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ORIGINAL ARTICLE

Serum Biomarkers in Alzheimer's Disease

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ABSTRACT

Background: AD is manifested by a gradually increasing impairment in cognitive functions and neurononal and synaptic loss with presence of senile plaques. Vitamin D has a function in neurotrophy, neurotransmission, neuroprotection, and neuroplasticity, its deficiency share in the pathogenesis of dementia and AD development. Serum albumin is an important human plasma protein and considered as a vital way for amyloid β declaration system as it binds from about 90% to 95% of the amyloid β in the blood. The goal of this work is to detect if there is a relationship between vitamin D, serum albumin levels in correlation with serum AB and the possibility of AD occurrence.

Methods: 64 individuals, 32 patients with dementia and 32 healthy individuals, they were subjected to complete general and neurological examination, Dementia Severity Rating Scale, MRI brain, serum vit D, albumin and AB levels.

Results: There was a statistically significance between patients and control groups concerning age, AB42, MMSE, DSRS, serum albumin, and vitamin D. A statistically significant negative correlation between vitamin D and all ages, AB42, and DSRS were found. There was a positive correlation between vitamin D and plasma albumin and MMSE. Also, there was a positive correlation between plasma albumin and all of vitamin D and MMSE was detected. There was a negative correlation between AB42 and MMSE and a statistically positive correlation between AB42 and DSRS.

Conclusions: Low serum albumin and vitamin D levels possibly will increase the possibility of AD dementia.

Keywords: AD; albumin; vitamin D; AB protein; Dementia.

INTRODUCTION

Alzheimer's disease (AD) is one of the most major etiological causes of dementia and account for 60% to70% of the cases. The World Health Organization discovered that high percentage about 60% of the patients suffering from dementia are in a lower income countries [1].

AD is manifested by gradually increasing cognitive dysfunctions with presence of senile plaques and neuronal loss. AD can be characterized by the existence of neurotic plaques consist of highly insoluble amyloid-β (Aβ) peptide in the brain cells. This suggests that the deposition of the plaques resulted from consequence of chronic inconsistency between the synthesis of amyloid-beta protein and its sequestration [2].

Vitamin D has a part in neurotrophy, transmission, protection, and plasticity mechanisms in the nervous system. So, vitamin D deficiency is considered to be implicated in the pathogenesis of AD [3]. Many clinical research detect the relation of vitamin D deficiency and cognitive dysfunction, A novel five cohort research studies approved that sufficient vitamin D supplementation was related with decrease dementia and AD incidence [4].

Albumin is considered as a most vital human plasma proteins which is considered as an important valuable factor for Aβ segregation systems as it binds with it by range from about 90% to 95% of the Aβ in plasma [5,7,8]. The balance of amyloid-β level in the brain and blood may be directed to blood leading to binding with peripheral serum albumin [9]. So, the reduction of blood serum albumin binding AB may affect the capability for Aβ sequestration into the blood from brain cells, which share in accumulation and deposition of Aβ protein in brain cells [10]. Aβ fibril formation may be inhibited serum albumin via binding Aβ monomers or oligomers [11].

Many research done on humans have reported that a low serum albumin shares in pathogenesis of AD dementia. Nevertheless, little data is existing on serum albumin level is implicated in Aβ accumulation in the human brain [12-13]. The aim of this study was to detect the relationship between serum vitamin D, serum albumin levels and serum B- amyloid protein with possibility of later development of AD.

METHODS

Study design and population

This study was done in the Neurology Department and Neurology outpatient clinic, faculty of medicine, Zagazig university hospital on patients with recent cognitive impairment and on patients diagnosed previously with Alzheimer disease. Approval by the Institutional Review Board was obtained to conduct the study. (IRB#371/1-july-2024), All patients signed full consent before enrollment in our study, this study was a case control study done on 32 patients and 32 normal control participants. The study was done according to the ethical guidelines of declaration of Helsinki. Written informed consents were signed from all participants. The study started from November 2023

to July 2024. The study was conducted on 64 adult participants. They were divided into two groups: group 1: those without dementia (cognitively normal) and group 2: those with cognitive impairment. Their ages ranged from 55 to 90 years. The cognitively normal participants with a Clinical Dementia Rating scale was 0 and not diagnosed as mild cognitive impairment or dementia. While individuals diagnosed as Alzheimer disease with cognitive impairment, according to National Institute on Aging (NIA) – Alzheimer's Association Guideline on Neuropathological Assessment of Alzheimer's as follows: 1-memory impairments established by their relatives, 2-objective memory problems, 3-conserved cognitive functions, 4-disability in daily activities, and 5-presence of dementia [14]. The exclusion criteria were presence of any psychiatric illness, other neurologic illness like, cerebrovascular diseases or medical conditions that might affect mental function, non-educated persons, presence of major visual, hearing and behavioral problems that can affect clinical examinations or brain imaging, taking any sedative and hypnotics drugs and patients and or relative rejection.

Clinical evaluations

Full medical and neurological history and detailed clinical examination were done, using Mini Mental State Examination (MMSE) interpretation of MMSE (25-30 normal, 20-25 Mild, 10-20 Moderate and 0-10 Severe) [15]. Dementia Severity Rating Scale (DSRS) interpretation were as the following: (0-18 Mild, 19-36 Moderate and 37-54 Severe).The test was done to all patients with cognitive impairment [16]. Data were collected and tabulated for statistical analysis

Radiological and Laboratory examinations

Radiological data including MRI brain. Laboratory tests were also done including serum Vitamin D Level, Serum albumin level and serum AB42 protein level. A venous blood samples (5 mL) were taken from the patients into plain tubes, serum samples were aliquoted in polypropylene tubes (two tubes, 250 µL in each tube) after centrifugated, and stored at −20 °C. serum was used to measure amyloid-β1-42 and vitamin D levels by using Sandwich ELISA method (EURO-IMMUN MedizinischeLabordiagnostika AG. Lubeck, Germany) depending on monoclonal anti-beta-amyloid antibodies. Other tube was used to measure albumin using BCG reagent on spectrophotometry.

Statistical Analysis

Microsoft Excel was used to code, process, and analyze data gathered from patient's clinical, laboratory tests, and scales measurements. Statistics for Social Sciences (SPSS) was then used to import data (SPSS version 27.0). According to the collected data, qualitative or quantitative was presented as number and percentage and mean ± SD, while non-parametric quantitative data is presented as range and median, and the Pearson correlation test was used to detect the correlation between the studied parameters. P value was set <0.05 for significant outcome and <0.001 for higher significant results.

RESULTS

In the study we find that there is a significant difference between the two studied groups concerning age, AB42, MMSE, DSRS as p value<0.001 (table 1).

There was a statistically non-significant difference between the studied groups regarding gender, smoking, co-mobile diabetes or hypertension (table 1).

In table (2) there was a statistically significant difference between the studied groups regarding albumin, and vitamin D p value 0.021 and <0.001 respectively.

Our result shows in table (3) The best cutoff value of plasma albumin in prediction of AD is ≤4.25 g/dl with area under curve 0.663 with 71.9% sensitivity and 56.2% specificity (figure 1).

The best cutoff value of vitamin D in prediction of AD is ≤19 with area under curve 1.0 with 100% sensitivity and 96.9% specificity (figure 2).

Table (4) approved that there was statistically significant negative correlation between vitamin D and all of age, AB42, and DSRS (r-0.325, -0.655, -0.885 respectively). There was a statistically significant positive correlation between vitamin D and plasma albumin (p value=0.036) and MMSE (p value <0.001).

There is statistically significant positive correlation between plasma albumin and all of vitamin D and MMSE (p value=0.046). There is statistically non-significant correlation between plasma albumin and either age, AB42, or DSRS (0.932, 0.381 and 0.148 respectively).

In table (5) there is a statistically significant negative correlation between AB42 and MMSE (r-0.685) and There is statistically significant positive correlation between AB42 and DSRS p value <0.001.

Table 1: Comparison between the studied groups regarding baseline data

	Case group (n=32)	**Control group (n=32)**	χ^2	**p**
Gender:				
Female	18 (56.3%)	19 (59.4%)	0.064	0.8
Male	14 (43.7%)	13 (40.6%)		
Smoker				
Yes	13 (40.6%)	12 (37.5%)	0.066	0.798
No	19 (59.4%)	20 (62.5%)		
Diabetes				
Yes	16 (50%)	15 (46.9%)	0.063	0.802
No	16 (50%)	17 (53.1%)		
Hypertension				
Yes	16 (50%)	12 (37.5%)	1.016	0.313
No	16 (50%)	20 (62.5%)		

	Mean ± SD	Mean ± SD	t	p
Age (year)	66.06 ± 6.09	61.97 ± 3.85	3.215	**<0.001****
AB42	11.94 ± 2.88	6.25 ± 2.73	8.114	**<0.001****
MMSE	12.66 ± 3.17	29.06 ± 1.24	-27.268	**<0.001****
	Median (IQR)	**Median (IQR)**	Z	**p**
DSRS	39.5(37 – 49)	0(0 – 10)	-6.947	**<0.001****

χ^2Chi square test t independent sample t test *p<0.05 is statistically significant **p≤0.001 is statistically highly significant Z Mann Whitney test

Table 2: Comparison between the studied groups regarding plasma albumin and vitamin D level

	Case group (n=32)	Control group (n=32)		p
	Mean ± SD	**Mean ± SD**	**t**	**p**
Albumin (g/dl)	3.93 ± 0.6	4.25 ± 0.48	-2.371	**0.021***
Vitamin D	9.91 ± 1.67	28.19 ± 4.6	-21.115	**<0.001****

t independent sample t test *p<0.05 is statistically significant **p≤0.001 is statistically highly significant

Table 3: performance of plasma albumin and vitamin D in prediction of Alzheimer disease

	Cutoff	AUC	95% CI	Sensitivity	Specificity	p
Albumin	≤4.25	0.663	0.529 - 798	71.9%	56.2%	0.025*
Vitamin D	≤19	1	1 – 1	100%	96.9%	<0.001**

*p<0.05 is statistically significant **p≤0.001 is statistically highly significant AUC area under curve CI Confidence interval

Table 4: Correlation between vitamin D, plasma albumin and the studied parameters

	Vitamin D		Plasma albumin	
	R	**p**	**r**	**p**
Age (year)	**-0.325**	**0.009***	-0.011	0.932
AB42	**-0.655**	**<0.001****	-0.111	0.381
MMSE	**0.89**	**<0.001****	**0.251**	**0.046***
DSRS	**-0.885**	**<0.001****	-0.183	0.148
Albumin (g/dl)	**0.263**	**0.036***	-	-
Vitamin D	-	-	**0.263**	**0.036***

r Pearson correlation coefficient *p<0.05 is statistically significant **p≤0.001 is statistically highly significant

Table 5: Correlation between AB42 and MMSE and DSRS

	AB42	
	r	**p**
MMSE	-0.685	<0.001**
DSRS	0.709	<0.001**

r Pearson correlation coefficient **p≤0.001 is statistically highly significant

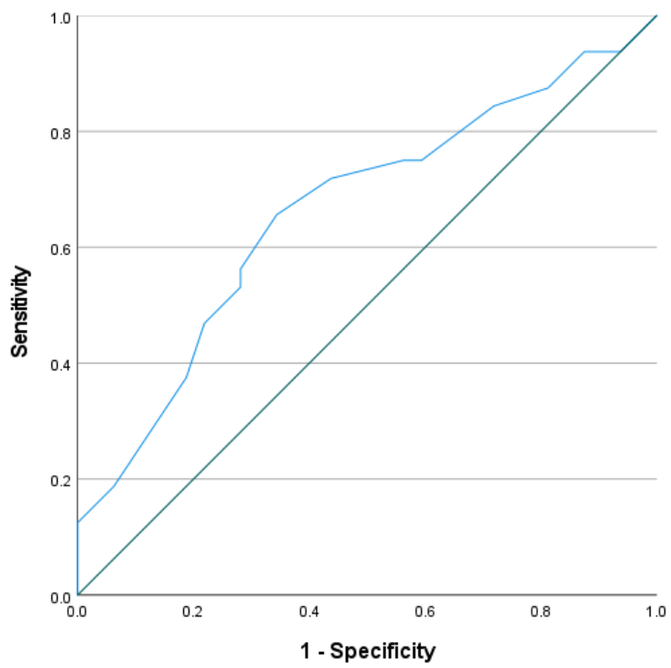

Figure 1: ROC curve showing performance of plasma albumin in prediction of Alzheimer disease

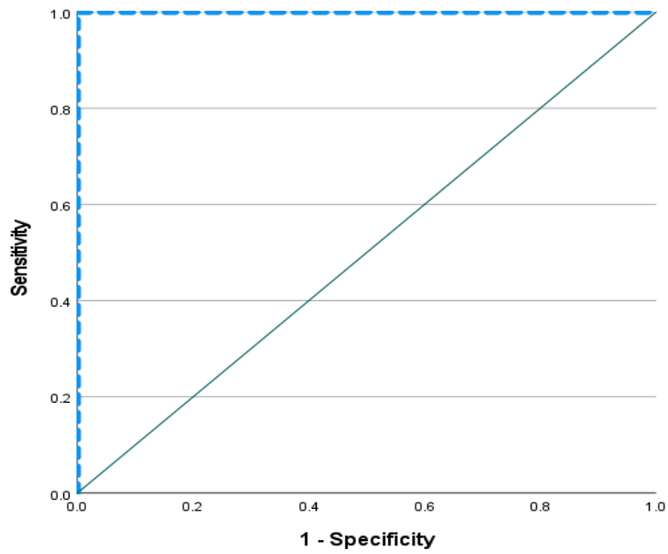

Figure 2: ROC curve showing performance of vitamin D in prediction of Alzheimer disease

DISCUSSION

Alzheimer's disease (AD) is one of the most important causes of dementia and account for about 70 percent of cases. Large numbers of cases were from low socioeconomic countries [17].

The present study revealed that there was low serum level of albumin and high level of AB42 in our patients group and this was in agreement with a study done by Kim et al. and Kuo et al. as they reported serum albumin is an independent risk marker for cognitive impairment in old people and this could be clarified by the low serum albumin level that is less binding to Aβ in blood, so increases in plasma Aβ concentration, leading to more deposition of Aβ in the brain parenchyma via decrease Aβ clearance because of its disequilibrium with plasma albumin [18-19].

Our study also was in accordance with Manafikhi et al. who also reported also plasma levels of both Aβ1-40 and Aβ1-42 were high in AD patients than people who were cognitively normal, they attributed this to normal facilitation of kidneys and liver to the systematic clearance of plasma AB via recognized transporter. So, an increase in serum amyloid B level occurs when there is a defect in the systematic clearance mechanism leading to more oxidative damage process through amyloid depositions that is taking place in Alzheimer's disease. Studies suggested that Aβ fibril formation may be inhibited by serum albumin by sequestrating Aβ monomers or oligomers. Many studies on humans have stated that a low level of serum albumin is related to cognitive dysfunction and AD disease [17-19].

One explanation is that malnutrition in dementia patients may contribute to low serum albumin level. Which may interpret the relationship between AD dementia and decrease serum albumin level [19].

Our study revealed that there was a low level vit D level in our patients and it was highly significant ,the level of prediction was ≤19 with area under curve 1.0 with 100% sensitivity and 96.9% specificity, these findings were in accordance with multiple studies (Schneider et al., Licher et al. and Olsson, et al. [20-21-22], they studied the relation between low vitamin D level and AD and a study done by Chai et al. to investigate the AD occurrence in relation to vitamin D deficiency. Many studies revealed that people with low serum vitamin D level (< 20ng/ml) had a more possibility of developing AD than people with sufficient vitamin D supplementation. Pinzon et al. (2023) mentioned in their meta-analysis showed the coincidence between vitamin D deficiency and the possibility of AD occurrence [23].

Vitamin D levels less than 25 ng/ml showed by the random effects model analysis are a potent risk factor for development of AD. This might be explained by the essential effect of vitamin D in cognitive function support and presence of receptors of vitamin D in the brain areas which play a role in cognitive functions and memory. The task of Vitamin D in neurotrophy, transmission, protection, and plasticity functions can explain the role of vitamin D deficiency in AD pathogenesis [24].

In our study , we found that serum albumin level had a significant difference between cognitively normal group and patients group (more in healthy than patients), while serum AB level was significantly higher in patient group (AD group) than cognitively normal group, these results were in agreement with Kim et al. who established that group with low serum albumin level has a positivity significant high Aβ level compared to the group with higher serum albumin level, they attributed this to the inverse relationships between serum albumin level with Aβ deposition into brain cells, potentiating the so-called sink theory which suggest the hypothesis of Aβ shifts from the brain to the plasma [19].

Conflict of interest

The authors declared that they have no conflicts of interest with respect to authorship and/or publication of this article.

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