Dicle Tıp Dergisi / Dicle Med J (2024) 51 (2) : 155-161

www.diclemedj.org

Original Article / Özgün Araştırma

Evaluation of ventricular arrhythmia in children with Wilson's disease; cardiac electrophysiological balance index (iCEB)

Kerem Ertas[1], **Ozlem Gul**[1], **Fatma Demirbas**[2]

1 Department of Pediatric Cardiology, Diyarbakir Children's Hospital, Diyarbakır, Turkey

2 Department of Pediatric Gastroenterology, Hepatology and Nutrition, Diyarbakir Children's Hospital, Diyarbakır, Turkey

Received: 02.12.2023; Revised: 06.04.2024; Accepted: 17.04.2024

Abstract

Aim: To evaluate cardiac involvement in Wilson's disease (WD) noninvasively by electrocardiography and to analyze it with the cardiac electrophysiological balance index (iCEB).

Method: Eighteen Wilson patients and 18 healthy child patients who were followed up in the Pediatric Gastroenterology department between 2022-2023 were included in the study.

Results: Wilson disease patients had normal ventricular and autonomic functions. QT-dispersion (QT-d) (22.61 (±11.47), p=0.000) and Tpe (66.50 (40-78), p=0.02) were found to be significantly higher in the WD group. QRS, QRS-dispersion (QRS-d), QT, QTc, Tpe/QT ratio, Tpe/QTc ratio, QT/QRS ratio, QTc/QRS ratio, Tpe/QRS ratio, Tpe/(QT*QRS) ratio both had similar values in the groups. Heart rate variability parameters (SDNN, SDNN-i, SDANN, rMSSD, pNN50, LF/HF ratio) were at similar values in both groups. rMSSD, pNN50, which indicates parasympathetic activity, was lower in Wilson patients than in the control group, but no statistical difference was detected. LF/HF ratio was significantly higher in WD patients.

Conclusions: Despite normal ventricular function and autonomic function in WD patients, they have an increased risk of ventricular arrhythmia. Although the cardiac electrophysiological balance index (iCEB) can provide useful information in the follow-up of WD patients, we recommend that depolarization, repolarization times, and repolarization dispersion times be evaluated separately in addition to iCEB.

Key words: Wilson disease; index of cardiac electrophysiological balance; autonomic dysfunction; Heart rate variability; repolarization dispersion

DOI: 10.5798/dicletip.1500899

Correspondence / Yazışma Adresi: *Ozlem Gul, Department of Pediatric Cardiology, Diyarbakir Children's Hospital, Diyarbakır, 21100 Yenişehir / Diyarbakır, Turkey e-mail: drsivasli@hotmail.com*

Wilson hastalığı olan çocuklarda ventriküler aritminin değerlendirilmesi; kardiyak elektrofizyolojik denge indeksi (iCEB)

Öz

Amaç: Wilson hastalığında (WH) kalp tutulumunu, noninvaziv olarak elektrokardiyografi ile değerlendirmek ve kardiyak elektrofizyolojik denge indeksi (iCEB) ile analiz etmek amaçlandı.

Yöntemler: Çalışmaya 2022-2023 yılları arasında Çocuk Gastroenteroloji bölümünde takip edilen 18 Wilson hastası ve 18 sağlıklı çocuk hasta dahil edildi.

Bulgular: Wilson Hastalığı olan çocuklarda ventriküler ve otonomik fonksiyonlar normaldi. QT dispersiyonu (QT-d) (22,61 (±11,47), p=0,000) ve Tpe (66,50 (40-78), p=0,02) WH grubunda anlamlı olarak yüksek bulundu. QRS, QRS dispersiyonu (QRS-d), QT, QTc, Tpe/QT oranı, Tpe/QTc oranı, QT/QRS oranı, QTc/QRS oranı, Tpe/QRS oranı, Tpe/(QT*QRS) oranları her iki grupta benzerdi. Kalp hızı değişkenliği parametreleri (SDNN, SDNN-i, SDANN, rMSSD, pNN50, LF/HF oranı) her iki grupta da benzer değerlerdeydi. Parasempatik aktiviteyi gösteren rMSSD, pNN50 Wilson hastalarında kontrol grubuna göre daha düşüktü ancak istatistiksel olarak fark saptanmadı. LF/HF oranı Wilson hastalarında anlamlı derecede yüksekti.

Sonuç: Wilson hastalarında ventriküler fonksiyon ve otonom fonksiyon normal olmasına rağmen ventriküler aritmi riski yüksektir. Kardiyak elektrofizyolojik denge indeksi (iCEB) WH hastalarının takibinde faydalı bilgiler sağlayabilse de iCEB'e ek olarak depolarizasyon, repolarizasyon süreleri ve repolarizasyon dispersiyon sürelerinin de ayrı ayrı değerlendirilmesini öneriyoruz.

Anahtar kelimeler: Wilson hastalığı; kardiyak elektrofizyoloji denge indeksi; otonomik disfonksiyon; kalp hızı değişkenliği; repolarizasyon dispersiyonu.

INTRODUCTION

Wilson's disease (WD) is an autosomal recessive disease in which copper accumulates in organs as a result of a defect in the protein (ATP7B) that provides transport in copper metabolism and excretion of copper from the liver[1].

Damage to organs in WD occurs mainly because of copper accumulation and damage as a result of free oxygen radicals[2,3]. Cardiomyopathy and arrhythmias may develop because of cardiovascular system involvement[4].

In postmortem studies of WDs; Histopathological findings, such as myocardial hypertrophy, fibrosis, and sclerotic changes, were detected. Cases of sudden death have been reported in WD[4,5].

There is very little evidence in the literature of cardiac arrhythmias in WD. In our study, we aimed to objectively evaluate the ventricular electrophysiological characteristics in WD using the index of cardiac electrophysiological balance (iCEB) in addition to conventional measurements.

METHOD

This was a prospective, case-control study. Approval was obtained from the local ethics committee (decision no: 558/2023).

Eighteen Wilson patients and 18 healthy pediatric patients followed up from the pediatric gastroenterology department were included in the study.

Wilson disease patients diagnosed according to Wilson's disease diagnostic criteria[6] were patients with hepatic involvement without central nervous system involvement and normal liver function tests at the time of evaluation. All Wilson disease patients underwent penicillamine therapy.

The body weight of all patients was expressed in

kilograms and the height in centimeters. Blood pressure was measured after the patients had rested for 15 minutes.

After a detailed examination of all patients, they were evaluated by transthoracic echocardiography (ECHO) (Vivid S60, General Electric Healthcare, GE, Vingmed, Norway)[7].

Left ventricular wall thickness and diameter, systolic and diastolic function parameters were measured in accordance with the recommended guidelines[7,8].

All patients were evaluated using 12-lead electrocardiography (ECG) (Econet Cardio M Plus, Germany; filtered 0.5–150 Hz, 25 mm/s, and 10 mm/mV). Holter ECG and ECG are commonly used to assess symptoms that may be associated with intermittent arrhythmias, such as syncope, dizziness, chest pain, palpitations. ECG recordings were evaluated offline by magnifying them 200 times on a computer.

Mean values were obtained by measuring at least five consecutive waves or intervals in lead DII or V5. QRS, QT, and Tpe were measured. A correction was made for the heart rate[9,10,11,12]. Thus, the QTc was obtained[13]. The difference between the maximum and minimum values of the measured time was defined as the dispersion value. Thus, QRS-d, QT-d, and QTc-d were obtained[9,14]. The cardiac electrophysiological balance index (iCEB), QT/QRS ratio, Tpe/QRS ratio, cardiac electrophysiological balance index corrected for heart rate (iCEB-c) QTc/QRS ratio were measured[15,16,17].

24-hour electrocardiography recording and heart rate variability (HRV) software based on Holter ECG recordings (Delmar Reynolds lifeCard CF; Impresario Software). Parameters derived from the time interval (SDNN (the standard deviation of all normal R-R intervals), SDNN index, rMSSD (the square root of the mean of the sum of the squares of differences between adjacent RR intervals), mean heart rate, pNN50 (the proportion of adjacent R-R intervals that differ by more than 50 ms in the 24-h recording)) and parameters derived from frequency (LF (low frequency), HF (high frequency), LF/HF ratio) were obtained[18,19].

Statistical analyses were performed using IBM SPSS (SPSS, Chicago, IL, USA). Continuous variables are expressed as mean±standard deviation or median (minimum-maximum), and categorical variables are expressed as percentages (%). Appropriate tests were selected on the basis of their distribution characteristics. Statistical significance was set at $p < 0.05$significant.

RESULTS

Wilson disease and control groups mean age values were 12.44 (± 4.15), and 12.49 (± 4.17) years, respectively. In this study, 44% of the Wilson and control group patients were male.

As a result of comparing the WD group and the control group, the values of age, sex, weight, height, SBP and DBP were similar in both groups and there was no statistical difference.

LVEDd, EF, FS, Tapse, mitral E and A velocities, E/A ratio, and DT values in the WD and control groups were similar in both groups, and no statistical difference was found (Table I).

Table I: Comparison of demographic data and transthoracic echocardiographic data of Wilson patients and control group

Parameter	Wilson group (n=18)	Control group (n=18)	p value
Gender (M/F, %)	44,56	44,56	1.00[3]
Age (year)	12.44 (± 4.15)	12.49 (± 4.17)	0.97[1]
Weight (kg)	40.39 (± 16.37)	41.88 (± 15.49)	0.32[1]
Height (cm)	144.88 (± 19.35)	151.22 (± 18.53)	0.25[1]
SBP (mmHg)	110.83 (± 13.23)	113.22 (± 11.11)	0.56[1]
DBP (mmHg)	62.88 (± 9.06)	65.44 (± 9.24)	0.40[1]
LVEDd (mm)	42.21 (± 5.47)	43.52 (± 5.40)	0.21[1]
EF (%)	66.88 (± 6.67)	69.94 (± 5.59)	0.14[1]
FS (%)	35.50 (30-52)	38.50 (32-49)	0.10[2]
TAPSE (mm)	22.40 (± 2.24)	22.71 (± 2.97)	0.70[1]
E wave (m/s)	0.92 (± 0.14)	0.99 (± 0.214)	0.15[1]
A wave (m/s)	0.62 (± 0.16)	0.58 (± 0.13)	0.50[1]
E/A ratio	1.56 (± 0.46)	1.74 (± 0.35)	0.18[1]
DT (ms)	126.27 (± 21.06)	140.27 (± 28.27)	0.11[1]

1: student T test, 2: Mann-Whitney U test, 3: chi-square test

The ECGs of all patients were in sinus rhythm, and none had a ventricular branch block. QRS duration, QRS-d, QT, QTc, QTc-d, Tpe/QT ratio, Tpe/QTc ratio, QT/QRS ratio, Tpe/QRS ratio, QTc/QRS ratio values in the WD and control groups were similar in both groups (Table II).

QTd and Tpe values were significantly higher in the WD group compared to the control group (p = 0.001 and 0.02, respectively) (Table II).

Table II: Wilson disease group and control group electrocardiography parameters comparison table

Parameter	Wilson group (n=18)	Control group (n=18)	p value
QRS (ms)	80 (79-100)	80 (80-86)	0.18[2]
QRS-d (ms)	0 (0-20)	0 (0-10)	0.23[2]
QT	357.80 (296-408)	322.00 (289-386)	0.05[2]
QT-d	22.61 (± 11.47)	11.66 (± 8.22)	**0.001[1]**
QTc	408.9 (± 32.66)	392.39 (± 22.87)	0.08[1]
QTc-d	41.59 (± 21.68)	35.19 (± 19.30)	0.35[1]
Tpe (ms)	66.50 (40-78)	57 (40-92)	**0.02[2]**
Tpe/QT ratio	0.18 (0.13-0.22)	0.16 (0.12-0.24)	0.18[2]
Tpe/QTc ratio	0.16 (± 0.02)	0.14 (± 0.03)	0.28[1]
QT/QRS ratio	4.16 (± 0.49)	4.07 (± 0.30)	0.49[1]
QTc/QRS ratio	4.88 (± 0.61)	4.86 (± 0.31)	0.93[1]
Tpe/QRS ratio	0.76 (± 0.11)	0.71 (± 0.14)	0.23[1]
Tpe/(QT*QRS)	0.0022 (± 0.0003)	0.0022 (± 0.0003)	0.79[1]

HR, SDNN, SDNN-i, SDANN, rMSSD, pNN50 and LF/HF ratio values were similar in both groups and no statistical differences were observed (Table III).

Table III: Comparison of heart rate variability parameters of WD group and control group

Parameter	Wilson group (n=18)	Control group (n=18)	p value
HR (beat/min)	89.88 (± 10.37)	88.80 (± 8.10)	0.77[1]
SDNN (ms)	163.53 (± 46.27)	151.31 (± 38.13)	0.53[1]
SDNN index (ms)	79.28 (± 29.33)	80.20 (± 32.00)	0.93[1]
SDANN (ms)	134.62 (± 44.04)	122.05 (± 32.42)	0.37[1]
rMSSD (ms)	76.35 (± 46.81)	81.05 (± 37.63)	0.75[1]
pNN50 (%)	22.70 (± 13.66)	28.36 (± 10.84)	0.19[1]
LF/HF	2.05 (± 0.82)	1.64 (± 0.51)	0.11[1]

1: student T test, 2: Mann-Whitney U test, HR: heart rate, SDNN: the standard deviation of all normal R–R intervals in the 24-h electrocardiogram (ECG) recording, SDNNindex: the mean of the

standard deviation of all R–R intervals for all 5-min segments of the 24-h ECG recording, SDANN: the standard deviation of the mean of R–R intervals in all 5-min segments of the 24-h ECG recording, rMSSD: the square root of the mean of the sum of the squares of differences between adjacent RR intervals, pNN50: the proportion of adjacent R–R intervals that differ by more than 50 ms in the 24-h recording, LF low frequency (0.04–0.15 Hz), HF high frequency (0.15–0.40 Hz)

DISCUSSION

Although ventricular and autonomic functions were normal in our study, the repolarization time and dispersion times were high in the WD group. The WD group was high-risk for ventricular arrhythmias.

The basic myocardial damage mechanism in WD is thought to result from copper deposition[3], damage from free oxygen radicals[2] and autonomic dysfunction[20,21]. Sudden cardiac death has been reported in WD in the literature[5] but there is insufficient evidence for ventricular arrhythmia.

In our study, ventricular electrophysiological features, depolarization properties, repolarization properties and repolarization-depolarization balance were examined under headings.

For depolarization analysis, QRS duration and QRS dispersion analysis were used. QRS interval ECG representation of ventricular depolarization. QRS dispersion is the difference between QRS-max and QRS-min according to the change in the cardiac rate[9]. The QRS dispersion is the reciprocal of spatial distribution of conduction velocity. An increased QRS dispersion may cause one-way block and reentry[22]. In one study, a high QRS duration was reported in Wilson disease patients[23]. In our study, in parallel with the literature[24-26], ventricular depolarization and dispersion of depolarization were found to be similar. Thus, in our study, copper did not cause conduction abnormalities due to myocardial accumulation during the early stages of WD.

The myocardium consists of three layers with different electrophysiological properties: endocardium, mid-myocardium (M cell), and epicardium. The epicardium had the shortest and the m cell had the longest duration of electrical activity. The electrical gradient between these layers increases the risk of arrhythmia[27].

In our study, in parallel with the literature[24,25], QT and QTc values were similar in both groups, but the QT dispersion was greater. In one study, QT and QTc interval values were higher in the WD group[26]. In this study, WD with high QT/QTc intervals had neurological involvement and this relationship was associated with autonomic dysfunction. In our study, autonomic function parameters were similar in Wilson disease patients without neurological involvement, which supports the results of the study. However, the fact that QT dispersion in this study had similar values in both neurological and non-neurological WDs, unlike in our study, makes the mechanism underlying QT dispersion prolongation controversial. Studies have shown that central[21,22] and peripheral involvement[28,29] occur in the development of autonomic dysfunction in WD. In our study, none of the patients had neurological involvement, and autonomic function parameters were normal.

An increase in the repolarisation dispersion time or transmural repolarisation dispersion time creates a predisposing condition for reentry. Sudden cardiac death (SCD) may ocur[11,12,30]. In our study, Tpe, a transmural repolarization dispersion parameter, was higher in the WD group than in previous studies[24,26]. This supports the existence of a ventricular transmural gradient difference in the early period and that they are especially risky for reentry ventricular arrhythmias.

The electrical wavelength (λ) is important for arrhythmia formation. An increase or decrease in the wavelength creates a predisposing condition for reentrant arrhythmias. Wavelength measurements (λ) can be

noninvasively displayed on an ECG. Lu et al. developed iCEB parameters to represent wavelength[15]. iCEB is a parameter based on (repolarization time/depolarization time). The QT/QRS ratio[15] can be used as an iCEB parameter and the QTc/QRS ratio[17] can be used as a corrected iCEB (iCEB-c) parameter. Tse et al. showed that the Tpe/QRS and Tpe/(QT*QRS) ratios can be used in addition to these parameters in iCEB evaluation[16].

The iCEB value should be within a certain range. An increase in iCEB causes torsadogenic, and a decrease causes non-torsadogenic ventricular tachyarrhythmias[1]. In our study, the iCEB and iCEB-c parameters were similar in both the groups. When the literature is reviewed, our study is the first to evaluate iCEB in Wilson's patients. The main reason for the normal iCEB in our study may be the long repolarization time in the WD group as well as the long depolarization time. In the study, mean QRS durations in the WD group and control group were 84.50 (±7.12) and 80.68 (±1.57), respectively. The use of iCEB in diseases that are likely to cause depolarization abnormalities, such as Wilson disease, is controversial. Mathematically considering the iCEB value, prolongation of the QRS period in the denominator may stabilize the iCEB ratio.

CONCLUSIONS

In our study, the risk of ventricular arrhythmia was high in Wilson disease patients with normal ventricular and autonomic function. This may be associated with myocardial copper accumulation, damage by free oxygen radicals, and altered ion channels in Wilson's disease independent of autonomic dysfunction mechanisms.

Although iCEB evaluation provides useful information for Wilson's patients, we recommend separately evaluating the depolarization and repolarization time and repolarization dispersion times in addition to iCEB.

The main limitations of our study are the limited number of patients and the lack of cardiac magnetic resonance imaging.

Ethics Committee Approval: This was a prospective, case-control study. Approval was obtained from the local ethics committee (decision no: 558/2023).

Conflict of Interest: The authors declared noconflicts of interest.

Financial Disclosure: The authors declared thatthis study has received no financial support.

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