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Original Article

Serum copper and ceruloplasmin levels in systemic sclerosis and various types of morphea in the Kashmir Valley

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Abstract

Objective To find the serum copper and ceruloplasmin levels in patients of systemic sclerosis and morphoea in the Kashmir Valley.

Methods This was a cross sectional study conducted in the department of dermatology of SKIMS Medical College over a period of one year involving 12 patients of systemic sclerosis and morphea and equal number of healthy controls. All the individuals were taken up for serum copper and ceruloplasmin levels.

Results In patients with systemic sclerosis, the mean levels of copper and ceruloplasmin were increased. No alterations were found in patients with morphea and healthy controls.

Conclusion The increase in serum copper is probably secondary to increase in ceruloplasmin level, which occurs as a nonspecific response to inflammation.

Key words
Systemic sclerosis, morphea, copper, ceruloplasmin.

Introduction

Abnormalities of serum copper and ceruloplasmin concentrations have been described frequently in patients of rheumatoid arthritis, ankylosing spondylitis, systemic sclerosis and morphea.[1,2] Since certain enzymes necessary for the synthesis of collagen are copper dependent, we thought it relevant to study the serum copper and ceruloplasmin in patients with systemic sclerosis and morphea, the two diseases which are not uncommon in the valley.

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Methods

The study was conducted in the departments of dermatology and biochemistry, SKIMS Medical College. Twelve patients of systemic sclerosis and various clinical types of morphea attending dermatology OPD were taken up for study. An equal number of healthy, age- and gender-matched controls were included in the study. Selection of the patients was done only after obtaining written informed consent. Clearance was obtained from the institutional ethical committee.

Exclusion criteria for the study group included patients suffering from any malignancy, decubitus ulcers, psoriasis, thyrotoxicosis, neurological diseases, rheumatoid arthritis and pregnancy. Detailed history was recorded and thorough clinical examination performed. A

proper history related to age, gender, residence, onset of illness and progression was taken. Patients were specifically asked for the history suggestive of connective tissue disorders like Raynaud's phenomenon, perniosis, dysphagia, breathlessness and renal symptoms like oliguria and puffiness of face. Based on history and clinical examination patients were grouped as: progressive systemic sclerosis, linear morphea, en coup de sabre, and pansclerotic morphea.

Serum copper measurement

Five milliliters of venous blood was collected in heparinized metal free polypropylene tubes in the fasting state from all subjects. Samples were centrifuged at 1500rmp for 10 minutes to separate the plasma that was diluted with an equal volume of 20% TCA to precipitate the proteins. The supernatant was then directly aspirated into GBC 902 double beam atomic absorption spectrophotometer for copper measurements.[3] Analytical reliability was determined by analyzing quality control sera obtained from Randox Lab Ardmore, UK.

Measurement of serum ceruloplasmin

Serum ceruloplasmin activity was measured according to the method of Sunderman Jr. and Nomoto.[4] The activity was measured as phenylenediamine oxidase activity of ceruloplasmin, with the spectrophotometer at 530nm wavelength. Mean concentration of ceruloplasmin in serum from healthy subjects was 27.5±0.041mg/dl with a range of 15-41.0 mg/dl.

Results

The age, gender distribution, clinical variants and serum values are shown in **Tables 1-3**. In the systemic sclerosis patients the serum copper was higher than in the controls. In morphea group, except for one pansclerotic variant, the levels did not differ from the controls. Ceruloplasmin levels were increased in systemic sclerosis patients but not in the morphea group. The highest ceruloplasmin levels were associated with the highest copper levels.

Table 1 Clinical characteristics, serum ceruloplasmin levels and copper levels in the study population.

Age (years)	*Gender*	*Clinical type*	*Serum ceruloplasmin (mg/dl) [Reference range 20-50]*	*Serum copper (µmoles/litre) [Reference range 11-25]*
36	F	Systemic sclerosis	66	37
3	M	Pansclerotic	55	30
8	F	En coup de saber	22	23
16	F	En coup de saber	39	19
18	M	Linear morphea	21	15
11	F	Morphea	20.6	17
30	F	Systemic sclerosis	57	29
8	F	Linear morphea	35	22
16	F	Linear morphea	44	14
18	F	Morphea	36	17
19	F	Linear morphea	27	12
22	F	Linear morphea	29	20

Table 2 Correlation of raised serum copper with systemic sclerosis and morphea.

Copper levels (µmoles/litre	*Morphea*	*Systemic sclerosis*
> 25	1	2
< 25	9	0

Table 3 Correlation of raised serum ceruloplasmin with systemic sclerosis and morphea.

Ceruloplasmin level	*Morphea*	*Systemic sclerosis*
< 50 mg/dl	9	0
> 50 mg/dl	1	2

Discussion

The fibrotic component of systemic sclerosis is believed to be due to the stimulation of fibroblasts by certain cytokines and growth factors and more recently due to connective tissue growth factor (CTGF).[5] Both collagen and elastin are fibrous proteins which require the formation of intermolecular crosslinks for their stability.[6] These crosslinks are formed by oxidative deamination of lysine oxidases which are copper dependent. Animals fed on copper deficient diets develop skeletal abnormalities and defects in vascular elastic tissue.[7]

After intestinal absorption small amount of plasma copper binds to albumin and gets transported to the liver. When released from the liver, copper specifically binds to a protein ceruloplasmin. The level of serum copper is therefore directly related to the level of ceruloplasmin.[1] The normal ranges of serum copper and ceruloplasmin are 11-25 µmoles/liter and 20-50 mg/dl, respectively.

Ceruloplasmin is one of the so called acute phase reactants which increase non-specifically in response to acute inflammation and it seems very likely that in our patients raised serum copper was a secondary result of high levels of caeruloplasmin rather than a primary disturbance of copper metabolism. This may also explain the raised levels in rheumatoid arthritis although increased urinary excretion of copper in the presence of normal plasma level has been reported in this condition.[2]

The mechanism and purpose of acute phase response are unknown but copper may have anti-inflammatory role, so that raised copper levels are actually protective in function, inhibiting production of the inflammatory prostaglandins like PGE2 and perhaps stimulating anti-inflammatory prostaglandin PGF2.[7] Sorenson has also produced evidence that copper enhances the anti-inflammatory properties of aspirin and other anti-inflammatory drugs.[8]

Our study revealed that serum copper and ceruloplasmin although raised in systemic sclerosis patients and also slightly higher in pansclerotic variants of morphea are otherwise not different from the controls. However, a larger sample number/study group is required to find out any definite relationship between serum copper and ceruloplasmin levels and systemic sclerosis plus different clinical variants of morphea.

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