Managing Abnormal Liver Blood Tests in Older People

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The prevalence of chronic liver disease is increasing in older people. The presentation of these diseases is often asymptomatic or nonspecific, so they easily go undiagnosed. Investigating the older person who has abnormal liver function is important in primary care, and the same vigilance should be applied to an older person as to a young person, even with mild abnormalities. Referral for specialist opinion in appropriate older people provides important diagnostic and prognostic information. Treatment options are similar for all age groups. Morbidity and age-adjusted mortality are often more severe in older people; therefore, early diagnosis and intervention are important.

Key words: chronic liver disease, aging, liver function tests

Introduction

As management of liver disease in older adults improves and the population ages, we will see increasing numbers of older people with longstanding liver disease and older people presenting with liver disease for the first time. The presentation and clinical course can be subtle and nonspecific and are easily overlooked; a high index of suspicion is required. No differences exist in the reference ranges for liver function tests (LFTs) between age groups. Diligence is required in their interpretation irrespective of age. The implications of mildly abnormal LFTs in older patients with no signs suggestive of liver disease, and what constitutes appropriate follow-up are unclear. It is, however, important to appreciate that in all age groups, early diagnosis of chronic liver disease can improve prognosis.

Common chronic liver diseases are featured in Figure 1.

Epidemiology

Twenty-eight percent of people with alcoholic liver disease are over the age of 60 years,\(^1\) as are 26% of individuals with nonalcoholic fatty liver disease.\(^2\) Chronic, autoimmune liver diseases such as primary biliary cirrhosis and autoimmune hepatitis also commonly present in older age.\(^3,4\) The exact prevalence of drug-induced liver disease is unknown, given its challenging diagnosis; however, it is almost certainly more common among older adults.\(^5\) Consequently, the demand for liver transplantation in older patients is increasing, with the proportion of liver transplant recipients over 60-year-olds being 10% during 1990–1991 and doubling to 21% between 1997–1999.\(^6\)

Viral hepatitis is less common in older age, but there are several important considerations relevant to older people. Fewer older people are vaccinated against hepatitis B virus,\(^7\) and outbreaks have been reported in long-term care residents, without typical blood-borne routes of transmission.\(^8\) Hepatitis C virus is also uncommon in older people, but there remain a significant few who received blood transfusion prior to screening for this virus.

Presentation and Clinical Features

Presentation in those with abnormal LFTs is, generally, nonspecific. Frequent symptoms among older people are fatigue, malaise, anorexia, nausea, and vomiting. Unless the primary care physician has a high degree of suspicion during the nonspecific symptom phase, older people often present with liver disease later, have more severe disease, or have had the disease for longer.\(^9,10\)

Inquiries

Liver function tests generally include alkaline phosphatase and hepatic transaminases (which are both enzymes) and also albumin and bilirubin. As there are no age-associated changes in alkaline phosphatase, hepatic transaminases, or bilirubin,\(^11\) all abnormalities in LFTs should be treated with diligence, regardless of the patient’s age. Local reference ranges will vary; here we refer to levels that fall above the upper limit of the local reference range. Abnormalities identified on LFTs generally fall into one of two groups; obstructive or hepatic. Alkaline phosphatase (which is found in the cells lining the bile ducts) and bilirubin tend to be disproportionately higher than the transaminases in obstructive liver disease (e.g. cholelithiasis). In hepatic disease the transaminases tend to be disproportionately higher as they are released from injured/diseased hepatocytes. However, these patterns are not always reliable and hepatic or biliary disease can cause any picture of abnormal liver function.

If clinical features do not direct further investigations (Table 1), a full liver screen should be considered. Ultrasonographic examination of the liver is useful to assess disease severity and identify focal liver lesions. If diagnostic doubt remains, referral for a specialist opinion and consideration of a liver biopsy are appropriate. In England and Wales, 6% of liver biopsies are performed on people over 80 years of age. Mortality in this age group is approx-
approximately 0.2%, with no increase in mortality seen with advancing age.\textsuperscript{12}

**Imaging**

If diagnostic doubt remains despite simple blood tests and an ultrasound examination, a referral to a specialist who may consider further imaging is required. The ultrasound examination is useful to assess the texture of the liver, whether it is smooth, nodular, and coarse or has focal lesions. It is particularly useful at imaging the extra-hepatic bile duct and identifying obstruction and gallstones. It can identify steatosis if approximately 30% of the liver is fatty. In addition it can identify ascites and splenomegaly (extra-hepatic signs of liver disease) and assess blood flow. Computed tomography of the liver may be used to complement ultrasound assessment and may identify smaller lesions of the liver or pancreas which may be missed on ultrasound. Endoscopic retrograde cholangiopancreatography (ERCP) may be used to visualise obstruction of the lower extrahepatic bile duct, with the advantage of being able to perform limited procedures during the procedure (e.g., removing obstructive gall stones). Magnetic resonance cholangiopancreatography is less invasive than ERCP, and is generally much quicker to perform.

Magnetic resonance imaging is useful in the assessment of steatosis and hepatic iron overload, but is not particularly sensitive or specific for diffuse liver disease. When used in conjunction with contrast it is particularly useful at identifying focal lesions and is more sensitive and specific than computed tomography at identifying and assessing malignancy.\textsuperscript{13}

**Considerations**

Mean cell volume may not be increased in chronic liver disease, particularly as the older person may show microcytosis due to chronic disease. Isolated increases in alkaline phosphatase may indicate bone or prostate pathology. Ferritin may be raised in inflammation. Often, the severity of the abnormality seen does not correlate with symptoms.

**Interpreting Abnormal Investigations**

When a patient presents in the clinic who has abnormal LFTs, there are a series of questions to consider: Is the abnormality acute? Might the abnormality be transient? Could the abnormality be due to systemic disease or medication? Are repeat LFTs persistently abnormal? This process is outlined in Figure 2.

**Is the Abnormality Acute?**

If there is a sudden development of signs or symptoms of acute liver failure or a suggestion of an obstructive lesion, urgent referral for a specialist opinion is necessary. Possible causes are drugs, infection, and obstruction.

**Might the Abnormality Be Transient?**

Possible causes of a transient abnormality are acute alcohol excess, a minor viral illness, or a drug reaction. A thorough history and examination help inform this etiology (Figure 2). In these circumstances, repeating LFTs after several weeks of alcohol abstention or drug withdrawal is the first step. The abnormality could of course be the first presentation of chronic disease, and repeat LFTs help determine this.

**Is the Abnormality Due to Systemic Disease or Medication?**

Consider whether the abnormality might

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pointers</th>
<th>Further Investigations</th>
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<tbody>
<tr>
<td>Alcoholic liver disease</td>
<td>53% of men and 38% of women aged &gt;60 years drink alcohol\textsuperscript{28}</td>
<td>Mean cell volume ↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gamma-glutamyl transferase disproportionately ↑</td>
</tr>
<tr>
<td>Nonalcoholic fatty liver disease</td>
<td>Other features of the metabolic syndrome</td>
<td>Body mass index ↑, serum lipids ↑, blood pressure ↑, blood glucose ↑</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>Family history, personal history of other autoimmune diseases, female</td>
<td>Immunoglobulin G ↑, autoantibodies (anti-nuclear ↑, anti-smooth muscle ↑, anti-liver-kidney-microsomal ↑)</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>Female, family history</td>
<td>Immunoglobulin M ↑, autoantibodies (antimitochondrial ↑)</td>
</tr>
<tr>
<td>Other</td>
<td>Sexual history, IV drugs, blood transfusions, respiratory disease, neurological symptoms</td>
<td>Hepatitis B and C antigens, antibodies and DNA</td>
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<td></td>
<td></td>
<td>Alpha fetoprotein</td>
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<td></td>
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<td>Ferritin and HFE gene analysis</td>
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<td></td>
<td></td>
<td>Alpha1-antitrypsin</td>
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<td></td>
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<td>Ceruloplasmin and urinary copper</td>
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\(\uparrow\) = raised; DNA = deoxyribonucleic acid; IV = intravenous.
Managing Abnormal Liver Blood Tests

Figure 1: Common Chronic Liver Diseases

**Healthy liver**

**Nonalcoholic fatty liver disease**
- Liver enlarges with fat deposits
- Scar tissue forms
- Can be severe and lead to cirrhosis

**Alcoholic liver disease**
- Fatty change, or steatosis
- Acute hepatitis or inflammatory reaction to the cells affected by fatty change
- May progress to cirrhosis

**Primary Biliary Cirrhosis**
- Inflammation and scarring destroy the small ducts within the liver, slowing or blocking normal flow of bile
- Inflammation spreads to nearby liver cells which are destroyed and then replaced by scar tissue (fibrosis)

**Viral Hepatitis B**
- Acute hepatitis causes inflammatory reaction to cell injury and necrosis
- Chronic hepatitis has sustained inflammation
- Includes cell necrosis, inflammation, fibrosis, and cirrhosis

**Autoimmune Hepatitis**
- Portal and periportal chronic inflammation
- Bile duct lesions may be present
- Connective tissue replaces the lost parenchyma
- Portal tract is expanded and assumes a "maple leaf" configuration
- Cirrhosis may follow
be attributable to systemic disease. For example, right heart failure resulting in liver congestion can lead to LFT abnormalities that reverse on treatment of the heart failure. Many medications can also affect LFTs—commonly, antidepressants, antibiotics, and statins. Do not forget to inquire about over-the-counter and herbal remedies. A clear history and examination inform clinical management. Stopping the use of the potentially problematic medication and then following up with appropriate repeat testing aid the diagnosis.

Are Repeat Liver Function Tests Persistently Abnormal?

Where abnormalities persist, the pattern of change can suggest a diagnosis. For example, an improving picture may indicate a transient viral infection; a static picture may indicate alcoholic liver disease or nonalcoholic fatty liver disease; and a worsening picture may indicate active inflammation from any cause. Hepatocellular carcinoma can complicate any chronic liver disease, and this should be borne in mind when faced with a deteriorating picture. However, even large increases can be nonspecific and do not always suggest worsening disease. When seeing patients in whom you suspect underlying liver disease, it is important to appreciate that LFTs do not exclude major chronic liver disease: interpret your investigations alongside your clinical judgment.

In those with persistently elevated LFTs, a cause should be sought. Investigate further with the suggestions in Table 1, and refer to a specialist for further assessment.

Referrals

Reasons for referral for a specialist opinion are highlighted in Table 2. Recent studies suggest that referral to other professionals such as physiotherapists and occupational therapists may be more appropriate than previously recognized.14,15

Common Chronic Liver Diseases

Alcoholic Liver Disease

Alcoholic liver disease is more severe on presentation in the older patient, and blood alcohol levels may be higher because of the lower body water content. Acute withdrawal may be easily missed, particularly in a population that may be judged to be less likely to consume alcohol.

Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease is more common and more severe among older adults.16 Patients typically display features of the metabolic syndrome. The diagnosis can be made clinically in the presence of risk factors (diabetes or insulin resistance, obesity, dyslipidemia, and hypertension) and ultrasonographic evidence with the absence of other causes, or on liver biopsy.

Autoimmune Hepatitis

Autoimmune hepatitis in older people is associated with fewer autoimmune diseases than in younger people. The commonest disease associations in older age are rheumatoid arthritis, autoimmune thyroid disease, and ulcerative colitis.17

Primary Biliary Cirrhosis

Primary biliary cirrhosis (PBC) is less likely to be diagnosed on liver biopsy in older people than in the young.18 Fatigue associated with PBC is a poor prognostic marker, being even more so in fatigued older people with PBC.7

Viral Hepatitis B

Viral hepatitis B is less likely to be treated in older people because markers of active viral replication tend to be low or absent in older age.20

Viral Hepatitis C

The most common reported presenting features of viral hepatitis C among people over the age of 65 years are abnormal LFTs of unknown cause, bleeding oesophageal varices, malaise, abdominal pain, edema and pruritis. This range of symptoms highlights both the nonspecific nature of chronic liver disease in older people but also the fact that it can present for the first time with complications of long term established disease.16 Recombinant interferon alone or combination with vibavirin are as successful in over 60 year olds as in younger age groups.21,22 Side-effects of interferon alone are more common in over 65 year olds but no significant differences in side-effects have been noted for combination treatment.

Hepatocellular Carcinoma

The commonest presentation of hepatocellular carcinoma is of deteriorating LFTs in the presence of pre-existing chronic liver disease.

Table 2: Reasons to Consider Referral to a Specialist

<table>
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<tr>
<th>Reason</th>
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<tr>
<td>Diagnostic doubt</td>
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<tr>
<td>Consideration of liver biopsy</td>
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<tr>
<td>Initiation and follow-up of specialist treatment</td>
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<tr>
<td>Initiation of long-term treatment</td>
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<tr>
<td>Resistant to usual treatment</td>
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<tr>
<td>Consideration of TIPS</td>
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</table>

TIPS = transjugular intrahepatic portosystemic shunt.
disease. Necessitating regular monitoring of LFTs, the alpha fetoprotein and liver ultrasound in people with chronic liver disease. Complication rates and length of survival following tumour resection are similar in older and younger age groups, but despite this, fewer older people are offered resection as a treatment. Transplantation offers the highest survival rates in the older adults with hepatocellular carcinoma, followed by resection, ablation and trans-arterial chemo-embolisation.

Drug-Induced Liver Disease
Drug-induced liver disease is a challenging diagnosis. It can only be made on the exclusion of other diseases and a corresponding time frame of drug to disease.

Management: General Principles
Orthostatic hypotension is more common in older people but may also arise as a consequence of liver disease–associated autonomic dysfunction. Fluid restriction, diuretics, laxatives, and anorexia can all exacerbate an already disturbed fluid balance. Polypharmacy often results when patients develop cirrhosis; beta-blockers, diuretics, laxatives, vitamin supplements, and disease-specific medications may all be prescribed. Incontinence may be exacerbated by the use of diuretics and laxatives, but may also be a result of adverse effects of medication such as ursodeoxycholic acid and cholestyramine.

Bone density may be affected when steroids are used. Osteoporosis is also common in PBC.

Management: Liver Transplantation
Following liver transplantation, people over 60 years old have no significant differences in length of hospital stay, repeat admissions, infections, rejection, repeat transplantation, or survival compared with younger people.

Conclusion
Clinicians can expect to see increasing numbers of older people with liver disease. Detecting liver disease, however, relies on a high index of suspicion given that presentation is often nonspecific, especially in older people. All hepatic investigations should be interpreted with diligence as there are no clinical changes resulting from age alone. There are several considerations when treating older people, and transplantation is an option. Early diagnosis and intervention in confirmed cases of liver disease are important to reduce the increased mortality seen in the older adult population.

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References
4. Parker D, Kingham J. Type 1 autoimmune hepatitis is primarily a disease of later life. QJM 1997;90:289–96.


