Protocol of a Thesis for Partial Fulfillment of Master Degree in Pediatrics

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Title:

Assessment of Subtle Myocardial Dysfunction in Children with Wilson's disease, A case control study

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What is already known on this subject? AND

What does this study add?

Wilson's disease (WD) is one of the most common metabolic liver diseases in older children. [1] The most frequent clinical presentation is liver disease. [2]

However, WD is a multisystem disorder. It is concluded that four modes of cardiac manifestations in WD include arrhythmias, cardiomyopathy, cardiac death, and autonomic dysfunction. Such possible cardiac involvement should be added to the clinical picture of WD involving the hepatic and central nervous system. [3]

The data on cardiac manifestations in children is very limited and only few adult studies are available. [1]

In this study, we aim to unveil subclinical cardiac dysfunction in children with Wilson's disease with apparently normal cardiac functions by conventional assessment.

1. INTRODUCTION:

Wilson's disease (WD) is an autosomal recessive disorder characterized by toxic accumulation of copper. [3] Copper accumulates not only in the liver and brain, but also in other organs [4] The clinical picture and presentation of WD depends largely on the predominantly affected system, amount of accumulated copper and resulting complications. The spectrum of the liver affection includes: acute hepatic failure with/without cirrhosis, chronic liver dysfunction, cirrhosis with asymptomatic or slowly progressive liver dysfunction, to fulminant hepatic failure and any type of liver injury. [5]

However, relatively little is known about the effects of copper accumulation on the heart. Myocardial copper accumulation was revealed by electron microscope. [6] Copper excess and copper deficiency are known to be associated with cardiovascular changes. [5] That may extend to the myocardium, resulting in electrocardiographic changes, arrhythmias, autonomic dysfunction, heart failure and sudden cardiac death. [3] WD was associated with subclinical diastolic dysfunction. It seems that this is related to the duration of the disease as more adults were reported to have diastolic dysfunction and concentric hypertrophy. Left ventricular cardiac mass correlated inversely with age at onset of symptoms of disease. [5] It may be the

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result of copper accumulation in the heart, and/or it could be due to a toxic effect of copper. [7]

A study highlighted that higher levels of ceruloplasmin and N-terminal pro b-type natriuretic peptide (NT-pro BNP) were independently associated with worse outcomes in heart failure patients. [8] The combined evaluation of ceruloplasmin and NT-proBNP had advantages over separate NT-proBNP and ceruloplasmin assessment. [9]

In early stages of the Wilson's disease, the LV appears apparently normal when evaluated by traditional 2D echocardiographic parameters. Fewer studies concerned with evaluation of children with WD by speckled tracking echocardiography. Despite apparently normal LV systolic function, the children with Wilson's disease demonstrated significantly lower peak longitudinal strain as an indicator for early affection of LV systolic function. [10]

2. AIM:

1. The primary aim is to asses LV dysfunction (systolic and diastolic functions) in children diagnosed with Wilson's disease by echocardiography.
2. The secondary aim is to correlate these findings with levels of serum Pro-Brain Natriuretic Peptide (pro-BNP) and serum ceruloplasmin.
3. The tertiary aim is to detect electrical cardiac abnormalities, including arrhythmias and ECG changes, in these patients.

3. METHODOLOGY:

- **Type of study:** A Case-Control Study.
- **Study duration:** 6 months.
- **Study setting:** The patients will be recruited from Pediatric Hepatology Clinic in National Hepatology and Tropical Medicine Research Institute (NHTMRI) in conjunction with Ain Shams University (ASU) children Hospital echocardiography lab., Cairo, Egypt.
- **Study Population:**
  They will be divided in to 2 groups:
  - **Group 1:** Patients confirmed Wilson's disease.

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- **Group 2:** Controls.

- **Patients group:**

  Patient diagnosed as WD, following up in Pediatric Hepatology Clinic in NHTMRI.

  Criteria of diagnosis based on Leipzig scoring system [11,12]: Typical clinical symptoms and signs, as: Kayser-Fleischer rings, neurological symptoms, serum ceruloplasmin, Coombs-negative hemolytic anemia.

  Other tests: Liver biopsy, 24hr urinary Cu, gene analysis.

- **Inclusion Criteria:**
  - The study will be conducted on patients aged from 4 years to 18 years, as it is the time of manifestation of the disease. [13]
  - Patients confirmed Wilson's disease whether there are neurological complications or not.
- **Exclusion Criteria:**
  - Children with Congenital Heart diseases.
  - Children with overt heart failure.
  - Children are known to have other liver diseases.
  - Children with clinical evidence of cardiac dysfunction.
  - Syndromic children.
  - Children who are suffering from Fulminant Hepatitis.

- Control group will be non-random convenient sampling technique selected, age and sex matched to main group, came from the outpatient clinic free from any chronic diseases.

- **Sampling Method:** Consecutive sampling.

- **Sample size:**

  Based on a study done by ***(Hlubocká et al., 2002)*** [14], assuming power of 80% with error margin of 0.05, a sample size of 36 patients in each group would be enough to detects an effect size for cardiac dimensions in WD patients compared to control of 0.6.

- **Ethical Considerations:**

  This study will start after approval of Research Ethics Committee of Ain Shams University Hospitals as well as Research Ethics Committee of General Organization of Teaching Hospitals and Institutes (GOTHI).

  An informed consent will be obtained from parents or caregivers before enrolment in the study.

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- **Study Tools:**

  All recruited patients will be subjected to:

  - **<u>Full history taking including:</u>**
    - Demographic data: age, sex, and consanguinity.
    - Duration of disease.
    - Family history of liver or heart disease.
    - Past history of similar condition.
    - Treatment given.
    - Markers of compliance.
    - Other comorbidities.
  - **<u>Clinical examination including:</u>**
    - General examination: anthropometric measure: weight and height.
    - Vital data (respiratory rate, heart rate, blood pressure, and O2 saturation)
    - Full abdominal examination.
    - Full cardiac examination.
    - Other system examination.
  - **<u>Investigations</u>**:
    - **Laboratory:**
      - Routine investigations: CBC, PT, PTT, INR, LFT, RFT.
      - Challenge test: 24-hr urinary Cu before and after D-Penicillamine.
      - Serum ceruloplasmin. (at time of diagnosis and within 6 months of assessment of cardiac function)
      - Cardiac markers: Serum Pro-Brain Natriuretic Peptide (pro-BNP) will be measured by using ELISA technique.
    - **Intervention:** Liver Biopsy. (at time of diagnosis if possible).
    - **Radiological:**
      - Pelviabdominal Ultrasound.
      - ECG.
      - ECHO, including:
        - <u>Conventional echo:</u>
          Dimensions of LA and LV, left ventricular mass index= LVM / height, Fractional shortening (FS %), ejection fraction (EF%), tricuspid annular plane systolic excursion (TAPSE) of RV, pulmonary artery pressure.
        - <u>Doppler imaging:</u>

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E/A, myocardial performance index (MPI), isovolumetric relaxation time (IVRT).

- Tissue doppler:
  To obtain early (Ea) and late diastolic (Aa) velocities ratio, LV filling pressure: The ratio of early mitral inflow velocity and mitral annular early diastolic velocity (E/e').
- Speckle tracking echocardiography (STE) on both LA and LV.

➢ Cardiac MRI if Feasible.

- **Statistical analysis:** The data will be collected, coded, tabulated and statistically analyzed by the last available certified version or statistical package for social sciences (SPSS).
- **Study outcome:** The outcome of this study is to detect LV dysfunction (Systolic and Diastolic functions) by Echocardiography in Wilson's disease patients, and assess the relation between serum Pro-Brain Natriuretic Peptide (pro-BNP) and serum ceruloplasmin in children with Wilson's disease.

4- References

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