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REVIEW ARTICLE

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Cardiac involvement in Wilson disease: Review of the literature and description of three cases of sudden death

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Abstract

Wilson disease (WD) is a rare genetic condition that results from a build-up of copper in the body. It requires life-long treatment and is mainly characterized by hepatic and neurological features. Copper accumulation has been reported to be related to the occurrence of heart disease, although little is known regarding this association. We have conducted a systematic review of the literature to document the association between WD and cardiac involvement. Thirty-two articles were retained. We also described three cases of sudden death. Cardiac manifestations in WD include cardiomyopathy (mainly left ventricular (LV) remodeling, hypertrophy, and LV diastolic dysfunction, and less frequently LV systolic dysfunction), increased levels of troponin, and/or brain natriuretic peptide, electrocardiogram (ECG) abnormalities, and rhythm or conduction abnormalities, which can be life-threatening. Dysautonomia has also been reported. The mechanism of cardiac damage in WD has not been elucidated. It may be the result of copper accumulation in the heart, and/or it could be due to a toxic effect of copper, resulting in the release of free oxygen radicals. Patients with signs and/or symptoms of cardiac involvement or who have cardiovascular risk factors should be examined by a cardiologist in addition to being assessed by their interdisciplinary treating team. Furthermore, ECG, cardiac biomarkers, echocardiography, and 24-hours or more of Holter monitoring at the diagnosis and/or during the follow-up of patients with WD need to be evaluated. Cardiac magnetic resonance imaging, although not always available, could also be a useful diagnostic tool, allowing assessment of the risk of ventricular arrhythmias and further guidance of the cardiac workup.

KEYWORDS

arrhythmias, cardiomyopathy, copper, dysautonomia, sudden death, Wilson disease

Synopsis

Cardiac manifestations in Wilson disease (WD) are not uncommon and can be life-threatening. The indications of electrocardiogram, cardiac biomarkers, echocardiography, and 24-hour Holter monitoring at the diagnosis and/or

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during the follow-up of patients with WD need to be evaluated. Cardiac magnetic resonance imaging, although less available, may provide valuable information regarding the amount of myocardial fibrosis, thereby allowing assessment of the risk of ventricular arrhythmias. As WD is a rare disease, there has been a paucity of large-scale studies, although they would nonetheless be particularly useful.

1 | INTRODUCTION

Wilson disease (WD) is a rare genetic condition, with fewer than 1000 patients in France,[1] that is due to a build-up of copper in the body. It requires life-long treatment and is mainly characterized by hepatic and neurological features due to copper accumulation. Copper accumulation has been reported to be related to the occurrence of heart disease.[2]

As early as 1987, it was stated in the literature that "Cardiac death in Wilson disease is a rare occurrence of historic interest. It is suggested that possible cardiac involvement should be added to the clinical picture of Wilson disease involving the hepatic and central nervous system."[3] For the first time, the patterns of cardiac involvement in WD were identified as cardiomyopathy, arrhythmias and conduction abnormalities, dysautonomia, and death from cardiac dysfunction.

However, the epidemiology of this condition has remained poorly characterized, probably due to the lack of routine cardiac evaluation in WD patients. Indeed, the largest cohort to date of WD patients did not include cardiac follow-up.[4] In a review of the literature, heart disease (cardiomyopathies and arrhythmias) was reported to be rare: "myocardial copper accumulation can cause cardiomyopathy and arrhythmias, even if clinical manifestations are rare."[5]

Conversely, in a study based on medico-administrative data including 463 WD patients, a 29% higher incidence of atrial fibrillation (AF) and a 55% higher risk of incident congestive heart failure (HF) were reported after adjusting for confounders. Moreover, HF occurred significantly earlier in WD patients compared with non-WD patients (mean age 66 ± 18 years and 72 ± 18 years respectively; $P < .0001$).[6]

The National Reference Center for Wilson's Disease in Paris (France) manages a significant number of WD patients, with a cohort of approximately 300 patients in 2019. During the follow-up of these patients, the occurrence of cardiac abnormalities such as HF, rhythm and conduction disorders, and cases of sudden death have been noted. Given the occurrence of three recent unexplained early sudden deaths (1/100 vs 1/1000 sudden deaths in the general population), we conducted a systematic review of the literature to better document the relationship between WD and cardiac involvement.

2 | MATERIALS AND METHOD

A systematic literature search was performed to identify the published case reports and studies regarding WD and its cardiac involvement. The literature search was conducted systematically using PubMed and it followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (http://www.prisma-statement.org). Studies published between 1959 and December 2020 were included. The following search terms, without any search filters, were used in PubMed: Wilson disease AND cardiac OR heart OR dysautonomia OR cardiomyopathy OR arrhythmia OR rhythmic OR sudden death NOT Wilson [Author]. Only publications in English and French were retained. Articles regarding adult and pediatric WD patients were included. The relevant articles were selected by considering the titles, followed by the abstracts. All of the titles and abstracts were screened and cross-checked by two authors (KC and NB). Articles unrelated to WD and/or to the cardiovascular system were excluded. Previous reviews of the literature and their related articles were included. This review was based on full-text articles only.

Three cases of WD patients who were regularly followed in our expert center and who die of sudden death were also described.

3 | RESULTS

In the first step, 568 publications were identified. Of these, 531 were excluded because they did not mention WD (N = 203), were not concerning the cardiovascular system (N = 52) or did not mention both WD and the cardiovascular system (N = 264). An abstract was not available for nine publications and the full text was not available for one publication. Duplicate articles (N = 2) were excluded. After reviewing the full texts, we excluded five articles (four did not mention cardiac involvement in WD and one was a response letter).

Ultimately, 32 publications were included in this review (Figure 1). The studies and case reports are summarized in Tables 1 and 2, respectively.

3.1 | Rhythm and conduction abnormalities

An electrocardiographic study that included 50 young WD patients (28 men and 22 women, mean age 22.92 ± 11.02 years, mean duration of the disease 4.84 ± 3.82 years),[31] reported sinus tachycardia in eight patients and sinus bradycardia in six. Other abnormalities included a bifid P wave in one, ST elevation in two, ST depression in two, T inversion in four, ventricular premature contractions in one, and a prominent U wave in one.

In a cohort of 125 patients, the QRS complex was significantly wider in WD patients than in healthy controls ($P < .0001$).[13]

In another study that included 35 WD patients (21 with neurological WD), compared to 30 healthy controls,[12] the QT intervals and the corrected QT intervals were significantly prolonged in the WD patients compared to controls ($P = .002$ for both the QT and the corrected QT intervals), without exceeding the pathological thresholds (450 ms in men and 470 ms in women).[32]

Higher maximal P-wave durations and P-wave dispersions on resting electrocardiograms (ECGs) have also been reported in 18 WD patients compared with 15 matched healthy controls.[7] The QT and P-wave dispersion values have also been reported to be significantly higher in children with WD compared to age- and gender-matched healthy controls ($P = .02$ and .04, respectively).[10] In another study,[9] 22 out of 51 children had at least one abnormality on the resting ECG. T-wave abnormalities were seen in 18 patients, sinus tachycardia in 12, sinus bradycardia in 8, bifid P waves in 2, ST-segment changes in 2, and premature ventricular contractions in 1 patient.

In the study by Quick et al,[2] 61 WD patients underwent a 24-hour electrocardiographic recording. Three patients had an ectopic atrial rhythm and one had atrial flutter. One patient required implantation of a pacemaker due to an atrioventricular block. Supraventricular and ventricular premature contractions (PSVC, PVC) were frequent (PSVC in 50 patients and PVC in 30). In another study,[18] 10 out of 23 WD patients who underwent a 24-hour ECG had rhythm abnormalities, mainly supraventricular tachycardias, and frequent supraventricular ectopic beats. A second-degree Mobitz type-1 atrioventricular block has also been reported in a 14-year-old female newly diagnosed with WD and suffering from episodes of light-headedness.[24] Of note, atrioventricular nodal degeneration was documented postmortem in one of nine WD cases in an autopsy study.[8]

3.2 | Heart failure, cardiac biomarkers, and cardiac imaging

In a longitudinal cohort study of WD based on medico-administrative data,[6] WD patients had a significantly increased risk of both AF and HF, before and after

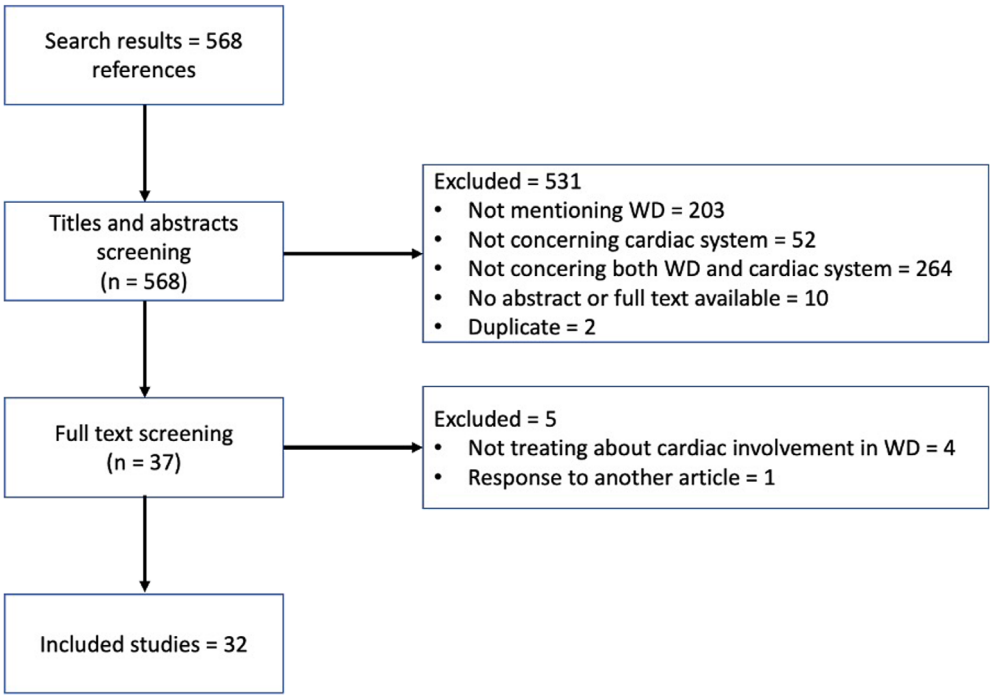

FIGURE 1 Flowchart of the literature review. WD, Wilson disease

TABLE 1 Cardiac manifestations in Wilson disease patients from the literature (population studies)

Reference	Number of patients	Gender (male/female)	Age (mean, y)	Diagnosis	Clinical form	Duration of illness (mean, y)	Treatment	Paraclinical exams	Cardiac involvement (number of patients, %)
Rhythm and conduction abnormalities									
Arat et al[7]	18	ND	49	Clinical manifestations Family history KFR Biology[a] Liver biopsy Quantitative liver copper assay	ND	9.6	D-Penicillamine: 17 Trientine: 1	ECG and TTE with Doppler	Higher P wave duration in WD patients than controls
Factor et al[8]	9	5/4	29.2	ND	Hepatic: 7 Neurologic: 2	6.2	D-Penicillamine: 9	Autopsy	Supraventricular tachycardia (1, 11.1%) Sudden death (2, 22.2%) Cardiac hypertrophy (5, 55.6%)
Hamdani et al[9]	51	28/23	11.19	Clinical manifestations Family history KFR Biology[a]	ND	1.48	ND	ECG	T wave abnormality (18, 35.3%) Sinus tachycardia (12, 23.5%) Sinus bradycardia (8, 15.7%) Bifid P wave (2, 3.9%) ST elevation (2, 3.9%) ST depression (2, 3.9%) Ventricular premature contraction (1, 2.0%)
Karhan et al[10]	42	ND	14.06	KFR Biology[a] Liver biopsy	Hepatic: 39 Neurologic: 3	7.0	All patients treated with D-penicillamine and zinc salts	ECG and TTE	Higher QT and P-wave dispersion values than controls Concentric LV remodeling (7, 16.7%)

TABLE 1 (Continued)

Reference	Number of patients	Gender (male/female)	Age (mean, y)	Diagnosis	Clinical form	Duration of illness (mean, y)	Treatment	Paraclinical exams	Cardiac involvement (number of patients, %)
Meenakshi-Sundaram et al[11]	50	28/22	20.94	Clinical manifestations KFR Family history Biology[a]	ND	8.36	All treated with copper chelating agent	ECG	Sinus tachycardia (8, 16%) Sinus bradycardia (6, 12%) Bifid P wave (1, 2%) ST elevation (2, 4%) ST depression (2, 4%) T inversion (4, 8%) VES (1, 2%) Prominent U wave (1, 2%)
Ozturk et al[12]	35	21/14	29.62	Clinical manifestations Biology[a] Liver biopsy	Hepatic: 14 Neurologic: 21	ND	D-Penicillamine: 28 Trientine: 3 Zinc: 34	ECG and TTE	Higher QT and QTC intervals in WD patients
Heart failure, cardiac biomarkers, and cardiac imaging									
Buksinka et al[13]	125	59/66	33.21	Clinical manifestations Biology[a] Genetics (117/125)	Hepatic:60 Neurologic: 59 Asymptomatic: 6	7.81	All treated (D-Penicillamine or Zinc)	ECG and TTE	Mild left ventricular hypertrophy Abnormal left ventricular diastolic function
Cheng et al[14]	97	58/39	20.74	Diagnosis criteria (Leipzig criteria ≥4[15])	Hepatic: 29 Neurologic: 68	4	D-Penicillamine: 82 Zinc: 61 None: 5	Biomarkers (BNP, MMP2, MMP9)	Higher serum levels of BNP, MMP2 or 9 in WD patients than controls. Neurologic forms had higher levels of biomarkers than hepatic forms. Negative correlation between cardiac markers and ceruloplasmin levels.

(Continues)

TABLE 1 (Continued)

Reference	Number of patients	Gender (male/female)	Age (mean, y)	Diagnosis	Clinical form	Duration of illness (mean, y)	Treatment	Paraclinical exams	Cardiac involvement (number of patients, %)
Efe et al[16]	30	18/12	31.7	Clinical manifestations Biology[a] Liver biopsy	Hepatic: 17 Neurologic: 13	11.6	D-Penicillamine: 26 Trientine: 1 Zinc: 29	ECG and TTE	No difference in left ventricular systolic or diastolic diameters or wall thickness or strain/strain rate between WD and controls.
Elkiran et al[17]	22	11/11	11.8	Clinical manifestations KFR Biology[a]	Hepatic: 13 Neurologic: 2 Asymptomatic: 7	2.95	D-Penicillamine + Zinc: 22		Mild significant differences in diastolic parameters measured by pulsed Doppler imaging
Hlubocka et al[18]	42	19/23		Clinical manifestations Biology[a] Liver biopsy Genetics	Hepatic: 16 Neurologic: 18 Asymptomatic: 8	12	ND	ECG TTE 24 h ECG monitoring	Increased thickness of interventricular septum Increased thickness of LV posterior Concentric LV remodeling (9, 21.4%) LV hypertrophy (1, 2.4%)
Karakurt et al[19]	21	11/10	11.04	Clinical manifestations KFR Biology[a] Liver biopsy	ND	2.04	ND	TTE	Diastolic dysfunction Regional deformation abnormalities (rotational strain and strain rate abnormalities)
Quick et al[2]	61	31/30	44.3	Diagnosis criteria (Leipzig score ≥ 4[15])	Hepatic: 25 Neurologic: 27 Asymptomatic: 9	24.9	D-Penicillamine: 37 Trientine: 13 Zinc: 7 None: 4	TTE 24 h ECG monitoring	Reduced RVEF (2, 3.3%) Reduced LVEF <50% (5, 8.2%) Myocardial LGE streak in interventricular septum (11, 18%) MRI pattern of myocarditis (5, 8.2%) Diastolic dysfunction (9, 14.8%)

TABLE 1 (Continued)

Reference	Number of patients	Gender (male/female)	Age (mean, y)	Diagnosis	Clinical form	Duration of illness (mean, y)	Treatment	Paraclinical exams	Cardiac involvement (number of patients, %)
Zhang et al[20]	61	ND	ND	Biology[a] Liver biopsy	ND	ND	ND	Cardiac MRI	Left ventricular cleft (12, 19.7%)
Grandis et al[6]	463 451 without prevalent AF 442 without prevalent HF	200/263	49	ICD-9 (Codes for WD)	ND	ND	ND	ICD-9 (Codes for AF and HF)	Significant increase risk of AF (38, 8.4%) and HF (59, 13.3%) in WD than in general population
Dysautonomia									
Kouvelas et al[21]	11	6/11	16	Biology[a] Liver biopsy Genetics	ND	8.5	D-Penicillamine:10 Trientine: 1	ECG TTE Mercury Sphygmomanometer	Significantly lower ABI in WD patients than controls
Li et al[22]	26	13/13	43.7	Clinical manifestations KFR Family history Biology[a] Liver biopsy Genetics	Hepatic: 5 Neurologic: 12 Asymptomatic: 9	2.9	D-Penicillamine: 17 Trientine: 5 Zinc: 5 None: 1	Cardiovascular autonomic function tests	Significant cardiovascular autonomic dysfunction in both sympathetic and parasympathetic branches in WD patients
Soni et al[23]	30	17/13	19	ND	Hepatic: 10 Neurologic: 20	4.48	ND	Cardiovascular autonomic function tests	At least one autonomic symptom (21, 70%)

Abbreviations: ABI, ankle-brachial index; AF, atrial fibrillation; BNP, brain natriuretic protein; ECG, electrocardiogram; HF, heart failure; ICD-9, International Classification of Diseases, ninth revision; KFR, Kayser-Fleisher Ring; LV, left ventricle; LVEF, left ventricular ejection fraction; MMP, matrix metalloproteinases; ND, no data; RVEF, right ventricular ejection fraction; TTE, transthoracic echocardiogram; VES, ventricular extrasystole; WD, Wilson's disease.

[a]"Biology" refers to low ceruloplasmin level, low total serum copper level, high urinary copper excretion.

TABLE 2 Cardiac manifestations in Wilson disease patients from the literature (case reports)

Reference	Number of patients	Gender (male/female)	Age (mean, y)	Diagnosis	Clinical form	Duration of illness (mean, y)	Treatment	Paraclinical exams	Cardiac involvement
Rhythm and conduction abnormalities									
Bajaj et al[24]	1	Female	14	Clinical manifestations KFR Biology[a]	Neurologic	0	None	ECG and TTE	Second degree Mobitz type 1 atrioventricular nodal black
Heart failure, cardiac biomarkers, and cardiac imaging									
Adar et al[25]	1	Female	16	Biology[a]	Hepatic	0	None	ECG and TTE	Takotsubo cardiomyopathy
Azevedo et al[26]	1	Male	10	Clinical manifestations Family history Biology[a]	Hepatic	0	D-Penicillamine	ECG Phonocardiogram Vectorcardiogram Myocardium biopsy	Signs of myocardial damage on ECG, vectorcardiogram, radioscopic and radiologic examinations High copper content in the myocardium
Böttiger and Mollerberg[27]	1	Male	17	Clinical manifestations KFR Biology[a] Autopsy	Neurologic	0	None	Autopsy	Hypertrophic left ventricle High copper content in the myocardium
Cardiac arrest or death from cardiac dysfunction									
Bobbio et al[28]	1	Male	38	ND	ND	ND	Liver transplantation	ECG TTE Implantable cardioverter defibrillator	Resuscitated cardiac arrest from ventricular fibrillation New episodes of ventricular fibrillation detected on implantable cardioverter defibrillator
Kaduk et al[29]	1	Male	14	Clinical manifestations Family history Biology[a] Liver biopsy	Hepatic	0.25	None	Autopsy	Biventricular heart failure leading to death
Kuan[30]	2	2/0	30	Clinical manifestations KFR Biology[a]	Neurologic	3,5	D-Penicillamine: 2	Autopsy	Death from ventricular fibrillation (1) Death from cardiac failure (1)

Abbreviations: ECG, electrocardiogram; KFR, Kayser-Fleisher Ring; ND, no data; TTE, transthoracic echocardiogram.

[a]"Biology" refers to low ceruloplasmin level, low total serum copper level, high urinary copper excretion.

adjusting for potential confounders. In this study, 463 WD patients have been identified. The incidence of HF in WD patients was 4.23 per 100 person-years (95% CI 3.22-5.46) vs 1.0 per 100 person-years (95% CI 1.00-1.01) in the non-WD population. After adjusting for confounders (age, gender, race, income, hypertension, diabetes, renal disease, hyperlipidemia, obesity, coronary disease, and obstructive sleep apnea), WD patients had a 55% higher risk of incident HF (HR 1.55, 95% CI 1.41-1.71, $P < .0001$).

On echocardiography, grade I diastolic dysfunction has been reported to be significantly more frequent in WD adult patients ($P = .001$),[2] and significant differences in diastolic parameters measured by pulsed-wave Doppler imaging compared to controls have been reported in WD children.[17] Echocardiographic left ventricular ejection fraction (LVEF) can be under 55%[18] and sometimes less than 50%.[2] However, to date, the LVEF has not been reported to be more altered compared to controls, perhaps due to a lack of well-conducted large-scale studies.

Concentric left ventricular (LV) remodeling and eccentric left ventricular hypertrophy (LVH) have been reported in WD patients.[18]

Deformation imaging was used in a small study by Karakurt et al[19] on 21 WD children (11 ± 3.6 years old) compared to 20 matched controls (10.5 ± 2.8 years old) who underwent transthoracic echocardiography (TTE). No significant differences were found in terms of global longitudinal strain and radial strain. A very recent study involving 30 WD adults also failed to detect altered deformation compared to controls.[16]

Conversely, echocardiography revealed apical ballooning, also called Takotsubo cardiomyopathy, complicating a fulminant hepatic failure, ultimately resulting in a diagnosis of WD in a 16-year-old female.[25]

In a study based on cardiac magnetic resonance imaging (MRI), 61 WD patients were compared to 61 age- and gender-matched controls.[2,33] The mean duration of WD was 24.9 ± 14.7 years. Five WD patients had an LVEF under 57%, which is the lower limit for normal MRI-LVEF. However, the MRI-LVEF was not significantly different between the groups. Conversely, the MRI right ventricular ejection fraction (RVEF) was significantly reduced in the WD group ($P < .001$). Two patients had an RVEF under 40%. Late gadolinium enhancement (LGE) and mid myocardial LGE streak in the interventricular septum were more frequent in WD. Interestingly, five WD patients had an MRI pattern of myocarditis, which normalized in one after decoppering therapy.

In a prospective controlled cardiac MRI trial,[20] LV clefts, also called crypts, defined as invaginations penetrating more than 50% of the wall thickness of the adjoining compact myocardium in diastole, were detected in 12 patients (20%) compared with 5% in healthy controls, the difference being statistically significant ($P = .013$). It is not clear whether these clefts are related to myocardial fiber or fascicle disarray, in WD. Their clinical significance in WD is not known.

Biological cardiac markers have also been measured.[2] Out of 18 patients with an acute exacerbation of WD, 4 had elevated troponin levels vs none in the absence of exacerbation. In one of them, the level of troponin decreased significantly under chelating agent.

Cheng et al[14] compared the levels of brain natriuretic peptide (BNP) and matrix metalloproteinases 2 and 9 (MMP2 and MMP9) in WD patients (34 patients with hepatic WD and 68 with neurological WD) and 33 age- and gender-matched healthy controls. All but five patients received treatments for WD. The serum levels of the three biomarkers, which reflect non-ischemic cardiovascular dysfunction, were higher in the WD patients than in healthy controls, especially in the patients with neurological WD (for BNP: $P = .033$ between neurological WD and controls; for MMP2: $P = .009$ and $P = .0004$ for hepatic and neurological WD, respectively, compared to controls; and for MMP9: $P = .03$ and $P = .00005$ for hepatic and neurological WD, respectively, compared to controls), and they were negatively correlated with the serum ceruloplasmin concentrations (for BNP: $P = .017$, $r = -0.215$; for MMP2: $P = .018$, $r = -0.221$; and for MMP9: $P = .011$, $r = -0.231$). These data suggest that BNP, MMP2, and MMP9 reflect the deposition of copper in the heart. Conversely, in the study by Quick et al,[2] none of the WD patients had a pathological elevation of NT-pro-BNP, although there was a positive correlation between the neurological severity of the disease severity (evaluated by the UWDRS score) and the NT-pro-BNP levels.

3.3 | Dysautonomia

Autonomic dysfunction has been reported in young WD patients (54% females, mean age and age at diagnosis of 16 ± 5.0 and 8.3 ± 4.0 years, respectively, compared to 11 healthy controls).[21] Blood pressure in a supine position and when upright after 3 minutes of standing as well as the ankle-brachial index (ABI) were measured. The ABI reflects endothelial function, with a value of less than 0.9 being pathological. While the systolic blood pressure declined in controls in an upright position compared to in a supine position, it increased significantly in WD patients. The ABI was significantly lower in WD patients and correlated with disease duration ($P < .03$, $r = -0.66$), suggesting early vascular deterioration in WD patients.

In another study, orthostatic hypotension was reported in 6 out of 50 WD patients.[11]

Cardiovascular autonomic reflexes were studied clinically and electrophysiologically in 30 WD patients who were compared with 30 age- and gender-matched controls.[23] The heart rate response to the Valsalva maneuver and RR interval variations were significantly abnormal in WD patients compared to controls, and the latency for the sympathetic skin response (SSR) was significantly prolonged.

In another study,[11] the SSR and RR interval variability on deep breathing were reported in 13 out of 50 WD patients. Dysautonomia was significantly more common among patients with a neurological presentation. This has been confirmed by another study.[22] The WD patients had a higher heart rate at rest, a lower Valsalva ratio, a smaller heart rate increase during isometric hand grips, and a lower baroreflex sensitivity during nearly all of the cardiovascular autonomic function examinations compared with healthy controls. Again, dysautonomia was more pronounced in patients with neurological symptoms.

3.4 | Cardiac arrest or death from cardiac dysfunction in WD

In 1982, two cardiac deaths in WD patients were reported by Kuan et al.[30] The first case was a 19-year-old boy with a 10-month history of tremor and a diagnosis of WD made 1 month before his admission. An ECG revealed atrial premature beats and ST elevation in most leads. He exhibited an episode of ventricular fibrillation that led to his death. The second case was a 41-year-old male whose cardiac clinical examination and ECG were normal. Despite a 6-year treatment with D-penicillamine, he developed cardiomyopathy and congestive HF that was refractory to medical therapy and that led to his death. More recently, cardiac arrest was reported in a 38-year-old man, 1 year after curative liver transplantation for WD.[28] The patient presented with ventricular fibrillation requiring advanced cardiopulmonary resuscitation and four defibrillations. TTE revealed a dilated left ventricle with global hypokinesia and an LVEF of 30%. Coronary angiography was normal. Three days after admission, a control TTE revealed normalized cardiac dimensions and function. Cardiac MRI revealed myocardial fibrosis. Endomyocardial biopsy confirmed the fibrosis, without inflammation. Furthermore, excessive deposition of copper and iron were documented: copper at 10.1 μg/g wet weight, with a normal range of 2.46-4.13 μg/g and iron at 163.3 μg/g wet weight, with a normal range of 35.2-71.3 μg/g. The patient received an implantable cardioverter-defibrillator. During 20 months of follow-up, he experienced a total of eight episodes of sustained ventricular tachycardia, which were successfully treated by the device.

The National Reference Center for Wilson's Disease in Paris (France) has encountered three unexplained sudden deaths in young WD patients in 2019 (over a cohort of 300 patients). These cases are described in Table 3.

Case 1 was a 33-year-old woman. WD was diagnosed as part of a familial screening. She had no other past medical history. Hepatic cytolysis was present at diagnosis. She first received D-penicillamine (Trolovol, 900 mg/d), switched to zinc acetate (Wilzin, 150 mg/d) after 1 year. The follow-up was uneventful. Abdominal ultrasound, Fibroscan, liver biology, and cerebral MRI were normal. The last biological results are included in Table 3. Neither ECG nor TTE was performed. Sudden death occurred 1 month after the last follow-up. The autopsy was not able to explain the reasons for death, and did not document any organic lesion. Hence, ventricular fibrillation was suspected to be responsible for the sudden unexplained death, as reported presciently.[28]

Case 2 was a 32-year-old man without past medical history. WD was diagnosed a year before as he complained of progressive dysarthria, hypophonia, moderate dysphagia, and depression. At diagnosis, total serum copper was 5.84 μmol/L ($N > 12.7$ μmol/L), exchangeable copper 3.86 μmol/L ($0.62 < N < 1.15$ μmol/L), relative exchangeable copper (REC) 66.1% ($N < 8\%$), and urinary copper excretion 2.1 μmol/24 hours ($0.30 < N < 0.60$ μmol/24 hours). Copper in the cerebrospinal fluid was increased (1.4 μmol/L for a normal range: 0.19-0.38 μmol/L). Bilateral Kayser Fleischer rings were present. UWDRS (Unified Wilson's Disease Rating Scale) was 21. Trientine dichlorhydrate (Trientine) was initiated. Despite medical therapy, the neurological state worsened progressively. Hence, liver transplantation was decided 1 year after WD diagnosis. Preoperative electrocardiogram and TTE were normal. The patient improved postoperatively and was discharged to a rehabilitation center. He died suddenly 3 months after the transplantation. Of note, he was seen in a good condition 3 hours before the discovery of the body. At autopsy, the only reported abnormalities were a small pulmonary embolism which cannot explain the sudden death and a known lesion of the right pallidum. Here again, sudden death from cardiac etiology was suspected.

Case 3 was a 45-year-old man. WD has been diagnosed at the age of 6, revealed by hepatic cytolysis. His past medical history was marked by alcohol dependence and chronic C hepatitis as a complication of the use of intravenous drugs. He was receiving D-Penicillamine (Trolovol 600 mg/d), allowing stabilization of the disease (no neurological symptoms, normal brain MRI and no Kayser-Fleischer rings). Hepatic steatosis was present.

TABLE 3 Clinical cases of Wilson disease (WD) with sudden unexplained death

Cases		Case 1	Case 2	Case 3
Gender		Female	Male	Male
Age at diagnosis (y)		11	31	6
Clinical form at diagnosis		Familial screening/ hepatic	Hepato-neurologic	Hepatic
ATP7B mutation		c.3909-2A > G intron 18 (homozygous)	c. 2333G > T exon 8, 2810delT exon 12	3083delA > G exon 14 (homozygous)
First line therapy		D-Penicillamine	TETA 2HCL	D-Penicillamine
Second line therapy		Zinc acetate	LT + TETA 2HCL	/
Data at death (or at last follow-up)				
Age (y)		33	32	45
Clinical form		Hepatic	Hepato-neurologic	Hepato-neurologic
Hepatic involvement	Hepatic score (0-6)	1	0 (LT)	2
	Liver biology	Normal	Normal	Hepatic cytolysis
	Abdominal ultrasound	Normal	Micronodular heterogeneous structure/ hepatomegaly	Steatosis
	Fibroscan (kPa)	6.3	8.8	8
Neurological involvement	Clinical symptoms	None	Parkinsonism, dystonia, dysarthria, executive dysfunction	None
	UWDRS	0	84	0
	Brain MRI	Normal	Basal ganglia T2 hyposignal and Putamen FLAIR hypersignal	Dural fistula and multiple hemorrhagic lesions
Biology	ExCu (μmol/L)	0.34	0.75	0.77
	UCu (μmol/L)	1.02	0.90	1.55
	Leukocytes (/mm^3)	4680	8500	5200
	Hemoglobin (g/dL)	13.1	11.1	14.9
	Platelets (G/mm^3)	264	295	255
	Prothrombin time (%)	95	91	85
	Factor V (%)	NC	NA	105
	Creatinine (μmol/L)	43	80	64
	ASAT (N < 35)	13	22	58
	ALAT (N < 35)	14	37	137
ECG		NA	Normal	NA
Transthoracic echocardiography		NA	Normal	NA
Autopsy study		Inconclusive. No organic lesion	Small pulmonary embolism and right pallidum lesion. Inconclusive for the cause of sudden death	Not performed

Abbreviations: ECG, electrocardiogram; ExCu, exchangeable copper (N: 0.62-1.15 μmol/L); LT, liver transplantation; MRI, magnetic resonance imaging; NA, not available; TETA 2HCL, trientine dihydrochloride; UCu, urinary copper excretion (N: 0.2-0.4 μmol/L); UWDRS, Unified Wilson's Disease Rating Scale.

The evolution was marked by fluctuant hepatic cytolysis due to chronic C hepatitis and alcoholism, without cirrhosis or hepatocarcinoma. In 2018, he had a generalized tonic-clonic seizure and the brain MRI showed cerebellar and frontal hemorrhagic lesions. A dural fistula was suspected. On last biological control, exchangeable copper was normal (0.77 μmol/L), liver enzymes were elevated (ASAT 58 UI/L [normal <34], ALAT 137 UI/L [normal <50]) and gamma GT at 340 UI/L (normal 12-64). No ECG or TTE was performed during the follow-up. The death occurred suddenly in jail, without any precursor symptom. The autopsy was not performed.

4 | DISCUSSION

This review of the literature and the description of the three sudden deaths demonstrate that cardiac involvement is not an uncommon finding in WD patients. Although the mechanisms of myocardial impairment in WD are still unclear, anatomopathological examinations are available and can help elucidate these mechanisms.

One of the first cases of cardiomyopathy associated with an increased copper content of the myocardium was reported by Böttiger and Möllerberg in 1959, in a postmortem examination of a 17-year-old boy suffering from hepatolenticular degeneration (HLD) who died after an unfortunate sternal puncture.[27] A relationship was suggested between copper deposition and cardiac damage. In 1978, the case of a 10-year-old boy with WD who had signs of myocardial damage (on ECG, vectorcardiogram, radioscopic and radiologic examinations, and hemodynamic study) was described by Azevedo et al. Biopsy of the myocardium by intracavitary puncture revealed a high level of copper deposition (155 μg/g of lyophilized tissue, which is 10 times the normal heart content).[26] In this short communication, the average copper contents of normal and WD heart tissues were reported. In another autopsy case report of a 14-year-old boy by Kaduk et al,[29] postmortem atomic absorption spectrophotometry of the myocardium revealed a 100-fold increase in copper, while ultrastructural examination revealed all the features of cardiomyopathy at the cellular level. Another autopsy study by Factor et al[8] analyzed nine WD patients, newly diagnosed (two patients) or chronically treated (seven patients, disease duration between 3 years and 17 years), compared with three controls. Cardiac hypertrophy was found in five of the nine WD patients, all chronically treated. All of the cases exhibited interstitial and replacement fibrosis, intramyocardial small vessel sclerosis, and focal inflammation. A 15-year-old boy had severe atherosclerosis of the left main coronary artery and one patient had atrioventricular nodal degeneration. Two patients, followed up and treated for 4 years, died suddenly. One of them had the most severe myocardial alterations. WD appears to be related to sudden cardiac death. This could be due to inflammation (myocarditis) secondary to copper deposits and copper accumulation in the heart[2,33] or metabolic changes similar to those observed in the liver of WD patients and animal models.[34] Like iron, copper can produce reactive oxygen species, thereby inducing DNA strand breaks and the oxidation of nucleotide bases.[35] In the heart, these oxygen radicals can damage cardiomyocytes.[18,35] Furthermore, as in hemochromatosis, iron deposits may be involved, since ceruloplasmin is also implicated in iron trafficking.[36,37] Hence, decoppering treatments can decrease the incidence of cardiomyopathy.[2]

There is a contrast between the studies that have reported no or mild cardiac involvement in WD, such as this series of 125 WD patients who underwent ECG plus echocardiography, and where the main cardiac manifestations were mild (LV hypertrophy, impaired LV diastolic function),[13,38] or that echocardiographic series using strain and strain rate in 30 WD patients,[16] and others,[2,18,33] vs the case reports of sudden cardiac death,[8,28,30] including our three case reports (see Table 3). This may be because some studies excluded severely ill patients[16] and because the patients included in the majority of these studies were mostly well treated, asymptomatic, or exhibited only mild symptoms, while cardiac damage may be more severe in less well-treated patients. Furthermore, cardiac involvement may be less prevalent in the relatively young patients who were included in these studies and may appear later during the progression of the disease. Therefore, we believe that cardiac explorations would be useful throughout the follow-up of these patients.

ECG abnormalities are frequent, they can occur at an early age,[9,10] and they can be secondary to the deposition of copper in the heart. A correlation between P-wave dispersion and serum copper levels has been reported.[7] Furthermore, P-wave dispersion has been associated with an increased risk of AF.[39-41] Indeed, in the Grandis et al population-based study,[6] the WD patients' incidence of AF was 2.59 per 100 person-years (95% CI 1.83-3.55) vs 0.74 per 100 person-years (95% CI 0.74-0.75) for the rest of the cohort, representing a 29% higher incidence of AF (HR 1.29, 95% CI 1.15-1.45, $P < .0001$). The reported higher risk of conduction abnormalities in WD patients could also be secondary to copper deposits in the intracardiac conduction pathways,[2,8,24] while cardiac fibrosis, as documented by cardiac MRI and endomyocardial biopsy, could be responsible for ventricular arrhythmias and predicted by QT dispersion.[28,30,42] Resting ECG is a widely available, easy to perform, and fast tool for rhythm assessment, and it should hence be performed in all WD patients at baseline and during follow-up. Cardiac monitoring for at least 24 hours would also be useful at the time of WD diagnosis and during follow-up, as this would help detect

rhythm and conduction abnormalities as well as stratification of the risk of severe ventricular arrhythmias.

Furthermore, morphological evaluation of myocardial involvement might be useful for patient care, as well as for epidemiological purposes, in systematic and large series. Indeed, there is a lack of data regarding myocardial involvement in WD patients, due to a lack of large-scale studies, as cardiac imaging is not routinely performed in WD patients. TTE is the most readily available tool for morphological analysis of cardiac structure and function, and it should hence be performed first, at baseline and during follow-up. It allows measurement of left atrial and ventricular volumes and function, LV mass, LV filling pressures, and pulmonary arterial pressures. To date, only sporadic LV systolic dysfunction has been reported in WD patients. Takotsubo cardiomyopathy can readily be diagnosed by TTE.[25] However, tissue Doppler imaging (DTI) for LV filling pressure evaluation and myocardial deformation, which may identify early myocardial alterations before LV systolic dysfunction, were not available in the majority of the reported studies. Cardiac MRI additionally allows documentation of cardiac fibrosis and quantification of LGE.

Finally, biomarkers of cardiac damage, mainly troponin and BNP, are thought to be associated with the severity of WD and should be assessed.[2] The duration of the disease appears to be related to the risk of cardiac involvement,[8,11] although neither the type of treatment nor the form of the disease (except for the association between neurological forms and dysautonomia) could be associated with the cardiac events. It has been hypothesized that myocardial copper overload may be responsible for inflammation of the myocardium (myocarditis), which would improve with appropriate therapy for WD.[2]

To date, the frequency with which one should schedule follow-up testing for the cardiac rhythm, morphology, and blood tests is not yet known. Large studies with a long observational period are needed to establish guidelines in this regard.

5 | CONCLUSION

The spectrum of cardiac involvement in WD is broad and can involve de novo patients or patients treated chronically irrespective of their clinical hepatic or neurological phenotype. The mechanism of cardiac damage in WD may be the consequence of copper accumulation in the heart and the consequence of a toxic effect of copper, with the release of free oxygen radicals.

We suggest that all WD patients should undergo at least one ECG and ECG monitoring, troponin, and BNP measurements, and a TTE at the time of diagnosis and during their follow-up, and patients with signs or symptoms suggestive of cardiac involvement or who have cardiovascular risk factors should be examined by a cardiologist in addition to assessment by their interdisciplinary treating team. When available, cardiac MRI may provide prognostic information. Prospective studies that include extensive and comprehensive cardiovascular evaluation of WD patients are warranted and would help with the specification of the spectrum of cardiac involvement in WD and how to document and treat them.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Kevin Chevalier and Nadia Benyounes wrote the manuscript. Aurélia Poujois supervised the drafting, edition, and revision of the manuscript. Michaël Alexandre Obadia, Clélie Van Der Vynckt, Erwan Morvan, and Thierry Tibi edited the manuscript.

INFORMED CONSENT

This article does not contain any studies with human or animal subjects performed by any of the authors.

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