How are abnormal results for liver function tests dealt with in primary care? Audit of yield and impact

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Abstract

Objective To determine whether abnormal results for liver function tests are investigated in primary care and findings on full investigation.
Design Retrospective audit and prospective clinical investigation.
Setting University hospital and surrounding general practices serving around 330 000 people.
Subjects Adults with abnormal results for liver function based on tests requested by their doctor between 1 January and 30 June 1995.
Interventions All patients with γ-glutamyltransferase, alanine aminotransferase, or alkaline phosphatase concentrations at least twice the upper limit of the reference range were studied. A median of 15 months later (range 12-21) records of hospital attendances and further investigations were examined. Where investigations were incomplete the records from the general practice were examined, and suitable patients were invited to attend the liver clinic.
Main outcome measures Investigations requested by the doctor and final diagnoses reached.
Results 933 patients with abnormal liver function tests were identified; follow up data were obtained in 873 (94%). 531 patients were already under hospital review. Of the remaining 342 patients, 157 were suitable for investigation; the others had died, moved away, were elderly, or had repeat liver function tests with normal results. No further tests were requested for 91 (58%) of these patients. 66 had been partially investigated by their doctor, and in seven patients results suggesting a treatable chronic liver disease had not been followed up. On investigation, 97 (62%) had an identifiable diagnosis requiring hospital intervention or follow up, or both.
Conclusions Abnormal results for liver function are often not adequately investigated, missing an important chance of identifying treatable chronic liver disease.

Introduction

Standard laboratory tests for liver function are often requested by doctors in patients with non-specific symptoms such as tiredness, abdominal pain, dyspepsia, and weight loss. Considerable uncertainty exists as to the appropriate follow up of mildly abnormal results in patients with no signs suggestive of liver disease, and there is a widespread assumption by both patients and doctors that all abnormal liver biochemistry is due to alcohol excess. Few data are currently available as to the yield of investigating mildly abnormal liver biochemistry in such a group. We aimed to follow up all abnormal results for liver function that were greater than twice the upper limit of normal from our clinical chemistry laboratory for a period of six months, requested by doctors serving around 50% of the population of Nottingham, to determine the underlying diagnosis.

Subjects and methods

We identified all adult patients from the Queen's Medical Centre who had an abnormal result for liver function based on a test requested by their doctor between 1 January and 30 June 1995, from the computer database of the clinical chemistry department. The results of liver function tests were defined as abnormal if any one of the concentrations of γ-glutamyltransferase, alanine aminotransferase, or alkaline phosphatase were at least twice the upper limit of the reference range. A median of 15 months later (range 12-21) we examined the hospital's computer databases for biochemical, virological, immunological, and radiological investigations, outpatient hospital attendances, and inpatient stays for these patients. We excluded from further analysis those patients who were under recent hospital follow up by a physician, oncologist, or general surgeon on the assumption that the abnormal results for liver function were part of the patients' current clinical problems.

Patients who did not fall into these categories were further investigated. Firstly, one of the investigators (PS or SR) visited each patient's doctor and examined the patient's notes, at least 12 months after the index abnormal result. Patients who had had no or incomplete investigations were then invited by letter from their doctor to attend for further investigation. An appointment for a liver clinic was requested if appropriate.

Ethics committee approval for this study was not sought. This was because further investigation of the index abnormal result for liver function, including examination of all relevant available medical records, was thought to be clinically indicated. Patients were offered further investigation on a voluntary basis after full consultation.

Results of investigations of patients with abnormal results for liver function

No of patients	Result
Review of doctors' notes for patients not under hospital follow up (n=342)	
38	Repeated liver function tests normal when requested by doctor
39	Died
30	Left practice (no follow up possible)
69	No further investigation appropriate (age, cancer, congestive heart failure)
9	Referred to hospital, awaiting outpatient appointment
157	Partial or no investigation
Positive test results in patients being managed by doctor (n=7)	
3	Antimitochondrial antibody
2	Increased ferritin concentration
1	Bile duct 9 mm on ultrasonography, stones in gall bladder
1	Smooth muscle antibody
Final diagnoses fully investigated (n=157)	
36	Normal result for repeated liver function test requested by liver clinic
18	Normal results for serological tests; declined liver biopsy
6	Normal liver on biopsy
42	Alcoholic liver disease (23 with cirrhosis)
26	Fatty liver or non-alcoholic steatohepatitis (11 fibrotic on biopsy)
5	Primary biliary cirrhosis
4	Primary haemochromatosis
2	Hepatitis B
6	Hepatitis C
2	Autoimmune hepatitis
2	Common bile duct stones
1	Primary sclerosing cholangitis
1	α_1 antitrypsin deficiency
6	Cryptogenic hepatitis

Results

Of 8208 tests for liver function requested by doctors in the six month period, we identified 933 patients with abnormal results that were twice the upper limit of the local reference range. Full follow up data were obtained in 873 (93.6%). Of the 933 patients, 497 (53.3%) had at least one result for liver function that was three times the upper limit of the local reference range, and 142 (15.2%) had at least one result that was four times the upper limit of the local reference range.

Tests had been requested for follow up of known liver disease in 531 patients, and the patients were already under hospital review. We examined the doctors' notes for the remaining 342 patients who were not under follow up at hospital (table). Of the 157 (46%) of these patients who were thought to require further investigation, no further tests had been requested for 91 (58%) and the other 66 had been partially investigated by their doctor: tests included autoantibody screen (28 patients), serology for hepatitis B (29) and C (22), serum ferritin concentration (10), and ultrasonography of the abdomen (18).

For seven patients a result suggesting a treatable chronic liver disease had been returned but not followed up, and no referral had been made to a gastroenterologist (table). All 157 patients were invited for repeat liver function tests, and, if required, further investigation was undertaken by the hospital's liver clinic. Overall, 101 (64%) patients had a liver biopsy, providing a diagnosis in 81 when serological tests gave normal results. Of these 157 patients, 97 (62%) had an identifiable diagnosis requiring hospital intervention or follow up, or both; eight of these had a viral hepatitis that was communicable and five had an inherited chronic liver disease (table). Of the 195 patients who had liver function tests repeated on request of their doctor or hospital, 74 (38%) showed spontaneous resolution of the abnormal test result.

Discussion

Commonly, liver function tests are transiently abnormal after acute alcohol excess, minor viral illness, or a drug reaction.[1] Liver enzyme concentrations that are chronically increased can result from chronic high alcohol consumption, obesity (particularly in men), and smoking (in women).[1 2] The pattern of changes in liver function tests can suggest a diagnosis, but even large increases are non-specific,[3] and liver biopsy is often required for a firm diagnosis.[4–6] As standard liver function tests are an inexpensive investigation, the first step towards discovery of an abnormal test result should be a repeat test after several weeks of alcohol abstention if no other clinical diagnostic clues are apparent. In our study the abnormal test result resolved spontaneously in 38% of patients.

We defined "abnormal" test results as those that were twice the upper limit of the local reference range. This arbitrary cut off point was chosen simply because an initial survey showed six times the number of abnormal test results if a more minor abnormality was considered; well beyond our means of investigation. Our study was not designed to define the sensitivity and specificity of liver function tests in primary care. Major chronic liver disease can exist with normal or near normal test results, and using our sampling method will clearly miss disease. In a study from the era before hepatitis C, Van Ness examined patients referred with one or more results for liver enzyme concentrations that were 1.5 times the upper limit of normal. He found that only 6 of 90 patients had normal sample results obtained by liver biopsy.[5]

Persistently abnormal test results for liver function require investigation as they can be associated with life threatening potentially communicable yet treatable diseases, as our study shows. Some of the more important diagnoses can be indicated by a relatively inexpensive battery of serological tests, comprising hepatitis B surface antigen, hepatitis C antibody, an autoantibody screen, and concentrations of immunoglobulins and ferritin. Early diagnosis of chronic viral hepatitis, haemochromatosis, autoimmune hepatitis, and possibly primary biliary cirrhosis can improve prognosis.

Many of the patients not investigated had been considered by their doctor, often correctly, as having alcoholic liver disease. It is important to note that alcoholics can have other liver diseases—for example, hepatitis B and C,[7–9] and previous studies have shown that liver biopsy can detect unsuspected liver diseases in patients with a known high alcohol consumption.[4] Furthermore, abnormal results for liver function in people who drink excess alcohol, even in those with normal synthetic function, may imply major liver disease, including cirrhosis. Many patients with alcohol problems may be referred to a multidisciplinary alcohol team. A physical assessment of patients with alcohol problems can help. Knowledge of the severity of a physical illness—for example, with biopsy staging of alcoholic liver disease—may impact on behaviour when other advice has failed.

What is already known on this topic

Investigating hospital patients with abnormal results for liver function often reveals important diagnoses

It is unclear whether patients with abnormal results detected by their doctor are adequately investigated and important diagnoses missed

What this study adds

An important minority of patients in primary care who have persistently abnormal test results for liver function do not have sufficient investigation and are not referred

Investigation of these patients yields important diagnoses, including communicable, potentially life threatening diseases

Medical complications of alcohol excess can also be anticipated and partly ameliorated.

The nature of our study's design meant that it highlighted instances where a diagnosis had been delayed, in particular in the seven patients who had a "diagnostic" test result but were not referred for treatment. Of 873 patients, 157 (18%) were not appropriately followed up and 97 (11%) with abnormal test results over six months had undetected major liver disease and would probably have benefited from follow up at hospital.

One strategy to improve follow up of abnormal test results would be to issue test reports that suggest further investigations, but as results should be interpreted within the clinical context this may be misleading, and to our knowledge no prospective evaluation of such a policy has been reported. Most studies using guidelines to attempt to change behaviour regarding requesting blood tests have been aimed at reducing usage of pathology services rather than avoiding missing treatable diagnoses, often with considerable success.[10 11] In a US study of supplementary blood tests in diabetic patients in primary care, less than 20% of patients received the recommended number of tests.[12] We aim to complete the audit cycle by reaudit after the publication of appropriate guidelines.

Conclusion

An important minority of patients with abnormal test results for liver function discovered by their doctor were not adequately investigated, resulting in missed treatable and sometimes communicable chronic liver disease. Patients with persistently abnormal test results should be referred to a hepatologist or gastroenterologist.

Contributors: PS helped plan the study, collected and analysed the hospital and general practice data, and wrote the paper. IL helped plan the study, collected the hospital data, and helped with the discussion section. SB produced the original patient sample and contributed to writing the paper. SR had the original idea for the study, helped plan it, collected and analysed the hospital and general practice data, and edited the paper; he will act as guarantor.

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1 Rosalki SB, McIntyre N. Biochemical investigations in the management of liver disease. In: Bircher J, Benhamou J-P, McIntyre N, Rizzetto M, Rodes J, eds. *Oxford textbook of hepatology*, 2nd ed. Oxford: Oxford University Press, 1999:506-9.
2 Steffensen FH, Sørensen HT, Brock A, Vilstrup H, Lauritzen T. Alcohol consumption and serum liver-derived enzymes in a Danish population aged 30-50 years. *Int J Epidemiol* 1997;26:92-9.
3 Johnston DE. Special considerations in interpreting liver function tests. *Am Fam Physician* 1999;59:2223-30.
4 Levin DM, Baker AL, Riddell RH, Rochman H, Boyer JL. Nonalcoholic liver disease. Overlooked causes of liver injury in patients with heavy alcohol consumption. *Am J Med* 1979;66:429-34.
5 Van Ness MM, Mae Diehl A. Is liver biopsy useful in the evaluation of patients with chronically elevated liver enzymes? *Ann Intern Med* 1989;111:473-8.
6 Hultcrantz R, Glaumann H, Lindberg G, Son Nilsson LH. Liver investigation in 149 asymptomatic patients with moderately elevated activities of serum aminotransferases. *Scand J Gastroenterol* 1986;21:109-13.
7 Mendenhall CL, Moritz T, Rouster S, Roselle G, Polito A, Quan S, et al. Epidemiology of hepatitis C among veterans with alcoholic liver disease. *Am J Gastroenterol* 1993;88:1022-6.
8 Nalpas B, Thiers V, Pol S, Driss F, Thepot V, Berthelot P, et al. Hepatitis C viremia and anti-HCV antibodies in alcoholics. *J Hepatol* 1992;14:381-4.
9 Mendenhall CL, Seeff L, Diehl AM, Ghosn SJ, French SW, Gartside PS, et al. Antibodies to hepatitis B virus and hepatitis C virus in alcoholic hepatitis and cirrhosis: their prevalence and clinical relevance. *Hepatology* 1991;14:581-9.
10 Sucov A, Bazarian JJ, Delahunta EA, Spillane L. Test ordering guidelines can alter ordering patterns in an academic emergency department. *J Emerg Med* 1999;17:391-7.
11 Guterman SJ, Van Rooyan MJ. Cost-effective medicine: the financial impact that practice guidelines have on outpatient hospital charges in the emergency department. *J Emerg Med* 1998;16:215-9.
12 Wisdom K, Fryzek JP, Havstad SL, Anderson RM, Dreiling MC, Tilley BC. Comparison of laboratory test frequency and test results between African-Americans and Caucasians with diabetes: opportunity for improvement. Findings from a large urban health maintenance organization. *Diabetes Care* 1997;20:971-7.

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A memorable patient

"Just my nerves"

Several years ago, before I permanently abandoned the clinic for the laboratory, I attended an elderly lady in the emergency department. She presented with "chest pain," always a guarantee of early attention, but this chest pain was due to a band of haemorrhagic skin vesicles over the distribution of the fifth right intercostal nerve. They were exquisitely tender and there was adjacent hyperaesthesia. I examined her for evidence of lymphoma or other predisposing condition and found none. I told her that she had shingles, and explained that the chickenpox virus, often dormant from a childhood illness, spreads from the spinal cord out along the nerve, and that the nerve involvement was why the condition was so painful. I remember thinking that my explanation had been especially good. She nodded in understanding, and I explained that I would recommend some pain medicine, do some blood tests, and talk to her family doctor about her condition.

As I left the room, I told her husband, waiting outside, that he could go in. As he entered, I heard him ask, "What did the doctor say?"

She replied, "He said it was just my nerves."

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We welcome articles of up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake*, or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk. Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.