

Blood alanine aminotransferase levels >1,000 IU/l – causes and outcomes

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ABSTRACT

Standard medical education dictates that the vast majority of cases of an alanine aminotransferase (ALT) level >1,000 IU/l will be due to acute ischaemia, acute drug-induced liver injury (DILI) (usually paracetamol) or acute viral hepatitis. There are very few references in the literature to other potential causes of an ALT >1,000 IU/l nor to the prognosis ascribed to each aetiology. In this study, we have confirmed that the main causes of a dramatic ALT rise are ischaemic liver injury, DILI and viral hepatitis. Common bile duct stones and hepatitis E are two causes for which there needs to be a high index of suspicion as the necessary tests may not be in the clinician's first-line investigation panel. Failing to find a cause and determining that the cause was ischaemic both have poor prognostic implications.

KEYWORDS: Alanine aminotransferase, transaminases, acute hepatitis, aetiology, prognosis

Introduction

Alanine aminotransferase (ALT) is an enzyme involved in the alanine cycle and is primarily found in muscle and the liver.¹ In clinical practice, ALT is measured as one of the liver function tests (LFTs) to screen for hepatocellular injury.² The differential diagnosis for elevated serum aminotransferases is broad and includes metabolic liver disease, alcohol-related liver disease, ischaemic hepatopathy, hepatotoxicity from drugs or toxins, autoimmune, hepatocellular and biliary injury, chronic viral hepatitis and malignant infiltration. Typically, ALT levels in these conditions can be two-to-five times the upper limit of normal, which is around 40 IU/l in most hospitals. Occasionally ALT levels can rise to levels of >1,000 IU/l. This will usually lead to an urgent referral to hospital or within hospital to

the gastroenterology or hepatology teams. Standard medical education dictates that the vast majority of these cases will be due to acute ischaemia or congestion, acute drug-induced liver injury (DILI) (usually paracetamol) or acute viral hepatitis.^{3–5} The requirement for admission to hospital and the prognostic and treatment implication for these three groups of conditions are very different and as such, it is important to determine the cause of the dramatic ALT elevation early.

Our aim was to review all the cases with an ALT level >1,000 IU/l in our city centre university hospital in order to determine cause and prognosis and improve urgent care pathways.

Materials and methods

This single-centre, retrospective, observational study was conducted in a tertiary referral university hospital over a two-year period. A retrospective chart review was performed on every patient who had presented to the hospital over this time period with an ALT >1,000 IU/l. This included reviewing, where applicable, the primary care referral letters for that episode, the written and electronic patient charts, patient medication records, intensive care unit (ICU) discharge summaries, hospital discharge summaries and death notifications. Where possible, aetiology was ascribed and prognosis (survival to hospital discharge) was recorded. In all cases, the aetiology ascribed in the patient notes was correlated with diagnostic criteria that had been established prior to the review (Table 1). All data were anonymised and recorded in a secure dedicated electronic database. Statistical data analysis was carried out using SPSS version 20. The study protocol was approved by the Research Ethics Committee of the Mater Misericordiae University Hospital (MMUH 1/378/1545 TMR).

Results

In total, 182 patients (56% (n=102) male and 44% (n=80) female) with an ALT >1,000 IU/l were identified.

The aetiology of the raised ALT is shown in Fig 1. As expected, ischaemic liver injury (61%, n=111), DILI (15.9%, n=29) and acute viral hepatitis (12.1%, n=22) were the most common causes accounting for nearly 90% of all cases. Interestingly, the next most common causes were idiopathic (5.0%, n=9) and acute cholelithiasis (4.4%, n=8). Autoimmune hepatitis (1.6%, n=3) made up the remaining cases.

Paracetamol toxicity accounted for almost half (13/29) of the DILI cases. The other common causes were anti-tuberculosis

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Table 1. Diagnostic features of acute liver injury (ALT >1,000 IU/l).

Acute liver injury	Diagnostic features
Ischaemic liver injury	<ul style="list-style-type: none"> > Appropriate clinical setting > Clinical impression from the patient's electronic or written medical record, and ICU and hospital discharge summaries > Other potential causes of acute hepatitis excluded
Viral liver injury	<ul style="list-style-type: none"> > Appropriate clinical setting > Patient records confirmed an acute viral cause > Other potential causes of acute hepatitis excluded
DILI	<ul style="list-style-type: none"> > Appropriate clinical setting > Clinical impression from the patient's electronic or written medical record, and ICU and hospital discharge summaries > Temporal relationship established between drug intake and onset of symptoms/transaminitis > Other potential causes of acute hepatitis excluded
Autoimmune hepatitis	<ul style="list-style-type: none"> > Pre-treatment international autoimmune hepatitis score $\geq 15^6$ > Other potential causes of acute hepatitis excluded
Cholelithiasis	<ul style="list-style-type: none"> > Appropriate clinical setting > Stones seen on imaging in common bile duct > Improvement in ALT once stone(s) removed > Other potential causes of acute hepatitis excluded
Idiopathic	<ul style="list-style-type: none"> > No other cause ascribed despite extensive review of the notes and consideration of all the diagnoses described above

ALT = alanine aminotransferase; DILI = drug-induced liver injury; ICU = intensive care unit.

medications (6/29) and other antibiotics (4/29). Other drugs were also implicated in smaller numbers (Table 2).

In order of frequency, the viral hepatitis causing ALT >1,000 IU/l were hepatitis B (7/22), hepatitis C (5/22), hepatitis E (4/22) and hepatitis A (3/22). Cytomegalovirus, Epstein–Barr virus and varicella zoster each accounted for one case.

9.3% (n=17) of patients had their acute hepatitis managed as outpatients, 54.9% (n=100) were admitted to the hospital and discharged home well and 35.7% (n=65) died during their admission (Fig 2A). Survival was highly dependent on the aetiology of the raised ALT. Ischaemic liver injury was the cause

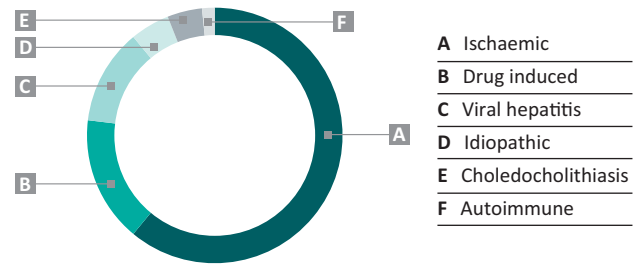


Fig 1. Aetiology of liver injury in patients with an ALT >1,000 IU/l (n=182). ALT = alanine aminotransferase.

of the ALT >1,000 IU/l in the vast majority of patients who died during the admission (93.8%, n=61) (Fig 2B). Overall mortality was 55% (61/111) in the ischaemic group, 6.9% (2/29) in DILI and 0% if the aetiology was viral hepatitis, stone disease or autoimmune hepatitis. 22.2% (2/9) of those patients in whom a cause could not be identified died.

Conclusions

We reviewed the investigations and outcomes of 182 cases where the ALT measurement was >1,000 IU/l. The results were generated by the biochemistry department attached to a tertiary referral university hospital and could come from the hospital in-patients or patients attending local general practitioners. The vast majority of these patients were admitted to hospital but some were managed in the community by primary care or in the hepatology out-patient department. There were some findings that reinforced standard teaching around 'acute hepatitis' and some that were surprising.

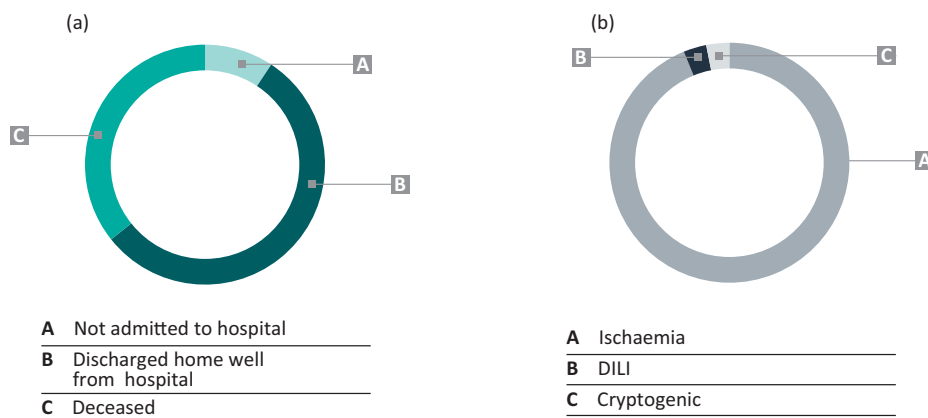
To the best of the authors knowledge, no similar case series has been published, however, a review of the literature reveals that ischaemia, drugs and toxins can cause elevations in ALT of greater than 40 times the upper limit of normal (ULN) while viral aetiology generally causes elevations of 10 to 40 times the ULN, ie any of these aetiologies can cause an ALT of >1,000 IU/l.^{7,8} Prognosis largely depends on aetiology and as such it is important to make the correct diagnosis from

Table 2. DILI causes of an ALT >1,000 IU/l (n=29).

Drug	n
Paracetamol	13
Tuberculosis medications	6
Antibiotics	4
Opiates	1
Chinese herbs	1
Bosentan	1
ARVs	1
Cocaine	1
Statin	1

ALT = alanine aminotransferase; ARVs = antiretrovirals; DILI = drug-induced liver injury.

Fig 2. (A) Outcome of patients who presented with an ALT >1,000 IU/l (%) (n=182). (B) Aetiology of ALT >1,000 IU/l in the deceased cohort (%) (n=65; 35.7% of total cohort).
ALT = alanine aminotransferase; DILI = drug-induced liver injury.



the outset. There are no specific blood tests for ischaemic or DILI and so detailed history taking and a thorough physical examination are essential in order to make the correct diagnosis. A number of laboratory tests and patterns may also be useful. In viral hepatitis, transaminases rarely increase to greater than 40 times ULN unlike that seen in ischaemic or DILI. Lactate dehydrogenase (LDH) activity often is higher than that of AST at presentation in ischaemic or drug-induced hepatic injury,^{8,9} as compared with viral hepatitis when the LDH level is generally normal or only slightly above the ULN.¹⁰ Cholelithiasis is a recognised but rare cause of severe transaminitis.¹¹ Agahi *et al* described three cases of cholelithiasis causing an ALT >1,000 IU/l, all of these cases had repeated investigation for liver disease before eventual identification of common bile duct stones with magnetic resonance cholangiopancreatogram.¹² Presentation of fulminant AIH has been described with transaminases of >1,000 IU/l, but it is rare.¹³ A recent single-centre review of all cases of AIH over a ten-year period identified 32 cases of acute severe AIH (defined as an international normalised ratio >1.5 without evidence of fibrosis). Although exact numbers were not given, the average AST was 619 IU/l (116–2,690 IU/l) indicating that very few patients had an AST of >1,000 IU/l.¹⁴

The proportion of patients that had ischaemic injury, DILI or viral hepatitis was exactly as we would have expected at around 90%. We were surprised to find cholelithiasis as the next most common cause of an ALT >1,000 IU/l (8/182 cases). This is significantly higher than the incidence rates seen in the literature and may confound admitting teams who would expect biliary colic due to bile duct obstruction to present with obstructive LFTs.

The second important clinically relevant finding from this study was that hepatitis E was more frequently detected than hepatitis A. This was in spite of hepatitis A serology being in the first-line viral screen and the need for hepatitis E serology to be requested separately if the first-line screen is negative. Hepatitis E is one of the most common causes of acute hepatitis worldwide, with the majority of cases occurring in Asia. In recent years, however, an increasing number of acute and chronic hepatitis E virus infections have been reported in industrialised countries.¹⁵ This has both clinical and treatment implications. In the first instance, a positive viral serology test allows the clinician to stop searching for other causes

and may avoid liver biopsy. In addition, hepatitis E infection can become chronic in immunocompromised patients and lead to hepatic fibrosis and cirrhosis. Treatment strategies are currently being evaluated and attempts are being made to develop effective hepatitis E virus vaccines.¹⁶ Physicians need to be aware of hepatitis E as a cause of both acute and chronic hepatitis in immunocompromised patients and this is particularly important if there may be a risk of pregnant women being exposed to infection given the high maternal mortality associated with the syndrome.

Nine patients had no cause identified for their acute transaminases. Four of these patients were not admitted to our institution nor were they referred to hepatology outpatient clinics. It was established that these patients were still alive but it was not possible to retrospectively establish the cause of the liver injury. They may have been referred to another local hospital or managed in the community. Despite extensively reviewing the clinical notes for the remaining five patients, it was not possible to confidently attribute a cause for the liver injury. There were no recorded hypotensive episodes, viral serology was negative and no incriminating drugs were recorded in the medical history. It is important to highlight that none of the patients were checked for hepatitis E. A retrospective effort to establish the hepatitis E virus status of these patients was not successful because samples were no longer available (stored for six months).

Finally, the clinical courses are very different for each of the aetiologies of liver injury. This has implications for follow-up. The prognosis in acute viral hepatitis, even with ALT >1,000 IU/l is extremely good and these patients can almost always be managed closely in the community. DILI has a well-defined mortality which will be drug-dependent and, certainly in the case of paracetamol, very predictable. Patients in whom the ALT rises to >1,000 IU/l due to ischaemic liver injury have a very poor prognosis. Often this is evident at the time, with the liver being simply another organ insulted in multi-organ failure. Sometimes, however, the ALT rise may be one of the earlier signs that augurs poorly for patient prognosis.

Limitations of this study are similar to those seen in other retrospective studies. This study depended on the availability, accuracy and comprehensiveness of the medical records. In the majority of cases it was possible to confidently attribute an aetiology to each patient; however there were a small number

of cases where an educated assumption needed to be made. It was not possible to retrospectively apply diagnostic criteria such as the CIOMS/RUCAM scale for DILI,¹⁷ to check LDH, or to complete the viral or autoimmune screens in those who had some missing results. There were nine cases where it was not possible to define an aetiology. The high mortality seen in the idiopathic group could possibly be explained by the fact that some of this group were in fact unrecognised ischaemic or drug-induced injuries.

In summary we have defined the main causes of a dramatic ALT rise and associated a prognosis with each aetiological group. Common bile duct gallstones and hepatitis E are two causes for which there needs to be a high index of suspicion, as the necessary tests may not be in the first-line investigation panel of the clinician. Failing to find a cause and determining that the cause was ischaemic both have poor prognostic implications. ■

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