Case report

CHOLESTATIC BRADYCARDIA: THE STORY OF RISING BILIRUBIN AND THE SLOWING HEART – A CASE REPORT OF A 74 YEARS OLD FEMALE PATIENT AT UNIVERSITY OF NIGERIA TEACHING HOSPITAL, ENUGU, NIGERIA

ABSTRACT

The association between Cholestatic jaundice and bradycardia has been well documented with reports of a variety of bradyarrhythmias. Although the actual mechanism by which jaundice leads to development of bradycardia or bradyarrhythmia has remained a puzzle to both physicians and surgeons for more than a century, it has however been known to complicate the course and outcome of obstructive jaundice.

Case description: Here we report the case of an elderly woman suffering from obstructive jaundice secondary to pancreatic malignancy (carcinoma of head of pancreas). She subsequently developed progressive bradycardia and other cardiac rhythm disorders as her serum bilirubin and bile acids continued to rise, and was referred to us, the cardiologists. Blood samples were taken about every three days for serum bilirubin and bile acids assay, and serial electrocardiogram (ECG) was done accordingly. The total/direct bilirubin rose progressively from 28.4/17.6 umol/L at the outset to 501.5/234.0 umol/L. The bile acids equally increased steadily from Aspartate Transaminases/ Alanine Transaminases/ Alkaline Phosphatase (AST/ALT/ALP) levels = 96/81/1037 IU/L to as high as AST/ALT/ALP = 580/400/7000 IU/L.Patient manifested cardiac rhythm disorders ranging from sinus bradycardia with first degree atrio-ventricular (AV) block and heart rate (HR) of 54/min, to Mobitz type 2 AV block (HR =40/min), and to Complete heart block (HR=33/min) over two weeks period. She was commenced on drugs that enhance bile acid elimination and counteract excessive vagal stimulation, and later on a decompressive surgery (biliary diversion) was carried out under temporary pace maker support. Consequently, patient showed some improvement in her cardiovascular parameters following intake of those drugs and much further improvement following the biliary decompressive surgery under temporary pace maker support, with the HR increasing steadily up to normal rate of 68 to 86 b/min over 3 weeks period.

Conclusion: This case has significantly demonstrated that the postulated mechanisms of cholestatic bradycardia hold some credence.

Keywords: Cholestatic jaundice, bradycardia, pancreatic malignancy.

INTRODUCTION

Jaundice (icterus) refers to yellow pigmentation of skin, sclerae and mucosa due to increased plasma bilirubin, usually detectable when plasma bilirubin is >35umol/L[1]. It is classified based on aetiology and type of circulating bilirubin. In terms of aetiology, it is divided into pre-hepatic, hepatocellular and cholestatic (obstructive) jaundice. By the type of circulating bilirubin, it is classified as conjugated (direct) and unconjugated (indirect) hyperbilirubinaemia[1]. Pancreatic malignancy, especially carcinoma of head of pancreas, is a known cause of obstructive jaundice among many other causes as it blocks the biliary channel by which bile (containing bilirubin) is excreted.

According to GLOBOCAN 2018 estimates, pancreatic carcinoma ranked the 11th most common cancer in the world and the 7th leading cause of global cancer deaths in industrialized countries[2]. It has been listed among the five topmost cancers with highest mortality for both sexes in Europe[3] and Africa including Nigeria, contributing 3.2% of all new cases of cancer and 7.8% of all cancer deaths. [4] It is rare in adults <40yrs of age, with a median age at diagnosis of 71years[5]. It usually has a late presentation as symptoms only appear when the disease has progressed, thus implying that 85-90% of patients have already advanced disease at diagnosis[6].

It has been found that 60-70% of pancreatic cancers are located in the pancreatic head,[5] leading to hyperbilirubinaemia due to obstruction of the central bile duct in 70-80% of these patients[7].

This biliary obstruction and consequent hyperbilirubinaemia usually lead to further complications of the disease because bilirubin induces systemic inflammatory response syndrome which may lead to multiple organ dysfunction syndrome.[8]

CASE PRESENTATION

We present a 74 year old female who presented to the gastroenterologists at University of Nigeria Teaching Hospital (UNTH) Enugu, Nigeria on account of progressively worsening generalized body weakness and jaundice. She also had anorexia, unintentional progressive weight loss, passage of dark-coloured urine and generalized pruritus. On initial evaluation, she was pale with jaundiced sclerae and skin. The rest of the general examination was unremarkable. Her pulse rate was 78bpm normal volume, regular and her BP was 140/70 mmHg, being a

known hypertensive patient on treatment. The abdomen was soft. Liver was palpable 4cm below right costal margin, firm and non- tender. Other aspects of the systemic examination were unremarkable. Abdomeno-pelvic ultrasound scan showed a mass in the head of pancreas with features of carcinoma and with obstructed bile ducts. A working diagnosis of obstructive jaundice secondary to cancer of head of pancreas was made. Some other investigations were the carried out and the results are as enumerated below.

1) Full blood count (FBC) showed anaemia with haemoglobin of 8.7g/dl and marked leucocytosis (total WBC= 22,200/$mm^{3)}$.
2) Liver function test (LFT) – total bilirubin 28.4mg/dl (0.2 – 1.03); conjugated bilirubin = 15.4mg/dl (normal is 0.1 – 0.5); Aspartate transaminase (AST) = 417.21U/L (normal is 0-40); Alanine transaminase (ALT) = 386.4U/L (normal is 0-34); Alanine transaminase; Alkaline transaminase (ALP) = 6418U/L (normal is 0-240)
3) Viral screenings (HBsA; Anti-HCV; HIV I &II) were all negative
4) Urinalysis – showed marked bilirubinuria
5) PT/INR - PT = 18secs (9.5 – 14.5); INR = 1.45
6) Fasting blood glucose (FBG) = 118mg/dl
7) Initial electrocardiogram (ECG) – showed normal sinus rhythm with HR of 74bpm. Other ECG parameters were normal.
8) Echocardiogram – showed aortic valve sclerosis with no functional impairment. Other echocardiographic parameters normal.
9) Abdominal Computed Tomography (CT) scan – confirmed cancer head of pancreas with a small solitary metastatic nodule in the right lung base.

She was referred to General Surgeons who reviewed and admitted her into the ward with a working diagnosis of obstructive jaundice secondary to Carcinoma of the head of pancreas and sepsis from ascending cholangitis. Further plan was to do work up for cholecystojejunostomy. In the meantime, her liver function test (LFT) continued to worsen with consequent cardiovascular abnormalities, mainly in form of bradycardia. Hence, we, the cardiologists, were invited to review and co-manage the patient. At this time, patient had a pulse rate (PR) of 33bpm, Bp of 130/70mmHg and heart sounds (HS) = $S_1S_2S_4$, no murmur. Bedside ECG then showed 1^{st} degree AV block with a HR of 36bpm. Plan was to relieve obstruction (biliary diversion) as soon as possible and she was commenced on the following medications: Tabs Ursodeoxycholic acid (UDCA) 250mg bd, Susp. Cholestyramine 4g bd, Tabs Salbutamol 4mg bd, IV Atropine 0.5mg diluted in 5mls of water for injection and given bolus (up to 2 doses of IV Atropine can be given in 5-10mins but not to exceed 3mg in a day), and Tabs Rifaximin 550mg bd, Susp. Lactulose 10mls bd for gut sterilization.

On commencement of the above regimen, pulse rate improved to 68b/m in 36hrs. However with worsening hyperbilirubinaemia, other cardiovascular and rythm abnormalities emerged.

Table1 below summarizes the findings (the relationship between rising bilirubin levels and cardiac dysfunction).

Several days later, with normalization of the PT/INR, she had a successful biliary decompression surgery (cholecystojejunostomy) under temporary (transcutaneous) pace maker support. Subsequent days post-operatively, there was remarkable reduction in total bilirubin levels with improvement of the heart rate. She was then referred back to the general surgeons and surgical oncologists for continued management of the primary disease, carcinoma of head of pancreas.

TABLE: 1 PRE- OPERATIVE VALUES, BEFORE CARDIOLOGISTS' REVIEW

Bilirubin (bil) Levels	**Transaminases**	**Pulse Rate**	**ECG Findings**
Day 1 Total bil = 28.4 Direct bil = 17.6	AST = 96 ALT = 81 ALP = 1037	76bpm	Sinus rhythm at 78bpm
Day 4 Total bil = 289 Direct bil = 287	AST = 325.4 ALT = 137 ALP = 1126	54bpm	1st degree AV block
Day 7 Total bil = 399.94 Direct bil = 292	AST = 364 ALT = 135 ALP = 1740	46bpm	High grade AV block
Day 9 Total bil = 411 Direct bil = 233	AST = 417.2 ALT = 386.4 ALP = 6418	40bpm	2nd degree AV block, Mobitz Type II
Day 12 Total bil = 501.8 Direct bil = 234.0	AST = 580 ALT = 400 ALP = 7000	33bpm	Complete heart block

The rising bilirubin and the slowing heart

TABLE: 2 FROM 36HRS AFTER CARDIOLOGISTS' REVIEW

Bilirubin Levels	**Transaminases**	**Pulse Rate**	**ECG Findings**
Day 14 Total bil = 345.4 Direct bil = 254.4	AST = 100 ALT = 81 ALP = 834	68bpm	Atrial bigeminy
POST – OP			
Day 18 Total bil = 262.6 Direct bil = 180.2	AST = 72 ALT = 64 ALP = 482	72bpm	Premature atrial and ventricular complexes
Day 21 Total bil = 208 Direct bil = 110	AST = 50 ALT = 36 ALP = 181	86bpm	Premature ventricular complexes

The falling bilirubin and the recovering heart rate

DISCUSSION

The association between obstructive jaundice and bradycardia has been known for over a centutry.[9] Increased recognition and awareness of this clinical problem have led to extensive clinical and laboratory investigations, culminating in a better appreciation and understanding between the liver and the cardiovascular system.[10] The history of cholestatic bradycardia dates as far back as 1863 when Rohrig demonstrated that bile acids are responsible for the bradycardia and hypotension of jaundice.[11] Detailed investigation into the relationship between bile acids, liver disorders and cardiac dysfunction was done by Kowalski et al., in 1953, who observed that patients with liver cirrhosis had a prolonged QTc interval. [12]

Cardiac Abnormalities in Cholestasis

Thus cardiac abnormalities associated with cholestasis include; Bradycardia[11], Hypotension[13,14], Hyporesponsiveness of the heart to adrenergic stimulation[15, 16] and QTc prolongation[17].

From our own observation from our patient, other cardiac abnormalities we noticed include; AV block (initial first degree AV block that progressed to complete heart block), Ventricular bigeminy, Premature atrial and ventricular contractions

Mechanisms of Cholestasis-induced Cardiac Abnormalities

The precise mechanisms of cholestasis-induced cardiac complications are not completely understood. However, the possible mechanisms and potential causative molecules of cardiovascular dysfunction in obstructive cholestasis are discussed below;

Bile Acids

Bile acids (BA) are amphiphilic, amphipathic steroids synthesized from free cholesterol in the hepatocytes and are essential for the solubilization of lipids in bile and the gastrointestinal tract, the induction and maintenance of bile flow and the absorption of fat from the gastrointestinal tract[18]. Several studies, both in vitro and in vivo, have demonstrated the negative chronotropic and inotropic effects of bile acids on the heart.[19,20,21] . Some other studies have suggested that the negative chronotropic effect induced by bile acids is mediated through vagal stimulation and can be antagonized by atropine.[21,22,23] .

Similarly, the proposed hypotheses by which bile acids induce bradycardia include; Formation of a monolayer on the cell membranes surface with consequent mechanical interference[21], Impairment of cell membrane action potentials by reducing inward current flow of calcium[24], and vagal stimulation.

These mechanisms have provided the basis of treatment regimen in affected patients. Atropine has been used with good results to counter the excessive vagal stimulation and improve inotropic heart characteristics. This was also demonstrated in our patient, in whom we used 0.5mg Atropine injections at critical periods to improve the heart rate. Bile acids are vasorelaxants[25]. The vasorelaxants action of bile acids is linked to their lipophilicity. Lipophilic bile acids exhibit greater vasoactivity than the modest to negligible vasoactivity exhibited by hydrophilic bile acids[26] One of the drugs approved for treatment of cholestasis is ursodeoxycholic acid (UDCA). UDCA is a relatively hydrophilic BA which is thought to displace more hydrophobic BAs in the BA pool and thus shift the composition to a less toxic one.[27,28,29] Hydrophobic BAs are cardiotoxic while hydrophilic BAs are cardioprotective, and cause enhanced cardiac contractility[30,31]; this informed the use of Tabs Ursodeoxycholic acid 250mg bd for our patient with an impressive result. The antiarrhythmic effect of UDCA is thought to be partially mediated by an increase in cardiac wavelength, due to the attenuation of conduction velocity slowing [32]. Also cholestyramine, a BA sequestrant, which was introduced in the patient management at some point, has been found to reverse the pathophysiological parameters in cholestasis.[33,34]

Bilirubin/Hyperbilirubinaemia

Our index patient showed a correlation between increasing serum bilirubin levels and worsening bradycardia and vice versa. This is illustrated in the figure below.

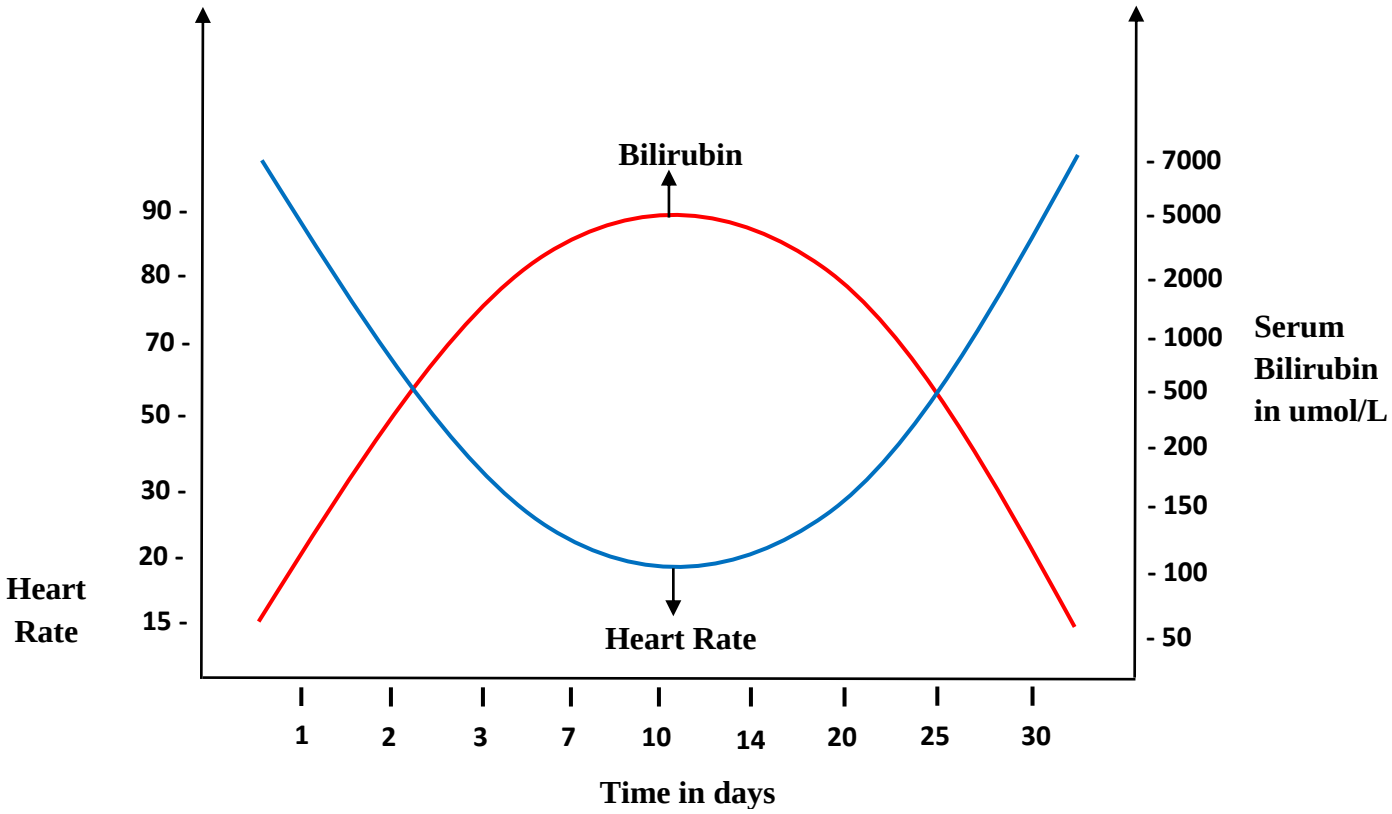

Figure 1: Relationship between Serum Bilirubin and Heart Rate

The graph in fig.1 above shows a steady fall in heart rate as the serum bilirubin level rose over the first ten days, followed by a period of gradual recovery of heart rate to normal from day10 to day 30 as serum bilirubin decreased following treatment.

This buttresses the fact that bilirubin is an important molecule implicated in cholestatic bradycardia. Thus major treatment option includes relief of obstruction as soon as possible as this helps in reducing bilirubin levels. Our patient had sustained gradual reduction of bilirubin levels following the cholecystojejunostomy with a consequent improvement in cardiovascular status.

Thirteen years ago (June 2010), Naveed Akhtar et al reported a case of cholestatic jaundice and bradycardia in a 21 year old lady with liver failure due to Hepatitis E viral infection in early postpartum period, who developed sinus bradycardia.[35] The pulse/ heart rate (PR/HR) crashed from 90 beats/min to 48 beats/min on the 5th day of her illness, and further deteriorated to hover between 40 – 45 beats/min as her serum bilirubin and liver enzyme levels continued to increase.

Their patient remained asymptomatic and the HR reverted spontaneously to a normal rate of 86 beats/min as the serum bilirubin and liver enzyme levels came down to normal.[35] This case is similar to that of our patient in that both patients had bradycardia in response to high rising levels of cholestasis with spontaneous reversal to normalcy as cholestasis improved. However, while their patient had sinus bradycardia, our patient demonstrated more core complex brady-arrhythmias and other cardiac rhythm abnormalities.

Nitric Oxide

The receptors of mRNA of endothelial type nitric oxide synthase are abundantly expressed in atrial and ventricular cardiomyocytes.[36] thus supporting the role of nitric oxide in regulating cardiac function.

Nitric oxide negatively regulates cardiac contractile function by altering calcium regulation in the heart. It impairs entry of calcium from extracellular space and its mobilization from internal stores. It also causes endothelial dysfunction and cholestasis-induced vasorelaxation as first reported by Utkan et al.[37]

Bilirubin inhibits the up-regulation of inducible nitric oxide synthase (NOS) by scavenging reactive oxygen species generated by the toll-like receptor 4-dependent activation of NADPH oxidase. [38] In this way, high levels of bilirubin indirectly encourages accumulation of nitric oxide which in turn causes depression of cardiac contractility with resultant bradyarrhythmias. Several studies have shown that in vivo use of nitric oxide synthase inhibitors such as L-NNA[39] and L-NAME[40] in rat models improved the bradycardia of those cholestatic rats.

Endogenous Opioid Peptides

There is increasing evidence that opioidergic system plays a role in the pathophysiology of cholestasis.[41] Opioid receptors are widely distributed in the cardiovascular system and their effects are mediated both centrally[42] and peripherally. [43]

They also modulate the autonomic nervous system,[44] cardiac rhythm[45] and cardiac contractility[46]. Several studies have explored the role of endogenous opioid peptides in cardiac abnormalities of cholestasis. In one of such studies, Leila et al[10] illustrated that the bradycardia of cholestatic rats was corrected with daily administration of naltrexone, a non-selective opioid receptor antagonist. They also demonstrated that naltrexone restored to normal the heart rate, blood pressure and susceptibility to arrhythmia in cholestatic animals with no significant effect on QT interval.

Atrial Natriuretic Peptide System (ANP System)

The involvement of ANP in cardiovascular abnormalities of cholestasis was suggested by Pereira et al.,[47] who noted that ANP levels increased shortly after common duct ligation in the rabbit. ANP at high levels has been shown to cause bradycardia. Studies by Allen et al showed that in supine and erect positions ANP has a dose dependent effect on heart rate; that at initial lower levels it causes increment in heart rate and lowers systolic blood pressure. But at higher levels it causes significant decreases in peak velocity and cardiac output with increases in index of systemic vascular resistance (ISVR) in both positions, but Heart rate slows down while diastolic pressure increases only when supine. [48]

Role of Tumour Necrosis Factors -α (TNF-α) in Cholestatic Cardiac Dysfunction

It has been reported that increased TNF-**α** acting via NF-**αB** – inducible nitric oxide synthase and p38 MAPK signaling pathways, plays an important role in the pathogenesis of cholestasis - induced cardiac dysfunction.[10] Also, TNF-**α** – accentuated endocannabinoid action and oxidative stress might also be involved in its negative inotropic effects in fibro-cholestatic hearts. [49]

CONCLUSION

Patients with advanced pancreatic malignancy tend to have hyperbilirubinaemia and these pose deleterious effects on the cardiovascular system, especially the heart itself. Therefore treatments of these individuals are complicated, requiring multidisciplinary approach. Our own experience together with the review of different articles, showed the possible mechanisms underlying cholestatic cardiac abnormalities and consequent treatment options. Our patient responded to treatment with improvement in cardiac function following administration of atropine, UDCA, cholestyramine and salbutamol at various times and in various combinations. This is very much in line with general consensus concerning treatment of cholestatic bradycardia. However the need to relieve the obstruction cannot be overemphasized and the mainstay of treatment still remains aggressive management of the primary cause of cholestasis which in this case is a pancreatic malignancy. Nevertheless the exact mechanism of action of bilirubin on cardiac function needs to be further elucidated.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

CONSENT

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

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