Cardiac assessment in Wilson's disease patients based on electrocardiography and echocardiography examination

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Abstract

Introduction: Wilson's disease (WD) is a rare genetic disorder that leads to impairments in copper metabolism. Patients principally exhibit liver and neuropsychiatric symptoms, but because copper also accumulates in all body organs, other (typically milder) clinical symptoms can occur. To date, cardiac involvement has not been thoroughly investigated in patients with WD. This study aimed to evaluate heart structure and function in patients with WD with commonly available diagnostic methods.
Material and methods: We compared 125 WD patients with an age- and sex-matched control group. Patients with WD were grouped according to their dominant symptoms – neurologic or hepatic. All subjects underwent clinical, electrocardiographic (ECG), and echocardiographic examinations.
Results: All subjects had sinus rhythm on electrocardiography. The only ECG parameter that differed between patients with WD and the control group was the QRS prolongation (92.0 vs. 86.4 ms; $p < 0.05$). On echocardiography patients with WD exhibited more hypertrophy in the left ventricle than controls (posterior wall in diastole: 1.0 vs. 0.93; $p < 0.01$) and the left ventricle hypertrophy was more pronounced in the neurologic than in the hepatic subgroup (1.05 vs. 0.96 cm; $p < 0.01$). Left ventricular systolic function was similar in the WD and the control group (ejection fraction: 67.5% vs. 67.7%). On tissue Doppler echocardiography patients with WD demonstrated slowing of myocardial relaxation, which was more evident in the neurologic group.
Conclusions: Heart involvement in WD was manifested mainly by mild left ventricular hypertrophy and subclinical changes in diastolic function, particularly in the patients with the neurologic form of disease.

Key words: left ventricular diastolic dysfunction, left ventricular hypertrophy, hepatolenticular degeneration.

Introduction

Wilson's disease (WD; OMIM: 277900) is a genetic disorder that results in impaired copper metabolism. Historically, the prevalence of WD was estimated as about 1 in 30 000 live births [1], but a recent genetic study suggested that it is underestimated and is really 1 in 7000 live births [2]. The most common presentations of WD are liver disease and neurologic symptoms [3, 4]. Apart from the liver and brain, copper also accumulates in other organs, bones, kidneys, and heart, which can lead

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to non-specific symptoms. In healthy individuals, the copper content in the heart is, on average 17 µg/g dry tissue [5]. Patients with WD have much higher heart copper contents, with an average of 157 µg/g (range: 79–298) [5].

A few reports have described a high risk of arrhythmias and sudden cardiac death associated with WD. Some studies have described variable degrees of cardiac changes, including cardiac hypertrophy, fibrosis, and small vessel sclerosis, in autopsies of patients with WD. A few reports have also described the various electrocardiography (ECG) and echocardiographic (ECHO) findings in patients with WD [6–10]. Nevertheless, there is no conclusive evidence on the effect of copper metabolism disorders on heart structure and function.

Therefore, in the present study, we performed a comprehensive analysis of cardiac abnormalities in a large group of patients with WD.

Material and methods

This is a retrospective analysis of all consecutive adult WD patients admitted to the 2nd Department of Neurology, Institute Psychiatry and Neurology, Warsaw, between July 2007 and February 2011. The study was approved by the local Ethics Committee in the Institute of Psychiatry and Neurology (Warsaw, Poland) and all procedures followed were in accordance with the ethical standards of the responsible Ethics Committee and with the Declaration of Helsinki (1975).

Subjects

One hundred twenty-five cardiologically asymptomatic patients with confirmed WD diagnosis and 125 healthy subjects as a control group were included in the study. All participants were hospitalized in the 2nd Department of Neurology, Institute Psychiatry and Neurology, Warsaw. All subjects (control as well as WD group) were asked about cardiac symptoms during routine examination performed by a cardiologist and all subjects had denied any manifestations of heart disease. Routine clinical examinations were performed in all subjects, including blood pressure (BP), pulse rate and the orthostatic hypotension test as a screening for dysautonomia. All subjects proven to have any cardiac problems, hypertension, diabetes mellitus, chronic obstructive pulmonary disease or chronic renal disease were excluded from the study [11, 12].

The diagnosis of WD was established previously on the basis of clinical manifestations and laboratory abnormalities (e.g., decreased serum ceruloplasmin and copper as well as increased urinary copper excretion). In selected cases (4/125; 3.2%), the diagnosis was based on a test with radioactive copper (assessment of serum copper radioactivity after intravenous loading of copper isotope in the context of disturbances of copper incorporation into apoceruloplasmin and release to blood and excretion to bile in WD patients) [13]. In most patients (117/125; 93%), the diagnosis was confirmed by genetic examination, as described previously [14]. Presymptomatic patients had never experienced symptoms of WD, but were diagnosed by screening their families. In further analyses, patients with WD were divided into two groups, based on the clinical presentation: the neurologic group, and the hepatic group. Based on the presence and intensity of individual signs of WD at diagnosis, the clinical form of WD was established. The predominance symptoms scoring system at diagnosis was the same as in previous WD papers [14]. Neurological symptoms were assessed and ranged from 0 = completely normal to 3 = severely impaired. Hepatic symptoms were assessed and assigned to four categories: 0 = completely normal; 1 = increased level of liver enzymes without signs of liver cirrhosis; 2 = compensated liver cirrhosis, 3 = decompensated liver cirrhosis or acute liver failure. Patients with a hepatic or neurological score of > 1 were classified according to a higher score; in the case of an equal result the patient was classified as a neurological case [14]. Additionally WD patients with neurological symptoms were assessed routinely with the Unified Wilson's Disease Rating Scale (UWDRS) in Part II (activity of daily living) and Part III (clinical examination) [15].

The control group consisted of healthy subjects who were hospitalized in our department finally due to subjective signs (mostly pain-like headache or back pain). All patients were diagnosed as healthy persons without neurological symptoms, and without any hepatic problems in the medical history and current results. Additionally these patients were matched for sex and age to the patients with WD.

ECG and ECHO measurements

Resting 12-lead ECGs were performed with typical parameters (amplitude: 1 mV/cm, speed: 50 mm/s) in all subjects. We evaluated the basic heart rhythm, arrhythmias, conduction disturbances, the amplitude and width of the P wave (lead II), and the duration of the PQ interval, the QRS complex and the QTc interval (mean from leads II, V5, V6). All measurements were repeated three times, and average values were calculated.

ECHO measurements were performed by a single cardiologist with a Vivid 7 (GE) ultrasound system in a standard position. The left ventricular diastolic and systolic diameters (LVDD and LVSD, respectively), the left atrial dimension (LA) and the left ventricular wall thicknesses in diastole,

including the interventricular septum (IVSD) and the posterior wall (PWD), were measured from the parasternal long axis in the M-mode. The left ventricular mass (LVM) and the left ventricular mass index (LVMI) were calculated with the American Society of Echocardiography formula [16]. The ejection fraction of the left ventricle (EF) was obtained with the modified Simpson's method [17]. Dysfunction of heart valves was assessed in color, pulsed wave (PW), and continuous wave (CW) Doppler imaging. The degree of dysfunction was classified as mild, moderate, or severe, based on European Association of Echocardiography (EAE) recommendations [18, 19]. Left ventricular (LV) inflow velocities, including the early diastolic wave peak velocity (E), the late diastolic wave peak velocity (A), the early-to-late velocities (E/A) ratio, and the E wave deceleration time (DecT), were measured from the apical four-chamber view, with the Doppler sample placed between the tips of the mitral leaflets. Mitral annular velocities were measured with PW tissue Doppler echocardiography (TDE) for assessments of global left ventricular systolic and diastolic functions. The longitudinal contraction of the LV was investigated by the peak systolic velocity of the mitral annulus (S) in two positions, septal and lateral. The diastolic function of the LV was assessed by the early diastolic (e'), and late diastolic (a') velocities of the mitral annulus; the early to late velocities (e'/a') ratio was calculated. The sample volume was positioned at about 1 cm within the septal and lateral edges of the mitral annulus, and the volume was adjusted to cover the longitudinal excursion in both systole and diastole. All measurements were performed in triplicate, and the results are expressed as the mean values.

Statistical analysis

The statistical analysis was performed as follows: WD patients vs. control group; and neurologic WD vs. hepatic WD. All data were analyzed with Statistica v. 10.0. The number of samples is expressed as n; continuous variables are expressed as the mean ± SD; and categorical variables are expressed as percentages. Comparisons of continuous variables between two groups were performed with the unpaired Student's t test. For all tests, $p < 0.05$ was considered statistically significant.

Results

Demographic and clinical data of the WD and control group are presented in Table I. There were no significant differences in age or gender between the study groups.

The majority of patients with WD (95.2%) presented typical (hepatic and/or neurologic) symptoms of the disease. Symptoms of WD occurred at an average age of 25.4 ± 9.74 years. The mean time that elapsed between the first symptoms and the disease diagnosis was 3.75 years. During the study, all patients with WD were treated with anti-copper drugs (d-penicillamine (DPA) or zinc sulfate (ZS)). The average duration of treatment was 4.04 years (range: 2 months to 35.4 years) in both WD subgroups. Among symptomatic patients, 59 (47.2%) presented with the neurologic form, and 60 (48%) presented with the hepatic form of WD. The mean severity of neurologic WD scored in UWDRS was in Part II 7 points (range: 0–12) and in Part III 34 points (range: 0–47). The stage of liver disease based on the scoring system used by us was as follows: in 15 cases – completely normal; in 30 cases – increased level of liver enzymes without signs of liver cirrhosis; in 65 cases – compensated liver cirrhosis; in 10 cases – decompensated liver cirrhosis. Symptoms of WD occurred at an average age of 28.5 ±9.26 years in the neurologic subgroup and at an average age of 22.0 ±7.1 years in the hepatic subgroup ($p < 0.05$).

ECG

All subjects had sinus rhythm. In patients with WD, the QRS complex was significantly wider than in the control group (92.0 vs. 86.49 ms, $p < 0.0001$). Other parameters were similar in both groups (the amplitude and width of the P wave and the PQ

Table I. Study group

Parameter	Wilson's disease ($n = 125$)	Control group ($n = 125$)	*P*-value
Gender, women/men, n	66/59	66/59	–
Age [years]	33.21 ±11.5	35.04 ±11.5	NS
Systolic blood pressure [mm Hg]	126.05 ±13.3	127.24 ±10.6	NS
Diastolic blood pressure [mm Hg]	76.64 ±8.6	76.76 ±8.4	NS
Pulse rate [bpm]	72.82 ±12.8	72.7 ±9.9	NS
BSA (body surface area) [m²]	1.82 ±0.2	1.8 ±0.21	NS

Data are presented as mean ± standard deviation. A p-value of < 0.05 is considered statistically significant.

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and QTc interval durations). Moreover, the ECG parameters were not significantly different between the hepatic and neurologic subgroups (data not shown).

ECHO

All echocardiographic results comparing WD patients with the control are shown in Table II. The comparison between the neurologic and hepatic forms of WD is presented in Table III.

The LV and LA dimensions were within normal limits and statistically similar in the patient and control groups. Only a few patients met the ESC criteria for the diagnosis of echocardiographic abnormalities; LV enlargement was found in 12 (9.6%) WD patients and 9 (7.2%) of the control group.

An assessment of the thickness of the left ventricle walls showed that the PWD was significantly greater in patients with WD than in the control group. Moreover, among the subgroups of patients with hepatic and neurologic WD, the thickness of the left ventricle (PWD and IVSD) was significantly greater in patients with neurologic WD than in those with hepatic WD. The calculated mean LVM was significantly larger in patients with WD than in the control group. However, when the left ventricular mass was indexed relative to the BSA, the difference between groups was only borderline significant ($p = 0.05$). The mean LVM was not significantly different between the two WD subgroups.

With regard to the LV systolic function, there was no significant difference in the EF between patients with WD and the control group, and nor did we find any significant difference in EF between the two forms of WD. Reduced EF (< 55%) was found only in 10 (8%) patients with WD and

Table II. Echocardiographic parameters in patients with Wilson's disease and control subjects

Parameter	Wilson's disease (*n* = 125)	Control group (*n* = 125)	*P*-value
LVDD [cm]	4.85 ±0.54	4.84 ±0.34	NS
LVSD [cm]	2.95 ±0.4	2.9 ±0.25	NS
IVSD [cm]	0.99 ±0.14	0.96 ±0.12	NS
PWD [cm]	1.0 ±0.13	0.93 ±0.12	0.00003
LA [cm]	3.55 ±0.49	3.56 ±0.3	NS
LVM [g]	174.89 ±48.31	162.8 ±39.14	0.037
LVMI [g/m^2]	96.58 ±22.64	90.72 ±19.76	0.05
EF [%]	67.5 ±6.5	67.7 ±5.3	NS
E [m/s]	0.76 ±0.13	0.76 ±0.12	NS
A [m/s]	0.51 ±0.09	0.54 ±0.1	0.04
E/A ratio	1.53 ±0.36	1.47 ±0.31	NS
DecT [ms]	199.5 ±32.25	194.15 ±26.33	NS
Septal S [m/s]	0.08 ±0.07	0.1 ±0.01	NS
Septal e' [m/s]	0.11 ±0.02	0.12 ±0.03	NS
Septal a' [m/s]	0.08 ±0.01	0.08 ±0.01	NS
e'/a' ratio	1.5 ±0.38	1.5 ±0.48	NS
E/septal e' ratio	6.9 ±1.52	6.83 ±1.54	NS
Lateral S [m/s]	0.11 ±0.02	0.11 ±0.02	NS
Lateral e' [m/s]	0.16 ±0.03	0.17 ±0.03	0.01
Lateral a' [m/s]	0.08 ±0.02	0.08 ±0.01	NS
Lateral e'/a' ratio	1.96 ±0.58	2.1 ±0.51	0.036

Data are presented as mean ± standard deviation. A p-value of < 0.05 is considered statistically significant. LVDD – left ventricular diastolic diameter, LVSD – left ventricular systolic diameter, IVSD – interventricular septum in diastole, PWD – posterior wall in diastole, LA – left atrial dimension, LVM – left ventricular mass, LVMI – left ventricular mass index, EF – ejection fraction of the left ventricle, E – peak early velocity of mitral inflow, A – peak late velocity of mitral inflow, DecT – E wave deceleration time, S – peak systolic velocity of the mitral annulus, e' – early diastolic velocity of the mitral annulus, a' – late diastolic velocity of the mitral annulus.

Table III. Echocardiographic parameters in hepatic and neurologic form of Wilson's disease

Parameter	Hepatic form (*n* = 60)	Neurologic form (*n* = 59)	*P*-value
LVDD [cm]	4.91 ±0.48	48 ±0.54	NS
LVSD [cm]	2.93 ±0.35	2.97 ±0.47	NS
IVSD [cm]	0.96 ±0.13	1.02 ±0.14	0.008
PWD [cm]	0.96 ±0.12	1.05 ±0.13	0.0002
LA [cm]	3.55 ±0.47	3.65 ±0.51	NS
LVM [g]	169.24 ±47.21	182.8 ±49.99	NS
LVMI [g/m^2]	93.61 ±19.1	98.17 ±24.62	NS
EF [%]	68.42 ±5.76	66.63 ±6.91	NS
E [m/s]	0.77 ±0.12	0.73 ±0.12	NS
A [m/s]	0.5 ±0.09	0.51 ±0.08	NS
E/A ratio	1.58 ±0.43	1.46 ±0.26	NS
DecT [ms]	198.7 ±30.7	199.2 ±33.6	NS
Septal S [m/s]	0.09 ±0.015	0.08 ±0.011	NS
Septal e' [m/s]	0.12 ±0.02	0.1 ±0.02	0.001
Septal a' [m/s]	0.07 ±0.01	0.08 ±0.01	NS
e'/a' ratio	1.63 ±0.47	1.34 ±0.43	0.0008
E/septal e' ratio	6.56 ±1.41	7.17 ±1.58	0.028
Lateral S [m/s]	0.11 ±0.02	0.10 ±0.01	0.0004
Lateral e' [m/s]	0.16 ±0.04	0.15 ±0.03	0.008
Lateral a' [m/s]	0.08 ±0.01	0.08 ±0.02	NS
Lateral e'/a' ratio	2.05 ±0.55	1.85 ±0.45	0.03

Data are presented as mean ± standard deviation. A p-value of < 0.05 is considered statistically significant.

in 3 (2.5%) of the control group, but WD patients with reduced EF were significantly older than the others (37.2 vs. 32.8 years). On TDE assessment, no difference was found between groups (patients with WD and control group) in terms of systolic velocities of mitral annulus (S). However, the analysis of this parameter in the subgroups showed slowing of the systolic velocity in the lateral part of the mitral annulus in patients with neurologic WD, reflecting early, subclinical changes in the left ventricular longitudinal systolic function.

The LV diastolic function was analyzed based on conventional Doppler and TDE. Mitral inflow parameters (E, A, E/A, DecT) remained within normal limits and were statistically similar in the patient and control group, and there was no statistically significant difference between the two clinical forms of WD. On TDE assessment, the left ventricular early diastolic velocity in the lateral part of the mitral annulus (lateral e') was significantly lower in patients with WD compared to the control group, and consequently this result affected the corresponding ratios (lateral e'/a' and E/e'). Furthermore, in the neurologic form of WD the slowing of myocardial relaxation was found on both edges of the mitral annulus.

In patients with WD, mitral regurgitation occurred significantly more frequently than in the control group (73.6 vs. 35.2%, *p* < 0.05). The degree of regurgitation was assessed as mild, except in one patient (moderate). Other valvular regurgitations occurred in both groups at similarly low rates. There was no significant difference in the incidence of valve regurgitations between the two subgroups of WD (data not shown).

Discussion

To our knowledge, this study included the largest group of patients with WD ever subjected to a thorough cardiological assessment.

The only ECG abnormality detected among the patients with WD was an increase in the width of the QRS complex. The QRS prolongation could indicate left ventricular hypertrophy or an

intraventricular conduction disturbance. Our results did not meet the criteria for a diagnosis of specific conduction disorders, and regarding the echocardiographic results, the QRS prolongation is probably a manifestation of LV hypertrophy. We speculate that our observation may be of clinical relevance, since QRS prolongation has been found to be an independent predictor of cardiovascular mortality in the general population [20]. In addition, hypertrophy of the LV may lead to cardiac dysfunction and consequently to heart failure. Therefore it could be reasonable to assess these parameters in WD, although patients die usually from non-cardiac causes [21].

In our study mild left ventricular hypertrophy and slowing of myocardial relaxation in patients with WD of the LV were found. The LV wall thickness depends on the size of cardiomyocytes, but it may also involve other cells or factors, including fibroblasts, vascular smooth muscle cells, and collagen [22, 23]. Heart hypertrophy may also be caused by intra- or extracellular pathological accumulations of various substances that lead to infiltrative or storage diseases [24, 25]. We do not know which of the above processes predominate in WD. Furthermore, copper acts as a co-factor for enzymes that catalyze many biochemical processes, including redox reactions [26]. Oxidative stress caused by the toxic effects of copper ions may result in cell damage. Copper stimulated the production of IL-6 and MAP-kinase, which played a role in inflammatory processes and cardiac hypertrophy [27]. Bruha et al. found that patients with WD exhibited increased levels of proinflammatory cytokines, interleukin-1β (IL-1β) and IL-6, in parallel with a reduction in total serum antioxidant capacity [28]. A polymorphism in the gene that encoded an IL-1 receptor antagonist had an impact on copper metabolism in patients with WD [29]. Functional polymorphisms in some genes that encoded enzymatic antioxidants were associated with the clinical manifestation of WD [30]. Anti-copper treatment improved antioxidant capacity parameters in WD [31]. On the other hand, copper activated sphingomyelin, which indirectly played a role in activating apoptosis [32]. Thus, many potential mechanisms may underlie the cardiological toxicity of copper.

In our study, only a mild abnormality in the mitral valve was found. We speculate that it could be related to the involvement of copper ions in collagen crosslinking [33]. This problem has not been discussed in previous studies. In our study the severity of valvular lesions was slight and did not cause any hemodynamic disturbances.

In our study, patients with neurologic WD had more severe heart abnormalities than patients with hepatic WD. This is in accordance with results published by Cheng et al., who found an elevated serum brain natriuretic peptide level (biomarker of congestive heart failure) in patients with neurologic WD, suggesting that cardiac changes were more severe in neurologic form [34]. This observation might be due to fact that the disease symptoms typically appear at a later age in neurologic WD than in hepatic WD [4, 35]. Thus, copper exposure may be undetected for a longer period in patients with neurologic WD than in patients with hepatic WD, which may explain the observed difference in the severity of cardiac changes.

Generally, we did not find any features of a serious structural heart disease in our study group. Results from the previous clinical studies were divergent. Historically, there were four models of cardiac manifestation in Wilson's disease described in the literature: arrhythmias, cardiomyopathy, cardiac death, and autonomic dysfunction [10]. The oldest studies that reported serious cardiologic problems in patients with WD referred mainly to young patients with severe clinical presentations in which LV hypertrophy and myocardial damage have been described in post-mortem examinations [6–8]. In more recent clinical studies the majority of researchers have observed normal size and wall thickness of the heart in WD, while Hlubocka et al. reported increased cardiac wall thickness [9]. Elkiran et al. investigated 22 pediatric patients with WD, and the only abnormality which they reported was subclinical diastolic dysfunction [36]. Arat et al. studied 18 patients with WD and found normal LV size and function, and the ECG showed only an increase in the P wave dispersion [37]. In another study from the same group of researchers, the abnormalities in two-dimensional echocardiographic grey-level distributions in patients with WD were described as a result of an early stage of cardiac involvement [38]. In a recently published study Karakurt et al. reported that pediatric patients with WD showed diastolic dysfunction and regional deformation abnormalities, especially rotational strain and strain rate abnormalities [39].

In our study, all patients received care from a specialist, and since diagnosis, they had systematically taken the recommended medications, which were known to modify the course of WD. Due to the case report from Bajaj et al., who described a patient who presented with a 2nd degree Mobitz type-1 atrioventricular block with complete resolution of atrioventricular disturbances after the initiation of typical WD therapy, we believe that an appropriate treatment reduced the risk of cardiac damage associated with abnormal copper metabolism [40].

The present study has several limitations: the limited number of patients (it being a rare disease), young population, potentially long period of WD treatment and lack of newly diagnosed and

un-treated WD patients. Another limitation is the lack of ability to assess the impact of kind and duration of WD treatment (DPA vs. ZS) on cardiological abnormalities; the treatment was initiated at various stages of the disease, almost 30% of patients freely switched from one WD drug to another (due to adverse drug reactions, patient's preferences, etc.) and the average duration of treatment was relatively short (less than 4 years) to verify the drug impact on heart tissue. The study was conducted in a neurological center, so there is possible overrepresentation of patients with neurologic WD. Additionally, the control group was collected as a generally healthy population (based on examinations and interview), and not according to positive liver damage; however, most studies comparing WD patients with a control group have used one homogeneous control group (without further division to avoid small, non-comparable groups) [41–43].

In conclusion, we demonstrated that WD may be associated only with minor, non-clinically-relevant heart involvement. None of the WD patients had a serious structural heart disease. Heart involvement in WD was manifested mainly by mild left ventricular hypertrophy. Systolic and diastolic function of LV may be classified as normal in the majority of WD patients. However, the lower diastolic velocities of the mitral annulus may reflect a slowing in myocardial relaxation in patients with WD as an early, subclinical change in diastolic function of the LV. All disturbances were more prominent in WD with neurologic presentation than in those with the hepatic form. Future studies should include populations with an older mean age and preferably non-treated naive patients to conduct follow-up. Those studies may be able to provide more detailed descriptions of heart involvement in WD.

Conflict of interest

The authors declare no conflict of interest.

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