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Unexplained High Activity of Aspartate Aminotransferase in an Asymptomatic Pediatric Patient

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Abstract

Elevated enzyme activities in plasma may at times be attributed to the presence of macro-enzymes. The macro-enzymes are often serum enzymes in complex with immunoglobulins, resulting in a greater molecular mass that cannot be filtered by renal glomeruli and are, hence, retained in the plasma. The aspartate aminotransferase (AST) can exist as a macro-enzyme, although it has been rarely reported.

We describe a pediatric patient with persistently elevated serum AST activity, due to macro-enzyme formation between AST and an immunoglobulin. This is to highlight the importance of early diagnosis of macro-AST in an otherwise asymptomatic pediatric patient with isolated AST-elevation and to avoid unnecessary costly testing.

***Key words*:** Alanine, Alkaline phosphatase, Aspartate aminotransferase, Child, Macro-Enzymes.

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1- INTRODUCTION

Macro aminotransferase (AST) is defined as a benign condition due to binding of AST to macromolecules like immunoglobulins or other plasma components. Due to their large size and mass, the macro-AST complexes are "entrapped" in the serum. They have reduced plasma clearance and consequently, have an extended half-life.

In most of the cases described in literature, AST was complexed with immunoglobulins (namely IgG, IgA and IgM). Macro-AST has to be considered in any child displaying isolated AST elevation (1); be it a healthy child or anyone with a co-morbid of chronic liver disease, autoimmune disease, malignancy or Medium-chain acyl-CoA dehydrogenase deficiency (MCAD). This will also ensure that unnecessary invasive and expensive evaluations do not take place (2). In addition to that, no treatment is required in an asymptomatic patient and regular follow-up is neither recommended nor required.

2- CASE REPORT

A 10 years old African-American boy, with no known past medical or family history, presented with elevated AST enzyme levels, ranging from 65 to 110 U/L, since past three years. His history was negative for abdominal pain, diarrhea, constipation, blood in stool, emesis, weight changes, fatigue, jaundice, rashes, arthralgias, and he had no reported allergies. He did not show any signs of inborn error of metabolism or fatty acid oxidation disease (or Medium Chain Acyl CoA-Dehydrogenase deficiency). His physical exam was unremarkable with normal growth and development. Initial evaluations such as Liver Function Test was positive for AST elevation only, with AST of 110 U/L, Alanine aminotransferase (ALT) 45 U/L, Alkaline Phosphatase 335 U/L, Albumin 4.6 g/dL. His complete blood count (CBC) was normal with Hemoglobin of 13.3 g/dL. His Celiac panel, thyroid tests, creatine phosphokinase (CPK), Lactate Dehydrogenase (LDH), alpha 1-antitrypsin, Renal Function Panel, hemoglobin electrophoresis, autoimmune studies and abdominal ultrasound were all within normal limits. His upper endoscopy revealed mild duodenitis by biopsy and he was started on oral proton pump inhibitor with no changes on his AST level. Some outside hospital work-up included a normal liver and muscle biopsy, normal echocardiography and electrocardiogram (EKG), along with a normal Computed Tomography (CT) scan of the abdomen and normal Magnetic Resonance Imaging (MRI) of brain.

Concomitant blood and urine AST tests carried out in our laboratory did not show decreased urinary AST level. The macro-AST pyridoxal phosphate level was 37 mcg/L (normal, since reference range is 5-50 mcg/L). Blood was also stored in a refrigerator for 6 days, and the level of serum AST remained the same before and after at 65 U/L. The marked elevation of AST with normal alanine aminotransferase (ALT) levels and a negative workup for the presence of liver disease lead to the consideration of presence of macro-AST in our patient. He continues to be asymptomatic with normal growth, and is seen in the Gastroenterology clinic every six months. His latest set of liver function tests showed an AST of 63 U/L, ALT of 12 U/L, alkaline phosphatase of 365 U/L, albumin of 5.0 g/dL and total bilirubin of 0.3 mg/dL.

3- DISCUSSION

The liver function tests (LFTs) include serum aminotransferases, bilirubin, alkaline phosphatase, prothrombin time and albumin. This term is misleading since most do not accurately depict how the liver is "functioning"; of the subset, only

albumin, bilirubin and prothrombin time truly assess liver function; elevation of serum aminotransferases indicates hepatocellular injury. Serum aminotransferases (formerly called transaminases) include alanine aminotransferase [ALT or serum glutamic pyruvic transaminase (SGPT)] and aspartate aminotransferase [AST or serum glutamic oxaloacetic transaminase (SGOT)].

ALT is found predominantly in the liver, with clinically negligible quantities found in the heart, kidneys and skeletal muscle. AST is found, in decreasing order of concentration, in the liver, cardiac muscle, skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes and erythrocytes (2). As a result, ALT is more specific for liver inflammation and disease than AST, as AST can be elevated in diseases affecting other organs, including trauma, burns, myocardial infarction, pancreatitis, acute kidney injury, acute hemolytic anemia and musculoskeletal diseases. In addition to that, clearance of serum aminotransferases involves catabolism by the reticuloendothelial system, and in that way, is very similar to the clearance of other serum proteins. AST is cleared more rapidly than ALT, and the major site of clearance is the hepatic sinusoidal cell. The phenomenon of macro-enzymes was first reported by Wilding et al. in 1964 (3).

Macro-enzymes are high-molecular weight complexes formed by the binding of an enzyme with a serum macromolecule (immunoglobulin or glycoprotein). Their large size does not allow them to be excreted by the kidneys and, therefore, their half-life is prolonged and there is an increase in the amount of circulating enzyme. Although they have been described to be present normally under physiologic conditions, they can be associated with pathological conditions such as infectious diseases, unspecified autoimmune disorders and even neoplastic transformations. Many case reports of the adult population have mentioned that elevated macro-AST levels spontaneously self-normalized in a few years. However, there have been varying mentions in literature as well, which have demonstrated both a fluctuating behavior of macro-enzyme levels as well as a persistent behavior for longer periods of time. Macro-enzymes are further classified into two types: Type I and Type II.

Type I macro-enzymes are formed when immunoglobulins-plasma enzyme complex is formed, and the immunoglobulins primarily involved are IgG, IgM and IgA (4). The pathogenesis is still unknown but may be due to autoimmunity via molecular mimicry. By contrast, Type II macro-enzymes arise through the process of self-polymerization or association with a foreign chemical, which is usually intravenously infused, such as a glycopeptide (4). Type II macro-enzymes are only transient.

Macro-enzymes are reported less frequently in children and adolescents than in adults. Also, they have been better described for most routinely measured enzymes like amylase and creatine kinase; with only a few reports of macro-AST, the first case of which was reported in 1978.
Macro-AST belongs to the class of Type I macro-enzymes (4). The prevalence of macro-AST, based upon referrals to tertiary centers for evaluation of isolated elevation of AST levels, has been reported to be between 13.1 and 60% for adults (5, 6) and 38.6% for children (5, 6).

Several methods for detecting macro-enzymes have been described, for example gel filtration chromatography, serum protein electrophoresis, polyethylene glycol (PEG) precipitation and immunoglobulin binding with protein A- or protein G-Sepharose beads. These tests are said to be highly sensitive and specific, but unfortunately, are not widely available. Also, the polyethylene glycol precipitation

method (7) reported that these authors observed a 90% decrease in AST activity in plasma after six days of refrigeration at 4°C. Similar findings of an over 60% loss of AST activity after two days of storage at 2° to 8°C (8). There was, however, a major discrepancy between the data of the literature and our own results since we did not observe any significant loss of AST activity under the same previously described conditions. On further review of literature, we were able to obtain a research article in which Chtioui et al. (9) confirmed our results and also, had not seen AST activity reduction despite re-measurements in pathologic controls and healthy controls. It is possible that structural differences of different complexes and probably their physiochemical properties (9) explain their different response to precipitation at 4°C storage.

4- CONCLUSION

The biochemical abnormality of persistent elevation of AST may be secondary to acute and/or chronic hepatitis (6), malignancies, autoimmune diseases, congenital disorders, hemolytic diseases, drugs, toxins as well as macro-AST. It is important to consider macro-AST elevation as a differential of isolated unexplained AST elevation in order to avoid unnecessary and costly invasive diagnostic workup (10). Also, it does not require any specific treatment and patient (and families) must be reassured regarding the benign nature and evolution of macro-AST (5, 11).

5- CONFLICT OF INTEREST

The authors had not any financial or personal relationships with other people or organizations during the study. So, there was no conflict of interests in this article.

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