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TANAFFOS

Relation of Cognitive Impairment with Number of Acute Exacerbations and Serum Level of VEGF among COPD Patients

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Background: Chronic obstructive pulmonary disease (COPD) is a main cause of morbidity and mortality in the world. Its complications are numerous and one of their most common extra-pulmonary ones is cognitive impairment which is directly related to its mortality and morbidity. A decrease in cerebral perfusion in these patients had been seen in previous studies considering the role of VEGF on angiogenesis and its role in the pathogenesis of COPD. This study was done to evaluate the relation of cognitive impairment with serum VEGF and the number of COPD exacerbations.

Materials and Methods: In the present study, 87 patients whom the pulmonologist confirmed their COPD disease based on spirometry testing were enrolled. The blood sample was received for serum VEGF level measurement and the Mini-Mental State Examination (MMSE) questionnaire was completed to assess the cognitive function. The number of exacerbations was also recorded. The blood sample was received from 87 other age and sex-matched persons without a history of pulmonary disease, CVA, or MI. Their VEGF level was also measured. The data was analyzed by SPSS version 20 software.

Results: In the COPD group, 42 (48.28%) had no cognitive impairment, 39 (44.83%) had mild, and 6(6.89%) had moderate cognitive impairment. In this group, there was a significant relation between the score of the MMSE questionnaire and the number of COPD exacerbations during the past year. However, there was no significant relation between VEGF and cognitive impairment.

Conclusion: According to the results of the present study, there was no significant relation between cognitive impairment and VEGF level. There was a significant relation between cognitive impairment and the number of COPD exacerbations. Also, there was a significant difference between the serum level of VEGF among COPD patients and the control group.

Keywords: COPD; Cognitive impairment; Serum VEGF; MMSE; Lung diseases

INTRODUCTION

COPD or chronic obstructive pulmonary disease is defined as irreversible restriction of air flow in the lung and decrease of FEV1/FVC ratio. It has three clinical subgroups: chronic bronchitis, emphysema, and small airway disease. The average age of incidence is 50 years old and more than 14% of the people aged more than 65 are affected (1). COPD has different risk factors including

environmental risk factors (cigarette smoking, air pollution, occupational exposure to dust and smoke) and genetic risk factors (2).

Emphysema is the enlargement of the lung because of the expansion of alveoli and atrophy of the septum. Vascular endothelial growth factor (VEGF) is a main modulator of physiologic and pathologic angiogenesis. In emphysema, the endothelial cells of the lung will experience apoptosis because of diminished VEGF and consequently, the sensitivity of the alveolar walls will increase for oxidant stress and proteinases (3). The serological level and also the number of VEGF receptors decrease in emphysema (4).

There is a hypothesis that the imbalance between VEGF and endostatin (VEGF antagonist) causes emphysema in COPD patients (5) and the increased serum VEGF causes remodeling of the airway in chronic bronchitis COPD patients (6). The recent studies have shown that VEGF is not only effective on angiogenesis in the CNS but also has direct neuroprotective effects on the neurons and has a neurotropic effect. It also increases the permeability of the blood-brain barrier to glucose and activates the anti-oxidants (7, 8). Many studies have shown increased VEGF levels among Alzheimer patients in comparison with normal people. The patients who had more rapid cognitive decline had more VEGF levels (9, 10).

VEGF has an important role in many diseases such as vasculitis and hematologic malignancies.

Beside its role as an essential regulator of physiologic and pathologic angiogenesis, VEGF triggers growth, survival, and migration of leukemia and multiple myeloma cells; plays a pivotal role in hematopoiesis; inhibits maturation of dendritic cells; and increases osteoclastic bone-resorbing activity as well as osteoclast chemotaxis. Dysregulation of VEGF expression and signaling pathways therefore plays an important role in the pathogenesis and clinical features of hematologic malignancies, in particular, multiple myeloma. (11) Increased plasma VEGF could be a useful marker for the diagnosis of vasculitis neuropathy and for monitoring a therapeutic effect (12). VEGF levels are raised in Wegner patients compared to normal controls and may be a marker of disease activity (13).

COPD is one of the main causes of mortality and morbidity in the world. Also, the most common presentation of COPD is diminished air flow, but it is related to many extrapulmonary manifestations which relate to morbidity, lower quality of life, and even mortality (14). It is linked with many extrapulmonary complications such as osteoporosis, anemia, and cardiovascular disease. Thus, it is considered a multi-system disease.

Cognitive impairment is one of the most common extrapulmonary manifestations of COPD and is related to mortality and morbidity (15). In a systematic review, it was shown that cognitive function is impaired in COPD patients compared to normal people (16). In the Valipour study, it is shown that the serum VEGF level in stable COPD patients is more than the control group (17).

In fact, by considering the relation of serum VEGF with the pathogenesis of COPD, the number of acute exacerbations of diseases, and the relation of VEGF with cognitive impairment, there is a question that if the VEGF levels could be the cause of more cognitive impairment among COPD patients? And does cognitive impairment correlate with the number of exacerbations in COPD patients?

MATERIALS AND METHODS

This study has the ethical confirmation from the Kerman Medical University Ethics Committee (k/95/178). In the present case-control study, from the patients with a history and presentations of COPD who were visited by a pulmonologist in Afzalipour hospital, Kerman, 87 Patients with stable disease, aged between 40-85 years and without a history of acute exacerbation during the past three months and confirmed COPD (FEV1/FVC < 0.7 that would not increase with two puffs of salbutamol spray and the FEV1 would not increase more than 12% or 200 cc, by the spirometry test (Spirolab III MIR, ITALY)) entered the study. 87 age and sex-matched family members of patients

from different parts of the hospital were selected as the control group. Exclusion criteria were illiteracy, cerebrovascular accident, and myocardial infarction. The goals of the study were described and informed consent was received. MMSE questionnaire was completed and O_2 saturation was measured by pulse oximeter (Zyklusmed, Germany) for the case and control group. A form for the history of kidney disease, diabetes mellitus, hypertension, hyperlipidemia, and number of COPD exacerbations during the past year was filled. Then, 2cc of venous blood was received, centrifuged, and stoked at -80 degrees centigrade to measure the serum VEGF level. The MMSE questionnaire is a 30-score questionnaire that is used for cognitive impairment and consists of 5 parts: attention and calculation (5 scores), recall (13 scores), language (9scores), orientation (10 scores), and recording (3 scores). The score equal or more than 25 is the normal range. 20-24 score shows mild cognitive impairment, below 9 shows severe, and 10-19 shows moderate cognitive impairment. Validity and accuracy of the Persian translation of this questionnaire is measured by Seyedian et al. with Cronbach's alpha of 81%. Its accordance with Wechsler adult intelligence scale was 85% with 90% sensitivity and 93.5% specificity (18).

After sample collection, the serum samples were evaluated with quantitative human VEGF kit (Bioassay Technology, China) and data was analyzed with SPSS20 software.

RESULTS

In the case group, 8 (9%) were female and 79 (91%) were male while in the control group 10 (11%) were female and 77 (89%) were male. The average age of COPD patients was 60.47 ± 9.8 years (between 43-83 years) and 60.41±7.8 years (between 45-80 years) in the control group. In the case group 42 (48.28%) had no cognitive impairment, 39 (44.83%) mild, and 6 (6.89%) had moderate cognitive impairment. In COPD group, there was a significant relation between the score of MMSE questionnaire and number of COPD exacerbations during the past year (correlation coefficient: -0.617) and the number of coexisting systemic diseases (correlation coefficient: -0.477, p-value<0.0001) (Figure 1).

Serum level of VEGF in COPD patients was 489.22±33.37 (range 117.1-980.8). There was no significant relation between serum VEGF level and the score of MMSE questionnaire (Pearson correlation: -0.109, p-value: 0.499).

Serum level of VEGF was 253±155.62 in the control group (range: 157.34-315.01). There was a significant difference between the serum VEGF level of the case and control group (p-value<0.0001).

In the control group, 75 (86.2%) patients had no cognitive impairment, 9 (10.34%) had mild, and 3 (3.46%) had moderate cognitive impairments. There was a significant difference between the MMSE scores of the cases and controls (p-value < 0.0001; mean difference: 1.12). The MMSE score was 23.63 ± 2.8 in the control group and 22.51 ± 2.4 in the case group.

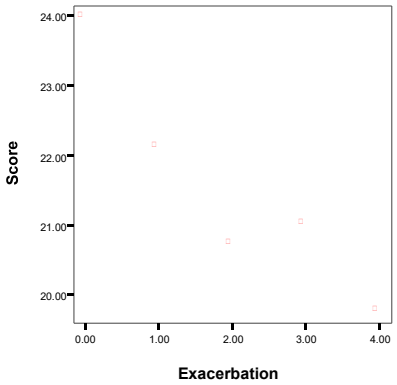

Figure 1. The relation of number of COPD exacerbation with MMSE score in COPD patients

There was also an inverse relationship between the number of exacerbations and MMSE score (p < 0.0001).

DISCUSSION

To our best knowledge, there was no study for evaluating the relation of VEGF and cognitive impairment in COPD patients. In the present study, 51.73% of COPD patients had a degree of cognitive impairment which has been reported variously in different studies. The prevalence of cognitive impairment among COPD patients

varies considering the sample selection, the considered age, the tests which were used to assess cognitive impairment such as MMSE, P 300, severity of COPD disease, and even the method of approving the COPD disease (a questionnaire for clinical presentations of COPD or spirometry). The results vary from no association between COPD and cognitive impairment in some studies (19) to 77% prevalence of cognitive impairment among COPD patients (20).

The present study did not show a relation between serum VEGF level and MMSE score as an indicator of cognitive impairment. Although, there was no relation between these two, but it can be due to specific VEGF level changes in different forms of COPD. As mentioned in the introduction, the serum VEGF level decreases in emphysema and increases in chronic bronchitis form of COPD (4,6,7). Considering this point that the present study didn't distinguish between two types of COPD because of the need for using advanced methods such as CT scan that was not feasible for us, so the relation between VEGF and cognitive impairment might be covered for this reason.

Similar to some studies (17, 20, 21, 22), in the present study, the level of serum VEGF was significantly higher in COPD patients in comparison with normal people. However, other study (23) did not find any difference between the VEGF levels of these two groups. The discrepancies could be because of a lack of differentiating chronic bronchitis from emphysema form (by noting their difference in VEGF levels).

By noting the adverse relation between serum VEGF and PaO_2, we can conclude that in acute exacerbation, hypoxia induces neo-angiogenesis and more perfusion and oxygenation using VEGF (22, 24). Although, another study says that the sputum VEGF level increases during the exacerbation, but there was no change in the serum level of VEGF (25).

Interestingly, Lee has reported that deletion of VEGF signal by activating Recombinant Luteinizing Hormone (RLH) caused more viral infections in COPD patients. It might be concluded that in fact, the increase of VEGF level is an immune response of body to the exacerbation (26).

In the study of Kirkil et al. in 2007 on 17 healthy, 30 stable COPD patients, and 30 COPD patients in exacerbation, it was shown that cognitive impairment was more among both groups of COPD compared to normal people and was more in exacerbations than stable COPD patients. It is mentioned that cognitive impairment and FEV1 and PaO_2 will regress to the basal level over time, after healing the exacerbation (27). However, in the study of Dodd et al. in 2013, it was mentioned that cognitive function will decrease in acute exacerbations and is related to the general condition and duration of hospitalization. It is also shown that this decrease in cognitive function had no significant healing in 3 months of follow-up (28). In two other studies, Federman et al. (29) and Ozyemisci-Taskiran et al. (30), it is shown that COPD patients experience cognitive impairment during the exacerbation of COPD.

There was also a significant adverse relation between the score of MMSE questionnaire with number of exacerbations and number of coexisting systemic diseases. For the relation of cognitive impairment with number of exacerbations many studies (24-27) are designed in a way that they have compared a group of stable COPD with a group of exacerbated COPD for cognitive impairment. Indeed, they have assessed their transient increase of cognitive impairment and not the long term effect of number of acute COPD exacerbations on cognitive impairment.

Although, one study had considered a three-month follow-up for the patients and it was mentioned that the induced cognitive impairment had no significant recovery in the three months of follow-up (25). However, in the present study, the patients were in stable situation and the number of COPD exacerbations during the past year was asked from the patient, retrospectively. There was a significant relation between the number of COPD exacerbations and cognitive impairment even in the stable state that could be an indicator of long term effects of each

previous acute exacerbation on cognitive status of the patient.

We could assess the relation of VEGF and cognitive impairment much better if we could distinguish the emphysema from chronic bronchitis type. The study could be better if we had a larger sample size.

CONCLUSION

According to the results of the present study, there was no significant relation between cognitive impairment and VEGF level. There was a significant relation between cognitive impairment and number of COPD exacerbations and there was a significant difference between the serum level of VEGF among COPD patients and the control group.

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