ORIGINAL ARTICLE

ELECTROCARDIOGRAPHIC MANIFESTATIONS IN PAEDIATRIC WILSON DISEASE

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Background: Wilson disease (WD) is one of the most common metabolic liver diseases in older children. It has a strong genetic background with autosomal recessive inheritance. WD is a multisystem disorder with predominant hepatic and neurological manifestations and variable age of presentation. The data on cardiac manifestations in children is very limited and only few adult studies are available in the literature. This study was planned to determine the frequency and spectrum of Electrocardiographic (ECG) changes in pediatric WD. **Methods:** This was an observational cross-sectional study conducted at The Children Hospital & the Institute of Child Health, Lahore, from January 2015 to January 2017. The children diagnosed as Wilson disease were enrolled for the recording of resting ECG. The ECG changes were seen and discussed with an experienced pediatric cardiologist who was involved and explained about the objectives of study. **Result:** Total 55 patients were enrolled but record of ECG was missing for 4 patients and excluded from the study. Out of 51 patients 22 had at least one ECG abnormality. Most frequent findings seen were T wave abnormality in 18 patients (35.2%) followed by sinus tachycardia and sinus bradycardia in 12 and 8 patients respectively. Other abnormalities included bifid P waves, ST segment changes each of 2 patients, and one premature ventricular contraction. QRS details including axis, complex, amplitude ratio and QT interval was normal in all the patients. There was no mortality during the study period due to cardiac cause. **Conclusion:** ECG abnormalities are not uncommon in pediatric WD but of mild nature. These are presumably related to underlying cardiomyopathy due to deposition of copper in heart which can be quantified by cardiac magnetic resonance imaging (MRI) and echocardiography is required to confirm ECG abnormalities detected.

Keyword: Wilson disease; ECG changes; Cardiomyopathy

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INTRODUCTION

Wilson Disease is a genetic disorder with progressive hepatolenticular degeneration and was first described in 1912 by Kinnear Wilson.[1,2] It is an autosomal recessive disorder caused by defect in copper transport in hepatic lysosomes and the gene was identified as ATP7B on chromosome 13.[3,4] The worldwide incidence is 1in 37000 with a carrier frequency of 1 in 90.[4]

Wilson Disease is a multisystem disorder with predominant hepatic and neurological manifestations with variable age of presentation.[5,6] Known for decades that WD has predilected sites for copper deposition including liver, brain, kidney and skeletal system, damaging these organs and leading to various presentations of the disease.[6,8] Cardiac involvements is one such manifestation supposed due to underlying copper deposition in the heart muscles generating different mode of presentations. These findings were highlighted and described in adults by Kaun who reported different modes of cardiac manifestations.[9] The data on cardiac manifestations in children is very limited and only few case reports are present in the literature. Serious cardiac complications are rare but reported and majority of WD patients have mild electrocardiographic manifestations.[1,9]

This study is being done to emphasize the importance of simple ECG test in all cases of Wilson disease so that any cardiac involvement may be detected early and treated promptly, thereby reducing mortality and morbidity.

MATERIAL AND METHODS

This was an observational cross-sectional study conducted at The Children Hospital & the Institute of Child Health, Lahore from January 2015 to January 2017 at the department of Pediatric Gastroenterology. The children, diagnosed as Wilson disease were enrolled for the recording of resting ECG from inpatient and clinics visiting as follow up. The sample size was calculated using world health organization (WHO) formula with 95% confidence interval and 13% margin of error estimating a population proportion with absolute precision (1 in 37000).[4] The children included were WD patients but not known to have any cardiac manifestations previously or on any cardiac medications. WD diagnosis was based on clinical manifestation, family history, slit-lamp examination for Kayser Fleischer

(KF) rings, low serum ceruloplasmin assay and increased 24 hours urinary excretion of copper.[5] All were on the treatment of WD including penicillamine and zinc therapy. Twelve leads resting ECG was recorded after standardization for the recruited children. The ECG changes were seen and discussed with an experienced pediatric cardiologist who was involved and explained about the objectives of study. Few patients underwent echocardiography for confirmation of ECG findings. Other causes like deranged electrolytes, drugs that could contribute to ECG abnormalities were excluded.

Statistical analysis was carried out by using the SPSS Chicago, IL, USA. Simple descriptive statistics were used. Mean and SD was calculated for quantitative variables like age, duration of illness and treatment time. Frequencies and percentages were calculated for qualitative variables like gender and clinical characteristics. The *p*-value less than 0.05 was taken as statistically significant in reference to age, gender, duration of illness, treatment and serum ceruloplasmin. This study was approved by institutional ethical committee and conducted according to the principles of the Helsinki Declaration.

RESULTS

Total 55 patients were enrolled but record of ECG was missing for 4 patients and excluded from the study. There were 28 males with a mean age of 11.19±2.34 years. Majority of patients with abnormal ECG's were older than 10 years of age (72.7%). The mean duration of illness and treatment at the time of study was 540±300 days and 491±292 days respectively. The mean serum ceruloplasmin and 24 hours urinary copper were significantly at abnormal values in both the groups. The table-1 describes about the demographic and clinical/ biochemical characteristics of the patients.

Out of 51 patients 22 had at least one ECG abnormality. Most frequent findings seen were T wave abnormality in 18 patients (35.2%) followed by sinus tachycardia and sinus bradycardia in 12 (23.5%) and 8 (15.6%) patients respectively. Various ECG abnormalities are shown in table-2. QRS details including axis, complex, amplitude ratio and QT interval was normal in all the patients. None of the patients had features of ventricular hypertrophy. There was no mortality during the study period due to cardiac cause. There was no statistically significant difference in ECG abnormalities in reference to age, gender, duration of illness, presence of KF rings, treatment and serum ceruloplasmin.

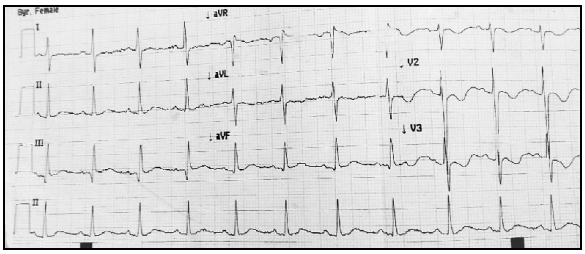

Figure 1: ECG of a patient showing bifid P Waves.

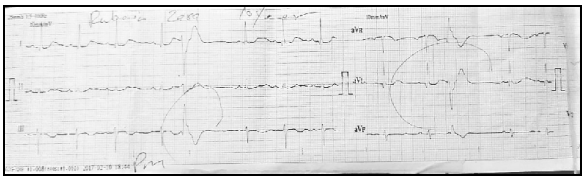

Figure 2: ECG of a patient showing premature ventricular contraction

Table-1: Demographic and clinical correlation with ECG manifestations

Parameter	Patients with normal ECG (n=29, 56.9%)	Patients with abnormal ECG (n=22, 43.1%)	*p*-value at <0.05
	Mean±SD	Mean±SD	
Male	n=18 (28), 64.2%	n=10 (28), 35.7%	0.191
Female	n=11 (23), 47.8%	n=12 (23), 52.1%	0.201
Age	10.8±2.4	11.6±2.23	0.242
Serum Ceruloplasmin	5.81±5.79	4.04±5.34	0.266
24 hour urinary Copper (ug/dl)	1546.62±1374.27	2647.54±2386.05	0.062
Duration of illness (days)	582.89±351.32	485±210.33	0.223
Duration of treatment (days)	495.31±346.8	393.63±191.92	0.189

Table-2: Electrocardiographic abnormalities in Wilson's disease (n=22)

ECG abnormality	n (%)
T wave abnormality	18 (35.2%)
Sinus tachycardia (>100/m)	12 (23.5%)
Sinus bradycardia (<60/m)	8 (15.6%)
Bifid P wave*	2 (3.9%)
ST Elevation (>1mm)	2 (3.9%)
ST Depression (<1mm)	2 (3.9%)
Ventricular premature contraction*	1 (1.9%)
Any other abnormality	6 (11.7%)

DISCUSSION

Wilson disease is an autosomal recessive genetic disorder due to defect in copper metabolism by hepatic lysosomes. WD is one of the leading cause of chronic liver disease in children especially in countries where consanguinity is prevalent like Pakistan. Various manifestations of the disease being known in the literature owing to copper deposition in different organs but cardiac manifestations are not reported in children. Up to our knowledge this has been the first study from Pakistan to see the ECG changes in WD patients and to highlight the abnormalities to lessen the mortality and morbidity in this cohort of children.

Kaun described the ECG abnormalities in adult patients with WD many decades ago. His study cohort showed 34% (18 out of 53) had ECG abnormalities which is almost similar to current study (43%). Kaun study was aimed to see ECG changes and confirmed on echocardiography and forwarded the conclusion that probably subclinical cardiomyopathy was the reason underlying these ECG changes.[9] In the present study, the aim was to see ECG changes so focus was not given on echocardiography.

Autonomic dysfunction has been reported in cases of WD patients which may manifest in the form of sinus tachycardia (Heart rate >100/minute) or sinus bradycardia (Herat rate <60/minute) and were noted in 12 and 8 patients in the present study respectively. Kaun[9], Meenakshi S[10] and Chu *et al*[11] also reported dysautonomia in WD patients and underlying mechanism was perhaps due to central autonomic dysregulation involving both sympathetic and parasympathetic systems[10,11]. Other factors like cardiotoxic drugs, electrolyte imbalance, dehydration and toxemic states leading to autonomic dysfunction were absent in all of our patients.

The most frequent ECG finding was T wave abnormalities and included peaked, flat and Inverted T waves but without any hemodynamic instability. Four patients had T wave inversion with no evidence of coronary artery disease and confirmed on echocardiography. Frequent T waves abnormalities were not seen in other studies. Moreover, none of children were on drugs like digoxin and other factors leading to T wave abnormalities like anxiety, fear, hyperventilation. U wave abnormality was seen in 7.5% of patients by Kaun and attributed to cardiomyopathy in WD but none of our patient showed any U wave.[9] ST segment abnormalities were noted in 4 (18.1%) patients which were also observed in other studies.

Other ECG findings observed in the study were bifid P waves and premature ventricular beat in 2 and one patients respectively. Cardiac arrhythmias, cardiomyopathy and heart blocks were also identified in few patients with WD.[12–14] In the present study, none of the patient had ventricular hypertrophy, prolonged QTc interval, arrhythmias, sinoatrial or atrioventricular block or low voltage QRS complexes.

Few recent studies in adults using echocardiography were published and showed different manifestations in WD including myocardial dysfunction, cardiac hypertrophy and interstitial fibrosis, left ventricle (LV) wall thickening and remodeling with relatively high frequency of extra-systolic beats and premature supraventricular contraction.[13–15] Mortalities and sudden deaths have been documented in WD patients due to cardiac manifestations but in the present study, cardiac findings were of mild nature and did not require any intervention or medications in reference to management. One possible explanation might be that all these patients were on chelation therapy with good compliance so there was no statistical difference in reference to age, gender and duration of illness and treatment time in both the groups.

Our study has limitations including observational, single center study and no control cases were examined but yet cases were identified with cardiac manifestations and an effort has been made to share the findings from a tertiary care center. More and large prospective, randomized studies are required to see the effect of copper deposition in heart with WD and advanced studies including cardiac MRI for quantification of copper and echocardiography for functional and structural damage to heart.

CONCLUSION

Cardiac manifestations were mild but these patients with changes on ECG should be looked up for cardiomyopathy or valvular involvement with echocardiography, and further work can be done on drugs which can help in effective chelation of patient with cardiac manifestation.

AUTHORS' CONTRIBUTION

SSBH: conceptualization, design and principle author, HAC: supervision, AS: editing of final manuscript, HSM: supervision and editing, TS: data interpretation on ECG's.

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