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INSIGHTS FROM SERUM CERULOPLASMIN AND COPPER VALUES OF PATIENTS AT A NATIONAL, TERTIARY CARE CENTRE FOR NEUROLOGICAL AND PSYCHIATRIC DISORDERS

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ABSTRACT

Background: Serum ceruloplasmin is a copper-containing ferroxidase and an acute-phase reactant. The most well-known cause for low levels of serum ceruloplasmin is probably Wilson's disease (WD). The other likely conditions include chronic liver disease, protein-losing disorders, copper deficiency, Menkes disease, hereditary aceruloplasminemia, etc. What is perhaps not well known is that some neuro-psychiatric conditions also present with low levels of serum ceruloplasmin. Since the symptoms of WD overlap with neuro-psychiatric disorders, there could be diagnostic dilemmas.

Aim: The reference interval for serum ceruloplasmin in healthy adults is 20-40 mg/dL. For WD, various lower limit reference interval cut-offs have been proposed, each with different sensitivity and specificity. This study aims to provide a cut-off value that will be diagnostic for WD in Indians presenting with neuro-psychiatric complaints.

Materials and Methods: This is a retrospective study using a laboratory database to establish reference intervals for serum ceruloplasmin and copper. Collected data included serum copper and ceruloplasmin test results of all patients between March 2013 to March 2014 collected from the Clinical Biochemistry Unit (under Department of Neurochemistry) at NIMHANS, Bengaluru. Data of 370 patients presenting with neuro-psychiatric conditions were collected. Healthy controls were not included. Reference intervals were established by the non-parametric method using percentiles (2.5th to 97.5th percentile) as recommended by CLSI (Clinical and Laboratory Standards Institute). IBM SPSS Statistics 21software was used for statistical analysis, which included chi-square test, Pearson correlation, P value, mean, sensitivity, specificity, etc. Copper and ceruloplasmin were analysed on the Beckman Coulter AU680 autoanalyser.

Results: In the WD group (107 patients), 77.5% had <5 mg/dL of serum ceruloplasmin. The 95% reference interval was <5 to 13.5 mg/dL. The mean serum copper was 29 µg/dL.

In patients with non-WD neuro-psychiatric disorders (263 patients), the 95% reference interval for serum ceruloplasmin was 14.4 to 31.7 mg/dL. The mean serum copper was 115 µg/dL.

Conclusion: The study data suggest that a serum ceruloplasmin of 14 mg/dL may be used as a WD diagnostic cut-off among Indian patients with neuro-psychiatric conditions, as it is 100% sensitive and 99% specific.

Keywords: Adenosine Triphosphatase, copper-binding protein, Dystonic Disorders, Mental Disorders, Seizures.

INTRODUCTION

Serum ceruloplasmin is a multifunctional protein. It is the main copper-binding glycoprotein accounting for 40-70% of total plasma copper, but it is not an essential copper transporter.[1,2] The other major copper-binding proteins in the blood include albumin (10-15%) and transcuprein/ α2 macroglobulin (5-15%). Both ceruloplasmin and transcuprein are seen in the α2 globulin band in serum protein electrophoresis.[2]

Ceruloplasmin is a member of the multicopper oxidase family, which utilizes copper to couple substrate oxidation. Therefore, it is the principal ferroxidase in the blood and helps transfer ferric iron to transferrin.[3] Ceruloplasmin is an acute-phase reactant that plays roles in antioxidant defence, the oxidative inactivation of nitric oxide, and the regulation of biogenic amines.[4]

Copper is an essential micronutrient that serves as a cofactor for many key metabolic enzymes, including cytochrome c oxidase, superoxide dismutase, ferroxidase (as part of proteins such as ceruloplasmin and hephaestin), tyrosinase, dopamine-β-hydroxylase, lysyl oxidase (for collagen synthesis), and monoamine oxidases (MAOs). Therefore, for optimal functioning of the biochemical processes, a normal level of systemic copper needs to be maintained.[5]

The largest contributor to copper in the serum is ceruloplasmin, and since copper is required to stabilize the structure of ceruloplasmin, the two influence each other's serum levels. Thus, the serum values change when either of these two components is affected. For example, pregnancy is associated with an increase in serum ceruloplasmin and hence serum copper, whereas dietary deficiency of copper leads to a decrease in both copper and ceruloplasmin levels.[6,7]

The commonly followed adult reference intervals for serum ceruloplasmin and copper are as follows: for serum ceruloplasmin, it is 20-40 mg/dL, for copper, it is 70-140 µg/dL (adult male) and 80-155 µg/dL (adult female).[8]

The most well-known cause for low levels of serum ceruloplasmin is probably Wilson's disease (WD). The other likely conditions include chronic liver disease, protein-losing disorders, copper deficiency, Menkes disease, hereditary aceruloplasminemia, etc. What is perhaps not well known is that some neuro-psychiatric conditions also present with low levels of serum ceruloplasmin. Since the symptoms of WD overlap with neuro-psychiatric disorders, there could be diagnostic dilemmas.[9]

In Wilson's disease (WD), serum ceruloplasmin is significantly reduced due to a genetic defect in the ATP7B gene, which encodes a copper-transporting P-type adenosine triphosphatase (ATPase) in the liver that functions to incorporate copper into ceruloplasmin and release it into the blood, and to remove excess copper by secreting it into the bile. Deficiency of ATP7B results in copper accumulation in the liver and also affects copper incorporation into ceruloplasmin, leading to its shorter half-life with rapid destruction. Consequently, there is excess circulating free copper, which accumulates in the liver and other organs, leading to complications of WD.[9]

The objective of this study is to analyze the trend of serum ceruloplasmin and copper levels among patients of a tertiary care, national-level neuro-psychiatric hospital. This is important because such data has not been adequately found in the literature for India. Data from a large Chinese study on the role of ceruloplasmin in the diagnosis of WD showed that the conventional cut-off of 20 mg/dL was associated with low specificity and a large number of false positives. They compared the serum ceruloplasmin in patients with WD and without WD and found that ceruloplasmin values less than the 20 mg/dL cut-off were found in neurologic, hepatic, nephrotic, and other disorders.[10]

Through a data distribution analysis of serum ceruloplasmin and copper values, the results of this study will help redefine the lower limit WD serum ceruloplasmin cut-off for Indian patients with neuro-psychiatric ailments. This is important since the symptoms of WD are often neurologic. This study could be expanded through further research.

MATERIALS AND METHODS

Study design: A retrospective study done to establish the reference interval among Indian patients visiting a tertiary-level neuro-psychiatric hospital. The study utilized the existing laboratory/ hospital database to arrive at the reference interval values for serum ceruloplasmin. Correlation of serum ceruloplasmin with serum copper was also done.

Setting and duration of study: The study was done at the Clinical Biochemistry Unit (under the Department of Neurochemistry) at NIMHANS, Bengaluru. Data were collected for all patients for whom both serum ceruloplasmin and copper were measured between March 2013 and March 2014. There were no ethical issues, and the institution approved it. Patient confidentiality was maintained throughout. There was no risk involved for the patients as the tests were done as part of their diagnostic work-up and not specifically for this study.[11] All the serum ceruloplasmin and copper data were tabulated between January and March 2014. Data analysis was done in 2025.

Inclusion and exclusion criteria: The subjects included patients presenting with various neuro-psychiatric complaints, including established cases of WD (diagnosed with the help of the WD Leipzig scoring system), who were screened with serum ceruloplasmin and copper tests. Data were included only if both serum ceruloplasmin and copper estimations were performed. Healthy controls were not included; with the study aim being to establish the

serum ceruloplasmin reference interval among non-WD neuro-psychiatric disorder patients.

Sample size: The total number of patient samples in whom both serum ceruloplasmin and copper were estimated was 370. This included both male and female patients in the age group range of 1-75 years.

Adequacy of sample size: For a retrospective study establishing a reference interval, the Clinical and Laboratory Standards Institute (CLSI) guideline EP28-A3c recommends a minimum sample size of 120 subjects.[12] A sample size greater than 120 has a confidence interval (CI) of 90%, while a sample size greater than 153 has a CI of 95%.[13] Therefore, the sample size of 263 patients with non-WD neuropsychiatric conditions in this study is adequate for establishing the reference interval for serum ceruloplasmin for this category of patients.

Methodology to estimate serum ceruloplasmin and copper: Serum ceruloplasmin was analysed using the ceruloplasmin kit (catalogue number: OSR6164) from Beckman Coulter (Beckman Coulter, Inc., USA) on the AU680 Clinical Chemistry Analyser (Beckman Coulter Inc., USA). The test employs the principle of immuno-turbidimetry utilising anti-human ceruloplasmin antibodies.[14] For serum copper, the Randox Copper assay kit (Randox Laboratories Ltd., UK) was used (catalogue number CU2340 for the assay kit and CAL2351 for the calibrator).[15] The test was programmed on the Beckman Coulter AU680 autoanalyser. It is a colourimetric assay based on the following principle: at pH 4.7, copper, which is bound to ceruloplasmin, is released by a reducing agent. It then reacts with a specific colour reagent, 3.5-Di-Br-PAESA 4-(3,5-Dibromo-2-pyridylazo)-N-Ethyl-N-(3 sulphopropyl) aniline, to form a stable, coloured chelate. Quality control (QC) was performed each time before processing the serum samples. QC materials used were assayed multi-sera (for copper), and specific protein control (for ceruloplasmin) from Randox Laboratories Ltd., UK.

For the statistical analysis, IBM SPSS Statistics 21 software was used. The Chi-square test, Pearson correlation, measures of significance (P-value, with a value <0.05 considered significant), mean, estimation of sensitivity & specificity of reference interval, etc., were employed. The non-parametric method using percentiles (2.5th to 97.5th) was employed to establish the 95% reference interval for serum ceruloplasmin, as recommended by the CLSI guideline EP28-A3c.

RESULTS

In all, the collected data included serum ceruloplasmin and copper values for 370 subjects. The age and sex distribution of the patients is shown in Table 1. The age group ranged from 1 to 75 years. Of the 370 patients, 232 were male and 138 were female. Among them, 107 patients had WD, while the remaining 263 patients had non-WD neuropsychiatric conditions. Healthy controls were included in this study.

Of the 107 WD cases, 70 were male and 37 were female. This has been represented in Table 2. Diagnosis of WD was based on the clinical, laboratory, and radiological findings, including the Leipzig score.[16] All patients presenting with WD were within 40 years of age. Table 3 is an age and sex-wise representation of patients with non-WD neuro-psychiatric conditions.

Table 4 is a further stratification of the age and sex-wise data based on serum ceruloplasmin levels.

Table 1: Age and sex composition of the patients in the study (total 370 patients)

Age group in years	Number of samples	No. of Males	No. of Females
1-10	54	32	22
11-15	72	43	29
16-20	56	40	16
21-40	142	86	56
41-75	46	31	15
Total	370	232	138

Table 2: Age and sex composition of Wilson's disease patients (total 107 patients)

Age group in years	Number of samples	No. of Males	No. of Females
1-10	10	4	6
11-15	29	18	11
16-20	22	17	5
21-40	46	32	14
41-75	0	0	0
TOTAL	107	71	36

Table 3: Age and sex composition of patients with non-WD neuro-psychiatric disorders (total 263 patients)

Age group in years	Number of samples	No. of Males	No. of Females
1-10	44	28	16
11-15	43	25	18
16-20	34	23	11
21-40	96	54	42

41-75	46	31	15
TOTAL	263	161	62

Table 4: Age and sex-wise distribution of serum ceruloplasmin and copper (370 patients)

Age in yrs	Ceruloplasmin (mg/dL)	Corresponding average Copper value (µg/dL)	No. of Males	No. of Females
1-10 n=54	<5	17	3	4
	5-15	65	2	2
	15-20	98	6	-
	20-30	141	18	12
	30-40	184	2	4
	40-45	241	1	-
11-15 n=72	<5	20	16	10
	5-15	68	3	1
	15-20	107	10	9
	20-30	135	14	9
	30-40	-	-	-
16-20 n=56	<5	18	10	5
	5-15	61	11	-
	15-20	91	11	3
	20-30	132	7	7
	30-40	204	1	1
21-40 n=142	<5	21	23	11
	5-15	57	14	4
	15-20	100	25	15
	20-30	129	24	24
	30-40	160	-	2
41-75 n=46	<5	14	1	-
	5-15	73	2	-
	15-20	101	13	8
	20-30	138	15	7
	30-40	-	-	-

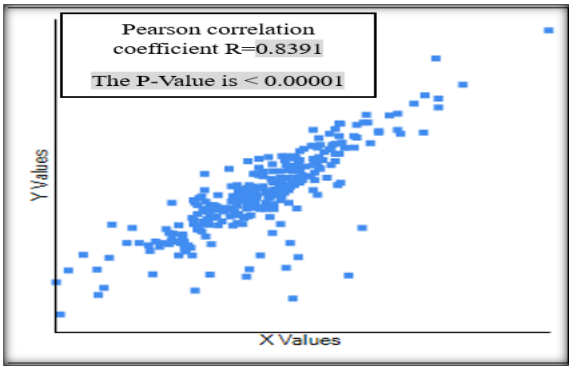

Figure 5: Correlation between serum ceruloplasmin and copper values (Serum Ceruloplasmin has been plotted on the X-axis and serum Copper on the Y-axis).

Figure 5 is a scatter diagram displaying the correlation between the serum ceruloplasmin and copper levels, and shows a very strong positive linear relationship between serum ceruloplasmin and copper (Pearson correlation coefficient R=0.8391 with P-Value < 0.00001).

Since normal healthy adult females usually have higher levels of ceruloplasmin as compared to healthy adult males,[17] the effect of sex on serum ceruloplasmin level was examined in our group of patients through the Chi-square test, as shown in Table 6. The data show no statistically significant difference between adult male and female ceruloplasmin levels among WD and non-WD patients with neuro-psychiatric symptoms.

Table 6: Correlation between sex and ceruloplasmin level among different age groups

AGE GROUP	Ceruloplasmin (mg/dL)	SEX		Total	P value
		F	M		
1-10 yrs	<10	4	3	7	**0.26**
	10-20	2	8	10	
	>20	16	21	37	
	Total	22	32	54	
11-20 yrs	<10	16	28	44	**0.26**
	10-20	12	33	45	
	>20	17	22	39	
Total		45	83	128	
21-40 yrs	<10	12	28	40	**0.07***
	10-20	18	34	52	
	>20	26	24	50	
Total		56	86	142	
>41 yrs	<10	0	1	1	**0.76**
	10-20	8	15	23	
	>20	7	15	22	
Total		15	31	46	
TOTAL		138	232	370	

**P-value <0.05 is considered significant*

Since the objective of this study is to find the optimal cut-off of serum ceruloplasmin to diagnose WD among patients with neuro-psychiatric symptoms, a ceruloplasmin reference interval specific to this group was established. This was done following the Clinical and Laboratory Standards Institute (CLSI) EP28-A3c document, which contains guidelines for determining reference values and reference intervals for quantitative clinical laboratory tests and is a guideline for global application developed through the Clinical and Laboratory Standards Institute consensus process [18]. The document also states, "One can use existing patient samples, even from subjects not known to be healthy". This premise was used to establish a reference interval using the CLSI guideline, according to which a minimum of 120 subjects per homogeneous subgroup is required for a nonparametric approach. The lower reference limits are estimated as the 2.5th percentile and the upper limits as the 97.5th percentile (corresponding to a 95% reference interval) of the distribution of test results for the reference population. The document also states that a sample size greater than 120 has a confidence interval (CI) of 90%, while a sample size greater than 153 has a CI of 95%. The sample size used here is 263 (number of non-WD neuro-psychiatric disease patients). Using this method, the reference interval (RI) for serum ceruloplasmin in this group was 14.4 to 31.7 mg/dL, and the mean value for serum copper was 115 µg/dL. Among the WD patients, 77.5% had <5 mg/dL of serum ceruloplasmin. The 95% reference interval was <5 to 13.5 mg/dL, and the mean value for serum copper was 29 µg/dL (most patients with WD were on copper chelation therapy).

The conventional serum ceruloplasmin lower limit cut-off among healthy adults is 20 mg/dL. While values <10 mg/dl strongly favour the diagnosis of WD, the values between 10-20 mg/dL have varying levels of sensitivity and specificity in diagnosing WD. The data from this study give the following sensitivity and specificity percentages.[Table 7]

Table 7: Sensitivity and specificity of ceruloplasmin cut-off value for Wilson's disease

Ceruloplasmin Cut-Off	Sensitivity %	Specificity%
20 mg/dL	100	56
10 mg/dL	86	100
14 mg/dL	**100**	**99**

As the upper limit of ceruloplasmin RI for WD and the lower limit of RI for non-WD neuro-psychiatric disease patients are both near 14 mg/dL, this value was chosen as the cut-off value as it has very high sensitivity and specificity.

DISCUSSION

Serum ceruloplasmin levels are lower in patients with non-WD neuro-psychiatric disorders as compared to healthy individuals, as has been demonstrated in the results of this study. The reference interval was found to be between 14.4 to 31.7 mg/dL with a WD cut-off of 14 mg/dL. Why the serum ceruloplasmin levels are lower in neuro-psychiatric conditions other than WD is not clearly known, though ceruloplasmin has been linked to neurodegenerative disorders through its role in copper and iron metabolism and as an antioxidant.[19,20] The results of this study also demonstrate that it is possible to differentiate between WD and other non-WD neurological conditions using a serum ceruloplasmin cut-off value of 14 mg/dl.

The well-known diseases associated with low ceruloplasmin include aceruloplasminemia, Menkes disease, Wilson's disease, severe liver or kidney disease, malnutrition or malabsorption.[21] This study highlights the lesser-known cause of low ceruloplasmin, i.e. non-WD neuro-psychiatric conditions. The most common early signs of WD include ataxia, dysarthria, hypersalivation, and personality changes. Later manifestations include dystonia, choreoathetosis, tremors, seizures, and Parkinsonism.[22] Since many signs and symptoms are common for both WD and certain neurological and psychiatric disorders, such patients were screened for WD as part of the diagnostic workup.

The findings of our study are similar to two large-scale Chinese studies.[10,23] The study by Yang Y et al retrospectively compared the ceruloplasmin levels of a large group of WD cases with three other groups: healthy subjects, heterozygous relatives of patients with WD and patients with various diseases other than WD, which included patients with hepatic dysfunction, neurological deficits, and other diseases. Among the patients with neurological deficits, lower than 20 mg/dL of serum ceruloplasmin was seen in conditions such as Parkinsonism, cerebral palsy, epilepsy, movement disorders like ataxia, dystonia, Huntington's disease, and mental (psychiatric) disorders. They established that a serum ceruloplasmin cut-off for differentiating WD from other conditions was 13 mg/dL.

Another study by Kelly D et al on 'The Clinical Utility of a Low Serum Ceruloplasmin Measurement in the Diagnosis of Wilson Disease' found that lowering the serum ceruloplasmin reference range to 14 mg/dL would have improved the test's performance without adversely impacting sensitivity.[24] This finding is in agreement with the results of the present study.

Salman HM et al, in their systematic review article on biochemical testing for the diagnosis of WD, analysed studies where the cut-off's were defined by

the Leipzig criteria. When using a cut-off of 20 mg/dL, a sensitivity of 77.1%–99% was achieved, and the specificity ranged from 55.9% to 82.8%. With the 10 mg/dL cut-off, the sensitivity ranged from 65% to 78.9%, whereas the specificity ranged from 96.6% to 100%. Accordingly, the highest sensitivity and specificity cut-off was suggested to be somewhere between 14 and 20 mg/dL.[25]

Limitation of this study: Inability to do a disease-wise reference interval calculation for specific neurological and psychiatric conditions, as the numbers were not statistically significant. No attempt was made to calculate the NCC copper or copper: ceruloplasmin ratio in WD cases, as the majority of patients were on chelation therapy.[26]

CONCLUSION

The majority of Indian patients with WD presented with a ceruloplasmin level <5 mg/dL. For patients with non-WD neuro-psychiatric disorders, the 95% reference interval for serum ceruloplasmin was 14.4 to 31.7 mg/dL. The mean serum copper was 115 µg/dL.

Serum ceruloplasmin of 14 mg/dL may be used as a WD diagnostic cut-off among Indian patients with neuro-psychiatric conditions, as it is 100% sensitive and 99% specific.

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