Charles Helsper, Gerrit van Essen, Bernard D Frijling and Niek J de Wit

Follow-up of mild alanine aminotransferase elevation identifies hidden hepatitis C in primary care

Abstract

Background
Hepatitis C (HCV) and hepatitis B (HBV) virus infection can lead to serious complications if left untreated, but often remain undetected in primary care. Mild alanine aminotransferase (ALT) elevations (30–100 IU/l) are commonly found and could be associated with viral hepatitis; unfortunately, these findings frequently remain without follow-up.

Aim
To determine if and how mild ALT elevation can be used to identify hidden HCV and HBV infection in primary care.

Design and setting
Primary care patients referred for liver enzyme testing were selected by a large primary care Diagnostic Centre (Saltro).

Method
First, 750 anonymous samples were collected in three categories of ALT elevation (30–50 IU/l, 50–70 IU/l, and 70–100 IU/l) and tested for HCV and HBV. Second, the national prevalence of each ALT elevation was estimated by analysing all annual ALT tests performed at Saltro.

Results
HCV prevalence was 1.6% and 1.2% in patients with an ALT of 50–70 IU/l and 70–100 IU/l respectively. In patients with an ALT of 30–50 IU/l, HCV prevalence was normal (≤0.1%). HBV prevalence was normal (≤0.4%) in all groups. The estimated number of ALT tests performed nationally each year in primary care was 1.1 million. An ALT of 30–50 IU/l was found in 21.1%, an ALT of 50–70 IU/l in 5.6%, and 2.6% had an ALT of 70–100 IU/l.

Conclusion
In primary care patients with an ALT level of 50–100 IU/l, HCV prevalence is tenfold the population prevalence, whereas HBV prevalence is not elevated. Therefore, diagnostic follow-up for HCV is indicated in these patients, even when other explanations for ALT elevation are present.

Keywords
alanine aminotransferase; hepatitis; hepatitis C virus; primary care; secondary prevention.

INTRODUCTION

Infection with viral hepatitis, especially hepatitis C virus (HCV), is increasingly considered as a serious health threat. Unfortunately, this disease still remains relatively unknown among the general population and GPs in countries with low infection rates. It is estimated that 2–3% of the worlds population (123–170 million people) is infected with HCV and 5–6% (350 million) with chronic hepatitis B (HBV), of which a large proportion remains undiagnosed.[1–3] If no treatment is started, approximately 20% of the chronic HCV and HBV carriers will develop liver cirrhosis, of whom roughly 5% will develop hepatocellular carcinoma.[4,5]

Fortunately, treatment outcomes of viral hepatitis have improved considerably in the past decade, especially for HCV. Success rates for HCV and HBV treatment are dependent on genotype. At present 50–80% of chronic HCV carriers can be cured. Chronic HBV can be suppressed in 35% HBV e-antigen (HBeAg loss) and cured in 7% of cases HBV surface antigen (HBsAg loss).[6]

Despite the serious consequences of infection, only a small proportion of HCV and HBV carriers are presently diagnosed. The main reasons are the lack of specific clinical symptoms and the limited awareness of viral hepatitis among physicians. The problem of underdiagnosing is most pressing for HCV carriers. At present, only a fraction of the estimated 15 000 to 60 000 chronic carriers in The Netherlands are diagnosed.[7] Since the virus is transmitted through blood-to-blood contact, current case finding strategies are based on the identification of risk groups. The most important risk groups for HCV are presented in Box 1.[8–10]

Even though identification and testing of these risk groups can improve case finding, this will lead to the detection of only a small sample of infected individuals. A recent survey showed that a national HCV campaign in the Netherlands is expected to detect an additional 500 HCV patients, still leaving the majority of the HCV-infected population undiagnosed.[11] Therefore, additional case finding strategies in clinical practice are required.

The alanine aminotransferase (ALT) test is the most frequently used test for liver disease in primary care. An ALT test result of >100 IU/l is a clear indicator of serious liver disease, but a mildly elevated ALT result (30–100 IU/l) is often ascribed to the use of medication (for example statins) or alcohol, obesity, or, for lower ALT levels (<50 IU/l), considered as part of the normal distribution of test results. As a consequence, abnormal ALT levels are frequently accepted without adequate diagnostic follow-up.[12]

Several international studies have reported a substantially increased risk of viral hepatitis in patients with mildly

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How this fits in

Hepatitis C (HCV) and hepatitis B (HBV) virus infection can lead to serious complications if left untreated, but often remain undetected in primary care. Mild alanine aminotransferase (ALT) elevations (30–100 IU/l) are commonly found, but frequently remain without follow-up. This study demonstrates that HCV prevalence is tenfold the population prevalence in primary care patients with an ALT level of 50 to 100 IU/l. Therefore, routine follow-up for testing HCV in these patients is indicated.

elevated ALT levels.[13–17] To explore if and how mild ALT elevation found in daily primary care practice can be used to detect hidden HCV and HBV infection, the prevalence of viral hepatitis and a cut-off point above which a substantially increased risk of viral hepatitis is present, need to be determined.

The aim of this study is to explore if primary care patients with mild ALT elevation are at increased risk for HCV and HBV infection, and, if so, to establish a cut-off point above which routine follow-up for viral hepatitis is effective in daily practice.

METHOD

A cross-sectional cohort study was performed among primary care patients referred for liver enzyme testing to the Saltro Diagnostic Centre, the leading primary care laboratory in the centre of the Netherlands. The Saltro Diagnostic Centre operates from 135 locations in the Netherlands, processes diagnostic applications for 600 000 patients annually, and offers laboratory facilities to approximately 750 primary care physicians in 350 surgeries.

As a first step, patients referred by their GP for liver enzyme testing with a mildly elevated ALT test result (30–100 IU/l) were identified anonymously. Patients for whom an additional HCV or HBV test was ordered were not included. Samples were collected in three groups with different ranges of mild ALT elevation (30–50 IU/l, 50–70 IU/l, 70–100 U/l). For each group, every third patient was selected for additional testing to prevent contamination bias, until each group contained 250 samples. Data collection for these 750 samples took place from January to June 2010. In these samples, HBV and HCV prevalence was assessed.

As the second step, to estimate the potential effect on hepatitis case finding at a national level, the prevalence of the different levels of mild ALT elevation in primary care patients who are referred for ALT testing was evaluated. For this purpose, all the ALT test results of patients referred by a GP to the Saltro Diagnostic Centre for an ALT test from July 2009 to June 2010 were analysed. These data were extrapolated based on the number of GPs in the Saltro database and the national number of GPs on 1 January 2010, as demonstrated by a national survey of GP registrations performed by the Netherlands Institute of Health Services Research (Nivel).[18] To validate the extrapolation, it was repeated based on the number of primary care surgeries both in the Saltro database and in the Netherlands, as found in the Nivel survey.[18]

Laboratory tests

All patients were tested for HCV using enzyme-linked immunosorbent assay (ELISA) testing for anti-HCV. Positive tests were confirmed by immunoblot analysis. Polymerase chain reaction was performed to determine if chronic infection had taken place. Chronic HBV was determined by ELISA testing for HBsAg and HBV surface antibody (anti-HBc). Chronic HBV was diagnosed if both tests had a positive result.

Data collection and analysis

Anonymous data were collected by staff employees at the Saltro Diagnostic Centre, through standardised procedures. Data were stored and analysed using the Excel statistical package. Where necessary due to low numbers, 95% confidence intervals (CIs) were determined based on the modified Wald method developed by Agresti and Coull.[19]

Ethical considerations

After consulting the medical ethics committee of the University Medical Centre Utrecht, it was decided to perform data collection and processing anonymously and to inform GPs affiliated to the Saltro Diagnostic Centre of the overall results of this study. It was left up to the GP whether or not to recall patients with a relevant ALT elevation to perform additional testing.

RESULTS

An overview of patient characteristics for the 750 samples used to determine the prevalence of hepatitis in the three levels of ALT elevation is shown in Table 1. Table 2 demonstrates the main findings for each range of ALT test results, including 95% CIs. Table 3 provides an overview of the annual ALT tests performed at Saltro, including the prevalence and characteristics of each level of elevation.

Box 1. Risk groups for hepatitis C[8–10]

- Past and present hard drug users, in particular injecting drug users
- Immigrants from highly endemic countries (prevalence >10%)
- Recipients of blood (-products) before 1992
- Travellers whose skin was pierced in endemic countries (prevalence >2%)
- Professionals at occupational risk
- HIV-infected men who have sex with men

The overall prevalence of confirmed anti-HCV-positive patients (once infected with HCV) and HCV-RNA-positive patients (chronic HCV infection) was 1.1% (95% CI = 0.5% to 2.1%) and 0.9% (95% CI = 0.4% to 2.0%) respectively. Prevalence of HCV was not elevated in patients with an ALT level of 30–50 IU/l. Prevalence of positive anti-HCV test results was 2.0% in the group with an ALT level of 50–70 IU/l and 1.2% in the group with an ALT level of 70–100 IU/l. Prevalence of positive HCV-RNA test results was 1.6% in the group with an ALT level of 50–70 IU/l and 1.2% in the group with an ALT level of 70–100 IU/l. Consequently, the prevalence of chronic HCV was 1.4% (95% CI = 0.6% to 2.9%) in patients with an ALT level of 50–100 IU/l.

Chronic HBV was found in one patient, who had an ALT level of 75 IU/l. This single finding indicates that there was no elevated HBV prevalence at all levels of mild ALT elevation.

Based on 93 637 ALT tests performed at Saltro Diagnostic Centre from July 2009 to June 2010, the number of ALT tests performed in primary care patients in the Netherlands was estimated at approximately 1.1 million annually. The tests performed at Saltro were applied for by 736 GPs in 356 surgeries. The national annual number of tests was calculated using the national number of practising GPs in 2010 ($n = 8921$), and confirmed by an extrapolation based on the number of GP surgeries ($n = 4088$). Of all ALT tests performed in general practice, 68.7% had a normal ALT level (0–30 IU/l), 21.1% had an ALT of 30–50 IU/l, 5.6% had 50–70 IU/l, 2.6% had 70–100 IU/l, and 2% had 100 IU/l or higher. In males, the prevalence of ALT elevation was approximately twice as high as in females, in all groups of ALT elevation.

When combining the national number of ALT tests with the estimated prevalence of ALT elevation of 50–100 IU/l in the Netherlands (8.2%), and the corresponding HCV prevalence in this group (1.4%), an estimated 1200 to 1300 hepatitis C patients could be identified annually if these patients were screened for HCV.

Table 1. Characteristics of the 750 blood samples used for hepatitis prevalence across three levels of ALT elevation.

	ALT 30–50 IU/l, *n* = 250	ALT 50–70 IU/l, *n* = 250	ALT 70–100 IU/l, *n* = 250	Total ALT 30–100 IU/l, *n* = 750
Sex — female, *n* (%)	96 (38.4)	66 (26.4)	74 (29.6)	236 (31.5)
Age, mean years (SD)	55.5 (14.7)	53.2 (15.3)	53.4 (14.5)	54.1 (14.5)
ALT, mean IU/l (SD)	37.6 (5.5)	58.1 (5.5)	81.8 (8.0)	59.2 (19.2)
ALT — median IU/l (range)	36.1 (30.1 to 49.8)	57.4 (50.1 to 69.9)	81.1 (70.1 to 99.5)	57.4 (30.1 to 99.5)

SD = standard deviation. ALT = alanine aminotransferase test.

Table 2. Prevalence of hepatitis at different levels of ALT elevation compared to population prevalence, *n*, % (95% CI)

	ALT 30–50 IU/l, *n* = 250	ALT 50–70 IU/l, *n* = 250	ALT 70–100 IU/l, *n* = 250	Population prevalence
Hepatitis C — once infected, *n*	0	5	3	0.2
% (95% CI)	0.0 (0.0 to 1.8)	2.0 (0.7 to 4.7)	1.2 (0.2 to 3.6)	
Hepatitis C — chronic infection, *n*	0	4	3	0.1
% (95% CI)	0.0 (0.0 to 1.8)	1.6 (0.5 to 4.2)	1.2 (0.2 to 3.6)	
Hepatitis B — chronic infection, *n*	0	0	1	0.4
% (95% CI)	0.0 (0.0 to 1.8)	0.0 (0.0 to 1.8)	0.4 (0.0 to 2.5)	

ALT = alanine aminotransferase test.

Table 3. Characteristics of the annual ALT tests performed at Saltro

	Total ALT tests	ALT 0–30 IU/l	ALT 30–50 IU/l	ALT 50–70 IU/l	ALT 70–100 IU/l	ALT ≥100 IU/l
Annual ALT tests and results	93 637	64 326	19 783	5246	2410	1872
Percentage of total ALT tests (95% CI)	100	68.7 (68.4 to 69.0)	21.1 (20.9 to 21.4)	5.6 (5.5 to 5.8)	2.6 (2.5 to 2.7)	2.0 (1.9 to 2.1)
Mean age, years (SD)	56 (20)	56 (21)	56 (16)	53 (15)	52 (15)	51 (19)
Sex — female, *n* (%)	52 836 (56.4)	42 037 (65.3)	7623 (38.5)	1700 (32.4)	749 (31.1)	727 (38.8)
Mean ALT, IU/l (SD)	31 (64)	19 (5)	37 (6)	58 (6)	81 (8)	233 (393)

SD = standard deviation. ALT = alanine aminotransferase test.

DISCUSSION

Summary

The prevalence of HCV in patients with an ALT elevation of 50–100 IU/l was over tenfold the population prevalence, whereas the prevalence of HBV was normal.[20,21]

In the Netherlands only, an estimated 1.1 million ALT tests were performed in the year 2009–2010, of which 8.2% are expected to have ALT levels of 50–100 IU/l. If ALT is used as a tool for the identification of hepatitis C patients, this could lead to the detection of an estimated 1200 to 1300 cases in the first year alone. This is more than twice the number expected in a large national hepatitis C campaign aimed at the general public and hard drug users.[11]

The prevalence of ALT elevation was relatively high in males as compared to females. This is consistent with previous findings, and can be attributed to a higher prevalence of conditions that lead to an

elevated ALT in males, such as cholesterol-mediated liver injury, metabolic syndrome, alcohol use, and the effect of higher haemoglobin levels.[22–24]

The GPs contributing to the Saltro database work in a relatively urbanised area. The authors do not expect this to have a large effect on the number of ALT tests performed, but the HCV prevalence might be slightly higher than the mean prevalence in the Netherlands. This could lead to an overestimation of the effect on a national level.

ALT prevalence found at an ALT level of 50–70 IU/l was 1.6%, versus 1.2% at the higher level of 70–100 IU/l, with largely overlapping confidence intervals. There is no apparent explanation for this and the authors think it is due to chance.

The fact that HCV is more prevalent among patients with elevated ALT levels does not mean that ALT is an appropriate test to detect HCV. Since ALT is normal in many HCV-infected patients, ALT is not suitable for HCV screening. Therefore, patients at risk for HCV should be tested with an anti-HCV test (ELISA), not with ALT.

Strengths and limitations

Due to ethical restrictions, data collection was performed anonymously, and therefore patient characteristics were not available. Knowledge of these characteristics, such as the presence of an increased risk based on risk groups, alcohol use and medication use, body mass index, and previous liver disease, is generally available to GPs.

This additional information, which needs to be used critically because it might also mislead GPs, provides a background that increases the diagnostic value of mild ALT elevation for the identification of hidden HCV. Since information regarding risk groups is particularly helpful to identify hidden HCV, it deserves strong recommendation to at least ask for the presence of an increased risk based on the known risk groups when an elevated ALT level is found, even when other explanations for the ALT elevation are present.

Since the researchers did not have access to patient histories, it is not possible to confirm that the patients with HCV identified in this study have not been diagnosed with HCV before. This might lead to an overestimation of the effect on case finding.

Comparison with existing literature

The study findings in the primary care population of the Netherlands are supported by findings in several international studies. Already in 2001, Sherwood and colleagues concluded that 'Abnormal results for liver function are often not adequately investigated, missing an important chance of identifying treatable chronic liver disease'.[12] Prati and colleagues demonstrated that the normal ranges for ALT are influenced by the presence of undiagnosed HCV.[24] Other international studies, performed in different populations, found an elevated prevalence of HCV in patients with elevated liver enzymes.[13–17] In these studies, 5–10% of the total tests for liver enzymes had abnormal results.[13,15,16] Results of these studies concerning the prevalence of HCV and ALT elevation are congruent with the present findings. This study specifies levels of ALT elevation at which HCV testing is indicated, and therefore facilitates the use of ALT as a tool to identify hidden hepatitis C in a primary care setting.

Implications for practice

In primary care patients with an ALT elevation between 50 IU/l and 100 IU/l, the risk of HCV infection is substantially elevated, whereas the risk of HBV infection is not. Therefore, it is recommended that in all these patients, particularly in those for whom no clear explanation for the ALT elevation is found, diagnostic follow-up for HCV is performed. In addition, the authors recommend enhancement of the guidelines for general practice, based on these findings.

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Ethical approval

The Medical Ethics Committee of the University Medical Centre Utrecht provided ethical approval.

Provenance

Freely submitted; externally peer reviewed.

Competing interests

The authors have stated that they have no competing interests.

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