JAUNDICE AND SINUS BRADYCARDIA 100 YEARS OF AN UNSOLVED MYSTERY

A CASE REPORT AND REVIEW OF LITERATURE

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ABSTRACT

The association of cholestatic jaundice and bradycardia is widely accepted. Several reports have documented a variety of arrhythmias including sinus bradycardia and cardiac asystole in patients with fulminant hepatitis. However the exact mechanism by which jaundice leads to development of bradycardia is still not known even after hundred years of publication of a land mark study in this connection by John. H. King in 1909. We report a case of severe bradycardia associated with fulminant Hepatitis E in a post-partum lady with review of literature.

INTRODUCTION

The heart is generally not affected directly in typical cases of acute viral hepatitis[1]. However in severe or fulminant viral hepatitis, cardiovascular derangements have been well documented. Several arrhythmias including ventricular ectopic beats, ventricular tachycardia, second and third degree AV block, sinus bradycardia and cardiac asystole have been reported in patients with fulminant hepatitis[2-5]. Cholestasis is still widely included in the differential diagnosis of bradycardia. John. H. King in 1909 showed that the injection of bile increases the vagal tone and that this action can be abolished by administration of atropine. Subsequent observers however held entirely different opinion regarding the mechanism by which bile salts exercise this function. The explanation for the bradycardia still remains unclear. We in this case reviewed the literature to highlight this unsolved mystery of more than 100 years.

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CASE REPORT

A 21 year old lady presented in the early postpartum period with a five day history of low grade fever, nausea and yellowish discoloration of skin and eyes. She had a normal vaginal delivery at another hospital and was discharged in a stable condition. On examination she had pallor, a puffy face and jaundiced skin and sclerae. Rest of the examination was unremarkable. On admission her pulse rate was 90 beats/min and regular. Blood Pressure was 110/70 and she was afebrile. Complete blood count showed white cell count 24800/ul, Hb 7.96 g/dl, platelets 205000/ul, Hct 23.7% . Results of initial biochemical and coagulation tests included Total Bilirubin 5.2 mg/dl, Direct Bilirubin 4.6mg/dl, AST 68, ALT 69, Alkaline Phosphatase 493, PT 21.9, INR 2.1, APTT 40.1, Cr 2.05, BUN 51, Urea 109. An ultrasound of pelvis did not show any retained products of conception. Patient was managed initially under provisional diagnosis of liver failure complicated by severe anemia, renal dysfunction and systemic infection. She was treated conservatively with I/V fluids, and broad spectrum antibiotics. Viral serological studies were positive for Hepatitis E Virus (HEV IgM) and negative for Hepatitis A (anti HAV IgG), Hepatitis B surface Antigen (HbsAg) and Hepatitis C (anti HCV) with enzyme immunoassay method.

A diagnosis of liver failure secondary to Hepatitis E was made. On 5th day of admission, cardiology department was consulted as she developed severe

bradycardia. ECG showed sinus rhythm with a pulse rate of 48. Blood pressure was normal and there were no symptoms associated with bradycardia. Echocardiographic examination was also normal. At that time the total bilirubin was 15.8, direct bilirubin 13.8, AST 107, ALT 367, Alkaline phosphatase 202. During the course of her illness her peak levels of total bilirubin and direct bilirubin were 20.15 and17.69 respectively. Her heart rate at that time was between 40-45. Bradycardia continued for 4 days without any symptoms and resolved spontaneously as the serum bilirubin levels gradually came down. On 12th day of her admission LFT'S were: total bilirubin 9.90, direct bilirubin 7.22, Heart rate after dipping down to 40/ min was once again 86 beats /min (as shown in Fig 1). Patient improved clinically and biochemically in 2 weeks time and was discharged and followed on outpatient basis. Her biochemical and coagulation tests returned to normal after about 9 weeks.

DISCUSSION

Cardiovascular complications in acute viral hepatitis have been reported in the past. These problems take three forms in patient with liver failure. The first is the appearance of a hyperkinetic circulation manifested by increased heart rate and cardiac output associated with decreased peripheral vascular resistance and arterial hypotension[6,7]. The pathogenesis of this syndrome is unclear and surprisingly little experimental study has been made of this phenomenon in acute hepatitis. The second and more clinically threatening cardiac complication is the onset of arrhythmias. Sinus bradycardia, premature ventricular complexes (PVCs), ventricular tachycardia, second and third degree AV block, and even cardiac asystole has been noted in patients with fulminant hepatitis[2-4]. The high incidence of arrythmias thus necessitates continuous electrocardiographic montoring of every patient with fulminant hepatitis. All forms of fulminant hepatitis, whether caused by hepatitis virus A, B, non-A, non-B, or drugs such as acetaminophen or halothane appear to be associated with arrhythmias[8-10]. In addition, cadiopathic viruses such as Coxsackie B can rarely cause concomitant icteric hepatitis with myocarditis[11], which is the third form of cardiac involvement in patients with severe liver disease.

Bradycardia can present in two ways: an absolute bradycardia i.e., a resting heart rate of less than 60 beats per minute and a "relative" bradycardia i.e., an inadequate tachycardiac response following sympathetic stimulation. The etiological factors responsible for these two phenomenon are unknown. Only a few clinical studies on the effects of cholestasis and cholemia on cardiovascular function have been published. The results of all experiments performed in laboratory animals indicate that bile acids have a negative ionotropic or chronotropic effect on heart[12,13]. Using anesthetized rats, Joubart demonstrated that intravenous administration of cholic acid elicited a dose dependent negative chronotropic effect[14]. Bogin et al and Enrique de Salamanca showed a negative chronotropic effect of bile acids on isolated rat cardiac myocytes and in the isolated perfused heart respectively[15]. Despite these evidences, however, this theory cannot be accepted in its entirety. Song and colleagues were unable to show a correlation between bile acid concentration and sinus bradycardia because the later was not observed[16]. Similarly Joubart (1978)[14] and Lee (1986)[17] found no existence of bradycardia in patients with jaundice. Furthermore the majority of investigators who showed bradycardia as an effect of bile acids did not measure plasma bile acid concentrations and most of the animal studies undertaken were in normal rats and this data may not correlate with the findings in jaundiced rats. The paucity of reports prompted Heaton to note that "bradycardia of obstructive jaundice attributable to bile acids does not seem to have been investigated by modern methods[18].

Hence there is much diversity of opinions, however three hypotheses have been proposed to explain the possible mechanism by which bile acids cause bradycardia : (1) Mechanical interference by forming a monolayer on the cell membrane surface[14], (2) interfering with the ability of the membrane to conduct action potentials by reducing the slow inward current of calcium[12] (3) Acting as antimuscarinic antagonist since their effects can be reversed by atropine or potentiated by physostigmine[14].

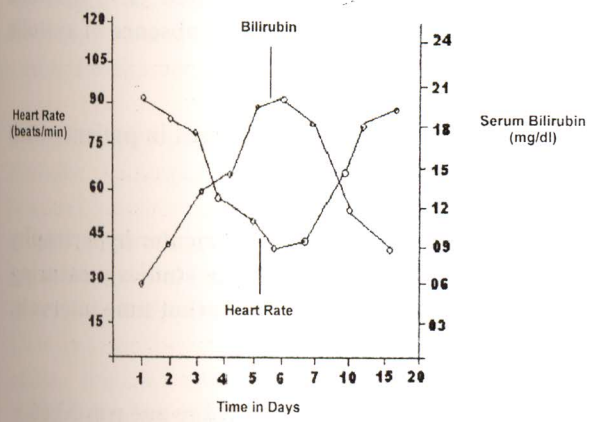
Our case, in line with the widely held concept, also showed a correlation of bradycardia with increasing serum bilirubin levels and provides a very needed impetus to investigate this effect in the light of modern sophisticated techniques which have led to an accurate description of mechanical, electrophysiological and

bichemical cardiac changes in the last two decades.

Nevertheless, In summarizing the cardiovascular effects of bile acids, the evidence so far suggests that bile acids probably are the etiological factors responsible for bradycardia and other cardiac dysfunction in patients with jaundice. However the exact mechanism of action of bile acids on cardiac function needs to be elucidated.

Annex - 1

Relationshio of Serum Bilirubin to Heart Rate



REFERENCES

1. Koff, R.S., and Galambos, J., Viral Hepatitis in Diseases of liver,5th ed., Lippincott, Philadelphia,1982 ; 461.
2. Hoagland, C.L. and Shank, R.E, Infectious Hepatitis, A review of 200 cases, J. Am. Med. Assoc.1946; (130): 615.
3. Ochn, H., Feil. H., and Rinderkencht, R., Electrocardiographic changes in cases of infectious hepatitis, Cardiologia, Am. Heart. J, 1946; (31):183.
4. Adler, E. and Lyon, E., Cardiac disorders associated with infectious hepatitis, 1947; (11): 111.
5. Saphir, O., Amromin,G.D., and yokoo , H., Myocarditis in viral hepatitis, Am. J. Med. 1956; (231) 168.
6. Ritt,. D., Whealan, G., Werner, Eigenbrodt, E., Schenker., Acute hepatic necrosis with stupor and coma, An analysis of 31patients, Medicine (Baltimore). 1979; (48):151.
7. Rueff, B. and Benhamou, J.P., Acute hepatic necrosis and fulminant hepatic failure. Gut. 1973; (14): 805.
8. Bell, H., Cardiac Menifestations of viral Hepatitis, J.Am.Med. Assoc. 1971;(218): 387.
9. Weston, M.J., Talbot, I.C., Howarth, P.J.N., Frequency of arrhythmias and other cardiac abnormalities in fulminant hepatic failure. Br. Heart. J., 1976;(38):1179.
10. Pimstone, B.L. and Uys,C.J., Liver necrosis and myocardiopathy following paracetamol overdosage, S.Afr. Med.J. 1968;(42): 259.
11. Sun, N.C., and Smith,V.M., Hepatitis associated with myocarditis. New Eng.J..Med, 1966;(274): 190.
12. Binah,O., Rubinstein,I., Effects of bile acids on ventricular muscle contraction and Electrophysiological properties. Arch. Pharmacol., 1987;(335)160.
13. Better. O.S. and Bomzon. A., The effects of cholemia on the renal and cardiovascular systems.,in The Kidney in Liver Disease, 3rd Ed, Williams and Wilkins. Baltimore.1988; 508.
14. Joubart. P., An in vivo investigation of the negative chronotopic effects of cholic acid in the rat. Clin.Exp.Physiol, Pharmacol., 1978; (9).
15. Enriquez de Salmanca. R., Toni. P., Negative chronotropic effects of cholic acid on rat heart cells. Experientia, 1983;(39):1307.
16. Song. E., Segal.I., Sinus bradycardia in obstructive jaundice. Correlation with total serum bile concentrations. S. Afr. Med. J., 1983;(64): 548.
17. Lee, S.S., Girod. C., Hemodynamic characterization of chronic bile duct-ligated rats. Effect of pentobarbital sodium. Am. J. Physiol. 1986; (251):176.
18. Heaton,K. W., Bile acids in Health and disease. Churchill Living stone, London, 1972.