Case Report **Open Access**

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Persistently raised aspartate aminotransferase (AST) due to macro-AST in a rheumatology clinic

Abstract: Macrocomplexes between immunoglobins and aspartate aminotransferase (macro-AST) may result in persistently increased AST concentration. The presence of macro-AST in patients has been implicated in unnecessary investigations of abnormal liver function tests. We report the case of a 44-year-old female who presented to the rheumatology clinic with a 12-months' history of constant widespread pain affecting her limbs and was found to have an elevated AST concentration. Further information from her GP revealed a 14-years' history of elevated AST with otherwise normal liver function. Previous abdominal ultrasound and two liver biopsies carried out 2 years apart were normal. This prompted further analytical investigation by the biochemistry department which identified macro-AST as the cause. This case illustrates that persistently raised isolated AST concentration with no other abnormal indices may warrant macroenzyme analysis potentially avoiding unnecessary invasive investigations.

Keywords: AST; liver enzymes; macro-AST; macroenzyme.

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Background

Patients taking potentially hepatotoxic medications such as disease modifying anti-rheumatic drugs (DMARD) and antiepileptics require monitoring of their liver function tests. Abnormal liver function tests in these patients often lead to further investigation or change in therapy. The presented patient underwent unnecessary investigations for elevated AST including two liver biopsies that were normal. These invasive investigations would have been avoided if the macroenzyme was identified earlier. The case highlights the need to consider this possibility in isolated persistently elevated AST.

Case presentation

A 44-year-old female presented to the rheumatology team with a 12-months' history of constant widespread pain affecting her limbs and trunk. She also reported poor sleep, irritable bowel and fatigue. Systemic enquiry did not reveal any symptoms of a connective tissue disorder. She had epilepsy diagnosed at 12 years, which was controlled on lamotrigine and sodium valproate. Her physical examination was unremarkable apart from multiple muscular tender points.

In the year preceding her attendance, she had extensive investigations carried out for persistently raised AST and a positive antinuclear antibody (ANA). Further information from her GP revealed that she had in fact had raised AST for 14 years, dating back to her sojourn in Germany where it was initially discovered. Her antiepileptic therapy at that time comprised of lamotrigine and sodium valproate. Her raised AST was attributed to the antiepileptic medications and her sodium valproate dose was subsequently reduced. This did not result in a normalisation of her AST. She reverted to her previous regime as she could not tolerate an increased lamotrigine dose. She was then referred to a gastroenterology team for further investigation.

Available results showed persistently raised AST dating back 10 years, with values ranging between

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278–524 IU/L (Reference range 5–35 IU/L). Other liver function tests including coagulation profile were normal as were the full blood picture, creatinine kinase and renal profile. Her liver antibody and hepatitis screen were negative. Although she had a positive ANA, which stained a centromere pattern, she described no features of connective tissue disease or Raynaud's phenomenon. No evidence of haemolysis was noted and abdominal ultrasound was normal. The two liver biopsies taken 2 years apart confirmed normal histology effectively excluding autoimmune and inflammatory disorders of the liver. She was referred to a hepatology unit in a tertiary centre where it was advised that the cause for her abnormal liver function had been fully investigated and no explanation could be found. The events leading up to the finding of macro-AST had put this patient through considerable anxiety, and the associated risks of invasive procedures.

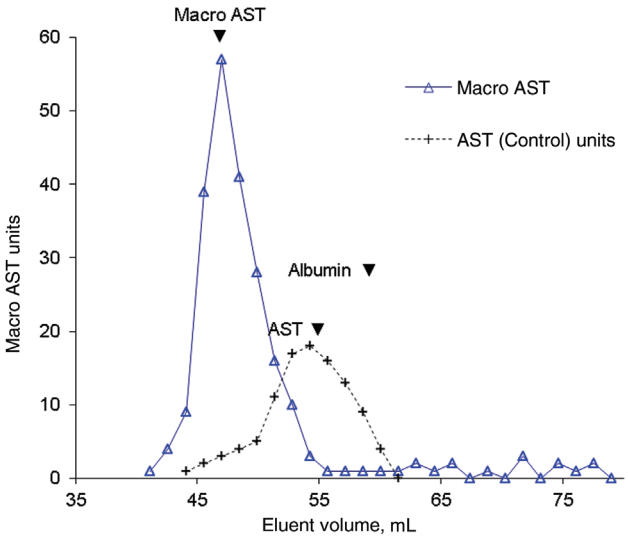

Figure 1 Gel filtration elution pattern of macro-AST sample and control.

AST laboratory method

AST was measured on the Beckman AU600 analyser. In this method, AST catalyzes the transamination of aspartate and α-oxoglutarate, forming L-glutamate and oxalacetate. The oxalacetate is then reduced to L-malate by malate dehydrogenase, while NADH is simultaneously converted to NAD^+. The decrease in absorbance due to the consumption of NADH is measured at 340 nm and is proportional to the AST activity in the sample.

Identification of macro-AST

After excluding non-hepatic causes for increased AST such as rhabdomyolysis, cardiac muscle damage and haemolysis in this patient, the possibility of macro-AST as a cause was considered by the biochemistry laboratory. Patient serum was screened for the presence of macro-AST using a polyethylene glycol (PEG) precipitation technique [1]. The serum treated with PEG immediately after venepuncture revealed low free AST activity. This finding suggested the presence of a macro-AST form. An aliquot of the patient's serum was subjected to gel filtration chromatography (GFC). Chromatograms confirmed the presence of a macro-AST form (Figure 1). The macro-AST complex was further characterised as an IgG type unstable at room temperature (Figure 2).

Discussion

Macroenzymes have been reported in cases since the 1990s. More recently, detection of macroenzymes of aspartate aminotransferase have been reported in children [1], adolescents and adults. Macroenzymes have a higher molecular mass and delayed clearance leading to increased concentration of measurable enzymes. They have been reported for a variety of hormones and enzymes including prolactin, creatinine kinase (CK) and amylase. These exist as a typical enzyme bound by immunoglobulin and are biologically inactive molecules.

Macrocomplexes can occur in association with immunologically related conditions [2, 3], neoplastic disease [4] and more so among the elderly [5]. Raised macro-AST has been reported in patients without existing or proven liver disease or damage when patients were followed up, and more frequently in young people [1, 5]. One long-term observation of a patient with raised macro-AST over 12 years showed fluctuating levels of AST between abnormal and normal ranges with an uneventful outcome [6]. A similar fluctuation in AST was observed in our patient and no obvious explanation for this was found. We postulate that fluctuation in immunoglobulin concentrations may contribute to this. In other cases, the incidental finding of a raised AST has prompted investigations of its cause with negative results [7]. Giannini et al. have published a schematic and systematic review of an approach to dissecting down an abnormal liver function test result, taking into consideration the geographical area and accounting for the timing of each abnormal result, including patients'

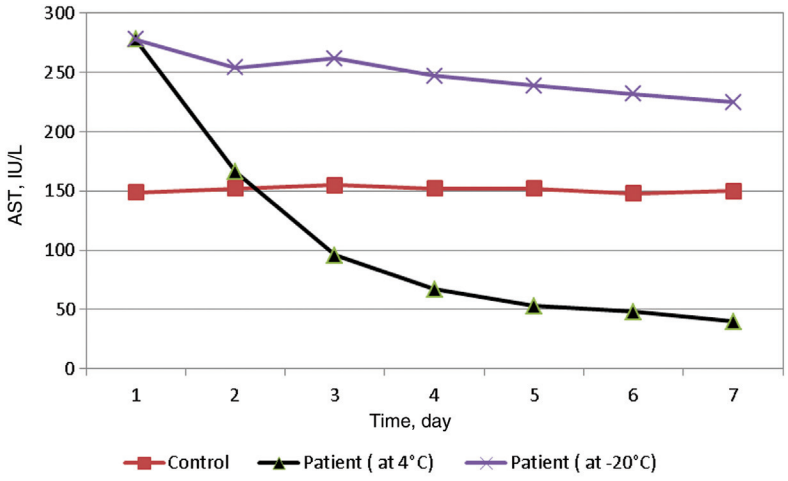

Figure 2 Change in AST activity in samples stored at different temperatures.

age [8]. This may serve as a useful reference point for rheumatologists.

Previous reports describe two forms of macro-AST complex; namely AST-IgG and AST-IgA. In our patient's sera the AST level decreased with time. This phenomenon has been reported in association with some cases of macro-AST complex and is not related to the type of complex. Mapplebeck et al. reported four cases of macro-AST of which two showed temperature instability [9]. Davidson and Watson have also described the instability of macro-AST with loss of AST activity in samples refrigerated at 4°C for 6 days [10]. The stability of AST at 4°C may be used as a simple method to evaluate the presence of macro-enzyme in samples. The unstable macro-AST complex in our patient made biochemical investigation elusive and necessitated fresh blood samples for confirmation. To avoid this situation, we suggest that if macro-AST is suspected, patient sera should be stored at –20°C immediately after venepuncture prior to analysis. Several methods for detection of the various macro-enzymes have been described. Polyethylene glycol precipitation (PEG) technique is widely used to screen for macro-enzymes in UK laboratories. This technique has its own limitations and a confirmatory method such as gel filtration chromatography (GFC) which is considered the reference method is necessary. Both techniques were used in our case.

An isolated macro-AST is a relatively rare phenomenon. It may result in persistently raised measurable AST which is relevant for patients that require regular liver function test monitoring. This should be considered as a possible cause as macro-enzymes are not routinely tested. In saying that, we would not recommend that patients with this biochemical finding should not have further investigations done. However, patients with persistently raised isolated AST without other abnormal indices, may benefit from a macro-enzyme test to preclude extensive or invasive investigations.

Learning points

An isolated macro-AST is a relatively rare phenomenon.

Patients with persistently raised isolated AST levels, where there are no other abnormal indices, may benefit from a macro-enzyme test to avoid extensive or invasive investigations.

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