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Prevalence of Wilson's disease in Kashmiri population: A tertiary care hospital-based assessment

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ABSTRACT

Background/Problem considered: The clinical symptoms and biochemical data are the most important factors in determining the diagnosis of Wilson's disease (WD). To reduce morbidity and mortality, it is required to establish the diagnosis effectively for its management. Therefore, the study aimed to determine the prevalence of WD and to measure copper and ceruloplasmin levels in the patients visiting Sher-i-Kashmir Institute of Medical Sciences, Srinagar (SKIMS).

Methods: It was a hospital-based observational descriptive study that lasted 5- years and involved a total of 1924 patients. Those subjects who visited the SKIMS (both in and out patient departments) with suspected Wilson's illness were included in the study.

Results: Out of 1924, males showed predominantly higher presentation than females (57.9% vs 42.1%). Out of 17 (0.8%) subjects initially suspected of having Wilsons's disease, only 02 subjects were actually positive for WD, and remaining 15 subjects were diagnosed with other illnesses. The overall median serum levels of copper and ceruloplasmin were 111ug/dl and 37 mg/dl respectively. However, the subjects with confirmed WD included 01 male and 01 female., Moreover these 02 patients diagnosed with WD, had serum ceruloplasmin levels as 13 and 10 mg/dl. The female subject was having positive history of WD, as her sibling had already died from this disease.

Conclusion: Serum copper and ceruloplasmin are still a better tool for diagnosis of the WD.

Introduction

Wilson's disease (WD), also named hepatolenticular degeneration is an inborn error of copper metabolism[1]. The disorder involves abnormal accumulation of copper in the liver, brain, kidneys, and other organs. Under normal conditions, most of the copper in plasma is contained in ceruloplasmin while "free" or (non-ceruloplasmin-bound) copper in plasma is low[2]. The dysfunction of the ATP7B protein leads to impaired biliary excretion of copper and thereby results in copper accumulation in the liver and extrahepatic tissues[2,3]. At the same time, plasma ceruloplasmin is typically lower than normal, and "free" copper becomes elevated. The manifold consequences of WD are highly variable with hepatic presentations more common in childhood, while neurologic presentations are usually diagnosed later[4].

World Health Organization (WHO) estimates that the global prevalence of WD is 1/10,000 to 1/30,000. The prevalence of WD is higher in China than in the West[5]. The prevalence is larger than expected, according to a recent large-scale genetic study[5]. The number

of patients living with the disease could significantly be underreported. Many cases of disability or death occur due to delays in timely diagnosis and treatment. So not only a comprehensive understanding of WD is required, but early diagnosis will also prove very beneficial for long-term prognosis[6,7]. The usual neurological or hepatic symptoms, low serum ceruloplasmin levels, the appearance of Kayser-Fleischer rings, and aberrant copper metabolism shown by laboratory tests make WD diagnosis simple. However, diagnosing WD in asymptomatic patients and people with only one of these signs is frequently difficult. Gene sequencing can give direct evidence for the diagnosis of WD, particularly in patients with unusual symptoms and those who are asymptomatic[8].

In India community-based WD incidence and prevalence studies are lacking, however in tertiary hepatobiliary centers, WD accounts for 7.6–19.7% of all paediatric liver disorders. Every year, 15 to 20 new cases of WD are reported in referral neurology facilities[9,10].

To the best of our knowledge, there has never been a single study in our population that could have provided a more accurate picture of the prevalence of WD. Because our community is geographically landlocked with distinct lifestyle and dietary patterns from the rest of the country, it would be fascinating to do a population-based study to provide more insight into WD for future effective disease management. More importantly, it presents there is no gold standard for diagnosis of WD, hence we decided to perform a hospital-based observational descriptive study of WD in Sher-i-Kashmir Institute of Medical Sciences (SKIMS) Srinagar, a tertiary care hospital.

Materials and Methods

Study Design: It was a five-year duration long retrospective study from 2015 – 2019 in which 1924 patients were included. The study was executed at SKIMS, Srinagar- a tertiary care hospital.

Subject selection: The subjects included those who visited SKIMS OPD and/or were admitted in different IPD sections of the hospital. All the subjects who were suspected of WD were included in the study and their Serum copper and ceruloplasmin levels were collected from the main Laboratory of Clinical Biochemistry, SKIMS. Other details like age, gender, recruitment section etc were collected from the database available in the Department of Clinical Biochemistry. The subjects who visited SKIMS OPD or were admitted to IPD sections for other than WD diseases were excluded from the study.

Biochemical investigations: Measurement of Serum copper and serum ceruloplasmin was done initially by a manual kit-based method. The manual method was later replaced and done with a fully automatic Biochemistry analyzer (Beckman coulter AU5800) via the Turbidimetery method.

Ethical Clearance: Institutional ethical clearance was not required as per the study design. We collected the data from the already available database in our department. The data include of those subjects who were advised by the doctor for copper and ceruloplasmin testing for diagnostic purposes.

Statistical analysis

The data was analyzed by using SPSS v26 and STATA 16 software. The data was not normally distributed, represented as median and percentages (for categorical data). Non-parametric Mann-Whitney test was used to obtain a *p*-value.

Results

In this 5-year study, a total of 1924 participants were enrolled, of which 1114 (57.9%) were males and 810 (42.1%) were females. 17(0.8%) patients had ceruloplasmin levels <20mg/dl. Out of 17 subjects initially suspected of having WD, 15 subjects were diagnosed with other illnesses related to the liver, rheumatoid arthritis, anemia, nervous system, and other health issues at later stages of study progression. These patients had a median serum ceruloplasmin level of 16 mg/dl. However, 2 patients (01 male and 01 female) diagnosed with WD, had serum ceruloplasmin levels of 13 and 10 mg/dl, for a male and female respectively. Moreover, the female was pre-symptomatic however, Wilson's sickness had already claimed the life of one of her siblings.

The overall median serum level of copper and ceruloplasmin was 111µg/dl and 37 mg/dl respectively. Male patients documented copper and ceruloplasmin levels was 110µg/dl and 37mg/dl, while as in females, the level was documented as 116 ug/dl for copper and 37mg/dl for ceruloplasmin. Furthermore, the ceruloplasmin level was found to be the same across the gender groups (Table 1).

Copper profile in patients with Wilsons, liver, neurological, and other disorders

Serum copper concentrations were also determined in the 17 patients whose median serum ceruloplasmin level was less than 20 mg/dl. The mean or median copper concentration in two patients with confirmed WD was 25.2 µg/dl. The median serum-free copper values for 15 people with liver, nervous system, and other disorders were 44 µg/dl, respectively.

Table 1: Gender wise distribution of ceruloplasmin levels among study subjects

	Copper		
Gender	**N**	**Mean Rank**	**p-value**
Male	1114	927.26	<0.001
Female	810	1009.83	
	Ceruloplasmin		
Male	1114	941.32	<0.05
Female	810	991.62	

On further stratification, it was observed that 1.7% (n= 33) subjects had both copper and ceruloplasmin levels lower than the normal range, whereas 82.4% (n=1585) corresponding to a maximum number of subjects, had serum levels of both the markers in the normal range. A statistically significant association was found between gender and serum copper ***(p-value <0.001)*** (Table 2).

A strong relationship between persons suspected of having WD and those with undetermined disease status was discovered after further categorization based on illness state.***(p-value<0.05).***

In addition, a statistically significant relationship was observed between patients suffering from various diseases other than WD ***(p-value< 0.001***), as shown in (Table 2). Moreover, a weak positive correlation was also obtained between serum copper and ceruloplasmin level ***(r=0.428, p-value<0.001)*** **Figure 1.**

Discussion

Scheinberg and Sternlieb published the first estimate of WD prevalence in 1984. It was the first study to suggest a figure of 1:30,000. However, due to the limited available data at that time, a number of positive cases were overlooked in the study[11]. The data relating to this disease was re-evaluated in 2020 by Dr. Tea Lund Laursen et al [13], and a total of 59 studies were evaluated. Despite the fact that genetic prevalence was shown to be 3-4 times greater than clinical findings in several population-based investigations, the overall estimate of illness prevalence of 1:30,000 - 1:50,000 was determined to be valid for the United States, Europe, and Asia and was as per the 1984 findings[11]. The first study on mortality from Wilson's illness was conducted in 2005, and it was an 11-year observational study in which 164 WD patients were observed for 11 years of which 20 (12.5%) died. Despite the treatment, the majority of the deaths were caused by liver and brain problems[12].

Table 2: Gender wise distribution of copper and ceruloplasmin levels among study subjects

		Ceruplasmin		
		Low (%)	Normal (%)	
copper	Low (%)	33(1.7)	303(15.7)	Chi2(1),140.2; p-value<0.001
	Normal (%)	3(0.2)	1585(82.4)	

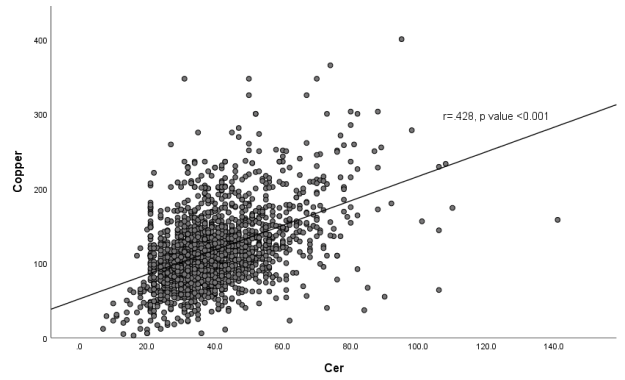

Figure 1: Correlation between serum copper and ceruloplasmin levels

In the present study, we considered it important to evaluate the levels of serum ceruloplasmin and free copper. Our study revealed that in our population 82.4% of the patients were found to have normal values of these markers. Only 33 (1.7%) of the total subjects were those having low ceruloplasmin and copper levels. Among 33 patients, the initial diagnosis of 13 patients was not available at the time of the study, because they were not admitted to the hospital, and were registered in the OPD section. Therefore, the follow-up of the patients was not possible. However, among the remaining 17 patients 2 patients were diagnosed with WD disease, and the other 15 patients were later diagnosed with liver, neurological diseases and followed on a regular basis.

In the two WD confirmed cases, we found low serum ceruloplasmin 11.5mg/dl and low free serum copper concentration 25.2µg/dl. Similar findings were reported in many studies conducted elsewhere[13,14]. Other 15 patients who were diagnosed with various liver and neurological diseases were also found to have low levels of serum ceruloplasmin and copper, which is a well-known fact now as copper gets deposited in the liver and various organs, because of low or absence of ceruloplasmin in serum as reported in a previous study[15].

Further we noted that females had more copper levels than men. The comparison was statistically significant (p value<0.005), however, the distribution of ceruloplasmin levels between gender groups did not show a comparable difference and neither has any study given any conclusive findings regarding serum copper and ceruloplasmin level with gender variation. A weak positive correlation was also noted between overall serum ceruloplasmin and copper concentration (r=0.428, p<0.001).

Table 3: Distribution of copper levels among subjects other than WD

Parameter	N	Mean Rank (Cu)	P -value	Mean Rank (Ce)	P -value
Wilsons's disease	2	3.00	>0.05	2.25	>0.05
Liver disease	3	3.00		3.50	
Suspected Wilson disease	15	127.47	0.001	22.40	0.001
Final disease status not available (OPD)	1903	966.06		967.39	
Liver disease	3	63.83	0.005	39.83	0.004
Final disease status not available (OPD)	1904	954.90		955.44	

When we compared ceruloplasmin and copper levels in patients with WD with those having liver disease, there was no statistically significant difference; however, when we compared patients with liver and suspected WD to patients with unknown disease status, there was a statistically significant difference (p= 0.005).

The disease condition of many patients was not known to us. If the disease status of those patients had been known, it would have been one of the study's strengths, but as the study went on, we lost track of them because the bulk of them were in the OPD and not admitted to wards, making it impossible to follow them.

Limitations of the study

The research included some flaws, keeping the sample size and prevalence of Wilson's illness in mind, determining the specificity and sensitivity of ceruloplasmin and copper to detect WD and further distinguish it from other diseases was not possible. Moreover, the amount of copper excreted in the urine was not assessed, and the follow-up treatment may have been far more effective.

Conclusion

To summarise, copper and ceruloplasmin are still superior diagnostic tools for Wilson's illness. However, the goal of this study was to assess the prevalence rather than to make a clinical diagnosis. Although we are first time reporting WD in the study population, it is too early to make any concrete inferences. A study with a larger sample size and full WD profile including 24-urinary copper analysis is of paramount importance to arrive at any conclusion regarding the prevalence and WD and prognostic importance of WD.

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Data availability: The data can be shared only on genuine request.

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