Dementia, Thyroid Function and Serum Level of S100B

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Abstract: Background: Dementia is a syndrome of acquired intellectual deficit resulting in significant impairment of social and/or occupational functions. This syndrome has shared clinical outcome that derives from multiple etiologies. Alzheimer's disease (AD) is the most common dementia in the elderly. The potential of peripheral biochemical markers as complementary tools to the neuropsychiatric evaluation of these patients has claimed further attention. Clinical hypo- and hyperthyroidism are recognized causes of reversible dementia but prior studies relating thyroid stimulating hormone (TSH) levels to cognitive performance in clinically euthyroid persons have yielded inconsistent results. Methods:We evaluated serum levels of S100B and thyroid functions in 58 community-dwelling dementia patients (28 AD patients, 10 vascular, 16 mixed dementia and 4 other degenerative dementias) and in 56 elderly controls. All participants were subjected to comprehensive geriatric assessment, and dementia stage and subtype were verified using assessment tools. S100B and TSH levels were measured in serum. Results: Patients with dementia were significantly older than controls. They also had significantly lower levels of S100B than controls (24.59 ± 8.282 vs. 30.07 ± 9.26 pg/ml) (P =0.001). Yet, the difference between S100B levels among dementia subtypes was insignificant. Among dementia subtypes; thyroid status was normal in all dementia subtypes except for AD. Patients with AD had significantly high prevalence of thyroid disorders (12/28). No significant correlation was found between S100B and thyroid status of the cases. Conclusion: S100B levels are significantly lower among patients with dementia but cannot be used for differentiation between dementia subtypes. Thyroid disorders- both hypothyroidism and hyperthyroidism- are common among patients with AD and should be routinely screened in such patients.

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1.Introduction

Dementia is a syndrome of acquired intellectual deficit resulting in significant impairment of social and/or occupational functions. This syndrome has shared clinical outcome that derives from multiple etiologies [1].

Alzheimer's disease (AD) is a progressive brain disorder that results in memory impairment, personality alterations, global cognitive dysfunction, and functional impairments [2]. It is the most common dementia subtype in the elderly, accounting for 60-80% of cases, and it is estimated to affect more than 4 million in USA [3]. The lifespan of individuals diagnosed with AD is reduced by about 50% as compared with those of similar age without the disease, and the survival expectancy is negatively associated with the severity of the disease at the time of diagnosis [4]. Despite its impact, there is no definitive ante-mortem diagnostic test for AD, and when the clinical diagnosis is made, it is difficult to assess and follow the course of neural cells loss [5].

S100B is a brain derived proteins extensively studied as peripheral biochemical markers for brain injury [6-9]. It is a calcium binding protein physiologically produced and released predominantly by astrocytes [10,11]. Since its levels may increase in CSF and/or blood in several brain pathologies, it has been considered to be used as a marker of astrocytic damage/reaction [12-14]. Considering the prominent neural death observed in the course of AD and other degenerative dementias, several studies have attempted to clinically evaluate the levels of these proteins but have yielded contradictory findings [15-19].Still, those studies have strengthened the belief that S100B is implicated in the mechanisms underlying neuro-degeneration in dementia [20-22].

There is also growing evidence linking alterations in the endocrine system to the pathogenesis of AD and other dementias. Clinical hypothyroidism and hyperthyroidism have long been recognized as a potentially reversible causes of cognitive impairment [23,24] and the serum thyroid stimulating hormone (TSH) level has become a standard screening test for the routine evaluation of patients with suspected dementia[25].Further, several cross-sectional studies have observed that high [26] or low [27] TSH levels within the normal (clinically euthyroid) range are both related to poor

cognitive performance, although some other investigations [28, 29] failed to demonstrate such associations. More recently, thyroid dysfunction has emerged as a possible risk factor for the development of irreversible dementia, with several epidemiological studies implicating both hypo [30,31] and hyperthyroidism [32].

S100B is also a marker of cerebral damage and/or reduced integrity of the blood brain barrier. So, in patients with stroke or global hypoxia; a positive correlation between S100B and cognitive outcome has been established [33].

The major aim of our study was to evaluate serum S100B and thyroid function in elderly dementia patients and controls.

2.Methods

Participants and study design

This is a case-control study enrolling 58 consecutive community-dwelling late-onset dementia patients and 56 elderly sex matched controls, all being recruited from outpatient clinics of the Geriatrics and Gerontology department of Ain Shams University Hospitals.

Comprehensive geriatric assessment of all participants including; full medical and personal history, functional assessment using Activities of Daily Living questionnaire (ADL) [34], and screening for depression was done using Geriatric depression scale-15 items (GDS-15) [35].

Cognitive function of all the participants was screened for the presence of cognitive impairment using the Mini Mental State Examination (MMSE) [36] and those positive for cognitive impairment were then assessed using the Clinical Dementia Rating (CDR) scale. The CDR is a scale in which CDR = 0 denotes no cognitive impairment, and the remaining points indicate various stages of dementia: CDR = 1 - mild dementia, CDR = 2 - moderate dementia, and CDR = 3 - severe dementia [37].Then diagnosis dementia subtype was done using the modified Hachinski ischemic index (HII) which differentiates vascular from degenerative dementia (patients with scores less than 5 are classified as AD, scores over 7 are classified as multi-infarct dementia) [38], the revised Addenbrooke's Cognitive Examination (ACE-R) which was used for differentiation between AD and fronto-temporal dementia(FTD) [39] and probable NINCDS ADRDA criteria were used to confirm AD diagnosis [25].

Exclusion criteria for cases included patients with impaired MMSE who score normal in any of the remaining cognitive tests, and those who refused to participate.

A control group was composed of 56 community-dwelling elderly individuals who have no history of endocrine disorders especially thyroid disease and have no subjective cognitive complaints.

Venous blood samples for S100B and thyroid function (TSH) were collected by venipuncture with a tube (vacuum system).

Lab testing

Serum protein S100B was measured(in pg/ml) using sandwich enzyme immunoassay technique (Human S100B ELISA kit) for quantitative measurement of S100 B protein.

As for TSH level, it was measured using (Nova ELISA kit) on Stat Fax ELISA reader and levels between 0.35-4.9 µIU/ml were considered normal.

Ethical considerations

The study was approved by the Ethical Committee of the Faculty of Medicine, Ain Shams University. Informed written consent was obtained from participants, their nearest relatives, or both depending on the patient's cognition.

Statistical analysis

Descriptive statistics are presented with mean ± standard deviation for parametric variables, and absolute and percentage frequency for categories. Comparison of S100B serum levels between groups was made using one-way ANOVA with Tukey test, and Student's t test for independent samples. Comparison ANOVA followed by Tukey test and Student t test were used to analyze differences between serum levels of S100B (AD and controls) and CDR groups. A p value < 0.05 was considered statistically significant. Statistical analyses were carried out with the SPSS 16.0 for Windows

3.Results:

The mean age of the case group was 73.52 ± 10.44 years while that of the controls was 66.89 ± 5.31 years and the difference between the 2 groups was highly statistically significant (P <0.001).

Of the case group, 51.7% were males and 48.3% were females while in the control group, 50% were males and 50% were females.

Table 1. Comparison between S100B levels in cases and controls.

S100B (pg/ml)	**Group**	**N**	**Mean**	**±SD**	*P*
	Cases	58	24.59	±8.282	0.001
	Controls	56	30.07	±9.260	

Comparison between mean S100B levels in the case and control groups revealed a higher level of S100B (30.07 ± 9.26 pg/ml) in the control group than that of the case group (24.59 ± 8.282 pg/ml) and that difference was highly significant (*P* =0.001) (Table 1). Further examination of the correlation of S100B to the dementia subtypes showed that its level was lowest among patients with other degenerative dementias (17 ± 1.4 pg/ml) and highest among patients with vascular dementia (37.6 ± 36.5 pg/ml) but the difference was not statistically significant (*P*=0.247) (Table 2).

Table 2. Comparison of S100B levels among different dementia subtypes.

Mean S100B level	Type of dementia				F	*P*
	Alzheimer	Vascular	Mixed	Others	1.4	0.247
	25.6 ± 9	37.6 ± 36.5	23.5 ± 8.6	17 ± 1.4		

Among dementia subtypes; thyroid status was normal in all patients with vascular , mixed and other degenerative dementias subtypes while 10 out of the 28 patients diagnosed with AD had hypothyroidism and 2 had hyperthyroidism revealing a highly statistically significant difference (*P*=0.013) (Table 3).

Table 3. Comparison of thyroid function among different dementia subtypes.

		Type of dementia				Total
		Alzheimer	Vascular	Mixed	Other degenerative dementias	
Thyroid function	Normal	16	10	16	4	46
	Hypofunction	10	0	0	0	10
	Hyperfunction	2	0	0	0	2
Total		28	10	16	4	58

P=0.013

When participants were categorized according to their thyroid status into normal, hypothyroid and hyperthyroid groups, there was no statistical significant difference between the levels of S100B among the 3 groups (*P*=0.48) (Table 4).

Table 4. Comparison of S100B level in the different thyroid function categories.

	N	Mean	±SD	±Std. Error	Minimum	Maximum	*P* value
Normal	46	23.96	±7.58	±1.117	15	40	0.48
Hypothyroid	10	27.40	±11.698	±3.697	16	48	
Hyperthyroid	2	25.00	±0.008	±0.000	25	25	
Total	58	24.59	±8.288	±1.088	15	48	

4.Discussion:

According to most research, age is the strongest risk factor for brain degeneration whether resulting from vascular and/or neurodegenerative mechanisms [40] and in this study cases were indeed significantly older than controls (*P* <0.001).

Ante-mortem biomarkers of dementia subtypes are a big area of research and S100B has been investigated as a marker among others. For example, Green and colleagues and Fox and Freeborough found that patients with AD and fronto-temporal lobe dementia have significantly higher levels of S100B protein [41,42]. On the other hand, Chaves, and colleagues concluded that serum S100B can be used as a marker of AD and that levels of S100B are lower among patients with AD when compared to controls [43].

There are reports of higher S100B levels in other degenerative dementias including Parkinson's disease dementia [7] and amyotrophic lateral sclerosis [44] as well.

In this study, patients with dementia had statistically significantly lower S100B levels than controls and the difference between S100B among dementia subtypes was statistically insignificant.

Theories explaining the role of S100B in dementia pathogenesis range between the hypothesis

that extracellular S100B might participate in brain inflammation by activating astrocytes, microglia and neurons [45] and that an association between S100B gene polymorphism "rs2300403 intron 2 single nucleotide polymorphism" and poorer cognitive function exists [46].

The controversy about S100B levels among dementia patients was explained by one study that measured and compared S100B levels in the different stages of AD dementia, they concluded that S100B is a more sensitive marker in mild/moderate stages of AD dementia and its level is much lower in the late stages of the disease [21]. Since most the cases in this study were at the late stages of dementia using CDR, this could explain the lower levels of S100B.

As for the correlation of dementia and thyroid status, only the relation between thyroid function and AD has been studied. For instance, a case-control study found that participants with hypothyroidism were at more than double the risk for developing AD as their euthyroid counterparts [47]. Also data from the Maastricht Aging Study (MAAS) revealed that hypothyroidism is a predictor of decreased cognitive performance [26]. Hyperthyroidism as well has been reported to affect the risk of AD in elderly, and that increased levels of T4 and free T4 increase one's risk of developing AD [32,48-49].

This study interestingly found abnormal thyroid function –both hypothyroidism and hyperthyroidism– exclusively in patients with AD in an alarming high prevalence (42.86%) in a population that is supposedly regularly screened for thyroid dysfunction. In the meanwhile, all other dementia subtypes – degenerative and vascular– had normal TSH levels.

No study; as far as the researchers of study know, correlated S100B and thyroid function among patients with dementia. The correlation between them in this study showed that S100B levels were not significantly different among patients with normal, increased and decreased TSH.

Conclusion:

S100B levels are significantly lower among patients with dementia but cannot be used for differentiation between dementia subtypes. Thyroid disorders- both hypothyroid and hyperthyroid- are common among patients with AD and should be routinely screened.

Recommendations:

Thyroid function should be specifically screened for in patients with probable AD

Studies that follow up changes in serum S100B levels during the course of dementia subtypes are mandatory to ascertain the role of this marker in the diagnosis and follow up of dementia patients.

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