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ABSTRACT

Background: Wilson's disease is an autosomal recessive disorder of hepatocyte copper trafficking caused by impaired function of P-type adenosine triphosphatase (ATPase), encoded by ATP7B gene located on chromosome 13q14. Although hepatic system involvement is the major presentation but various systemic and CNS presentations have been known to occur. Various autonomic disturbances have been reported, but not much have been studied in detail. We evaluated the relationship between the disease severity and autonomic disturbances in affected patients.

Methods: This study was conducted during 2011-2013 in the department of pediatrics. All the patients under 16 years of age with Wilson disease were included. We evaluated cardiovascular ANS function, including changes in heart rate and blood pressure after performing Valsalva maneuver, tilt test, and cold pressor test. P value<0.05 was considered statistically significant.

Results: In this study 21 patients with Wilson’s disease were assessed. The mean (±SD) age of the patients was 10 years (±3.4, range: 1-16).Cardiovascular ANS function in the patients was significantly increased compared with normal values (P<0.05). The correlation between Wilson’s index and some of the indices of cardiovascular ANS function was significant.

Conclusion: Wilson’s disease scoring system can be beneficial in predicting patients’ outcome between the severities of ANS involvement and patients’ prognosis, and helping in therapeutic decision making.

KEYWORDS: Wilson’s disease, Autonomic disturbances, Wilson scoring system.
INTRODUCTION

Wilson disease is a rare autosomal recessive inherited disorder of copper metabolism that is characterized by excessive deposition of copper in the liver, brain, cornea and other tissues. Wilson disease is often fatal if not recognized and treated when symptomatic. Its incidence is one per 5,000 to 100,000 births. Rapid diagnosis and investigating the possibility of the disease in patients affected by any types of liver disease, especially those who are over 5 years of age, not only can facilitate the treatment but can also provide the possibility of appropriate treatment for other types of hepatic disease.[1-3] Various forms of hepatic Wilson diseases include asymptomatic hepatomegaly (with or without splenomegaly), subacute or chronic hepatitis, and acute hepatic failure (with or without hemolytic anemia). Cryptogenic cirrhosis, portal hypertension, ascites, edema, visceral bleeding, or other signs of hepatic dysfunction (such as delayed puberty, amenorrhea, coagulation defect) can be other clinical manifestations of Wilson disease.[1,2,4]

Neurological manifestations of the disease include temors, dysarthria, dystonia, parkinsonism, chorea form movements, lack of motor coordination, deterioration in school performance, and behavioral changes. Although, Kayser-Fleischer rings may not exist in young patients with hepatic involvement, they are always present in patients with neurological symptoms.[5]

Early involvement of basal ganglia and brainstem in Wilson’s disease could lead to dysfunction of autonomic nervous system (ANS) before the patient becomes symptomatic. ANS dysfunction can be diagnosed at this stage based on different signs including changes in arterial blood pressure and heart rate in various physiological conditions in asymptomatic patients. Actually neurological involvement can be anticipated using this method and appropriate treatment can be started before the neurological symptoms appear.

ANS involvement is often subclinical; besides, the sympathetic system is more involved than the parasympathetic system [6-8]. ANS involvement in patients presenting with neurological symptoms is more frequent than those presenting with non-neurological symptoms.

In 2005, by using more advanced statistical formulae, Dhawan and colleagues[8] could propose a new index with 93% sensitivity and 98% specificity. The new index had a positive predictive value (the probability of being sick after having a positive test result) of 93%. Most importantly, all the children with a score more than 11, who did not undergo liver
transplantation, died; whereas all those with a score lower than 11 survived. This fact indicates the significant applicability of Wilson Index in identifying the necessity of liver transplantation. Wilson index will be scored (0-4) based on the paraclinical status described in table 1, and the scores from each item are summed to obtain a final score for each patient. The final score ranges from 0 to 20.\[9\]

**Table1: Wilson's Scoring System**

<table>
<thead>
<tr>
<th>Wilson score for each item</th>
<th>Bilirubin (µmol/L)</th>
<th>INR(^1)</th>
<th>AST(^2) (IU/L)</th>
<th>WBC(^3)/L(^10^9)</th>
<th>Albumin (g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0-100</td>
<td>0-1/29</td>
<td>0-000</td>
<td>0-6/7</td>
<td>45&gt;</td>
</tr>
<tr>
<td>1</td>
<td>101-150</td>
<td>1/3-1/6</td>
<td>101-150</td>
<td>6/8-8/3</td>
<td>34-44</td>
</tr>
<tr>
<td>2</td>
<td>151-200</td>
<td>1/7-0/9</td>
<td>151-300</td>
<td>8/4-10/3</td>
<td>25-33</td>
</tr>
<tr>
<td>3</td>
<td>201-300</td>
<td>2/0-2/4</td>
<td>301-400</td>
<td>10/4-15/3</td>
<td>21-24</td>
</tr>
<tr>
<td>4</td>
<td>300&gt;</td>
<td>2/5&lt;</td>
<td>400&lt;</td>
<td>15/4&lt;</td>
<td>&lt;20</td>
</tr>
</tbody>
</table>

1-INR: International Normalized Ratio  
2-AST: Aspartate Aminotransferase  
3- WBC: White Blood Cell

To predict the outcome of patients with Wilson’s disease, Nazer and colleagues\[9\] developed a scoring system combining clinical symptoms and paraclinical parameters. In a study by Chu and colleagues, ANS involvement was assessed using sympathetic skin response and RR interval variability. Sympathetic skin response was impaired in 52% of the patients; whereas, parasympathetic functions, which was checked by examining RR interval after Valsalva maneuver, was abnormal in only 3 patients. Such finding suggests more sympathetic involvement compared with parasympathetic system in patients with Wilson’s disease.\[10\] Meenakshi-Sundaram and colleagues reported that ANS dysfunction exists in 38% of patients affected by different levels of the disease severity.\[11\]

Matarazzo and colleagues studied abnormal and spontaneous changes in the rhythm of body temperature, pulse rate, and blood pressure in patients with the disease. They found that because of ANS dysfunction, some patients had fever in the absence of infection.\[7\]
There are controversies over the mechanism of ANS dysfunction in patients with Wilson’s disease. Some reports mentioned abnormalities in central nervous system (CNS).\cite{4, 9-11} Soni and colleagues\cite{12} evaluated autonomic cardiovascular reflexes in 30 patients with the disease who had neurological symptoms and compared them with equal number of age and sex matched healthy participants. They found that patients with Wilson’s disease had significant decrease in autonomic cardiovascular function in response to Valsalva maneuver. Sympathetic skin response was also significantly delayed. However, no significant correlation was found between severity of Wilson’s disease and ANS dysfunction. Chu and colleagues noted significant delays in CNS conduction.\cite{10}

This study aimed to evaluate the relationship between severity of the disease and ANS function in the affected patients. In case, we could prove such changes in the patients, we would use non-invasive tests to diagnose the disease before it leads to irreversible neurological sequelae.

**PATIENTS AND METHODS**

This study was conducted between 2011 to 2013 in department of pediatrics. All patients under 16 years of age with Wilson’s disease whose disease was confirmed by clinical and/or laboratory methods. Following clinical assessment, patients’ ANS was assessed as well as cardiovascular system using electrocardiography and echocardiography.

ANS function of cardiovascular system was evaluated by checking changes in heart rate and blood pressure after Valsalva maneuver, tilt test (in which the patients were held in a controlled condition at 60° angle for 50 minutes), and cold pressor test (in which the patients ‘hands were put into the water at 4°C for 90 seconds). At the same time, laboratory findings were recorded in a check list. The patients were excluded from the study if they could not tolerate tests assessing cardiovascular ANS function. Mean and standard deviation was calculated for each index of cardiovascular ANS function. Degree of patients’ response to various tests was compared with normal response to specify the frequency of abnormal responses.\cite{13} The collected data were analyzed using SPSS software, version 20. Chi-square and t tests were used as appropriated. The significance level was set at P <0.05.

**RESULTS**

In this study, 21 patients with Wilson’s disease were evaluated. The mean (±SD) age of these patients was 10 years (±3.4, range: 1-16) of whom 10 were male and 11 were female. The
mean (±SD) age of men and women were 10.8 (±4.3) and 11.6 (±2.2) years respectively (P=0.22).

The mean (± SD) systolic blood pressure in the studied patients was 109.7 (±11) mmHg at rest and 118.5 (±13.9) mmHg after Valsalva maneuver. It was 117.6 (±9.7), 118.4 (±11.3), and 118.8 (±12.6) mmHg within one, two, and three minutes after the tilt test respectively. Repeated measure ANOVA showed no significant changes in systolic blood pressure in the patients (P=0.11).

The mean (±SD) diastolic blood pressure in the studied patients was 63.7 (±5.5) mmHg at rest and 69.5 (±11) mmHg after Valsalva maneuver. However, there was no significant difference between mean diastolic blood pressure before and after Valsalva maneuver (P=0.07, paired t test). The mean (±SD) diastolic blood pressure was 73.8 (±8.5), 73.9 (±11.3), and 74.5 (±10.7) mmHg within one, two, and three minutes after the tilt test, respectively. Changes in diastolic blood pressure was statistically significant (P=0.023).

The mean maximum RR interval in the studied patients was 17.4 (±3.3) and the mean minimum RR interval was 13.8 (±3.5) after Valsalva maneuver. The mean RR interval at rest was 17.9 (±3.1). Mean of the first RR interval was 17.9 (±4.3) at rest. It was 14.9 (±3.4), 14.9 (±2.7), and 15.9 (±3.7) within one, two, and three minutes after rest respectively. There was a statistically significant differences between the RR intervals at the mentioned times (P<0.001, repeated measure ANOVA.

The mean (±SD) systolic blood pressure after the cold pressor test was 113 (±11.3, range: 94-143) mmHg. In the same situation, the mean (±SD) diastolic blood pressure was 63.7 (±9.7, range: 51-89) mmHg and the mean RR interval was 16.2 (±3.4, range: 11-25) (table 2).

Table 2: Mean and SD, range of blood pressure, and RR interval in patients with Wilson’s disease after cold pressor test

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
<th>Maximum</th>
<th>Minimum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>113</td>
<td>11.3</td>
<td>143</td>
<td>94</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>63.7</td>
<td>9.7</td>
<td>51</td>
<td>89</td>
</tr>
<tr>
<td>RR interval</td>
<td>16.2</td>
<td>3.4</td>
<td>11</td>
<td>25</td>
</tr>
</tbody>
</table>
The mean (±SD) heart rate changes during phase 2 of Valsalva maneuver in the studied patients was 44 (±31) beats per minute. The mean (±SD) RR interval ratio of the phase 4 to phase 2 of the maneuver was 1.16 (±0.15, min= 0.53, max= 1.34).

The frequency distribution of RR interval ratios of phase 4 to phase 2 of the maneuver, recorded in the patients’ electrocardiogram, Based on these findings obtained in 10 patients this ratio was ≤1.2, and actually no normal response from cardiovascular ANS was achieved (P<0.05).

Mean (±SD) heart rate increase after tilt maneuver in the studied patients was 33 (±35) beats per minute; while, he mean increased diastolic and systolic blood pressure was 4 (±12) and 3 (±5) mmHg, respectively.

Only in one patient, the systolic blood pressure increased more than 20 mmHg after cold pressor test and in other patients, the response to cardiovascular ANS was not normal. Mean (±SD) total score of Wilson disease in studied patients was 5.7 (±2, range 0-10).

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There were positive correlations between the score of Wilson’s disease with systolic blood pressure after tilt maneuver (r=0.07), heart rate (r=0.135) and systolic blood pressure after cold pressore test (r=0.22). However, such correlation was not statistically significant (P >0.05). The highest positive correlation was with systolic blood pressure after cold pressor test.
Wilson’s score was negatively correlated with increased heart rate during phase 2 of Valsalva maneuver ($r=0.12$), RR interval ratio of the phase 4 to the phase 2 of the maneuver ($r=0.055$), increased diastolic blood pressure ($r=0.12$), and increased heart rate after tilting the patient ($r=0.15$, $P>0.05$).

**DISCUSSION**

Early involvement of basal ganglia and brainstem in Wilson’s disease could lead to dysfunction of autonomic nervous system (ANS) before the patient becomes symptomatic. ANS dysfunction can be diagnosed at this stage based on different signs including changes in arterial blood pressure and heart rate in various physiological conditions in asymptomatic patients. Meenakshi-Sundaram and colleagues have mentioned the existence of dysfunctions in the CNS because peripheral nerve conduction was normal in all their patients.[11]

Kuan and colleagues conducted a prospective study to evaluate cardiovascular involvement in patients with Wilson’s disease. They found that 34% and 20% of patients suffered from electrocardiographic abnormalities and orthostatic hypotension respectively. Besides, one-third of the patients showed abnormal response to the Valsalva maneuver.[14]

Soni and colleagues[12] evaluated autonomic cardiovascular reflexes both clinically and electrophysiologically in 30 patients with Wilson’s disease presenting with neurological symptoms and compared them with equal number of age and sex matched control healthy participants. They observed statistically significant abnormal response to the Valsalva maneuver and RR interval ratio in the patients compared with healthy controls ($P<0.05$). Latency for sympathetic skin response was significant as well in such patients ($P<0.02$). The result of their study, similar to ours, showed that there was no significant correlation between autonomic dysfunction and clinical severity of Wilson’s disease.

However, parasympathetic functions were more affected than the sympathetic functions. In another study, Chu and colleagues assessed ANS dysfunction using sympathetic skin response and RR interval variability. They observed that sympathetic skin response was impaired in 52% of the patients; whereas, parasympathetic functions that was evaluated by examining RR interval after Valsalva maneuver, was abnormal in only 3 patients. Such finding suggests that sympathetic nervous system is more affected than parasympathetic system in patients with Wilson’s disease.[10]
In our study, mean (±SD) total score of Wilson’s disease was 5.7 (±2), and the highest and the lowest total scores were 0 and 10 respectively. Wilson’s disease can make neurological symptoms in affected patients through autonomic dysfunction. Types of symptoms (parasympathetic or sympathetic), their intensity, their correlation with clinical status, survival, Wilson’s score, and treatments have been discussed in several studies. It is important to note that dysautonomia is associated with various and sometimes dangerous disorders. Therefore, preventing, controlling, and treatment of such disorders can be beneficial for the patients and their family.

There was a positive correlation between Wilson’s score, and increased systolic blood pressure after tilting, increased heart rate, and systolic blood pressure after cold pressor test. However, such correlation was not statistically significant (P >0.05). In some of the studied patients, such factors were increased as the score increased and vice versa. The score had the highest positive correlation with systolic blood pressure after cold pressor test.

Wilson’s score was negatively correlated with increased heart rate in phase 2 of Valsalva maneuver, RR interval ratio of phase 4 to phase 2 of the maneuver, increased diastolic blood pressure, and increased heart rate after tilting. But this correlation was not statistically significant.

The defect in response to Valsalva maneuver in patients with Wilson’s disease may result from defects in baroreceptors, brain stem, beta 2 receptor reflex, and efferent pathways of vagus nerve reflex or cardiac sympathetic nervous system (Ref). Defects in Reflex Arc sensory neuron, and spinothalamic, suprapontine, and intrathalamic neural pathways could also affect the patients’ response to the cold pressor test.

**CONCLUSION**

Since there is a significant correlation between the severity of the disease based on the Wilson’s score and dysautonomia, the severity of ANS dysfunction is also correlated with the severity of the disease. So evaluation of ANS function can be used as an appropriate non-invasive test along with the Wilson’s score for better evaluation of the affected patients. This evaluation can especially be effective in patients with predominant neurological symptoms, in whom the disease is severe but Wilson’s score has not proportionally increased. To confirm the correlation between Wilson’s disease scoring system and autonomic symptoms, more multicentral studies with bigger sample size and more efficient control of confounding factors
is recommended. Performing a case-control study and comparing the Wilson’s scores of the affected patients with healthy controls can be beneficial in defining the sensitivity and specificity of Wilson index for predicting the patients’ outcome, and to correlate the severity of ANS involvement with prognosis of the disease. It can also help in more efficient decision making for therapeutic approaches.

**CONFLICT OF INTEREST:** None

**FUNDING:** None

**REFERENCES**

