Original Article

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The Relationship between Serum Copper Level with Cognitive Disorders in Elderly

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ABSTRACT

BACKGROUND AND OBJECTIVE: Copper is a metal element which plays a pivotal role in the pathology of various neurological disorders including cognitive disorders. Previous studies have shown different relationships between serum levels of copper and cognitive impairment. This study aimed to investigate the relationship between serum levels of copper and cognitive disorders in the elderly in Amirkola.

METHODS: This cross-sectional study is a part of Amirkola Health and Ageing Project performed on all the population is 60 years and older. According to the Mini-Mental State Examination (MMSE), people were divided into two groups with impaired cognitive status (N=347) and normal (N=657). People with cognitive impairment were classified in mild, moderate, severe subgroups. In this test, point more than or equal to 25 (30-25) was considered as natural and score less than 25 as a person with cognitive impairment. Serum copper level was measured in venous blood samples and was compared between two groups.

FINDINGS: In this study, of 1616 elderly people, 1004 people in the age group 60-90 years were examined. 518 men and 486 women were existed with a significant difference in serum level of copper between the sexes ($p<0.0001$). The average serum level of copper in people without cognitive impairment (129.43±54.83) was different from an average copper level in patients with cognitive impairment (135.06±57.38), but was not statistically significant. There was a significant difference in serum levels of copper in the MMSE subgroups ($p=0.009$).

CONCLUSION: The results showed that cognitive impairment is associated with serum levels of copper.

KEY WORDS: *Cognitive Disorders, Elderly, Serum Level of Copper.*

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Introduction

Cognitive disorders based on the International Classification DSM-IV-TR are a group of neuro-psychiatric disorders basically influence on learning, memory, perception and problem solving (1, 2). Considering that the elderly population (aged 60 years and above) is increasing globally (5-3), cognitive disorders as major problems are necessary to be prevented and managed (6, 7). Several factors were introduced in the development or progression of cognitive disorders, including chronic diseases (diabetes), metabolic syndrome, diet status, serum folate and metals (8).

In previous studies, the relationship between body metal balances with progression of cognitive impairment has been assessed, and new approaches were obtained in the field of balance of these metals interfering with nerve damage and its progression, increase in aluminum, iron, copper and reduction of manganese, zinc and selenium can be found in patients with cognitive disorders (particularly dementia) (9, 10). Neuroactive elements such as copper can be released in synapses during neuronal activity (11). In several studies, serum copper status was evaluated in cognitive disorders among the elderly (23-12). In a study, it was announced that divalent copper in contrast to univalent copper that can be found in food, is not absorbable.

After copper absorption from the digestive system to the liver, a part of divalent copper bypasses the liver system and goes directly into the blood. In this study appears to confirm that the accumulation of copper in the brain is involved in cognitive disorders and also leads to oxidative damage in the brain. Some meta-analyzes show that levels of non-ceruloplasmin-bound copper (which is defined as the free copper), is higher in patients with Alzheimer's disease than healthy patients (23, 15).

In a study, it was shown that serum free copper considered as an important factor for converting of mild cognitive impairment to Alzheimer's disease and for each micromoles per liter of serum free copper results in approximately 20% increased risk (15). In another study, no significant differences was observed in serum levels of copper group who has Alzheimer's disease compared with control subjects (21). Given that different results were obtained regarding to relationship between serum levels of copper in cognitive disorders in various studies, as well as, because the serum level of copper status and its association with cognitive impairment has been evaluated in Iran in very limited level (24), this study aimed to investigate the relationship between serum levels of copper and cognitive disorders in the elderly people of Amirkola.

Methods

This study is a part of a comprehensive plan to evaluate the health status of elderly people of Amirkola (25) which was done during 2010-2011 years on 1616 elderly individuals (60 years or older) after the approval of the ethics committee of Babol University of Medical Sciences.

Elderly patients with hypothyroidism and diabetes, multiple sclerosis, congestive heart failure, drug abuse and drugs affecting copper metabolism such as anticonvulsants, contraceptives, glucocorticoids and those with incomplete records were excluded from study. Of the total cases, 1004 patients were eligible for inclusion in the study, which were divided into two groups with cognitive impairment (N=347) and without cognitive impairment (N=657) according to the Mini-Mental State Examination (MMSE) score. MMSE is a clinical applied short questionnaire with 30 points which is used to screening of cognitive impairment. In this test, the test scores of 21-24, 10-20 and under 9 are classified as mild cognitive impairment, moderate signs of cognitive impairment and severe cognitive impairment, respectively. Validity and reliability of the Persian version of this questionnaire has been approved in the country (26). According to previous studies (28, 27), MMSE score greater than or equal to 25 (30-25) as natural and score less than 25 was considered as a person with cognitive impairment and based on this definition, the elderly were divided into two groups of patients with cognitive impairment and without cognitive impairment.

Venous blood samples were collected from elderly people for measurement of serum concentration of copper. Serum levels of copper were measured using bionex kit based on previous studies (29) and serum copper levels 140-70 dl was considered as the normal range. Laboratory evaluation of all samples was conducted in the laboratory of biochemistry of Babol University of Medical Sciences.

Data were analyzed using SPSS 22 software by T-Test and Chi-Square tests and $p<0.05$ was considered statistically significant.

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Results

Of the total cases, 1004 patients aged 60-99 years were eligible for inclusion in the study. The presence of cognitive impairment in the elderly with age, sex, education level, marital status, living alone was statistically significant (table 1) (p<0.05). 6.1% of women rated based on MMSE had severe cognitive impairment, whereas only 6.0% of men had severe cognitive impairment (p<0.0001). MMSE score was significantly associated with the level of education so that with increasing educational level, the number of seniors who had normal MMSE was added (p=0.001). The mean age of the patients with normal MMSE was 68.29±6.85 years and in the group with abnormal MMSE was 72.74±7.99 years and the difference was statistically significant (p<0.0001). Based on serum levels of copper, there was a significant difference between the sexes (p<0.00001). 220 men (42.5%) and 241 women (49.6%) had abnormal amounts (increase or decrease) serum levels of copper (table 2). The average serum level of copper in people with normal MMSE was 129.43±54.83 and in the group with abnormal MMSE was 135.06±57.38. This difference was not statistically significant (p=0.12). A significant difference in serum level of copper status was found in subgroups of MMSE (table 3) (p=0.009).

Table 1. Frequency of cognitive impairment on the basis of separation of basic variables studied in the elderly people of Amirkola

MMSE / Variable	Normal N (%)	Abnormal N (%)		P-value
Sex	man	396(76.4)	122(23.6)	0.0001
	Woman	261(53.7)	225(46.3)	
Level of education	Illiterate	354(53.6)	307(46.4)	0.0001
	Primary and secondary school	234(85.4)	4.(14.6)	
	High School and university	69(100)	–	
Live alone	Yes	42(52.5)	38(47.5)	0.014
	No	615(66.6)	3.9(33.4)	
Marital status	single	573(67.7)	273(32.3)	0.001
	Married	84(53.2)	74(46.8)	
Age (year)	60-64	254(77.2)	75(22.8)	0.0001
	65-69	153(73.2)	56(26.8)	
	70-74	119(66.5)	60(33.5)	
	75-79	82(47.7)	90(52.3)	
	80-84	34(45.9)	40(54.1)	
	85-99	15(36.6)	26(63.4)	

Table 2. Distribution of serum levels of copper according to sex in the elderly people of Amirkola

Gender / serum level of copper) ug(	Man N(%)	Woman N(%)
≥70	64(64.6)	35(35.4)
70-140	298(54.9)	245(45.1)
≤140	156(43.1)	206(56.9)

p<0.0001

MMSE / serum level of copper (ug)	Normal N(%)	Mild cognitive disorder N(%)	Moderate cognitive disorder N(%)	Severe cognitive disorder N(%)
<70	62(62.6)	24(24.2)	12(12.1)	1(1.1)
70-140	380(70)	118(21.7)	42(7.7)	3(0.6)
>140	215(59.4)	112(30.9)	28(7.7)	7(1.9)

p=0.009

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Discussion

In this study, significant difference between the sexes in terms of serum copper was detected. However, in both sexes, the copper level was mainly in the normal range, but in men, 12/4% was lower than normal range of serum copper level and 1/30% higher than normal range; whereas in the elderly women, 7/2% had serum copper levels of under 70 and 42/4% had levels higher than 140.

In addition, in study of Squitti and colleagues, serum free copper levels had a significant relationship with age, sex and decrease in MMSE score. The average serum level of copper in people with normal MMSE (no cognitive impairment) was different from an average copper levels in the group with abnormal MMSE, but this difference was not statistically significant. Also no significant differences was found in serum copper status in subgroups of MMSE. Among the 11 elderly people with severe cognitive impairment, 7 of them (63/6%) had serum levels of copper higher than normal, whereas this condition was not found in moderate or mild cognitive impairment in the elderly (18).

Review of previous research shows a different relationship between the copper statuses with cognitive disorders in different studies. In a study by Agarwal et al., The mean serum concentration of copper in patients with Alzheimer's disease and vascular dementia patients had a significant increase compared to the control group (30).

Bucossi and colleagues reported in the meta-analysis study that among studies regarding the effects of copper and Alzheimer's, there are some challenges, showing that copper deficiency and toxicity, both can have a role in the occurrence and progression of the disease. Therefore, it is concluded that for the treatment and prevention of Alzheimer's disease, balancing and copper homeostasis is essential (31). In the study of Rembach and colleagues, no significant difference was observed in serum levels of copper within the group with Alzheimer's compared to control subjects (21). Pajonk and colleagues in a study that was conducted on 32 patients with mild to moderate alzheimer's disease, although all patients had serum levels of copper in the physiological range, a negative correlation was observed between serum levels of copper and cognitive impairment, so that in people with lower levels of serum copper, there was a higher risk index of Alzheimer's disease (32).

The difference in the relationship between serum levels of copper with cognitive disorders in different studies could be related to the method of study (cross-sectional or longitudinal studies), and demographic characteristics of the studied population, sample size and the area of study. Since the change in the balance and the metabolism of copper is one of the pathological mechanisms of Alzheimer's disease and the general population primarily receiving copper through eating (75%) and drinking (25%), a low copper diet in elderly that their copper metabolism has modified, can decrease the risk of severe cognitive disorders (Alzheimer's) in them(16).

The strengths of this study are high sample size and comparison of two groups with cognitive impairment and without cognitive impairment and the limitations of this study include the lack of reviewing the duration of cognitive impairment, lack of reviewing other associated diseases, lack of evaluation of diet and used drugs in the elderly. It is also recommended that, serum free copper and ceruloplasmin-bound copper be analyzed separately in future studies.

According to results of this study, cognitive disorders in the elderly has been linked with serum levels of copper.

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