resistance no more prevalent in the older group [45].

Mortality

Older patients have a much greater chance of developing hepatocellular carcinoma (HCC)—927/100,000 in 60–69 year olds, compared to 197/100,000 in 30–39 year olds [46].

Viral hepatitis—hepatitis C

Clinical features and investigations

In a study of 25 patients aged over 65, the presenting features in order of occurrence were abnormal LFTs, bleeding oesophageal varices, malaise, abdominal pain, oedema and
pruritus. Each patient had abnormal LFTs. Twenty underwent liver biopsy at presentation: 60% had cirrhosis, 30% had cirrhosis and HCC and 10% had chronic hepatitis [47].

**Treatment**

Recombinant interferon has a response rate (normalised ALT, improved liver histology) of 62% in the over 65s, compared to 57% in under 65 year olds. Side-effects, however, are more common in the older patients (23%) compared to the young (19%) [48]. Combination interferon and ribavirin is as successful in the over 60s as the under 60s, with a sustained virological response of 38% in the under 60s and 32% in the over 60s (P = 0.36). Combination is also more effective than interferon alone and is not associated with more side-effects than the under 60s [49].

**Mortality**

In a 10-year follow-up of an elderly population, 34% died and of those only 17% were related to liver disease (liver failure, HCC) [50].

**Hepatocellular carcinoma**

**Clinical features**

Signs and symptoms at presentation are similar for older and younger patients. Typical presentation is of an acute deterioration in an existing chronic liver disease, necessitating the need for screening [LFTs, alpha-fetoprotein (AFP), liver ultrasound]. In patients over 65 years, the commonest presenting symptoms are weakness, abdominal pain, anorexia, weight loss and nausea. Presenting clinical signs in one retrospective study of the over 65s were hepatomegaly (in 85%), jaundice and ascites (in 35% of patients) [51].

**Investigations**

AP, AST and albumin are abnormal in over 80% of over 65 year olds, and bilirubin and ALT abnormal in over 60%. AFP is >10 ng/ml in 90% of over 65 year olds, and >200 in 63%. HBsAg can be found in 13% of over 70 year olds with HCC, which is significantly less than those aged under 70 years [52]. Sixty-nine per cent of over 65 year olds have cirrhosis, a similar figure to a younger group [51]. The stage of HCC (Okuda: bilirubin, albumin, ascites, tumour size) was not different between age groups [51].

**Treatment**

No significant differences in complications, survival months, intensive care admissions and mortality is seen between age groups receiving liver resection [53]. Potentially curative therapies exist for patients with HCC, including resection, transplantation and local ablation. In addition to these treatment methods, trans-arterial chemo embolisation (TACE) can palliate and prolong survival. One large, population-based study of older patients with HCC (compared to younger patients in brackets) were treated as follows: transplant 0.9% (1.5%), tumour resection 8.4% (5.9%), ablation 4.1% (4.4%), TACE 4.2% (6.3%) [54].

**Mortality**

In the above study, 3-year survival was best in transplanted patients (40.7%), followed by resection (30.9%), ablation (9.8%) and TACE (6.1%) [54].

**Other chronic liver diseases**

**Haemochromatosis**

Hereditary haemochromatosis (HH) is classically diagnosed in middle age, with an average survival of 21 years (with treatment) [55]. However, recent case reports and genetic studies confirm that it can present in old age, and males who are homozygous for the C282Y gene (the commonest genetic abnormality identified) are surviving into old age without clinical or biochemical abnormalities. This is of importance to the geriatrician who should recognise that patients can present much later than previously thought [56]. As might be expected, females who undergo earlier menopause have a greater concentration of hepatic iron than females who undergo the menopause after the age of 50, as a result of therapeutic menstruation [57].

HH must also be considered in older patients presenting with neurological complications, as iron overload may be misdiagnosed with movement disorders such as Parkinson’s disease or cerebellar syndromes [58].

Treatment of HH by venesection may induce orthostatic hypotension as a result of volume loss which is likely to be more severe in the elderly; concomitant infusion of intravenous fluids may reduce this risk.

**α-1 Antitrypsin deficiency (A1ATD)**

A1ATD is recognised as a possible cause of cirrhosis in older age. In one case review describing three patients aged over 65, only one had obstructive Airways disease, but each had abdominal swelling or hepatomegaly, with a raised ALP. A1AT is an inflammatory marker making interpretation of levels less useful for diagnosis which is confirmed on liver biopsy [59]. A1ATD can also present with respiratory disease in the elderly and is more likely to present later in age in life-long non-smokers [60].

**Wilson’s disease (WD)**

The commonest presentation in adulthood is neuropsychiatric compared to hepatic dysfunction in childhood [61]. Case reports of WD presenting in the elderly, however, are less typical. Reports vary from neurological dysfunction in the absence of liver disease and Kaser–Fleischer rings [62], liver disease with no neurological dysfunction [63], to non-specific presentation (weight loss) [64]. In one review comparing recent diagnoses of WD (1994–2003) to past diagnoses (1976–93), the age at presentation was greater in the most recent period (35.1 vs. 16.7 years) [65].
Conclusions

It is important that geriatricians recognise that the prevalence of liver disease is increasing in older age groups, including rarer liver diseases. Awareness of vague symptoms and signs which could indicate liver abnormalities and interpretation of investigations such as LFTs is vital. The same vigilance should be applied to older patients as it is to younger patients when interpreting abnormal LFTs, no matter how mild the abnormality. In diagnostic uncertainty, liver biopsy is safe, but often overlooked, and may lead to appropriate treatment. Special attention should be paid to those who are prescribed diuretics, lactulose and benzodiazepines as adverse effects are more common in the elderly. The science behind the ageing liver would suggest that it is less able to cope with insults and may contribute to more severe disease or decompensate existing disease.

Key points

- Prevalence of chronic liver disease is increasing in the elderly.
- Onset is more insidious in older patients.
- Abnormal LFTs should be investigated thoroughly (unless inappropriate); liver biopsy is safe in the elderly.
- There are some subtle differences in treatment.
- Age-adjusted mortality is often greater in the elderly.

Conflicts of interest

There are no conflicts of interest.

Supplementary data

Supplementary data are available at Age and Ageing online.

References

(The very long list of references supporting this review has meant that only the most important are listed here and are represented by bold type throughout the text. The full list of references is available on the journal website as Appendix 2)


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