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Original Article

Structural and Functional Cardiac Changes in Children with Wilson Disease

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Abstract:

Background: Wilson disease (WD) is an autosomal recessive disease with copper overload. Its clinical picture depends on specific tissue/system damage by the excess copper.

Aim of the work: We aimed to study prospectively the phenotypic spectrum of structural and functional cardiac changes among children with WD.

Methods: 16 children with confirmed WD underwent electrocardiography (ECG), conventional and tissue Doppler echocardiography.

Results: ECG was normal in 11 patients (68.7%), inverted T was detected in 2 (12.5%), ST elevation in 2 (12.5%) while P-pulmonale and inverted T were detected in 1 (6.25%). Five patients (31.25%) had mild and one (6.25%) had severe tricuspid regurgitation. Two girls (12.5%) with WD had underlying congenital heart defects, one had atrial septal defect (ASD) and another had double inlet left ventricle (DILV), malposed great vessels and severe pulmonary stenosis. There was a positive correlation between LV mass and duration of treatment (r=0.559, p=0.030), and a negative correlation between age of onset and LV mass index (r=0.600, p=0.018). There was no significant correlation between age of onset and duration of treatment with myocardial perfusion imaging (MPI) or tissue Doppler parameters.

Conclusion: WD in children is associated with cardiac structural and functional changes including congenital structural heart malformations; ASD and DILV. Future research is needed to verify if ASD and DILV in WD are embryonic presentations of copper overload in WD.

Level of Evidence of Study: IIB (*1*).

Keywords: atrial septal defect; conventional and tissue Doppler echocardiography; copper overload; double inlet left ventricle; electrocardiography; Wilson disease.

Abbreviations: ASD: atrial septal defect; DILV: double inlet left ventricle; ECG: electrocardiography; LV: left ventricle; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; IVS: interventricular septum; PW: posterior wall; FS: fraction shortening; MPI: myocardial performance index; TDI: tissue doppler imaging; IVRT: Isovolumetric relaxation time; SBP: systolic blood pressure; DBP: diastolic blood pressure; AO: aorta; LA: left atrium: RV: right ventricle; EF: ejection fraction; WD: Wilson disease.

Introduction

Wilson disease (WD) is an autosomal recessive disease characterized by copper overload. The mutations of copper transporting gene *ATP7B* in WD are various with poor genotype-phenotype correlation(*2*). The clinical picture and presentation of WD depends largely on the predominantly affected system, amount of accumulated copper and resulting complications. Copper overload damage is not limited to liver, central nervous system, eyes, kidneys, bones, hemolysis, bone marrow and heart (*3*).

The spectrum of the liver affection includes acute hepatic failure without cirrhosis, chronic liver dysfunction, cirrhosis with asymptomatic or slowly progressive liver dysfunction, to fulminant hepatic failure and any type of liver injury (*4*). Central nervous system clinical

presentation and complications in WD include headache, tremor, dystonia, ataxia, dizziness, numbness in the hands and acute weakness, seizures, syncope, dysarthria, Parkinsonism (*5*), subtle mood instability, depression deterioration in school performance or behavioral changes up to schizophrenia (*6*). Eye involvement in WD presents as sunflower cataracts, Kayser-Fleischer rings of copper deposition in Descemet membrane of the cornea at the limbus and findings similar to intraocular copper bodies (chalcosis) (*7*) and optic neuropathy (*8*). Renal involvement in WD is not rare. It includes copper renal nephropathy and copper-chelator penicillamine related nephropathy. Children may present with renal impairment, gross hematuria, acute renal failure on top of acute hemolysis, proteinuria, renal tubular acidosis (RTA), renal stones and diffuse mesangial proliferation and IgA deposition in mesangium (*9*).

Osteopenia and osteoporosis secondary to copper overload or to RTA manifest as bone pain, peripheral fractures and common radiological vertebral fractures (*10*). Bone marrow is often involved in WD afflicted subjects, either as a part of copper overload, copper-chelator penicillamine related or subsequent to over-chelation. It presents by cytopenia, marrow trilineage dysplasia (*11*) and bone marrow aplasia (*12*).

Cardiac involvement in WD has been reported among adults, with up to 30%-42% having at least a single electrocardiographic abnormality, mild parietal left ventricular (LV) thickening and concentric LV remodeling in up to 21% (*13*). Diastolic dysfunction was reported to be rare among children with WD, and presents in the form of cardiomyopathy and sudden death due to copper overload in heart tissue (*14*). It is interesting that the clinical picture of WD is almost always atypical and the diagnosis should be suspected in a variety of clinical settings. We aimed to study prospectively the spectrum of structural and functional cardiac changes in WD.

Subjects and Methods

This cross-sectional study was carried out at the Hepatology Clinic, Pediatric Hospital, Cairo University during the period between March 2017 and March 2018. The study was approved by Higher Studies Research Committee of Faculty of Medicine, Cairo University, in compliance with Helsinki declaration guidelines (*15*).

Participants

The study comprised 16 children diagnosed with WD and 15 healthy control subjects of matched age and sex. Their medical history was documented along with family history, clinical examination including general and local examination of all body systems, diagnostic investigations including 24 hours urinary copper before and after penicillamine challenge (normal range 20-50 μg after penicillamine challenge) (*16*). Only cases with confirmed diagnosis of WD based on clinical manifestations and laboratory tests including increased 24-hours urinary excretion of copper ± low serum ceruloplasmin were included in the study. Patients known to have other liver disease were excluded from the study. Heart examination, ECG and echocardiographic findings of enrolled children with WD were compared to findings of healthy age and gender matched children with normal cardiac structure and function.

Methods

Cardiac Structural and Functional Assessment Studies

Conventional & Tissue Doppler Echocardiography:

All enrolled children underwent conventional & tissue Doppler echocardiography. Echocardiography examination was performed at the Echocardiography Laboratory, Pediatric Cardiology Unit, New Children Hospital, Faculty of Medicine, Cairo University.

- Trans-thoracic two dimensional (2D), (M mode) and Doppler echocardiogram were performed using GE vivid 5 (GE Medical System, Horten, Norway with a 3.5-MHz multifrequency transducer) ultrasonic machine phased array sector scanner.
- Linear measurements of left ventricle (LV) cavity were attained: Left ventricular dimensions were measured from M-mode; LV end diastolic diameter (LVEDD), LV end systolic diameter (LVESD), walls (interventricular septum [IVS] and posterior wall [PW]).

- LV systolic function assessment followed the recommendations of the American Society of Echocardiography. Fractional shortening (FS %) was considered as an indicator of LV systolic function. FS value < 28% was considered as impaired LV systolic function (*17*).

Myocardial performance index (MPI):

- Left ventricular global function was evaluated by assessing MPI, which is a nongeometric quantitative index that reflects myocardial performance. It is the ratio of total time spent in isovolumic activity to the ejection time. In normal children, the published left ventricular MPI is 0.35+ 0.03 (*18*, *19*).
- MPI, is an index of global ventricular function that is independent of ventricular structure.
- MPI was the calculated average of 3 cycles (for the left ventricle) according to the formula MPI = a – b /b.
- Where: "a" value = time from closure to opening of the mitral valve, and "b" value: ejection time of the left ventricle.
- Left ventricular mass and mass index were measured using the following equation: (LVM)=0.8*(1.04*(IVS+LVEDD+LVPW)3- (LVEDD)+0.6(gram) (*20*).
- Left ventricular mass index= LVM / height 2.7(gram/meter) (*21*).
- Echocardiographic parameters were compared to those of a control group of matched age and sex.

Tissue Doppler imaging (TDI)

- TDI was done typically using the 4-chamber view where the ultrasound beam was directed perpendicular to the mitral annular planes. The 5-mm pulsed TD sample volume was sited at both aspects of the mitral annulus and at the lateral aspect of the tricuspid annulus. We adopted Mostafa and coworkers technique in assessment of the global LV systolic and diastolic function; average velocities of 6 LV walls, peak systolic myocardial function, peak early diastolic filling velocity, and late peak diastolic myocardial filling velocity. Isovolumetric relaxation time (IVRT), early (Ea) and late diastolic (Aa) velocities ratio at the lateral and septal mitral and at the free-wall tricuspid annulus were measured. The ratio of early mitral inflow velocity and mitral annular early diastolic velocity (E/e') was evaluated as a representative of LV filling pressure (*22*).

Electrocardiograph:

- A 12 lead ECG was performed for all patients and was systemically analyzed by a consultant cardiologist after excluding other conditions that might predispose to ECG abnormalities.

Statistical Analysis

The collected data were revised, coded, tabulated and introduced to a PC using statistical package for social sciences (SPSS 16.0 for windows; SPSS Inc., Chicago, IL, 2001). Data were presented and the suitable analysis was done according to the type of data obtained for each parameter. Descriptive data were presented as mean, standard deviation (±SD), range for numerical data and frequency and percentage for non-numerical data. For independent samples t test was used to assess the statistical significance of the difference between means. Chi-square test was used to examine the relations between qualitative variables. One way ANOVA test was used to assess the statistical significance of the difference between means. $P < 0.05$ was the level of significance employed in study.

Results

Among the studied children with WD there was no gender predilection. (Table 1). The earliest age for initial symptoms was 16 months with 6 children presenting before 3 years. Children with WD did not have a typical clinical picture, and cardiac involvement was not limited to acquired cardiac affliction, as two children had underlying congenital heart disease (one had univentricular heart and the other had atrial septal defect). (Figure 1). Normal ALT was encountered in 8 (50%) of the children with Wilson, and 7 had normal AST level. Growth was affected in children with WD as well, where 5 were below the 10th percentile of weight and height expected for age. (Table 1). All children were on copper chelation therapy, vitamin B, D and E supplementation and a copper-restricted diet. Zinc sulfate was the mainstay of copper chelation

among all studied children, with the dose guided by the level of copper excreted in urine. The aim was to achieve target copper excretion in urine in 24 hours of 30-40 µg.

Table 1: Demographic data of studied cohort with Wilson Disease

		Number	%
Gender	Male	8	50
	Female	8	50
Family history	Absent	4	25
	Present	12	75
Consanguinity	Non consanguineous	7	43.75
	Consanguineous	9	56.25
Onset of Disease	Symptomatic Cases	11	68.75
	Screened pre symptomatic cases*	5	31.25
Ceruloplasmin	Normal	3	18.75
	Reduced	13	81.25

	Mean	Standard Deviation	Median	Minimum	Maximum
Age (months)	97.07	50.59	102.00	16.00	180.00
Age at onset of symptoms (months)	63.80	36.04	60.00	16.00	125.00
Percentile % (weight for age)	42.67	32.51	50.00	5.00	90.00
Percentile (height for age)	45.53	35.70	50.00	3.00	97.00
SBP (percentile)	53	4.31	55	52.5	55
DBP (percentile)	50.1	3.8	51.5	36.8	70.00
Duration of treatment (months)	27.47	40.19	22.00	.00	144.00
Urinary Copper in 24 hours urine (in µg)	71.33	64.20	50.00	10.00	212.50
Urinary Copper in 24 hours post-D- penicillamine challenge (µg)	475.45	425.03	340.00	112.00	1798.00

SBP: systolic blood pressure, DBP: diastolic blood pressure.
*Screened presymptomatic case: Child diagnosed as having Wilson disease after screening of family members of an index case that presented by symptomatic Wilson Disease.

Cardiac Affection Encountered Among The Studied Case Series:

ECG findings were as follows:

- The QRS axis, PR interval, QRS complex, R/S amplitude ratio and QT interval were normal in all. ECG was normal in 11cases (68.7%), inverted T detected in 2(12.5%) in V1 and V2 leads (may be considered normal), ST elevation in 2 children (12.5%) in AVF lead while P-pulmonale and inverted T were detected in 1 case (6.25%) in lead II.

Structural Cardiac Affection among Studied Children with confirmed WD:

- One child had moderate LV hypertrophy (6.25%), and 5 (31.2%) had concentric remodeling pattern. Mild grade tricuspid regurgitation in 5 cases (31.25%), while severe tricuspid regurgitation was recorded only in 1 case (6.25%) who suffered from infective endocarditis. Tricuspid regurgitation was absent in 10 cases (62.5%). (Table 2). One girl had underlying congenital atrial septal defect (6.25%) and another had underlying congenital double inlet left ventricle (DILV), malposed great vessels and severe pulmonary stenosis (6.25%). The latter underwent Blalock Taussig right pulmonary artery shunt placement and bilateral Glenn procedures. She presented with cholestasis and liver cell failure at 8 years of age. Her total bilirubin exceeded 24mg/dL and she responded to chelation by zinc sulfate by reaching near normal values within 6 months of initiation of therapy.
- There was a significant positive correlation between age of onset and copper in urine (µg/24h) after penicillamine challenge ($r = 0.741$, $p=0.002$), between LV mass and duration of treatment ($r=0.559$, $p=0.030$), and a significant negative correlation between age of onset and

LV mass index (r=0.600, p=0.018), while there was no significant correlation between age of onset and duration of treatment with MPI or tissue Doppler parameters.

- None of the 5 children with WD who were diagnosed during screening of family of index case had structural or functional cardiac affection.

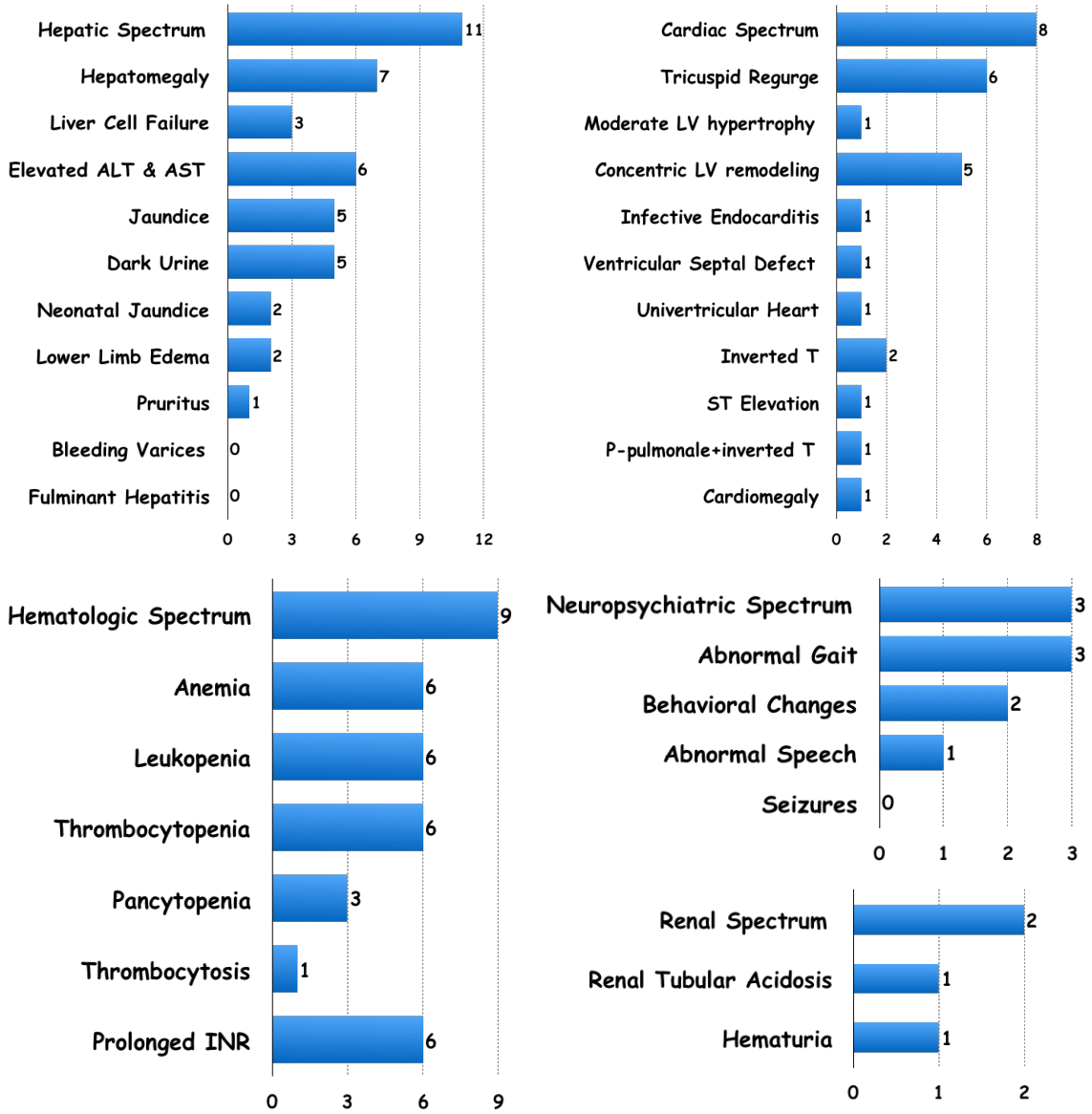

Figure 1: System Affection Spectrum of Studied Cohort of Children with Wilson Disease.

Functional Cardiac Affection among Studied Children with confirmed WD:

- Ejection faction was significantly lower among cases (p=0.029), however, clinically relevant decrease in EF (<50%) was not noted.
- Among diastolic filling parameters, there was significant decrease in the deceleration time of early diastolic transmitral flow (p=0.02) among patients. Myocardial performance index (MPI), that incorporates systolic and diastolic time intervals in expressing global systolic and diastolic ventricular function, was significantly higher in patients (p=0.001) than in controls using conventional echocardiography. Also tissue Doppler showed significant difference among the two groups regarding the MPI (p=0.001).

Other system affection encountered among the studied case series:

- The studied cohort suffered from multi-system disease, with various degrees of liver, heart, kidneys, neuropsychiatric and hematologic involvement. (Figures 1 and 2).

Table 2: Conventional and tissue Doppler echocardiography imaging values of children with Wilson disease and control group

	Cases					Control					P value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
AO	1.89	.38	1.90	1.10	2.60	1.94	.32	1.90	1.30	2.50	0.683
LA	2.07	.43	2.00	1.20	2.60	2.17	0.31	2.10	1.70	2.60	0.595
RV	1.81	.36	1.80	1.20	2.60	1.67	0.25	1.70	1.20	2.00	0.305
PA	1.70	.20	1.70	1.20	2.00	1.86	0.20	1.90	1.40	2.10	.029*
IVS	0.71	0.11	0.70	0.60	0.90	0.69	0.10	0.70	0.50	0.80	0.744
LVPW	0.71	0.14	0.70	0.50	1.00	.65	0.11	0.70	0.50	0.80	0.345
LVEDD	3.57	0.58	3.60	2.50	4.40	3.75	0.49	3.60	2.80	4.50	0.389
LVESD	2.13	.50	2.20	1.10	2.90	2.39	.32	2.40	1.80	3.00	0.089
EF %	64.47	4.56	64.00	60.00	75.00	69.80	7.26	70.00	60.00	88.00	0.029*
FS %	38.73	6.30	38.00	31.00	56.00	34.47	3.54	34.00	30.00	42.00	0.037*
EV mitral	0.99	0.17	1.00	0.60	1.20	0.98	0.08	1.00	0.76	1.12	0.512
AV	0.61	0.24	0.53	0.43	1.43	0.54	0.08	0.50	0.40	0.69	0.683
DT	95.27	23.80	89.00	61.00	140.0	122.9	18.00	130.0	90.00	150.0	0.002*
MPI	.37	0.17	0.36	0.10	0.69	0.18	0.10	0.17	0.06	0.36	0.001*
E/A	1.72	0.39	1.71	0.79	2.30	1.84	.32	1.85	1.37	2.65	0.567
EV LV post.	0.18	0.03	0.19	0.12	0.23	0.18	0.04	0.16	0.12	0.24	0.436
AV post.	0.08	0.03	0.08	0.05	0.15	0.07	0.01	0.07	0.05	0.10	0.325
S post.	0.10	0.02	0.09	0.07	0.17	0.09	0.02	0.10	0.07	0.11	0.653
MPI post.	0.50	0.12	0.49	0.20	0.70	0.33	0.04	0.34	0.26	0.40	0.001*
E/A post.	2.34	.60	2.40	1.20	3.10	2.56	0.50	2.66	1.60	3.00	0.325
EV septum	0.12	0.04	0.12	0.02	0.18	0.16	0.03	0.16	0.12	0.20	0.003*
AV septum	0.08	0.03	0.07	0.04	0.14	0.07	0.01	0.06	0.05	0.11	0.436
S septum	0.08	0.02	0.09	0.02	0.10	0.08	0.01	0.08	0.07	0.10	0.870
MPI septum	0.51	0.09	0.52	0.34	0.64	0.33	0.05	0.34	0.23	0.45	0.001*
E/A septum	1.80	0.73	2.00	0.14	3.20	2.52	0.67	2.50	1.27	3.30	0.007*
Average E	0.16	0.03	0.16	0.10	0.21	0.17	0.03	0.16	0.12	0.22	0.567
E/E prime	6.48	1.85	6.35	3.33	10.00	5.95	0.93	6.14	4.54	7.22	0.461
LV mass (g)	68.67	27.71	62.00	34.00	128.0	69.53	27.07	66.00	28.00	114.0	0.935
LV mass index (g/m2)	72.87	21.51	67.00	40.00	119.0	72.93	14.45	69.00	54.00	96.00	0.806
RWT	0.40	0.10	0.37	0.31	0.64	0.34	0.03	0.33	0.29	0.39	0.126

*: Statistically significant at $p< 0.05$. AO: aorta, AV: peak velocity of late transmitral flow, DT: deceleration time, EF: ejection fraction, E: peak velocity of early diastolic mitral annular motion, E/A: Early diastolic ventricular filling/late filling due to atrial contration; EV: peak velocity of early diastolic transmitral flow, FS: fractional shortening, IVS: interventricular septum, LA: left atrium, LV: left ventricular, LVEDD: left ventricular end diastolic diameter, LVESD: left ventricular end systolic diameter, LVPW: left ventricular posterior wall, MPI: myocardial performance index, PA: pulmonary artery, Post: posterior, RV: right ventricle, RWT: relative wall thickness, S: peak velocity of systolic pulmonary vein flow.

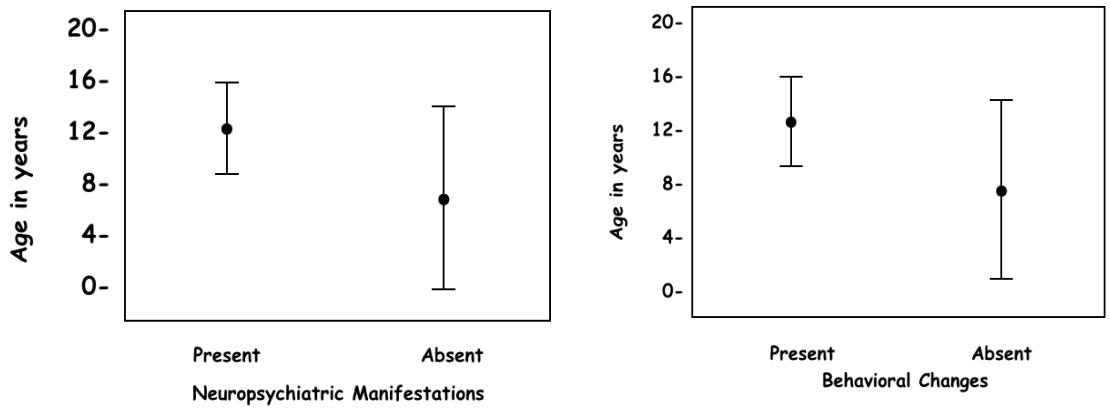

Figure 2: Neuropsychiatric manifestations (p value =.048) and behavioral changes (p value =.038) had an older age of presentation.

Discussion

WD affects the heart structurally and functionally in the pediatric age. Children with symptomatic WD had cardiac affection, but none of the asymptomatic children with WD who were diagnosed by screening following diagnosis of an index case had any cardiac affection. Left ventricular cardiac mass correlated inversely with age at onset of symptoms of disease. Copper excess and copper deficiency are known to be associated with cardiovascular changes (*23*). None of our studied cohort had copper deficiency yet the functional changes were detected among 68.7% of the cases. Hence the cardiac changes were attributed to the excess copper load. It is interesting that the threshold for cardiac affection is related to symptoms of WD as none of the screened pre-symptomatic cases had cardiac structural or functional changes.

WD was associated with subclinical diastolic dysfunction among our studied group. Five had concentric remodeling (31.1%). It seems that this is related to the duration of the disease as more adults were reported to have diastolic dysfunction and concentric hypertrophy (*13*). A long term prospective study is needed to verify this assumption.

WD was associated with congenital cardiac malformation among two of our studied cohort; one case had only atrial septal defect and the other had double inlet left ventricle, malposed great vessels and severe pulmonary stenosis. In children with congenital cardiac malformations who suffer from hepatic complications, WD should be suspected. This is the first report of double inlet left ventricle, malposed great vessels and severe pulmonary stenosis associated with WD.

Copper excess during embryogenesis among hamsters and other animals is known to be associated with atrial septal defects and ventricular septal defects (*24*). Among humans univentricular heart disease is known to be associated with liver disease (*25*), but it was never suspected to be due to copper excess. Evidence supports that the liver disease precedes the shunt operation, as supported by liver pathology (*26*). Our reported structural heart deformities suggest that embryonic WD is a possibility.

The age at presentation of WD around 5 years was argued by evidence that support that WD can present earlier, by age of 2 years (*27*). Again the lack of typical liver pathology findings in WD (*28*) might explain why copper excess was not suspected in those with univentricular heart, double inlet left ventricle, malposed great vessels and severe pulmonary stenosis and liver disease. Our work suggests that cardiac clinical spectrum of WD might include an embryonic presentation with abnormal congenital cardiac structure.

In view of our findings, it seems logical to check for copper overload in children with univentricular hearts, ASD, DILV or other congenital structural defect presenting with liver disease, as this is a treatable condition. We believe it is a rare association yet might be under diagnosed. However, cardiac birth defects in off-springs of mothers with known WD and copper excess are rare (1.5%). The later include atrial septal defects and persistent foramen ovale (*29*). Also, among hamsters excess copper was reported to cause 58 major cardiac malformations in 56% of embryos (*24*). The underlying pathogenesis is not clear. It is not clear if our studied child with atrial septal defect and the other with DILV were exposed to excess copper during

embryogenesis, and it is not clear if the excess copper is teratogenic among humans. It is also not clear if the cardiac malformations in both girls was related to copper excess or deficiency, given that copper deficiency is known to cause cardiac malformations among embryos of animals (*30*). The association of cardiac anomalies in both girls with WD is extremely intriguing and highlights the need to study effects of micronutrients on embryogenesis in humans.

There was no "typical" clinical picture of WD in the study group. Presentation comprises various clinical compositions that are atypical. WD is a treatable condition that should be diagnosed in any child with multisystem disease, neurologic disease, liver, bone, kidney or heart disease.

We report that cardiac involvement was subtle and was complicated by infective endocarditis with severe affection of tricuspid valve in one child.

Children with WD having underlying cardiac affection are susceptible to infective endocarditis. The child awaits tricuspid valve replacement, though she is clinically compensated with no clinical abnormality apart from tricuspid valve serious and severe regurgitation.

Our study has limitations. Our study, being cross-sectional and not prospective did not allow us to assess the effect of copper levels and its chelation therapy on cardiac remodeling. Again, the small sample size is another limitation.

Conclusion

Wilson disease in children is associated with cardiac structural and functional changes. We came across children with underlying congenital structural heart malformations; identified as atrial septal defects and double inlet left ventricle. Future research is needed to verify if ASD in WD is an embryonic presentation of embryonic copper overload/WD.

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Author Contributions:

All authors shared in conceptualization, supervising, data curation, data analysis, writing original draft, data interpretation, writing original draft, supervising and revising. All authors reviewed the final manuscript. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in connection with the study.

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