AST/ALT Ratio In Acute, Uncomplicated Falciparum Malaria Infection: Comparison In Relation To The AST/ALT Ratios In Diseases Of The Liver

I Garba, U Gregory

Citation

I Garba, U Gregory. *AST/ALT Ratio In Acute, Uncomplicated Falciparum Malaria Infection: Comparison In Relation To The AST/ALT Ratios In Diseases Of The Liver*. The Internet Journal of Anesthesiology. 2006 Volume 14 Number 2.

Abstract

Introduction: Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities were assayed in 110 adult patients (age range 18-40 years) presenting with acute, uncomplicated falciparum malaria infection and a control group of 80 age and sex-matched adults.
Methods: Patient selection was done by simple random sampling of adult males and females presenting at the Bauchi State Specialist Hospital with a history of fever and malaise not lasting more that seven days and who were subsequently confirmed to be malaria-positive by microscopic examination of Giemsa-stained thin blood slides.
Results: The mean serum AST and ALT activities were found to increase significantly relative to the AST and ALT values in the control group. Serum AST activity was 38.29 ± 1.37 IU in the falciparum malaria patients and 30.19 ± 1.37 IU in the healthy controls, $p < 0.05$. Similarly serum ALT activity was 31.06 ± 0.58 IU in falciparum malaria patients and 24.96 ± 0.92 IU in the control group, $p < 0.05$. The mean AST/ALT ratio in acute falciparum malaria infection was found to be 1.22 ± 0.14. This ratio differs significantly from the AST/ALT ratios reported for patients with Non-alcoholic steatohepatitis, chronic hepatitis C, alcoholic liver disease, hepatitis B and cirrhosis, $p < 0.05$.
Conclusion:An AST/ALT ratio greater than 1 during acute falciparum infection contradicts earlier reports that the ratio is highly specific to cirrhosis alone or has application as marker of liver disease only. Therefore the application the AST/ALT ratio as a non-invasive means of assessing liver disease must be done with caution in the tropics where P. falciparum malaria infection is among the leading causes of hospital attendance.

INTRODUCTION

The transaminases are two closely related enzymes of clinical significance [1], particularly in the assessment of liver function. Among the duo, aspartate aminotransferase (AST) is known to exist in two electrophoretically distinct forms; a cationic isoenzyme associated with the mitochondria [2] and the anionic form associated with the cytoplasm [3]. Tissue levels of AST are highest in the heart and liver [4]. Significant amount are also found in skeletal muscle and kidney, with lower levels in pancreas, spleen and lung. Low levels of AST are also found in erythrocytes [5]. Alanine aminotransferase (ALT) is present in varying concentrations in the liver, heart, skeletal muscle, kidney, pancreas, spleen, lung and red blood cells [6]. Both enzymes increase in many disorders related to the liver damage; hence they have been proven to be sensitive indicators of liver-cell injury [7]. In particular, patients with viral hepatitis present with marked increases in the serum activities of both ALT and AST frequently before clinical symptoms of the disease become apparent [8,9]. ALT is more elevated than AST in various necro-inflammatory conditions of the liver, reflecting its greater efficiency as a liver disease marker [10]. Other conditions associated with increased serum ALT are infectious mononucleosis and intra-hepatic cholestasis. Serum AST levels are found to increase in myocardial infarction, muscle disease and hemolytic anemia [11]. Other reported causes of elevated serum aminotransferase activities include alcohol abuse [12,13], medication [7] autoimmune hepatitis [14,15], hepatic steatosis and non-alcoholic steatohepatitis, hemochromatosis [18], Wilson's disease and alpha1-antitrypsin deficiency [7]. However, it is not only diseases affecting the liver that are associated with elevated serum aminotransferases. Non-hepatic causes of raised serum aminotransferases include occult celiac sprue [7], muscular dystrophy [19,20], acute appendicitis [21] obesity [22] and circulating aminotransferase-immunoglobulin complexes

(macro-enzymes) [23]. Because of their usefulness as serum markers of liver diseases, the AST/ALT ratio has been postulated to be good indicators of hepatic diseases in adults [24,25]. In particular, the AST/ALT ratio has been used to distinguish cirrhotic from non-cirrhotic patients [26] and patients with non-alcoholic steatohepatitis from those with alcoholic liver disease [17]. In this study we assayed for the serum activities of both AST and ALT in adult presenting with acute P. falciparum malaria infection and compared the AST/ALT ratio obtained with the AST/ALT ratios reported for other diseases. The aim was to assess if the predictive and differential diagnostic value of this ratio is unique only to the diseases of the liver.

SUBJECTS AND METHODS

Study Locale: The southern and northern limits of Bauchi State where the study was conducted are demarcated by latitudes 9°30' North and 10°30' North respectively. Its Western and Eastern limits are bounded by longitudes 8°45' East and 11°0' East respectively. Two thirds of the land area is in the south of latitude 11°15'. Mean daily temperature in August, the month in which the study was conducted is 29.2° C and a humidity range of 68 %. August is the month of year where the incidence of falciparum malaria endemicity is at its highest peak because the highest average rainfall occurs in that month.

Patients and Study Design: Patient selection and pre-qualification was done by simple random sampling of individuals presenting at the Bauchi Specialist Hospital Outpatient Department with a history of fever and malaise within a period of 1-8 days, and who were confirmed to be infected with the falciparum malaria parasite by microscopic examination of Giemsa stained thin blood slides. Based on the following selection criteria, only 111 patients were found to be qualified for participation in the study. The age of patients is within the range of 18 – 40 years.

Patient Selection Criteria: Patients whose case history showed a concomitant presentation with the following conditions: Anemia, liver cirrhosis, hepatitis and other liver diseases, alcoholism and kidney disorders and those with a body-mass index > 25 were excluded from this study. Similarly patients on self-medication with any antimalarial drug prior to presentation were also excluded from the study.

Controls: For comparative purposes, a control group of 48 healthy adults (age interval, 18 – 40 years) were also enrolled in the study.

Serum: Venous blood (5 ml) was obtained from each of the patients by venepuncture of the antecubital vein using a sterile needle and syringe between the hours of 9 – 11.00 am local time. The blood samples were then transferred into clean, sterile centrifuge tubes and allowed to clot. Each clotted sample was centrifuged at 3000g for 10 minutes to obtain the sera. Enzyme assay was carried out within 24 hours of collection.

Enzyme assays: Serum AST and ALT activities were assayed according to the method described in Stoeve and Makarova [27]. All the reagents used in the work were of analaR grade.

Data analysis: Data was analyzed using the Openstat4 statistical software (Version 6, mod 3). The difference between the mean serum AST and ALT activities in healthy controls and infected adult falciparum malaria patients was analyzed using the Student's t-test for correlated samples. The difference between AST/ALT ratios in acute falciparum malaria infection and other diseases were analyzed using the Student's t-test for independent samples. p values < 0.05 were considered significant.

Ethics: This work was conducted in accordance with the following ethical declarations: World Medical Association's Declaration of Helsinki [28], APA Ethical Principles in the Conduct of Research with Human Participants [29], World Medical Association's Declaration of Lisbon on the Rights of the Patient [30] and CIOMS / WHO International Guidelines for the Conduct of Research Involving Human Subjects [31].

RESULTS

Figure 1

Table 1: AST and ALT activities in adult malaria patients and control (IU).

Enzymes	Mean ± SD	
	Patients	Control
ALT	31.06 ± 0.56[a]	24.96 ± 0.92[a]
AST	38.29 ± 1.37[b]	30.19 ± 1.37[b]
AST/ALT Ratio	1.23	1.21
% increase in serum ALT activity relative to controls = 20.43		
% increase in serum AST activity relative to controls = 26.83		

Values with the same superscript on a row differ significantly at p < 0.05

Figure 2

Table 2: Relative AST/ALT Ratios in acute malaria infection and some selected diseases.

Diseases REFERENCE	AST/ALT Ratio
Acute *falciparum* malaria infection	1.22[a]
Alcoholic liver disease 17	2.60[b]
Non-alcoholic steatohepatitis 17	0.90[c]
Chronic hepatitis C infection 26	0.99[d]
Hepatitis B 32	0.80[e]
Cirrhosis 33	0.93[f]
P. *Vivax* infection 34	0.90[g]

a-b, a-c, a-d, a-e, a-f, a-g (Differences significant at p = 0.003)

The normal healthy reference values for both aspartate and alanine aminotransferases in the selected study locale are as follows: 30.19 ± 1.37 IU (AST) and 24.96 ± 0.92 IU (ALT), table 1. ALT and AST values in acute falciparum malaria infection were found to be as follows: 31.06 ± 0.58 IU and 38.29 ± 1.37 IU respectively as shown in table 1. Relative to the healthy reference values, the activities of both ALT and AST were found to be significantly higher in acute falciparum malaria patients, $p < 0.05$. These values represent 20.43 % and 26.83 % increases in the serum activities of ALT and AST respectively. Table 2 shows the AST/ALT ratios in acute falciparum malaria patients and other disease conditions. The AST/ALT ratio of 1.22 in malaria patients is significantly higher than the AST/ALT ratio in all the other diseases except alcoholic liver disease, $P < 0.05$, which has the highest AST/ALT ratio.

DISCUSSION

The normal, healthy values for serum AST and ALT as reported by Pratt and Kaplan[7] and later supported by Prati et al., [35]are in the range of less than 30-40 U per liter. These values are above the normal range obtained in our study as shown in table 1. The differences in the normal, healthy ranges are not unexpected. This is because the normal, healthy ranges differ from one laboratory to another[7]. The possible reasons for such variations include environmental, nutritional status and anthropometric indices [36]. Acute P falciparum malaria infection is the leading cause of death and disability, particularly in tropical Africa. The pathogenesis of this parasitic infection involves the liver stage where infective sporozoites invade and multiply in the hepatocytes and an erythrocytic stage where merozoites cause the destruction of infected red blood cells prior to their differentiation into male and female gametocytes [37,38]. Since both the liver and erythrocytes are rich sources of AST and ALT, the activities of the invading P falciparum parasites in these organs/tissues can lead to damage to the membranes of these organs/tissues and the consequent release of AST and ALT, resulting in the observed increase in the serum activities of these enzymes. The lower AST/ALT ratio observed in P. vivax infection is a reflection of the differences in the degree of pathogenesis between vivax and falciparum malaria infection. It is also suggestive that parasite activities in P. vivax infection is associated with a lesser degree of hepatocytes and red cell damage and a confirmation that falciparum malaria is the most lethal of all the human malaria parasites. In relation to alcoholic liver disease, the AST/ALT ratio in falciparum malaria infection is significantly lower.

This is not an unexpected finding since alcohol consumption has a more damaging effect on centriportal liver cells which are rich in AST. In addition, this high AST/ALT ratio in alcoholic liver disease is a reflection of the low serum activity of ALT in patients with this disease [12]. The comparatively low AST/ALT ratios in the other disease can be explained by the differences in the etiologies of these conditions relative to that of falciparum malaria infection. Considering earlier reports which indicates that an AST/ALT ratio > or = 1 is unique and indicative of cirrhosis [25,26], the finding of an AST/ALT ratio > 1 in acute P. falciparum malaria infection is a justification that changes in AST/ALT ratios in disease should be interpreted with caution, particularly in malaria-endemic areas. This is more so since there is no unanimity in the predictive value of AST/ALT ratio in cirrhosis [39,40]. Furthermore, the interpretation of an AST/ALT ratio in a tropical setting where falciparum infection is endemic could be indicative of malaria infection not cirrhosis.

CORRESPONDENCE TO

Ibrahim Hassan Garba EMAIL: ihgarba2002@yahoo.com
Telephone: 0804-5252-720

References

1. Huncrantz R. Galuman H. Lindberg G. Nilsson LH. Liver investigation in 149 asymptomatic patients with moderately elevated activities of serum aminotransferases. Scand J Gastroentrol 1986; 21: 109-113
2. Watazu Y. Uji Y. Suguichi H. Okabe KH. Murao S. New automated measurement of mitochondrial aspartate aminotransferase with use of protease 401. Clin Chem 1990; 3: 687-689
3. Grostadt M. Rej R. Huseby NE. Mitochondrial aspartate aminotransferase determined by Fast-Protein liquid

chromatography. Clin Chem 1980; 36: 348-350
4. Calbreath D F. Clinical Chemistry. Philadelphia, W.B. Saunders Company. 1992; 468p
5. Ono K. Ono T. Matsumata T. The pathogenesis of decreased aspartate aminotransferase and alanine aminotransferase activity in the plasma of hemodialysis patients: the role of vitamin B6 deficiency. Clin Nephrol 1995; 43: 405-408.
6. Sherman KE. Alanine aminotransferase in clinical practice. A review. Arch Intern Med 1991; 151:260-265
7. Pratt DS, Kaplan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients. NEJM 2000; 1266-1271
8. Schiff ER. De Medina M. Kahn RS. New perspectives in the diagnosis of Hepatitis C. Semin Liver Dis 1999; 19: Suppl 1: 3-15
9. Jensen D, Dickerson DD, Linderman MA, Kessler H. Serum alanine aminotransferase levels and prevalence of hepatitis A, B and Delta in outpatients. Arch Intern Med 1987; 147: 1734-1737
10. Rosenthal P, Haight M. Aminotransferase as a prognostic index in infants with liver disease. Clin Chem 1989; 36: 346 -348.
11. Carrion-matinez M, Barber B, Pazole SP. On the determination of aspartate aminotransferase. Biochim Biophys Acta 1977; 4: 382
12. Cohen JA, Kaplan MM. The SGOT/SGPT ratio - an indicator of alcoholic liver disease. Dig Dis Sci 1979; 24:835-838
13. Diehl AM, Goodman Z, Ishak KG. Alcohol-like liver disease in non-alcoholics: a clinical and histologic comparison with alcohol-induced liver injury. Gastroenterol 1988; 95: 1056-1062.
14. Czaja AJ, Natural history, clinical features, and treatment of autoimmune hepatitis. Semin Liver Dis 1984; 4: 1-12.
15. Krawitt EL. Autoimmune hepatitis. NEJM 1996; 334: 897-903.
16. Bacon BR, Farahvash MJ, Janney CG, Newschwander-Tetri BA. Non-alcoholic steatohepatitis: an expanded clinical entity. Gastroenterol 1994; 107:1103-1109.
17. Sorbi D, Boynton J, Lindor KD. The ratio of aspartate amino-transferase to alanine aminotransferase: Potential value in differentiating non- alcoholic steatohepatitis from alcoholic liver disease. Am J Gastroenterol 1999: 94: 1018-22
18. Powell LW, George DK, McDonnel SM, Kowdley KV. Diagnosis of hemochromatosis. Ann Intern Med 1998; 129: 925-931.
19. Zamora S, Adams C, Butzner JD, Machida H, Scott RB. Elevated aminotransferase activity as an indicator of muscular dystrophy: case reports and review of the literature. Can J Gastroenterol 1996; 10: 389-393.
20. Kamath BM, Dhawan A, Mieli-Vergani G. Raised serum transaminases: not always liver disease. Arch Dis Child 2000; 82: 266
21. Kundrotas LW, Clement DJ. Serum alanine aminotransferase (ALT) elevation in asymptomatic US Air Force basic trainee blood donors. Dig Dis Sci 1993; 38: 2145-2150.
22. Burns CJ, Boswell JM, Olsen GW. Liver enzyme activity and body-mass index. J Occup Environ Med 1996; 38: 1248-1252.
23. Buffet C, Corrriat A, Soni T, Pelletier G, Lemonier A, Etienne JP. (1987) Macroaspartate aminotransferase: Unusual cause of increased serum aspartate aminotransferase activity. Dig Dis Sci 1987; 32:1059-1060.
24. Rosenthal P. Haight M. Aminotransferase as a prognostic index in infants with liver disease. Clin Chem 1989; 36: 346 -348.
25. Sheth SG, Flamm SL, Gordon FD, Chopra S. AST/ALT ratio predicts cirrhosis in patients with chronic hepatitis C virus infection. Am J Gastroenterol 1998; 93: 44-48.
26. Park GJ, Lin BP, Ngu DB, Katelaris PH. Aspartate aminotransferase: alanine aminotransferase ratio in chronic hepatitis C infection: is it a useful predictor of cirrhosis? J Gastroenterol Hepatol 2000; 15: 386-390.
27. Strove EA, Makarova VG. Laboratory Manual in Biochemistry. Moscow. MIR Publishers. 1989; 234p
28. World Medical Association's Declaration of Helsinki. Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects. Adopted by the 18th World Medical Assembly, Helsinki; Finland, June1964 and amended by the 48th General Assembly, Somerset West, Republic of South Africa, October 1996
29. American Psychological Association (APA). Committee for the Protectionof Human Participants in Research . Ethical Principles in the Conduct of Research with Human Participants. American Psychological Association,Washington D.C. 1982.
30. World Medical Association. Declaration on the Rights of the Patient, Amended by the 43rd General Assembly, Bali, Indonesia. 1995.
31. Council of International Organization of Medical Sciences / World HealthOrganization (CIOMS/WHO). International Ethical Guidelines for Biomedical Research Involving Human Subjects. Geneva, Switzerland.1993.
32. Park JH, Park CK, Kim ES, Park SY, Jo CM, Tak WY, Kweon YO, Kim SK, Choi YW. The diagnostic value of serum hyaluronic acid, 7S domain of type IV collagen and AST/ALT ratio as markers of hepatic fibrosis in chronic hepatitis B and Cirrhosis patients. Taehan Kan Hakkoe Chi 2003; 9: 79-88.
33. Reedy DW, Loo AT, Levine RA. AST/ALT ratio > or = 1 is not diagnostic of cirrhosis in patients with chronic hepatitis C. Dig Dis Sci 1998; 43: 215 - 219
34. Kochar DK, Visnal S, Singh N, Kochar SK, Kumar VS, Das A. Plasmodium vivax malaria. Emerg Infect Dis 2005; 11:132-134.
35. Prati D, Taioli E, Zanella A, et al. Updated definitions of healthy ranges for serum alanine aminotransferase levels. Ann Intern Med 2002; 137: 1-9.
36. Piton A, Poynard T, Imbert-Bismut F, et al. Factors associated with serum Alanine transaminase activity in healthy subjects: consequences for the definition of normal values, for selection of blood donors, and for patients with chronic hepatitis C. Hepatology 1998; 27: 1213-1219.
37. Miller LH, Baruch DI, Marsh K, Doumbo OK. The pathogenic basis of malaria. Nature 2002; 415: 673 - 679.
38. Sinden RE. The biology of plasmodium in the mosquito. Experientia 1984; 40:1330 - 1343.
39. Pohl A, Behling C, Olivier D, Kilani M, Momson P, Hassanein T. Serum Aminotransferase levels and platelet count as predictor of degree of fibrosis in chronic hepatitis C patients. Am J Gastroenterol 2001; 11: 3053-3055.
40. Imperiale TF, Said AT, Cummings OW, Born LJ. Need for validation of clinical decision aids: use of the AST/ALT ratio in predicting cirrhosis in chronic hepatitis C. Am J Gastroenterol 2001; 3: 918-919.

Author Information

Ibrahim Hassan Garba, BSc, MSc
Chemistry Programme, School of Science, Abubakar Tafawa Balewa University

Ubom Gregory, BSc, MSc, PhD
Department of Biochemistry, Faculty of Medical Sciences, University of Jos