Ambulatory Electrocardiogram Changes with Chelation Therapy in 28 Wilson's Disease Patients

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Abstract: **Background**: Wilson's disease (WD)'s cardiovascular involvement has gained more attention. That are caused by direct copper accumulation in the heart, central and peripheral autonomicnerve dysfunction, and cardiomyopathy that is secondary to liver cirrhosis. Twenty-four-hour ambulatory electrocardiogram (AECG) can detect abnormal electrocardiogram (ECG) changes in real-time by recording ECG continuously for 24 hours. It also indicates autonomic nerve function by reviewing heart rate variations (HRV). Limited results have shown that up to 43-63% of WD patients have abnormal AECG changes, but HRV and changes with chelation therapy have been reported rarely. **Objective** To evaluate the AECG changes and the relationship between clinical outcomes and AECG changes after chelation therapy in 28 patients with WD. **Methods** standard 12-lead electrocardiogram (ECG) and AECG were recorded in 28 WD patients (16 male, 12 female; mean age 18.5 +/- 7.5 years) in three days after admission and after anti-copper treatment for eight weeks respectively. The clinical outcomes were evaluated by the same observer, according to the Unified Wilson's Disease Rating Scale (UWDRS). **Results** Before chelation, ten out of 28 (35.7%) patients had abnormal ECGs, that mainly included arrhythmia, left ventricular high voltage, ST depression and T wave abnormalities, eighteen patients (64.3%) had at least one abnormality in the AECG, that mainly included arrhythmia, ST depression and T wave abnormalities, and time-dependent measures of heart rate variability (HRV), SDNN and RMSSD values were 135.786 ± 57.304 and 57.357 ± 34.193 respectively. Despite the significant clinical improvement (Clinical score: t=3.138, p=0.004), the ECG, AECG and heart rate variation parameters (SDNN and RMSSD) did not change significantly (P>0.05) after chelation therapy for 8 weeks. **Conclusions** Although the clinical symptoms improved with eight weeks of chelation therapy, the ECG and AECG did not improve accordingly.
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1. Introduction

Hepatolenticular degeneration, also known as Wilson's disease (WD), is an autosomal recessive genetic metabolic disorder that causes copper to accumulate in tissues. Recently, its cardiovascular involvement has gained more attention. In the 2008 WD diagnostic and treatment guidelines, the cardiovascular involvement was viewed as an important atypical clinical manifestation (Roberts and Michael, 2008) Up to 34-50% WD patients are found to have abnormal electrocardiogram (ECG) changes, in particular cardiac arrhythmias and ST-T changes (Meenakshi-Sundaram et al., 2004; Yang, 1995; Huang et al., 1999; Hao, 1997). Twenty-four-hour ambulatory electrocardiogram (AECG) is superior in detecting these changes because the ECG is recorded continuously for 24 hours. It also indicates autonomic nerve function by reviewing heart rate variations (HRV). WD's cardiac involvements are caused by direct copper accumulation in the heart, central and peripheral autonomic nerve dysfunction, and cardiomyopathy that is secondary to liver cirrhosis. Currently, studies on WD with AECG are uncommonly conducted. Limited results have shown that up to 43-63% of WD patient have abnormal AECG changes (Hlubocká et al., 2002; Yang, 2009) but HRV and changes with chelation therapy have been reported rarely (Liu and Zhang, 2013). We studied the AECG of 28 WD patients and developed a clinical scoring system to evaluate patients' clinic outcomes before and after chelation therapy. It correlations between changes in AECG readings and clinical outcomes were analyzed in 28 WD patients.

2. Materials and Methods

Subjects: Twenty-eight WD patients (16 male, and 12 female, mean age: 18.5 ± 7.5 years, range 7–40 years) who were treated at Zhengzhou People's Hospital from October 2011 to August 2012 were included in the study. The patients had been diagnosed with WD for 6 months to 15 years earlier, with an average 3.1±1.9 years. Grouping criteria:

Subjects were required to meet the WD diagnostic criteria developed by the Chinese medical association, neurological disease chapter, Parkinson's disease and motion disorder group and genetic neurological disorder grou (2008). They were evaluated by a designated physician according to Evaluation of the Unified Wilson's Disease Rating Scale (UWDRS) within 3 days of hospital admission and again 8 weeks after chelation therapy (Leinweber et al., 2008) The WD diagnostic criteria were as follows: (1) liver damage or neurological symptoms; (2) low serum level of ceruloplasmin (<0.2 g/L); (3) high 24-hour urine copper excretion (> 100 ug); (4) corneal Kayser–Fleischer rings (KF rings) visible on slit lamp examination. Evaluation standards: The UWDRS included a clinical scoring table with the following three components: neurological score with 206 points being the highest score; liver function with 36 points being the highest score; psychological function with 76 points being the highest score. Total score is 320 points. All patients were informed about the study purposes. Consent was signed by all participating patients.

Methods: All patients had a standard 12-lead ECG and 12-lead 24-hour AECG within 3 days after admission and at 8 weeks post chelation treatment. ECGs were acquired with Nihon Kohden EKG 1205 with patients in the supine position after a 3-5 minute rest. If arrhythmias were seen, a three minutes rhythm strip was added. AECGs were obtained with the Version 12.5 system made by DMS. Tracing was replayed and artifacts were removed with software under manual commands. Premature supraventricular and ventricular beats were identified. Maximum and minimum heart rates and ST segment changes were analyzed. Heart rate variation parameters, such as SDNN and RMSSD, were automatically calculated by the system. Rare premature beats and early repolarization were not viewed as abnormalities. The analyzers were blind to group randomization.

Statistical analysis: Statistical analyses were carried out using SPSS (version 16.0). Continuous variables are expressed as mean ± SD, and categorical variables are expressed as percentages. Comparisons of continuous variables between two groups were performed by means of matching Student's t test. Categorical variables were compared using the Pearson Chi-square test. The Fisher's exact test was used when the theoretical frequency was less than 5. For all tests, $P < 0.05$ was considered statistically significant.

3. Results

ECG changes before and after chelation therapy: Before chelation, ten out of 28 (35.7%) patients had abnormal ECGs. The abnormal ECGs were as follows: six cases with sinus tachycardia or bradycardia; four cases with left ventricular high voltage (LVHV), four cases with T wave abnormalities; heart block in 2 cases. After 8 weeks of chelation therapy, six out of the ten patients with abnormal ECGs had complete or significant improvement of their ECG findings. The remaining four patients had no ECG improvement after chelation. Another four patients developed new abnormalities on ECG, including sinus tachycardia and bradycardia. Clinically, the patients' symptoms had improved significantly after chelation therapy. (Clinical score: $t = 3.138$, $p = 0.004$), ECG changes did not reach statistical significance. Table 1 shows the details of there sult.

Table 1. ECG changes pre- and post chelation therapy in 28 WD patients

Items	Cases	Score	Arrhythmia		T wave abnormality	LVHV
			T/B*	HB**		
Pre-Chelation	28	28.4+27.6	6	2	4	4
Post-Chelation	28	19.9+19.5	10	2	1	3
P value		0.004	0.375	1.000	0.352	1.000

T/B*: tachycardia or bradycardia; HB**: heart block.

AECG changes pre- and post chelation therapy: AECG was abnormal in 18 out of 28 patients (64.3%). After 8 weeks of treatment, of the 18 patients with abnormal findings, eight had complete or significant recovery, six had no significant changes, and the remaining four patients developed new sinus tachycardia. Another three patients who had normal AECGs before chelation therapy developed new ST-T changes on AECG after therapy. Despite the significant clinical improvement (Clinical score: $t=3.138$, $p=0.004$), the AECG and heart rate variation parameters (SDNN and RMSSD) did not change significantly with chelation therapy ($P>0.05$). See Table 2 for details.

Table 2. AECG changes pre- and post chelation therapy in 28 WD patients

Items	Cases	Score	Arrhythmia			ST-T Changes	SDNN	RMSSD
			T/B*	HB**	FPVC***			
Pre-Chelation	28	28.4+27.6	6	6	2	14	135.8±57.3	57.4±34.2
Post-Chelation	28	19.9+19.5	8	4	2	14	139.6±35.3	58.5±29.0
P value		0.004	0.537	0.485	1.000	1.000	0.668	0.866

T/B*: tachycardia or bradycardia; HB**: heart block; FPVC***: frequent premature beats.

4. Discussion

WD is an autosomal recessive disorder affecting copper metabolism. The WD gene codes for a copper transporting P-type ATPase (ATP7B) are located on chromosome 13q14.3. Mutation of this gene disrupts copper homeostasis, resulting in the accumulation of copper in the liver, brain, kidneys, and corneas and in copper toxicity at these sites. WD particularly affects the liver and nervous system. Heart involvement in Wilson's disease, however, has rarely been recorded.

Kuan (1987) and his colleagues have categorized cardiac involvements in WD into four groups: cardiac arrhythmia, cardiomyopathy, sudden cardiac death and autonomic nerve dysfunction. Along with liver and neurological involvement, cardiac symptoms are viewed as one of the major WD symptoms. We studied the ECGs for 28 WD patients and found abnormalities in 35.7%. These abnormalities included cardiac arrhythmia, ST-T changes and LVHV. The results were similar to previously reported findings (Meenakshi-Sundaram et al., 2004; Yang, 1995; Huang et al., 1999; Hao, 1997; Kuan, 1987) After eight weeks of chelation therapy, six out of ten patients with abnormal ECG changes had complete or significant improvements. The cardiac involvements in WD patient are generally caused by several mechanisms including direct copper deposition in the cardiovascular system, central and peripheral autonomic nerve dysfunction and cardiomyopathy secondary to liver cirrhosis (Liu and Han, 2011) With chelation therapy, copper is removed from the heart and other organs, which explains the ECG improvement in some patients. Four patients developed new abnormalities on ECG after chelation, which may be due to copper redistribution from high concentration organs to low concentration organs during the early phases of chelation therapy. Such copper redistribution to neurological system or other new tissues has been observed in at least one previous study (Yang and Li, 2011).

AECG offers 24-hour continuous cardiac information for patients in various positions. The information includes heart rate and its variation, premature beats, tachycardia and ST-T changes. Compared to regular 12-lead ECG, AECG is superior in detecting cardiac arrhythmias and ST-T changes. AECG was found to be abnormal in 64.3% of all studied patients, which is much higher than the abnormal ECG rate. Our results are consistent with those reported by Yang Guange, but slightly higher than those reported by Hlubocka. These results indicate that ECG is not sensitive enough to discover the cardiac involvement in WD patients, and that AECG is required to accomplish that.

One of the problems that can cause the cardiac abnormalities seen in WD patients is central and peripheral autonomic nerve dysfunction (Liu and Han, 2011). Soni and others have recently studied 30 WD patients with electrophysiological tests. Significantly more abnormal responses to the Valsalva maneuver and RR interval variation were observed in patients than in age- and gender-matched healthy controls. It is felt that the vagal nerve was more affected than the sympathetic nerve in WD patients, but this did not correlate with the severity of adverse clinical outcomes (Soni et al., 2009) The heart rate variations seen on AECG indirectly reflect the level of autonomic nerve dysfunction. SDNN indicates the overall sympathetic and parasympathetic nerve tension and modulation, while RMSSD primarily indicates the parasympathetic cardiac effects. In our study, the means of SDNN and RMSSD were both lower than normal references (Guo, 2002). After chelation therapy, the means had increased slightly, but did not reach statistical significance.

Of note, the lead system of AECG is a simulated system. AECG has lower accuracy in diagnosing myocardial infarction or LVH. Thus the LVHV diagnosis was not made in our study.

By using the UWDRS, we calculated clinic scores for all 28 patients before and after chelation therapy. Our results showed that despite the fact that clinical symptoms had significantly improved with 8 weeks of chelation, the changes on ECG, AECG, hear rate variation SDNN and RMSSD were not significant. No significant difference in the improvement of their clinic symptoms was observed between patients who showed improved ECG and

AECG readings and patients who showed improved ECG and AECG readings underwent chelation therapy. We have also noticed that in four patients with worsened ECG and seven patients with worsened AECG after chelation therapy, clinic symptoms had improved. This indicates that short-term chelation is able to improved clinical symptoms; however, the cardiac damage is irreversible.

5. Conclusion

We studied the ECG and AECG changes of 28 WD patients pre- and post chelation therapy, and we found that AECG is more sensitive in detecting cardiac involvement seen in WD. AECG offers information on 24-hour heart rate variations, which indirectly reflect the level of autonomic nerve dysfunction. Although the clinical symptoms improved with eight weeks of chelation therapy, the ECG and AECG did not improve accordingly.

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