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IRON DEFICIENCY CAN CAUSE COGNITIVE IMPAIRMENT IN GERIATRIC PATIENTS

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Abstract: *Objectives:* Deficiency of iron, which plays an important role in oxygen transport and storage, may lead to cerebral hypoxia and cognitive decline. This relationship which was studied in children and adults was not evaluated in the elderly. The objective of this study is to examine the effect of iron deficiency on cognitive function in the elderly. *Design, Setting, Participants:* This is a cross-sectional study conducted in a geriatric medicine outpatient clinic of a university hospital. Consecutive 2009 patients admitted to Geriatric Medicine outpatient clinic were examined and 622 patients who fulfilled the inclusion criteria were enrolled in the study. *Measurements:* Comprehensive geriatric assessment, cognitive assessment and laboratory analysis including blood count, iron, total iron binding capacity, ferritin, and transferrin saturation were performed. *Results:* Mean age of the study group was 72.5±6.5 and 439 (70.6%) were women. MMSE scores were moderately and significantly correlated with iron levels ($r=0.33$, $p<0.001$) and transferrin saturation ($r=0.32$, $p<0.001$). Transferrin saturation was significantly lower in the patients with dementia ($p=0.040$). It was found that patients with iron deficiency had lower MMSE scores ($p<0.001$) and this relationship was also present in patients without anemia ($p=0.004$). *Conclusion:* The results of this study revealed a negative influence of iron deficiency on cognitive function and this influence was independent from the presence of anemia. As iron deficiency can be easily diagnosed and treated, detecting its effect on cognitive function is of importance. Screening for iron deficiency and initiating appropriate treatment should be a routine part of comprehensive geriatric assessment.

Key words: Iron deficiency, cognitive function, dementia, anemia, elderly.

Introduction

Iron deficiency (ID) with and without anemia are among the most important health problems affecting the elderly population. Iron deficiency anemia (IDA), either alone or in combination with folate and/or vitamin B12 deficiency, accounts for nearly 20% of all anemias in elderly individuals (1). Furthermore, ID remains the most prevalent single nutrient deficiency in both developing and developed countries for all ages (2).

It was hypothesized that chronic deficiency of iron, which plays an important role in oxygen transport and storage, could lead to cerebral hypoxia and cognitive decline (3, 4). This association which was previously studied in the children and adults was not examined in the geriatric population. Previous studies suggested that ID and anemia leads to cognitive decline, dysfunction in intellectual performance, and behavioral abnormalities in children, cancer patients, women at reproductive age, and some young adults (3-6). However, the association between iron deficiency and cognitive function in the elderly was not clearly defined. Some studies showed an association between anemia and dementia. A meta-analysis of two studies examining the relationship between anemia and dementia, showed a significantly increased risk of incident dementia with anemia (7). However, in those studies, the etiology of anemia was either not defined or was mostly due to vitamin B12 deficiency which is a very well known cause for cognitive decline in any patient (8). Effect of the iron deficiency anemia solely on cognitive functions in the elderly has not yet been studied.

The aim of this study is to examine how ID and IDA influences cognitive function in the geriatric patients aged 65 years and older. Furthermore, we intended to find out whether the influence of ID on cognitive function is independent from the presence of anemia.

Methods

Study Population

Consecutive 2009 geriatric patients aged 65 years and older who were admitted to our outpatient geriatric medicine clinic for comprehensive geriatric assessment were enrolled into this study. After performing comprehensive geriatric assessment including cognitive assessment and laboratory analyses, 622 patients who did not meet the exclusion criteria were included into this study (9). Exclusion criteria were as follows:

- Metabolic and endocrinologic diseases that may cause cognitive dysfunction, including vitamin B12 deficiency, folate deficiency and hypothyroidism.
- Severe dementia (Stage 6 and 7 in Global Deterioration Scale).
- Patients to whom MMSE test could not be performed due to poor cooperation because of visual problems, auditory problems, severe dementia, and decompansation in general

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situation.

- Patients who were previously diagnosed with iron deficiency, so were on iron treatment.
- Beta thalassemia trait and other hemoglobinopathies
- Myelodysplastic syndrome
- Transferrin saturation >50%

For the cognitive assessment, after complaint of memory loss was questioned, standardized Mini-Mental State Examination (MMSE) and clock drawing tests were performed (10, 11). Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria were used to ascertain diagnosis of dementia (12, 13). Patients who did not meet DSM-IV, NINCDS-ARDRA and Petersen criteria, with normal clock drawing test and an MMSE score>24 were considered as cognitively intact. The study protocol was consistent with the Declaration of Helsinki.

Laboratory Analyses

Blood samples were obtained by venipuncture from the antecubital vein after 12 hours fast. Laboratory analysis for total blood count, plasma iron, total iron binding capacity (TIBC) and ferritin levels, thyroid function tests, vitamin B12 and folate levels were performed. Turbidimetric immunoassay (The Beckman IMMAGE FER Test) was used for the determination of ferritin levels. Transferrin saturation was calculated by the classical formula (plasma iron/TIBC × 100).

Anemia diagnosis was made according to WHO criteria (Hb<12g/dl for women, <13g/dl for men). Patients with transferrin saturation lower than 15% or ferritin level lower than 15ng/ml were diagnosed as IDA.

Statistical Analyses

Categorical variables are presented as percentages, normally distributed continuous variables are presented as mean±SD, and skew distributed variables are presented as median (minimum-maximum). For comparison between groups, chi-square test was used for categorical variables, Student t test was used for normal distributed continuous variables and Mann Whitney-U test was used for skew distributed variables. For correlation analysis Pearson correlation test was used for normal distributed variables and Spearman correlation test was used for skew distributed variables. Multivariate regression analyses were performed in order to find out the independent effect of iron deficiency on MMSE scores.

For conducting the statistical analysis SPSS 15.0 for Windows was used and a p value <0.05 was considered as statistically significant.

Results

Demographic, Clinical and Laboratory Results

The mean age of the study population consisting 622 elderly subjects was 72.5±6.5, and 439 (70.6%) subjects were female. Twenty seven patients (4.3%) had dementia and 177 (28.5%) had mild cognitive impairment. Anemia was present in 64 patients (10.3%) and iron deficiency was present in 64 (10.3%) patients. Twenty nine patients with iron deficiency (45.3%) had anemia. The clinical and laboratory features of the study population are given in Table 1.

Table 1
The Clinical and Laboratory Features of the Study Population

	Study population (n=622)
Age (mean±SD)	72.5±6.5
Gender (Female/Male)	439 (70.6%)/183 (29.4%)
MMSE score	28 (4-30)
Dementia	27 (4.3%)
Mild cognitive impairment	177 (28.5%)
Anemia	64 (10.3%)
Iron deficiency	64 (10.3%)
Hemoglobin	13.7 (8.5-17.8)
Hematocrit	40.8 (27.8-53.6)
Iron (mcg/dl)	79.7±22.8
Total iron binding capacity (mcg/dl)	281.2±57.2
Ferritin (ng/ml)	59.6 (3.9-487)
Transferrin saturation (%)	28.9 (3.7-49.8)
Vitamin B12 (pg/ml)	305 (200-2000)
Folat (ng/ml)	24.4 (12-861)

Results of the Relationship between Iron Deficiency, Anemia and Cognitive Function

Correlation analysis between MMSE scores and iron parameters including iron, total iron binding capacity, transferrin saturation, ferritin, and hemoglobin were performed. Results revealed that iron (r=0.33, p<0.001) and transferrin saturation (r=0.32, p<0.001) were moderately and significantly correlated with MMSE score. These relationships are shown in Figures 1a and 1b. Other parameters did not show a correlation with MMSE scores.

Comparison of iron parameters with regard to cognitive status was performed and it was found that transferrin saturation was significantly lower in patients with dementia (25.7 (12.8-44.3) in patients with dementia, 29.1 (3.7-49.8) in patients without dementia; p=0.040). Iron, total iron binding capacity, ferritin, and hemoglobin levels were not different between groups. Although TS was found to be significantly lower in dementia, it still remained within the normal ranges. Therefore ROC curve analysis was performed to determine whether the standard cut off value of TS for iron deficiency is also accurate for dementia, or a different cut off value would be more appropriate. ROC analysis revealed that the cut off 19.19 for TS has an effect on dementia (sensitivity 40.7%, specificity 84.5%).

Effect of anemia on cognitive function was tested and no significant relationship between anemia and dementia was found. However, MMSE scores were significantly lower in patients with anemia, compared with the patients without (27 (5-30) vs. 28 (4-30); p=0.022).

Figure 1

1a. Relationship between Mini Mental State Examination (MMSE) test and transferrin saturation (TS). 1b. Relationship between Mini Mental State Examination (MMSE) test and iron levels

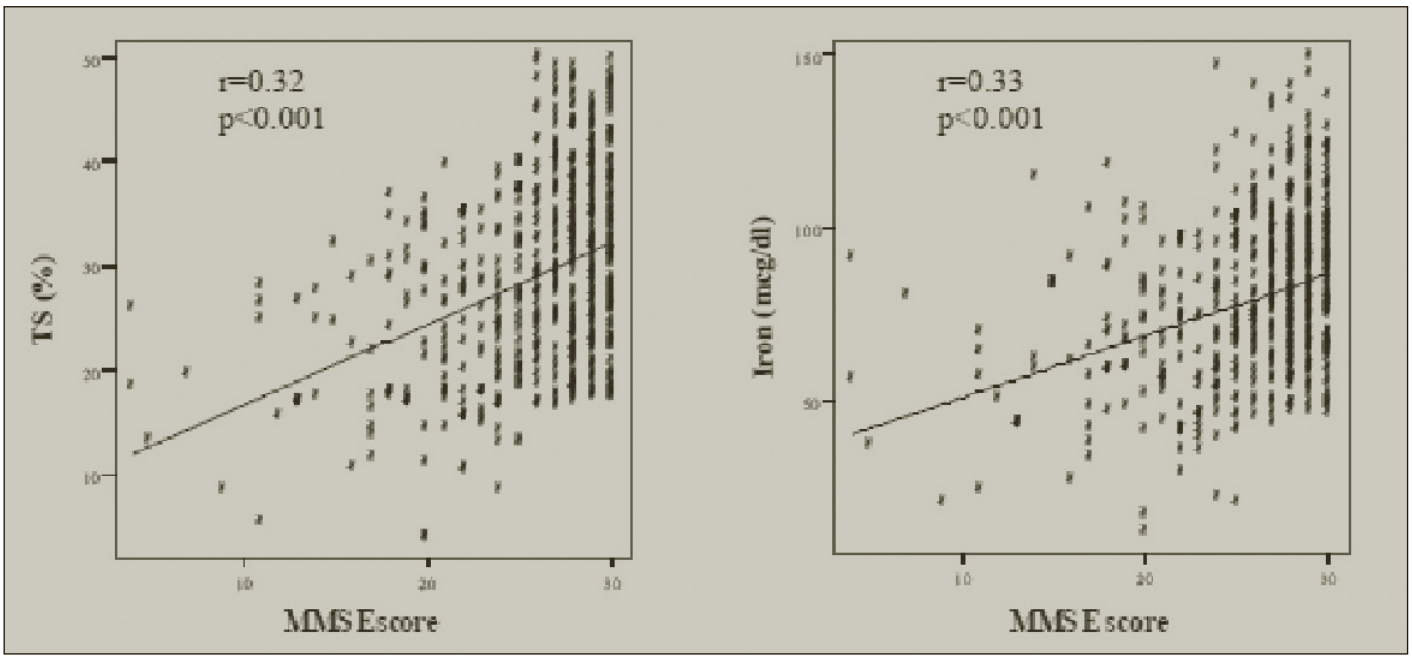
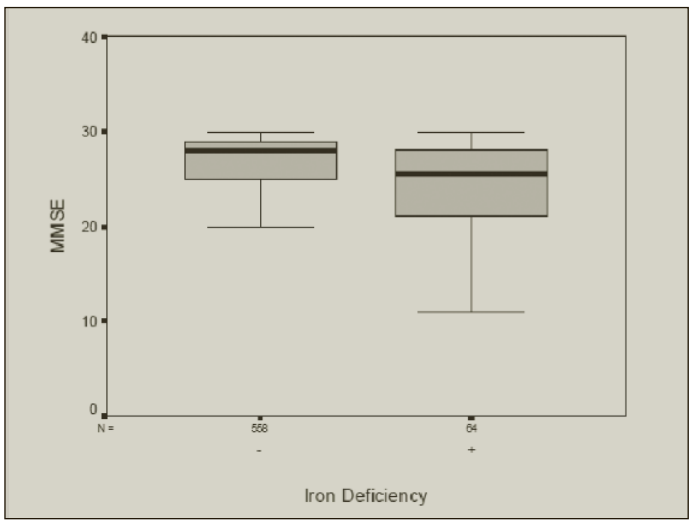


Figure 2

Mini Mental State Examination (MMSE) test scores in patients with iron deficiency and without. MMSE score was 25.5 (5-30) in patients with iron deficiency, 28 (4-30) in patients without (p<0.001)



When patients with and without iron deficiency were compared, MMSE score was found to be significantly lower in patients with iron deficiency (25.5 (5-30) vs. 28 (4-30); p<0.001) (Figure 2). Frequency of dementia was higher in patients with iron deficiency (9.4% vs. 3.8%; p=0.037). In order to find out if this influence of iron deficiency on cognitive function is independent from anemia or not, patients without anemia were analyzed. Within nonanemic patients, MMSE score was significantly lower in patients with iron deficiency when compared to patients without iron deficiency (25 (14-30), 28 (4-30); p=0.004). Furthermore, transferrin saturation showed a moderate and significant relationship (r=0.32, p<0.001), and iron showed weak but significant relationship (r=0.27, p<0.001) with MMSE scores.

Multivariate regression analyses performed with the parameters age, sex, education, depression, vitamin B12, TSH, drugs that could affect cognitive function, iron, transferrin saturation, and anemia revealed the independent effect of transferrin saturation on MMSE scores. The results of multivariate analyses are demonstrated on Table 2.

Table 2

Results of multivariate regression analyses of the parameters those are potentially associated with MMSE scores. The parameters age, sex, education, depression, vitamin B12, TSH, drugs that could affect cognitive function, iron and transferrin saturation were put into equation

	Beta	t	p	CI
Transferrin saturation	0.28	7.95	<0.001	0.099; 0.163
Education	0.34	9.67	<0.001	0.731; 1.103
Age	-0.18	-5.08	<0.001	-0158; -0.070

Discussion

The results of this study revealed a significant decline in cognitive function in patients with iron deficiency (ID). MMSE test scores were significantly lower and dementia frequency was significantly higher in patients with ID. This negative influence of ID on cognitive function was independent from the

presence of anemia. This study is the first to examine the relationship between iron status and cognitive function in the geriatric age group. To determine the influence of ID on cognitive function is of importance because ID is very common in the elderly and is mostly easily treatable. According to the results of this study, ID has a negative influence on cognitive function even before reaching the level of anemia.

In this present study, in order to examine the direct effect of pure ID on cognitive function, other conditions that could cause cognitive dysfunction were excluded. As hypothyroidism, vitamin B12 and folate deficiency are well known causes of cognitive decline, patients with these conditions were excluded. Furthermore, iron overload is associated with Alzheimer's disease. Therefore, transferrin saturation >50%, the level that iron overload in the tissues begins, was another exclusion criteria (14).

The association of iron status and cognitive skills is recently attracting interest. Iron is necessary for the oxygenation and energy production of the cerebral parenchyma, and for the synthesis of neurotransmitters and myelin (15). Iron is also a cofactor in biochemical processes, including mitochondrial electron transport, catecholamine metabolism and DNA synthesis (3). It has previously been suggested that anemia has great influence on cognitive functions via cerebral hypoxia and other possible mechanisms (3, 4) and deficiency of iron may cause cognitive decline by these mechanisms (3, 4, 16). Although it is not clear whether cognitive dysfunction due to ID or anemia is reversible, the general opinion is that as duration and severity of ID or anemia increases, reversibility of cognitive dysfunction becomes more difficult (5, 17-19). Therefore, it is important to screen the elderly for ID in order to make the diagnosis and initiate the treatment on time.

Although the influence of ID on cognitive function has been studied in infants, children, and some young adults, its effect in the elderly has not yet been studied. In various studies examining children and patients with cancer, it was shown that ID and anemia causes cognitive dysfunction, decline in intellectual performance, and behavioral abnormalities (3-6). On the other hand, there is no clear evidence regarding the effect of ID on cognition in the geriatric age group, which is the age group that cognitive decline is most frequently seen. The association of ID with dementia also needs further evidence. Although some studies showed a relationship between anemia and dementia, anemia was mostly due to vitamin B12 deficiency and the direct effect of pure ID on dementia was not studied (8).

Iron deficiency is linked to attention-deficit/hyperactivity disorder, memory, and behavioral abnormalities in children and infantile iron deficiency anemia leads to perturbation of the development of cognitive functions (6, 15, 20). Lubach and Coe demonstrated slower cognitive performance in iron deficient infant monkeys (21). In human studies, there is compelling evidence that 6 to 24 month-old infants with iron deficiency anemia are at risk for poorer cognitive and neurophysiologic development (22). Various studies in children showed that the severity of cognitive dysfunction is due to the severity and duration of ID (16- 18). It was also demonstrated that treatment of ID in children is together with increase in intellectual performance and improvement in cognition (5, 23).

Studies regarding the association between ID and cognition in adults were performed in cancer patients, women of reproductive age, pregnant women, and renal dialysis patients (4, 24-26). It was suggested that iron deficiency anemia results in cognitive deterioration and alteration of neurological functions in cancer patients. Moreover, correction of anemia improved cognitive abilities in these patients. Likewise, cognitive performance of young women with iron deficiency anemia improved after iron supplementation (2). These studies made it clear that the effects of ID on cognition are not limited to the developing brain, but it also has critical role in the adult brain.

The results of these studies conducted in children and adults puts forward the importance of iron in developed brain, as well as developing brain; and they show that its effect on the elderly brain is worth examining. An association between anemia and cognitive impairment in the elderly subjects was determined by Chaves et al, Zamboni et al, and Argyriadou et al (16, 27, 28). However, in the latter anemia was mostly due to vitamin B12 deficiency, and none of them specifically examined iron deficiency anemia.

Another important point is that, level of improvement is depended on duration of anemia (4, 29-31). This shows that early diagnosis and treatment of ID is crucial for improving cognitive functions. The present study demonstrates that iron deficiency results in cognitive decline in the elderly. However, as this is a cross-sectional study, effects of correcting iron deficiency in the elderly group on cognitive function could not be determined.

Future studies should be conducted to support these findings and to obtain evidence about how iron deficiency treatment affects cognitive function. This present study furthers our understanding of the consequences of iron deficiency in the elderly and points out that iron deficiency has cognitive consequences even without reaching the level of anemia. In the light of these findings iron deficiency should be screened and appropriately treated in the individuals at geriatric age group.

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