Original Article

Electrocardiographic and Echocardiographic Findings in Pre-Liver Transplant Pediatric and Young Adult Patients With Wilson's Disease: A Case-Control Study

Hamid Amoozgar[1], MD; Sahar Azadi[2*], MD; Mozhgan Zahmatkeshan[3], MD; Ali Reza Safarpour[3], PhD

ABSTRACT

Background: Wilson's cardiac involvement causes cardiomyopathy, arrhythmia, autonomic nervous system dysfunction, and sudden cardiac death. This study aimed to evaluate cardiac dysfunction in pre-liver transplant patients suffering from Wilson's disease and to classify their risk of arrhythmia and sudden cardiac death.

Methods: This case-control study was performed in the Transplant Coordination Center at Namazi Hospital, Shiraz University of Medical Sciences, between 2012 and 2014. The cardiac function was evaluated with 12-lead electrocardiography and echocardiography (M-mode, color Doppler, and tissue Doppler imaging). P-wave dispersion, QT dispersion, and T peak to T end-dispersion were measured in the patient group, and these values were compared with those in the control group.

Results: Totally, 23 patients with Wilson's disease and 47 healthy individuals were included in this study. P-wave dispersion and QT dispersion were significantly increased in the patients with Wilson's disease ($P<0.05$). Pulsed Doppler echocardiographic findings showed significantly increased E and A peak velocities of the mitral and tricuspid annuli in the patient group ($P<0.05$). Tissue Doppler imaging was in favor of a significant increase in systolic and early and late diastolic velocities of the mitral and tricuspid annuli.

Conclusions: The prolongation of P-wave dispersion and QT dispersion renders patients with Wilson's disease susceptible to atrial and ventricular arrhythmias and sudden cardiac death. The evaluation of the cardiac function of such patients should include color Doppler and tissue Doppler imaging to assess diastolic dysfunction as one of the initial cardiac involvements. ***(Iranian Heart Journal 2022; 23(1): 118-128)***

KEYWORDS: Cardiac evaluation, Wilson's disease, Diastolic dysfunction, Echocardiography, Electrocardiography

[1] Neonatology and Cardiac Research Center, Shiraz University of Medical Science, Shiraz, IR Iran.
[2] Department of Pediatrics, Shiraz University of Medical Sciences, Shiraz, IR Iran.
[3] Gastroenterhepatology Research Center, Shiraz University of Medical Science, Shiraz, IR Iran.

*** Corresponding Author:** Sahar Azadi, MD; Department of Pediatrics, Shiraz University of Medical Sciences, Shiraz, IR Iran.
Email: saharazadi917@gmail.com **Tel:** +987137266811

Received: September 30, 2020 **Accepted:** December 20, 2020

Wilson's disease (hepatolenticular degeneration) is a rare autosomal recessive and multisystemic disorder. [1] Different genetic mutations in the 13q chromosome lead to the malfunctioning of the protein-encoding gene, *ATP7B*. [2] This results in decreased biliary excretion and the accumulation of copper in several organs, including the liver, brain, and kidney, as well as the cardiovascular and endocrine systems. [3,4] Genetic studies in different populations have shown multiple genetic mutations, with more than 250 gene mutations leading to reduced copper binding to ceruloplasmin and reduced copper bile excretion, responsible for the accumulation of copper in the liver. [5,6]

Wilson's disease is categorized into 4 groups: cardiomyopathy, arrhythmia, autonomic nervous system dysfunction, and cardiac death. [7,8]

This disease is rare at the age of less than 5 years, although there have been reports of cases at the age of 2 to 3 years. [9-11] It is much more common in childhood than in adulthood, with hepatic manifestations. The symptoms of Wilson's disease may be vague and nonspecific. The hepatic symptoms of Wilson's disease may be similar in children and adolescents to the symptoms of autoimmune hepatitis and viral hepatitis. [12,13]

Nowadays, several electrocardiographic (ECG) and echocardiographic indices can help us predict cardiac dysfunction. P-wave dispersion (the difference between the maximum and minimum P-wave duration), [14] QT dispersion (the difference between the maximum and minimum QT duration), [15] and T peak to T end dispersion (the difference between the maximum and minimum T peak to T end duration) in standard 12-lead ECG are the predictors of the occurrence of atrial and ventricular arrhythmias, respectively. [16]

Systolic and diastolic cardiac dysfunction has also been evaluated in different diseases with accumulative nature such as Wilson's disease and thalassemia in several studies. [17] With the introduction of novel treatment modalities for Wilson's disease and improvements in patients' survival, the early diagnosis of the specific organ involved can decrease morbidity and mortality.

In the present study, we aimed to evaluate ECG and echocardiographic findings in pre-liver transplant patients suffering from Wilson's disease and to compare the findings with those in a healthy control group.

METHODS

Study Design and Setting

This case-control study was conducted on patients with Wilson's disease who were candidates for liver transplantation and healthy controls. The participants consulted the Transplant Coordination Center at Namazi Hospital, Shiraz University of Medical Sciences, Shiraz, Iran, between January 2012 and May 2014. All experimental procedures were approved by the Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran (CMRC code number: 7912) and followed the Helsinki Declaration of 1964, as revised in 2013. A written consent form was obtained from all the individuals in the test and control groups.

Participants

Wilson's disease was diagnosed through evaluations of serum copper, ceruloplasmin, the 24-hour urine copper test, the penicillamine challenge test, the Kayser–Fleischer ring, and liver biopsies. All the patients were referred to the center according to their Nazer prognostic index scores for Wilson's disease, [18] and those suffering from Wilson's disease were treated with trientine or penicillamine and zinc acetate (Table 1).

Table 1. Wilson's scoring system according to the Nazer criteria

Wilson's score	Albumin (g/L)	WBC (10^9/L)	AST (Iu/L)	INR	(Bilirubin µmol/L)
0	>45	0-6.79	0-100	0-1.29	0-100
1	34-44	6.8-8.39	101-150	1.3-1.69	101-150
2	25-33	8.4-10.39	151-300	1.7-1.99	151-200
3	21-24	10.4-15.39	301-400	2-2.49	201-300
4	<20	>15.4	>401	>2.5	>300

Patients were excluded if they had a past medical history of congenital heart disease, systemic or pulmonary hypertension, diabetes mellitus, chronic kidney disease, and consumption of any cardiac or anti-arrhythmic drugs.

Data Sources/ECG Measurement

Standard 12-lead ECGs at a rate of 25 mm/s and an amplitude of 10 mv/cm were recorded for all the participants in supine position with the aid of a digital, single-channel ECG machine (Aras-630), operated by a professional operator. All the ECGs were evaluated on-screen with a digital clipper in Corel Draw X5. P-wave duration, QT duration, T peak to T end duration, P-wave dispersion, QT dispersion, TPE (T peak to T end) dispersion, and QTC (the corrected QT interval) were calculated in all the ECGs. The ECG was accepted for our study only if there were at least 8 out of 12 measurable leads for our variables.

P-wave dispersion is the difference between the maximum and minimum P-wave duration in a standard 12-lead ECG. The QT interval is the distance between the first deflection of the QRS complex from the isoelectric line to the end of the T wave or the nadir between the T and U waves if a U wave exists. QT dispersion is the range of maximum and minimum QT intervals in a standard ECG. The corrected QT interval (QTC) was measured via the Bazett formula. The TPE interval is the distance between the T wave's peak to the end of the T wave, and the difference between the maximum and minimum TPE intervals in the precordial leads stands for TPE dispersion.

Echocardiography

Echocardiography was performed with a GE Vivid 3 system (GE Vingmed, Horten, Norway), equipped with a 3 MHz transducer. All the echocardiographic measurements in the patient and control groups were taken by a single pediatric cardiologist. Several parameters of the cardiac function were assessed to raise the intraobserver reliability. The echocardiographic studies included the M-mode, Doppler, and tissue Doppler echocardiography. The M-mode echocardiography measured/examined the interventricular septum and the diameter of the left ventricular wall in the systole and diastole. The ejection fraction and fractional shortening were measured in the long-axis view. With the aid of pulsed-wave Doppler at the leaflet (mitral [M] and tricuspid [T]) tips, early diastolic inflow velocity (E), velocity during active atrial contraction (A), and the E-to-A wave (E/A) ratio were measured. Pulsed-wave tissue Doppler velocities were obtained at the cardiac base in the apical 4-chamber orientation from 3 locations: the lateral mitral annulus, the interventricular septum, and the lateral tricuspid annulus: the peak systolic annular velocity (S), the peak early diastolic annular velocity (E′), and the peak late diastolic annular velocity (A′).

Study Size

The sample size was determined based on a study conducted in 2008 by Arat et al. [19] Accordingly, 23 individuals were estimated for each group.

Statistical Analysis

Statistical analysis was performed with SPSS software, version 19 (SPSS Inc, Chicago, IL, USA). Quantitative variables were presented as the mean ± the standard deviation of the mean (SD), and qualitative variables were presented as frequencies and percentages. An independent Student *t* test was used for the comparison of the quantitative variables between the groups. The χ^2, Fisher exact, and Mann–Whitney tests were employed to compare proportions. In all the analyses, a 2-tailed *P* value of less than 0.05 was considered statistically significant.

RESULTS

The current study enrolled 23 patients with Wilson's disease admitted to the Transplant Coordination Center and 47 healthy controls. The average age of the patient group and the control group was 16.87± 5.16 years and 16.27±5.38 years, respectively. The demographic characteristics of both groups are presented in Table 2.

No significant difference was observed in the heart rate between the test and control groups (81.466±6.73 bpm vs 80.377±5.442 bpm; *P*=0.21). The patients indicated no significant difference in P-wave amplitude, P-wave duration, and P-wave interval in lead II with the controls. The measurements of QRS duration, R-wave amplitudes, S-wave amplitudes, and QT and QTC duration also showed no significant differences (Table 3).

On the other hand, P-wave dispersion and QT dispersion were significantly longer in the patients than in the control group (42.17±11.8 vs 26.93±9.62; *P*<0.001 and 67.826±30.3 vs 52.425±17.61; *P*=0.009, respectively). However, no significant difference in TPE dispersion was observed between these groups (52.45±28.95 vs 44.47±20.52; *P*=0.24) (Fig. 1 & Table 3).

The ECG findings were compared between the patients with Wilson's disease and the control group. The abnormal findings are mentioned in Table 3. No arrhythmia was detected in the control group, but one of the participants in the test group showed Wolff–Parkinson–White (WPW) syndrome. The M-mode echocardiography study also showed no significant differences in both groups (Table 3). The pulsed-wave Doppler echocardiography showed that EM, AM, ET, and AT were significantly longer in the patients with Wilson's disease than in the control group (Table 4). The tissue Doppler imaging was in favor of significant prolongation in SM, EaM, Aam, Ss, Aas, Eas, ST, EaT, and AaT in the test group in comparison with the controls (Table 4).

The Pearson correlation analysis showed statistically significant correlations between P-wave dispersion and EM, AM, ET, AT, EaM, Ss, Eas, ST, and EaT (Fig. 2, Fig. 3 & Table 5). The mean Wilson score according to the Nazer criteria in the test group was 4.565±1.2 (range =0–10), which had a reverse relationship with the ejection fraction and a statistically significant correlation with AaS and E to AT (Fig. 4 & Table 6).

Table 2. Demographic and anthropometric characteristics of the study groups

	Case Group (n=23)	Control Group (n=47)	*P* value
Age (y) (range)	16.87±5.163 (6-28)	16.277±5.388 (8-27)	0.663
Weight (kg)	47.9±19.53	48.333±19.34	0.51
Height (cm)	157.88±18.139	160.125±21.144	0.323
Sex (%) Female Male	8 (53.33%) 15(46.67%)	18 (72%) 25(28%)	

Table 3. Electrocardiographic characteristics of the study groups

	Case Group (n=23)	Control Group (n=47)	*P* value
Heart rate (bpm)	81.466±6.73	80.377±5.442	0.21
P-wave duration in lead II (ms)	106.02±19.148	109.412±14.152	0.411
P-wave amplitude in lead II (mv)	0.154±0.051	0.171±0.046	0.17
PR interval in lead II (ms)	172.92±23.96	183.04±33.8	0.204
P-wave Dispersion (ms)	42.173±11.8	26.936±9.622	0.000
QRS duration in lead V_5 (ms)	109.548±24.677	108.952±15.387	0.902
R-wave amplitude in lead V_1 (mv)	0.23±0.127	0.216±0.166	0.652
R-wave amplitude in lead V_6 (mv)	0.998±0.342	1.138±0.434	0.181
S-wave amplitude in lead V_1 (mv)	-0.679±0.342	-0.749±0.283	0.362
S-wave amplitude in lead V_6 (mv)	-0.125±082/0	-0.165±0.131	0.193
QT interval in lead II (ms)	378.452±40.156	381.064±26.255	0.745
QTC in lead II (ms)	0.43±0.021	0.433±0.02	0.604
QT dispersion (ms)	67.826±30.3	52.425±17.61	0.009
TPE dispersion (ms)	52.452±28.953	44.476±20.527	0.188
SV (cm^3)	72.056±18.092	70.296±18.594	0.755
EF (%)	74.789±5.287	73.553±6.043	0.452
LVPWs (cm)	1.043±0.287	1.077±0.231	0.632
LVPWd (cm)	0.852±0.179	0.85±0.163	0.969
LVIDS (cm)	2.527±0.402	2.579±0.453	0.673
LVIDd (cm)	4.483±0.551	4.495±0.596	0.941
IV Ss (cm)	1.341±0.25	1.328±0.244	0.862
IV Sd (cm)	1.011±0.235	0.984±0.228	0.684
Sinus tachycardia	2 (8.695%)	1 (2.127%)	0.755
Biphasic T wave	0	2 (4.255%)	
Prominent U wave	1 (4.347%)	1 (2.127%)	
Tall R wave in lead V_1	0	0	
Tall R wave in lead V_6	0	0	
Deep S wave in lead V_1	0	1 (2.127%)	
Deep S wave in lead V_6	1 (4.347%)	2 (4.255%)	

PWD, P-wave dispersion; QTD, QT dispersion; TPED, T Peak to T end dispersion; QTC, Corrected QT interval; SV, Stroke volume; EF, Ejection fraction; LVPWS, Left ventricular end-systolic posterior wall dimension; LVPWd, Left ventricular end-diastolic posterior wall dimension; LVIDS, Left ventricular end-systolic posterior wall dimension; LVIDd, Left ventricular end-diastolic posterior wall dimension, IV Ss, Interventricular septal diameter in the systole; IV Sd, Interventricular septal diameter in the systole

Table 4. Color Doppler echocardiographic findings of the study groups

	Case Group (n=23)	Control Group (n=47)	*P* value
EM (cm/s)	0.89±0.469	25.209±38.56	0.008
AM (cm/s)	0.654±0.332	17.942±27.456	0.008
ET (cm/s)	0.678±0.127	21.554±34.657	0.011
AT (cm/s)	0.521±0.209	17.368±28.014	0.012
SM (cm/s)	0.088±0.029	3.636±5.52	0.007
EaM (cm/s)	0.142±0.06	4.589±6.878	0.007
AaM (cm/s)	0.082±0.031	3.506±5.535	0.009
Ss (cm/s)	0.085±0.023	2.503±3.795	0.008
EaS (cm/s)	0.138±0.028	3.012±4.653	0.01
AaS (cm/s)	0.137±0.209	2.397±3.755	0.012
ST(cm/s)	0.133±0.028	3.902±5.787	0.006
EaT(cm/s)	0.13±0.055	3.586±5.418	0.008
AaT (cm/s)	0.142±0.042	3.336±5.097	0.009
E to AM (cm/s)	1.719±0.972	1.683±0.771	0.877
E to AT (cm/s)	1.506±0.571	1.48±0.513	0.896
E to Aa (cm/s)	10.175±19.106	8.264±14.4	0.669

EM, Early diastolic velocity of the mitral valve; AM, Late diastolic velocity of the mitral valve; ET, Early diastolic velocity of the tricuspid valve; AT, Late diastolic velocity of the tricuspid valve; SM, Peak systolic velocity of the mitral valve; EaM, Peak early diastolic velocity of the mitral valve; AaM, Velocity of the A wave of the mitral valve; Ss, Peak systolic velocity of the septum; EaS, Peak early diastolic velocity of the septum; AaS, Peak atrial velocity of the septum; ST, Peak systolic velocity of the tricuspid valve; EaT, Peak early diastolic velocity of the tricuspid valve; AaT, Peak systolic velocity

Table 5. Pearson correlation between P-wave dispersion and electrocardiographic findings in the patients with Wilson's disease

P-Wave Dispersion	*r* value	*P* value
EM (cm/s)	-0.271	0.036
AM (cm/s)	-0.265	0.041
ET (cm/s)	-0.275	0.035
AT (cm/s)	-0.273	0.037
EaM (cm/s)	-0.263	0.04
Ss (cm/s)	-0.266	0.04
EaS (cm/s)	-0.272	0.035
ST (cm/s)	-0.257	0.046
EaT (cm/s)	-0.275	0.032

EaM, Peak early diastolic velocity of the mitral valve; Ss, Peak systolic velocity of the septum; EaS, Peak early diastolic velocity of the septum; ST, Peak systolic velocity of the tricuspid valve; EaT, Peak early diastolic velocity of the tricuspid valve

Table 6. Pearson correlation between the Wilson scores and the electrocardiographic findings in the patients with Wilson's disease

Wilson Score	*r* value	*P* value
EF (%)	-0.297	0.04
AaS (cm/s)	0.399	0.005
E to AT	0.338	0.019

AaS, Peak atrial velocity of the septum

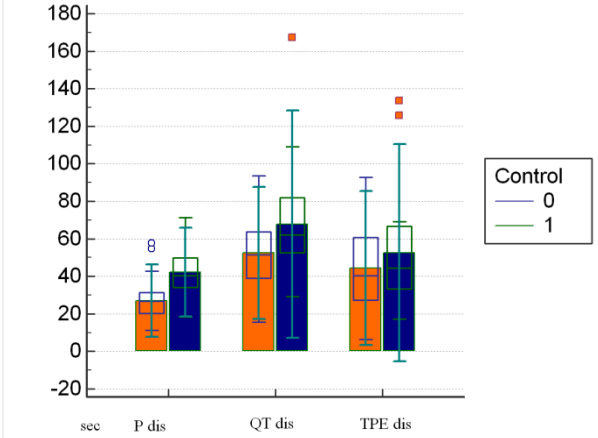

Figure 1. The image displays P-wave dispersion, QT dispersion, and TPE dispersion in the case and control groups.

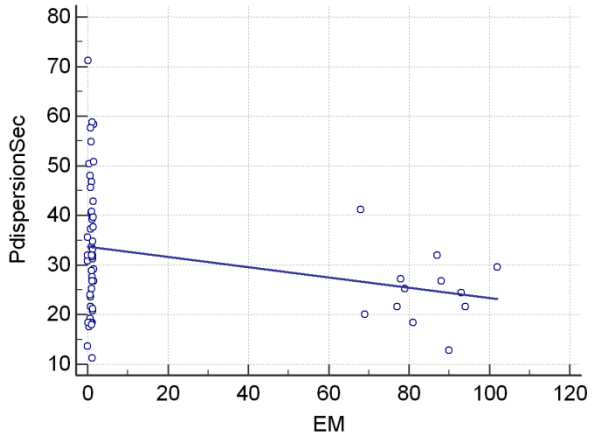

Figure 2. The image displays linear regression between P-wave dispersion and EM.

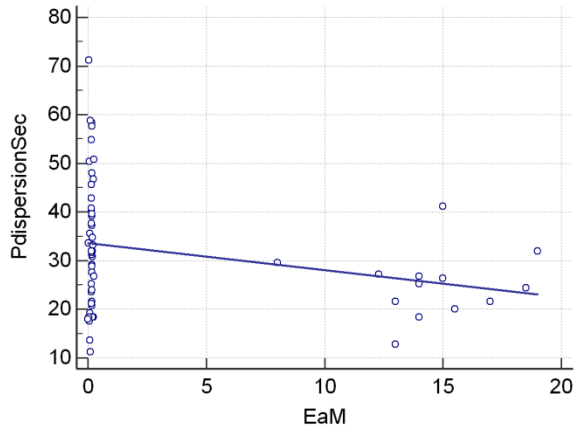

Figure 3. The image displays linear regression between P-wave dispersion and EaM.

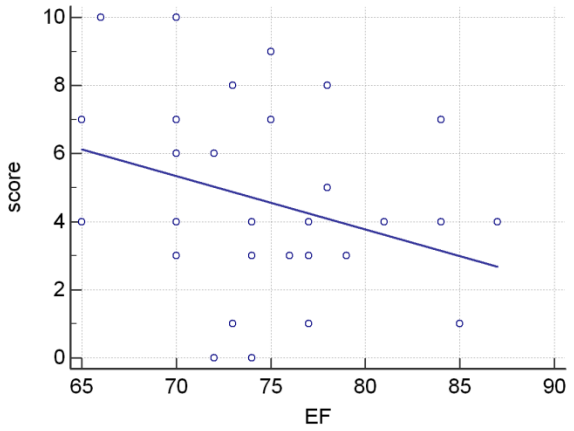

Figure 4. The image displays linear regression between EF and the Wilson score.

DISCUSSION

Wilson's disease is a rare genetic disease, with a prevalence of 1 in 30 000 people. Although liver, nerve, and psychological involvements are the main manifestations of Wilson's disease, the diagnosis and treatment of other organs as soon as possible is one of the goals to reduce morbidity and mortality. Cardiomyopathy, arrhythmia, autonomic nervous dysfunction, and cardiac death have been reported in patients with Wilson's disease in several studies. [20,21] P-wave dispersion is known a predictor of the occurrence of atrial arrhythmias, including atrial fibrillation and flutter, [21,22] especially in several cardiac (eg, coronary artery disease and post-coronary bypass surgery) and noncardiac (eg, acute pancreatitis, prehypertension, obesity, subarachnoid hemorrhage, metabolic syndrome, and diabetes mellitus) diseases. [23,24] P-wave dispersion is longer in patients with Wilson's disease than in the normal population, and it renders patients with Wilson's disease prone to atrial arrhythmias and confirms the findings of this study. [22,24,25]

QT dispersion has been introduced as a predictor of intraventricular conduction defects, ventricular arrhythmias, and sudden cardiac death in previous studies conducted by Cagli et al [22] and Cevik et al. [26] The results of this study showed that QT dispersion was significantly longer in patients with Wilson's disease than in the control group, rendering the former group prone to ventricular arrhythmias.

TPE (T peak to T end) dispersion is an index of repolarization defects in the ventricular myocardium and can be a predictor of ventricular arrhythmias and sudden cardiac death. [16] This correlation has been reported in patients with hypertrophic cardiomyopathy and Brugada syndrome. [21,27] Topilski et al [28] also showed that QTC and TPE intervals could predict torsade de pointes. In our study, there was no significant difference in TPE dispersion between the patients with Wilson's disease and the healthy control group.

Systolic and diastolic cardiac dysfunction has been evaluated in patients suffering from Wilson's disease in several studies. Our findings by M-mode echocardiography in this regard showed no significant difference between the patients with Wilson's disease and the control group, in contrast to the data reported by Meenakshi–Sundaram et al. [7] Such variations can arise because of different criteria considered in selecting the study population. Meenakshi–Sundaram et al [7] chose patients with either more

advanced diseases or poor compliance for oral chelating agents as their study group.

Our Doppler echocardiographic measurements showed that the patients with Wilson's disease had significantly longer EM, AM, ET, and AT, in favor of diastolic dysfunction. Our tissue Doppler imaging measurements also demonstrated significantly longer SM, EaM, AaM, Ss, EaS, Aas, ST, EaT, and AaT in the patients with Wilson's disease than in the control group, which is in close agreement with the results reported by Elkiran et al. [29]

Although we found no significant difference in the ejection fraction between the 2 study groups, the other findings from color Doppler and tissue Doppler imaging were in favor of diastolic dysfunction in the group with Wilson's disease. These results confirm Elkiran's theory of the introduction of diastolic dysfunction as a predictor of Wilson's cardiac involvement. [29] According to the Nazer criteria, the Wilson score is a grading system for the appropriate referral of patients with Wilson disease to liver transplantation centers. [18] Our results showed that the Wilson score was related to AaS and E to AT and was reversely correlated with the ejection fraction.

CONCLUSIONS

P-wave dispersion and QT dispersion were significantly longer in our patients with Wilson's disease than in our normal control group. This finding can predict atrial and ventricular arrhythmias and sudden cardiac death. Diastolic dysfunction might be the initial presentation of Wilson's cardiac involvement. In light of our findings, we conclude that the progression of Wilson's disease and further accumulation of copper in body organs and systems, including the cardiovascular system, could result in increased risks of arrhythmias and systolic and diastolic dysfunction and in the future.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgments

The present article was extracted from a thesis written by Sahar Azadi and was financially supported by Shiraz University of Medical Sciences (grant No: 93-01-01-7912).

REFERENCES

1. Carta M, Mura G, Sorbello O, Farina G, Demelia L. Quality of Life and Psychiatric Symptoms in Wilson's Disease: the Relevance of Bipolar Disorders. Clin Pract Epidemiol Ment Health 2012; 8:102-109.
2. EASL Clinical Practice Guidelines: Wilson's disease. J Hepatol 2012; 56:671-685.
3. Hedera P. Wilson's disease: A master of disguise. Parkinsonism Relat Disord 2019; 59:140-145.
4. Pfeiffer RF. Wilson's disease. Handb Clin Neurol 2011; 100:681-709.
5. Bandmann O, Weiss KH, Kaler SG. Wilson's disease and other neurological copper disorders. Lancet Neurol 2015; 14:103-113.
6. Poujois A, Woimant F. Wilson's disease: A 2017 update. Clin Res Hepatol Gastroenterol 2018; 42:512-520.
7. Meenakshi-Sundaram S, Sinha S, Rao M, Prashanth LK, Arunodaya GR, Rao S, et al. Cardiac involvement in Wilson's disease--an electrocardiographic observation. J Assoc Physicians India 2004; 52:294-296.
8. Kuan P. Cardiac Wilson's disease. Chest 1987;91:579-583.
9. Lim CT, Choo KE. Wilson's disease--in a 2 year old child. J Singapore Paediatr Soc 1979; 21:99-102.
10. Ko S, Lee T, Ng S, Lin J, Cheng Y. Unusual liver MR findings of Wilson's disease in an asymptomatic 2-year-old girl. Abdom Imaging 1998; 23:56-59.
11. Nakayama K, Kubota M, Katoh Y, Sawada Y, Saito A, Nishimura K, et al. Early and presymptomatic detection of Wilson's disease at the mandatory 3-year-old medical health care examination in Hokkaido Prefecture with the use of a novel automated

urinary ceruloplasmin assay. Mol Genet Metab 2008; 94:363-367.

12. Hermann W, Eggers B, Wagner A. The indication for liver transplant to improve neurological symptoms in a patient with Wilson's disease. J Neurol 2002; 249:1733-1734.

13. Grümayer ER, Weippl G. [Acute hemolysis and liver cirrhosis as leading symptoms of Wilson's disease in childhood]. Klin Padiatr 1983; 195:355-357.

14. Dilaveris PE, Gialafos JE. P-wave dispersion: a novel predictor of paroxysmal atrial fibrillation. Ann Noninvasive Electrocardiol 2001; 6:159-165.

15. Gurok MG, Korkmaz H, Yıldız S, Bakış D, Atmaca M. QT and P-wave dispersion during the manic phase of bipolar disorder. Neuropsychiatr Dis Treat 2019; 15:1805-1811.

16. Milberg P, Reinsch N, Wasmer K, Mönnig G, Stypmann J, Osada N, et al. Transmural dispersion of repolarization as a key factor of arrhythmogenicity in a novel intact heart model of LQT3. Cardiovasc Res 2005; 65:397-404.

17. Rodrigues A, Guimarães-Filho FV, Braga JC, Rodrigues CS, Waib P, Fabron-Junior A, et al. Echocardiography in thalassemic patients on blood transfusions and chelation without heart failure. Arq Bras Cardiol 2013; 100:75-81.

18. Nazer H, Ede R, Mowat A, Williams R. Wilson's disease: clinical presentation and use of prognostic index. Gut 1986; 27:1377-1381.

19. Arat N, Kacar S, Golbasi Z, Akdogan M, Sokmen Y, Kuran S, et al. P wave dispersion is prolonged in patients with Wilson's disease. World journal of gastroenterology: WJG 2008; 14:1252.

20. Meenakshi-Sundaram S, Sinha S, Rao M, Prashanth L, Arunodaya G, Rao S, et al. Cardiac involvement in Wilson's disease-an electrocardiographic observation. JAPI 2004; 52.

21. Dilaveris PE, Gialafos JE. P-wave dispersion: A novel predictor of paroxysmal atrial fibrillation. Annals of Noninvasive Electrocardiology 2001;6:159-165.

22. Çağlı K, Ergün K, Lafçı G, Gedik HS, Ulaş MM. QT and P wave dispersion. Journal of Ankara University Faculty of Medicine 2005; 58.

23. Soliman RA, Battah AA, Hekaal A, Ashraf MM, Wadei A. The Relationship between P Wave Dispersion and Diastolic Dysfunction in Patients with Significant and Insignificant Coronary Artery Disease. J Am Sci 2010; 6:438-445.

24. KHOSROUPANAH S, Nemati M, BAZARGAN LO, Zare N. Effect of CABG on P-wave Dispersion and the Relationship between AF and P-wave Dispersion 2009.

25. DEDEOĞLU E, BAYRAM B, ÖMÜ D, Hanci V. The P-wave dispersion and QTC durations in the patients with acute pancreatitis. Acta Medica 2014; 30:869.

26. Cevik Y, Tanriverdi F, Delice O, Kavalci C, Sezigen S. Reversible increases in QT dispersion and P wave dispersion during carbon monoxide intoxication. Hong Kong Journal of Emergency Medicine 2010; 17:441-450.

27. Castro H. Antzelevitch C. T peak–T end and T peak–T end dispersion as risk factor for Ventricular tachycardia/Ventricular fibrillation in patients with Brugada syndrome. J Am Coll Cardiol 2006; 47:1828-1834.

28. Topilski I, Rogowski O, Rosso R, Justo D, Copperman Y, Glikson M, et al. The morphology of the QT interval predicts torsade de pointes during acquired bradyarrhythmias. Journal of the American College of Cardiology 2007; 49:320-328.

29. Elkiran O, Karakurt C, Selimoglu A, Karabiber H, Kocak G, Celik SF, et al. Subclinical diastolic dysfunction in children with Wilson's disease assessed by tissue Doppler echocardiography: a possible early predictor of cardiac involvement. Acta cardiologica 2013; 68:181-187.