Evaluation of Pediatric Bradycardia: A Single Center Experience

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ABSTRACT

Background: Heart rate is an integral part of the clinical assessment of the children with acute illness and is commonly used in pediatric early warning scores.

Objective: The aim of this study was to assess our current practice for evaluation and management of bradycardia in children.

Patients and methods: The study was conducted in Pediatric Arrhythmia Clinic, Neonatal Intensive Care Unit and Pediatric Intensive Care Unit from March 2020 to August 2021. 61 Neonates and children aged from 1 day to 18 years presenting with bradycardia were included in this study. Predeath bradycardia was excluded. Full medical history, physical examination, basic investigations, 12 leads ECG and echocardiography were performed to all patients. Thyroid function tests, 24 hours Holter monitoring, and stress ECG were done if indicated.

Results: 61 patients were included in the study. Heart rate ranged from 44 to 94 beat/minute with mean 69.44 beat/minute, the most common form of presentation was abnormal echocardiography. Hypocalcemia was present in 85.2% of patients. 70.5% of patients had sinus bradycardia, 13% had complete heart block (CHB),10% of patients had long QTc Syndrome with sinus bradycardia, 3.3% had 1st and 2nd degree heart block, 1.6% had ECG changes of ALCAPA with sinus bradycardia and 1.6% had ventricular ectopic.

Conclusion: It could be concluded that bradycardia in children needs accurate assessment to rule out the need of acute intervention and to decrease the risk of life-threatening conditions.

Keywords: Pediatric, bradycardia, hypocalcemia, ECG.

INTRODUCTION

Heart rate is frequently applied in pediatric early warning scores. In pediatric population age related anatomical and physiological changes produce normal ranges for electrocardiogram parameters that differ from adults and vary with age, heart rate below the lowest normal value regarding age is defined as bradycardia. Sinus bradycardia, junctional bradycardia, or atrioventricular block are the most common manifestation of pediatric bradycardia. Due to several different etiologies, it may occur in a completely structurally normal heart or in presence of associated congenital heart disease. Recently mutation in multiple genes has been involved as a cause of inherited sinus node dysfunction or progressive cardiac conduction abnormalities. Treatment and prognosis of bradycardia in pediatrics are completely dependent upon the underlying cause. Management of bradycardia is indicated when it is related to symptoms and/or there is a risk of heart failure or pause-dependent tachyarrhythmia. Rapid diagnosis and suitable treatment are crucial in most cases to avoid sudden death [(1)].

Because there is an overlap of heart rate ranges with non-pathologic changes, evaluation of symptoms is a very important aspect in the assessment and treatment of bradycardia. In the 2018 ACC/AHA/HRS Guideline on the assessment and treatment of Patients with Bradycardia and Cardiac Conduction Delay, there was a great change from prior guidelines that recommend device-based implantation to a focus on evaluation and treatment of disease states [(2)].

The aim of this study was to assess our current practice for evaluation and management of bradycardia in neonates and children.

PATIENTS AND METHODS

This prospective cohort observational study included a total of 61 neonates and children aged from 1 day to 18 years presenting with bradycardia, attending at Pediatric Arrhythmia Clinic, Neonatal Intensive Care Unit and Pediatric Intensive Care Unit, Sohag University Hospital. This study was conducted between March 2020 to August 2021. Predeath bradycardia was excluded.

All patients underwent accurate evaluation, which included: detailed medical history included Socio-demographic factors. Cardiac symptoms, such as feeding difficulties, exercise intolerance, syncope, medication history and chronic maternal disease, physical examination included general condition, anthropometric measures, vital signs. (Including HR, BP, RR, Body temperature). Cardiac examination (including any associated murmur, Heart failure). Basic investigations (CBC, serum electrolytes including total and ionized calcium level).12-lead electrocardiogram 12 leads ECG were performed to all included children using (Fukuda Denshi CardiMax ECG device model FCP-7101).

The electrocardiograms were reviewed through the creation of descriptive reports and determination of the following variables: heart rate, PR interval and QRS duration, The QT interval was measured from the beginning of the QRS complex to the end of the T wave,

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defined by the return of the terminal T wave to the isoelectric T-P baseline. Thereafter QT interval was adjusted for heart rate using Bazett's formula. Interpretation of every ECG paper was done using specific centile tables for normal values of ECG waves and intervals according to age [3]. Bradycardia is considered as a heart rate below the lowest of normal for age [1].

Abnormal heart rhythm and manifestations of ischemia were also reported. Echocardiography: All patients had 2-D and M-mode echocardiographic examinations in accordance with the American Society of Echocardiography standards. Thyroid function tests, 24-hour Holter monitoring using Mortara 2016 American made H3 and stress ECG if indicated.

***Ethical Consideration*:**

This study was ethically approved by Sohag University's Research Ethics Committee. Written informed consent of all the participants' parents was obtained. This work has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Quantitative data were expressed as mean ± SD (Standard deviation). Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). P value < 0.05 was considered significant.

RESULTS

The study included 61 patients. About 53% of them were males. Age ranged from 1 day to 14 years with median 4 years.

Table (1): Distribution of the studied patients according to demographic data:

	N=61	%
Gender: Female Male	 29 32	 47.5 52.5
Age (year): Median Min – Max	 4 years 1 day – 14 years	

Table (2): Heart rate of the studied patients:

	Mean ± SD	**Range**
Heart rate	69.44 ± 13.97	44 – 94

Table (3): Distribution of the studied patients according to clinical presentation (n=61):

Clinical presentation	**Number**	**Percent**
Abnormal echocardiography	17	28
Abnormal examination	10	16.4
Syncope	10	16.4
Medication toxicity	6	9.8
Disturbed conscious level	5	8.2
Gastro-enteritis	3	5
Malnutrition	3	5
Prematurity	2	3.3
Shock	2	3.3
Renal failure	1	1.6
Nephrotic syndrome	1	1.6
Viral infection	1	1.6

Regarding presenting symptoms, 28% had abnormal echocardiography. Abnormal examination and syncopal attacks were the presentation of 16.4% of cases for each, medication toxicity (one of them was due to digitalis toxicity) were present in 9.8% of cases. Disturbed consciousness was the presentation in 8.2% of cases. Gastroenteritis and malnutrition were present in 5% of cases for each, prematurity and shock due to bradycardia were the presenting symptoms in 3.3% for each. Renal failure, nephrotic syndrome and viral infection were evident in 1.6% of cases for each.

Table (4): Laboratory data of the studied patients (n=61):

	Mean ± SD
Hemoglobin (g/dL)	11.63 ± 1.87
Sodium (mmol/L)	132.72 ± 4.76
Potassium (mmol/L)	3.45 ± 0.6
Ionized calcium (mg/dl)	1.01 ± 0.11
Total calcium (mg/dl)	8.2 ± 0.81

Hemoglobin level of the studied patients ranged from 8.5 to 18.6 g/dL with mean 11.63 g/dL. Sodium level ranged from 126 to 156 mmol/L with mean 132.72. Potassium level ranged from 2.2 to 4.92 mmol/L with mean 3.45 mg/dL. Ionized calcium level ranged from 0.82 to 1.32 mg/dL with mean 1.01 mg/dL. Total calcium level ranged from 5.5 to 9.5 mg/dL with mean 8.2 mg/dL.

Table (5): Distribution of the studied patients according to presence of hypocalcemia:

	N=61	**%**
Hypocalcemia Present Absent	 52 9	 85.2 14.8

Hypocalcemia was present in 85.2% of the studied patients.

Table (6): ECG findings of studied patients (n=61):

ECG findings	Number	Percent
Sinus bradycardia	43	70.5
CHB	8	13
Long QTc	6	9.8
1st and 2nd degree HB	2	3.3
Changes of ALCAPA	1	1.6
Ventricular ectopics	1	1.6

Regarding ECG findings of studied children with bradycardia,70.5% of them had sinus bradycardia, 13% had CHB, about 10% of patients had long QTc interval with sinus bradycardia, 3.3% had 1st and 2nd degree heart block, 1.6% had ECG changes of ALCAPA with sinus bradycardia and 1.6% had ventricular ectopic.

Table (7): ECG findings in patients with abnormal echocardiography (n=17):

Echocardiographic findings	ECG findings	Number
Mild left ventricular dilatation	Sinus bradycardia	3
L-TGA	CHB	1
Operated TGA	Sinus bradycardia	1
Complete AV canal defect	CHB	1
ASD Patch closure	1st, 2nd degree HB	2
VSD	CHB	1
VSD patch closure	CHB	1
Operated Fallot tetralogy	CHB	1
Operated Fallot tetralogy	Sinus bradycardia	1
Situs inversus, VSD	CHB	1
Dilated cardiomyopathy	ECG changes of ALCAPA	1
Restrictive cardiomyopathy	Sinus bradycardia	1
Decreased systolic function	CHB	1
Normal echo cardiography with bradycardia	CHB	1

Regarding ECG findings in bradycardic patients with abnormal echocardiography, heart block was present in 10 children with CHD pre and post operative (16.4% of bradycardia cases) and 2 patients with congenital complete heart block (3.3% of bradycardia cases), sinus bradycardia was present in 2 post operative cases for CHD, in 2 patients with cardiomyopathy (3.3% of bradycardia cases) and in 3 patients with mild left ventricular dilatation (5% of bradycardia cases).

Table (8): Distribution of the studied patients according to result of Holter monitoring:

Holter findings	N=17	%
CHB	**8**	**13**
Sinus bradycardia	**6**	**9.8**
1st and 2nd degree heart block	**2**	**3.3**
polymorphic ventricular tachycardia	**1**	**1.6**

Holter monitoring was performed for 17 patients. Sinus bradycardia was confirmed in two post operative cardiac patients, one patient with restrictive cardiomyopathy and in 3 patients with syncope. Heart block was confirmed in 10 patients. One patient with syncope had sinus bradycardia on his ECG showed polymorphic ventricular tachycardia in his Holter study.

Table (9): Distribution of the studied patients according to Possible cause of sinus bradycardia (n=43):

Cause	Number	Percent
Hypocalcemia	18	42%
Effect of drugs	6	14
Hypothermia	5	11.6
Increased ICP	5	11.6
Electrolyte disturbances	3	7
Post cardiac surgery cardiomyopathy	2	4.7
Hypothyroidism	1	2.3
CPVT	1	2.3
Viral infection	1	2.3

Hypocalcemia was the only possible cause of sinus bradycardia in 42% of cases of sinus bradycardia. Sinus bradycardia was due to effect of drugs (1 patient with digitalis toxicity) in 14% of cases with sinus bradycardia. Elevated intracranial pressure and hypothermia in children with severe protein energy malnutrition and prematurity in 11.6% of cases Electrolyte disturbances were the cause of bradycardia in 7% of cases. Sinus bradycardia was present in 4.7 % of cases late after cardiac surgery due to sick sinus syndrome and in one patient with restrictive cardiomyopathy.

Sinus bradycardia was present in one 11 years old patient presenting with recurrent syncope (2.3% of sinus bradycardia cases) due to CPVT diagnosed by stress ECG, in one patient 1.5 years old presented by marked sinus bradycardia diagnosed to have hypothyroidism he needed inotropic support and improved on thyroid replacement hormone therapy and in one patient 9 years old with fever diagnosed to have covid 19 infection, he had marked persistent sinus bradycardia, he was shocked and needed inotropic support till sinus bradycardia improved.

Table (10): Distribution of the studied patients according to treatment:

Treatment	N	%
Ca and vitamin D	52	85
Anti-failure medications	1	1.6
Propranolol	7	11.5
Inotropes	2	3.3
Atropine	1	1.6
Thyroxin replacement therapy	1	1.6
Correction of electrolytes	3	5
Measures to decrease ICP	5	8.2
Correction of hypothermia	5	8.2
Referral to EP center	13	21.3
Surgery for ALCAPA	1	1.6
Follow up	7	11.5

Regarding treatment provided, 85% of patients received vitamin D and calcium supplementation. one case with persistent hypocalcemia needed endocrinological consultation. 13 patients (21.3%) 11 patients with heart block, 2 patients with postoperative sinus bradycardia were referred to electrophysiology center for further evaluation. B- blocker therapy was indicated in 7 patients (6 patients with long QT syndrome and one patient with CPVT). 2 patients (3.3%) needed inotropic support. Correction of electrolytes in 5% of patients. Correction of hypothermia and measures to decreases intracranial pressure resulted in improvement of bradycardia in 8.2% of patients. One patient 3 years old with restrictive cardiomyopathy was on treatment for heart failure. One patient with ALCAPA referred for surgery. Thyroid replacement therapy corrected bradycardia in one patient with hypothyroidism. One patient with covid 19 improved on inotropic support. One patient with digitalis toxicity received IV atropine. Follow up of bradycardia enrolled in 5 patients with other medication toxicity, one patient with asymptomatic congenital complete heart block and normal echocardiographic examination, one patient with asymptomatic ventricular ectopic and normal echocardiography.

DISCUSSION

Bradycardia is defined as a heart rate below the lowest normal value for age [(4)]. Proper identification of rhythm and etiology and appropriate immediate therapeutic measures are necessary when assessing the child with a low heart rate [(5)]. Heart rate is an integral part of the clinical assessment of the child with acute illness and is commonly used in pediatric early warning scores [(6)]. Compared with **Choi *et al.*** [(7)] who studied 271 children in whom acute response system (ARS) was activated because of bradycardia and found most common diagnosis among the included children were for hematological causes (55.4%) followed by endocrinological causes (10.7%), and gastroenterological causes (9.2%). **Choi *et al.*** [(7)] reported that 13.3% of patients with bradycardia was related to the administration of certain medications such as beta blockers, calcium channel blockers, digoxin or clonidine. Hypoxia, poisoning, electrolyte disorders, infection, sleep apnea, drug effects, hypoglycemia, hypothyroidism, and increased intracranial pressure are the main pathologic causes of sinus bradycardia [(8)].

Congenital complete heart block may occur in a structurally normal heart or in association with CHD. Heart block occurs in 1–3% cases of surgically treated hearts especially after closure of ventricular septal defects, after TOF repair, left ventricular outflow tract surgery, and left-sided valve surgery. A recent multicenter study demonstrated highest incidences of AV block and pacemaker placement after the double switch operation (15.6%), tricuspid valve (7.8%) and mitral valve (7.4%) replacement, atrial switch with ventricular septal defect repair (6.4%) and Rastelli operation (4.8%). Late-onset AV block may be due to progressive fibrosis and sclerosis involving specialized conduction pathways which are fragile in CHD [(9)]. Dysfunction of the sinus node include a wide varieties of disturbances in impulse production of the sinus node and its conduction to the nearby atrial tissues. It may be a result of specific congenital structural abnormalities such as left atrial isomerism and left-sided juxtaposition of the atrial appendages. In most patients, SND is secondary to surgical procedures such as repair of sinus venosus ASDs, Glenn shunts, Fontan operation, and Senning or Mustard procedures. Post-operative SND may result from direct damage to the sinus node or its blood supply[(9)].

A study conducted on a large Japanese population to assess arrhythmias late after repair of tetralogy of Fallot, showed a prevalence of brady arrhythmias of about 8%, with an incidence of 2nd and 3rd degree AV block respectively around 4% and 3%. Most of cases with 3rd degree AV block had perimembranous ventricular septal defect. Conduction disturbance didn't persist in any of the patients who had perioperative complete A-V block , and one patient with complete AV block, who did not receive pacemaker implantation, died on follow-up [(10)]. A study which assessed the results of patients after surgical repair of ventricular septal defect at young age concluded that, although the precise mechanism linking surgical repair of an isolated ventricular septal defect and the late occurrence of sick sinus syndrome is unknown, cannulation of the right atrium for cardiopulmonary bypass has been proposed as a possible cause [(11)].

Wilders and Verkerk [(12)] concluded that nearly most of the ion channels affected by the different types of LQTS gene mutations are also expressed in the human sinoatrial node (SAN). LQTS is commonly associated with a change in basal heart rate (HR). They provide an overview of known LQTS mutations with

effects on HR and the underlying changes in expression and kinetics of ion channels. They reported a large number of LQTS mutations that were related to sinus bradycardia and concluded that the occurrence of both QT prolongation and sinus bradycardia on a family basis is completely limited to LQTS types 3 and 4 (LQT3 and Ankyrin-B syndrome, respectively). They also emphasized that a causative role of this sinus bradycardia in cardiac events seems reserved to mutations underlying LQT3[12].

Lapierre and Hugues [13] presented a 5-day-old child who was referred to the department of cardiology for bradycardia without any other cardiac symptoms. ECG was normal. Cardiac echography demonstrated a reverse flow inside the interventricular branch of the left coronary artery suggesting ALCAPA.

Walsh *et al.* [14] postulated that Pediatric restrictive cardiomyopathy carries a poor prognosis secondary to a high risk of sudden death previously attributed to ventricular tachyarrhythmias. The extent of conduction abnormalities in this population and their relationship to life-threatening events has not been previously reported and concluded that Pediatric patients with restrictive cardiomyopathy have a high risk for acute high-grade heart block, and bradycardic events represented a significant portion of all arrhythmic events. They concluded that ECG monitoring strategies diagnosing conduction system disease should be performed in all patients with restrictive cardiomyopathy.

Holter monitoring is an important tool in the assessment of bradycardia. Pacemaker insertion in AV block is based on average heart rates, determined by a 24-h monitor. Holter monitoring gives important information about the range of ventricular rates attained by the junctional escape rhythm in complete AV block [1].

Loewe *et al.* [15] in his study about Hypocalcemia-Induced Slowing of Human Sinus Node pace making postulated that Each heartbeat is initiated by cyclic spontaneous depolarization of cardiomyocytes in the sinus node forming the primary natural pacemaker. In patients with chronic kidney failure on hemodialysis, the heart rate drops to very low values before they suffer from sudden cardiac death and hypothesized that the electrolyte disturbance that occur mostly in these patients affect sinus node beating rate and may cause severe bradycardia. To examine this hypothesis, they widened the **Fabbri *et al.*** [15] computerized model of human sinus node cells to account for the dynamic balance of intracellular ion concentrations. They tested the effect of altered extracellular potassium, calcium, and sodium concentrations. They found that sodium changes had unremarkable effects (0.15 bpm/mM) and potassium changes mild effects (8 bpm/mM) but calcium changes markedly affected the beating rate (46 bpm/mM ionized calcium without autonomic control). Their findings are complemented and substantiated by an empirical database study comprising 22,501 pairs of blood samples and in vivo heart rate measurements in hemodialysis patients and healthy individuals. A reduction of extracellular calcium had a strong correlation with a decrease of heartrate by 9.9 bpm/mM total serum calcium ($p < 0.001$) with intact autonomic control in the cross-sectional population [16].

Acute malnutrition has been recognized as causing cardiac myofibrils to be thinned with impaired contractility. Bradycardia due to hypothermia and hypoglycemia. Hypotension are also common in severe cases. The combination of bradycardia, impaired cardiac contractility, and electrolyte imbalances predisposes to arrhythmias [17]. Reports of COVID-19 infection related bradycardia are few but increasing in number [18]. **Choi *et al.*** [7] found that arrhythmia associated with bradycardia was found in 25 cases, but no case was treated with pacemarker insertion or with other interventions by a cardiologist. Endocrinology department patients with bradycardia caused by clonidine required fluid therapy if they had simultaneous hypotension. In the gastroenterology department, many patients suffered anorexia nervosa, which led to a low BMI and bradycardia. Some patients in hemato-oncology department show bradycardia during night, which was associated with sleep but none of them received any intervention.

Patients with CHD and post-operative SND or high degree or complete AV block—even when the underlying defects are ‘structurally repaired’ have a high risk of SCD. Accordingly, there is a lower threshold for pacemaker insertion even in asymptomatic patients. One year of mortality of patients with complete post-surgical AV block who did not receive permanent pacemaker implantation has been reported ranging from 28 to 100% in several studies from 30-years ago underscoring undisputable need for permanent pacemaker therapy [9].

Ventricular ectopic is frequently identified in healthy children with structurally normal hearts has a benign clinical course often disappearing spontaneously. A small percentage of children may develop cardiomyopathy. Asymptomatic children with normal ventricular function and a low ectopy burden can be followed without any intervention and generally reassured. Children with an ectopy burden more than 30% are at some risk of developing LV dysfunction and should be more closely followed with noninvasive imaging. Development of symptoms attributed to the ectopy or signs of increasing LV dimensions or LV dysfunction should be treated with medication or catheter ablation[19].

CONCLUSION:

It could be concluded that bradycardia in children needs accurate assessment to role out the need of acute intervention and to decrease the risk of life-threatening conditions.

RECOMMENDATIONS

1. Bradycardia among children can be caused by different conditions rather than cardiac causes. ECG followed by Echocardiography and Holter ECG have an important role in evaluation of children with bradycardia.
2. Further longitudinal studies with large sample size are needed to evaluate hypocalcemia as a cause of sinus bradycardia in children.

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