

Thyroid Hormones and Antibodies: An Economic Risk Factor to Remember

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Abstract

Background

Thyroid metabolites play an important role in cognitive functions. It is absolutely recommended to evaluate thyroid function tests (TFT) in the etiologic examination of cognitive disorders in dementia. In this study, we aimed to compare laboratory and cognitive data of patients aged under 65 years who presented to the other clinics with memory loss and who had been diagnosed with Alzheimer disease (AD).

Methods

We retrospectively reviewed the findings of patients aged under 65 years meeting the inclusion criteria of the study. Before admitting to our clinic, the patients who had memory problems were diagnosed with AD without screening TFT and started medications in different centers were screened. After performing thyroid screening for differential diagnosis in our first evaluation, patients who had diagnosed with disorders of thyroid hormones or/and antibodies and started to treat with thyroid medical therapy, included in our study.

There were three groups. GroupI patients had elevated values of fT3 and anti-TPO, normal anti-TG levels. GroupII patients had decreased fT3 and fT4 levels and normal values of antibodies. GroupIII patients had normal fT3-fT4 and elevated values of anti-TPO and anti-TG.

The patients of medications for AD (donepezil/rivastigmine/memantine/irregular medications) were recorded. The patients were followed-up for at 1st and 24th weeks after starting thyroid medical treatment. Follow-up of the patients was performed by the standardized mini mental state examination (MMSE), Verbal memory process, Boston naming test (BNT), Frontal assessment battery (FAB), Barthel activities of daily life index (BI) and Ideomotor apraxia test (IAT).

Results

We identified 55 (30 female-25 male) patients who could be included. The mean age of patients was 51.8 ± 7.6 (35-65). There were 40 (72.7%) patients in GroupI, 11 (20.2%) in GroupII, and 4 (7.1%) in GroupIII.

MMSE, BNT, FAB (similarities go-no-go and lexical fluency), IAT were found statistically significant differences in all groups. Cognitive tests were found to be improved in patients. Although BI was found significant improvement in GroupII at 24th week.

Conclusion

If there is a disorder of thyroid hormones and antibodies in patients with memory loss, the treatment of thyroid dysfunction should be planned before onset of anti-dementia medications.

Background

The thyroid gland controls the body's metabolic function. Glands produce hormones that regulate various functions in the body. Thyroid metabolites play an important role in the central nervous system, especially for cognitive functions [1]. Thyroid dysfunction, which may develop with aging, may have a negative effect on quality of life with impaired cognition. Hypothyroidism is a common cause of treatable cognitive impairment. The diagnosis of hypothyroidism in the elderly may be difficult, because hypothyroidism-associated symptoms of cognitive dysfunction may occur in older ages is generally attributed to the aging process or a neurodegenerative disease as likely Alzheimer disease (AD). A number of other reasons that bear similarity to AD must be excluded on clinical or laboratory grounds. Inadequate investigation of differential diagnosis of AD can result with starting to anti-dementia medications. Thus, the patient not only takes an unnecessary medication, but also health insurance faces an unnecessary economic cost. Moreover, while the disease is treatable, it remains untreated.

Therefore, it is absolutely recommended to evaluate thyroid function tests in the etiologic examination of cognitive disorders in dementia guidelines [2, 3]. However, it is seen that the patients who had memory problems in clinical practice are diagnosed with AD without testing any thyroid hormone and antibody analysis.

In this study, we aimed to compare laboratory and cognitive data of patients aged under 65 years who presented to the other clinics with the symptoms of memory loss and who had been diagnosed with AD and started treatment for AD, regardless of clinical or subclinical thyroid dysfunctions. Also, cognitive functions of the patients which had no response to AD therapy, had improvement with medical therapy for thyroid dysfunction.

Methods

We retrospectively reviewed the findings of patients aged under 65 years meeting the inclusion criteria of the study. Before admitting to our clinic, the patients diagnosed with AD and started medications in different centers were screened in our datas. These patients were admitted to the centers with memory problems, however, the functions of the thyroid glands were not evaluated because they were not considered as a cause of memory problems. After performing thyroid screening for differential diagnosis in our first evaluation, patients who had diagnosed with disorders of thyroid hormones or/and antibodies and started to treat with thyroid medical therapy, included in our study.

The patients were divided into three groups according to serum thyroid values. Group I patients had elevated values of free triiodothyronine (fT3) and anti-thyroid peroxidase antibody (anti-TPO), normal anti-thyroglobulin antibody (anti-TG) levels. Group II patients had decreased fT3 and free thyroxine (fT4) levels and normal values of antibodies. Group III patients had normal fT3-fT4 and elevated values of anti-TPO and anti-TG.

Optimum value ranges of the patients were evaluated; thyroid stimulating hormone (TSH) 0.45–5.33 µIU/mL, fT3 2.5–3.9 pg/mL, fT4 0.62–1.13 ng/dL, anti-TPO < 9.0 IU/mL, anti-TG 0–4.0 IU/mL in the laboratory for serum examinations.

The patients of medications for AD (donepezil 10 mg/day, rivastigmine 9,5 mg/day, memantine 20 mg/day) were recorded. The patients who take their medications irregularly or not use instead of physicians' recommendation were included as another group for medical treatment evaluation. The certain duration of anti-dementia drugs therapy could not be recorded because the anti-dementia drugs were started in other centers. We had no detailed information about exact duration.

Data of the patients who attended the outpatient clinic follow-up regularly and whose neuropsychological tests were performed both at the first admission and at 24th week were recorded. The patients with other causes of dementia were excluded from the study.

The patients were followed-up for at least 6 months after starting thyroid medical treatment. Follow-up of the patients was performed by the standardized mini mental state examination (MMSE), Verbal memory process test (VMPT), Boston naming test (BNT), Frontal assessment battery (FAB), Barthel activities of daily life index (BI) and Ideomotor apraxia test (IAT). MMSE is a simple screening test that is important for cognitive impairment [4]. In this study, it was evaluated over 30 points depending on literacy status of the patients. VMPT involve tasks measuring verbal memory capacity including learning of word lists, story recall or logical memory and learning sequence of paired words [5] In the evaluation, immediate memory score, complete learning points (number of attempts ensuring complete learning), total learning score (total number of words recalled in each trial) and long-term recall scores are determined. In this study, to evaluate verbal learning and working memory (verbal), immediate learning, delayed recall and total recall criteria scores were used. The objective of BNT is to measure a person's ability to name illustrated objects in 20 seconds [6]. The FAB examines similarities (conceptualization), lexical fluency (mental flexibility), motor series (programming), conflicting instructions (sensitivity to interference), go-no go (inhibitory control), prehension behaviour (environmental autonomy). In similarities test, the patient is asked to comprehend the relationship between two objects of the same category. Patients with dysfunction of the frontal lobe can not establish a relationship between objects and can not establish concrete features or similarity. In lexical fluency, people must recall as many words as possible according to a given one letter in one minute. In the motor series test, the patient is asked to do the "punch-edge-palm" sequence (Luria's three step test). In the go-no go test, if the researcher hits twice in the conflicting instructions test, the patient should strike once. Thus, cases should follow verbal commands and avoid doing what they see. In this test, case should inhibit the previous response with the same stimulus.

BI is a scale used to measure the individual's performance in daily living activities. Nutrition, self-care, toilet activities, bathing, stair-climbing, dressing, bowel care, bladder care, mobility, and transfer are evaluated over 100 points in 10 categories.

IAT consists of 20 items in 4 different categories (facial, upper extremity, instrumental and complex) each containing 5 items. Each item is given by verbal instruction and the patient is asked to do it. When it is not

correct or the patient does not react, the patient is shown movement and asked to mimic. The patient's score is presented from a scale one to 60 points [7].

Statistical analysis

The Kolmogorov-Smirnov test was used to test the normality of the distribution of variables. Continuous parametric variables were compared using the independent-sample t-test. Continuous nonparametric variables were compared using the Mann-Whitney U-test. The continuous variables were reported as mean \pm standard deviation. Pearson's chi-squared test was used to detect the relationship between the two categories of variables. Statistical significance was set at $p < 0.05$. All analyses were performed using IBM SPSS Statistics, Version 13.0. (Armonk, NY: IBM Corp.)

Results

Patients

We identified 55 (30 female-25 male) patients who could be included in the study. All cases were between the age of 35–65 (the mean age; 51.8 ± 7.6). There were 40 (72.7%) patients in Group I, 11 (20.2%) patients in Group II, and 4 (7.1%) patients in Group III. (Table 1) The distribution of patients with memory loss according to age was 4, 9, 8, 11, 18, 5 patients respectively. (35–40, 41–45, 46–50, 51–55, 56–60, 61–65 years) (Table 1)

Table 1
Number and percentage of patients' gender and age distribution.

	N
Group I (increased fT3 and anti-TPO)	40 (%72.7)
Donepezil	23
Rivastigmine	7
Memantine	4
Irregularly or not use treatment	6
Group II (decreased fT3 and fT4)	11 (%20.2)
Donepezil	3
Rivastigmine	1
Memantine	1
Irregularly or not use treatment	6
Group III (increased anti-TPO and anti-TG)	4 (%7.1)
Donepezil	2
Irregularly or not use treatment	2
fT3: free triiodothyronine, fT4: free thyroxine, anti-TPO: anti-thyroid peroxidase antibody, anti-TG: anti-thyroglobulin antibody	

Also, the groups had detailed information about medical treatment for memory problems. In Group I, the patients continued to use donepezil (n = 23), rivastigmine (7) and memantine (4). Six patients who used the medical treatments irregularly or not take any medications in Group I. In Group II, 3 patients were treated with donepezil, one patient was treated with rivastigmine, and one memantine. Six patients had irregular medical treatment in Group II. In Group III, two patients were treated with donepezil. Table 2 shows the distribution of the patients according to anti-dementia drugs.

Table 2

Groups for serum levels of thyroid hormones and antibodies and medications for memory loss.

GROUP I (n = 40)	1st week	24th week	p
Mini Mental State Examination	18.22 ± 4.17	21.6 ± 3.11	0.001
Boston Naming Test	11.23 ± 2.36	13.1 ± 1.4	0.004
Verbal Memory Processes Test			
Immediate Learning	2,90 ± 1,19	3,12 ± 1,40	ns
Delayed Recall	5,54 ± 1,12	6,80 ± 1,74	ns
Total Recall	5,25 ± 1,19	6,75 ± 2.65	ns
Frontal Assessment Battery			
Similarities	1.27 ± 0.10	2.12 ± 0.81	0.001
Go-no go	0.90 ± 1.20	1.52 ± 1.02	0.001
Lexical fluency	1.21 ± 1.1	2.02 ± 0.91	0.001
Barthel Activities of Daily Life Index	81.2 ± 2.02	85.41 ± 3.21	ns
Ideomotor Apraxia Test	41,02 ± 13,05	46,62 ± 10,63	0.001
ns: p > 0.05			

Cognitive Evaluation

The cognitive tests including MMSE, VMPT, BNT, FAB, BI and IAT performed at the 1st week and 24th week were compared in all groups.

MMSE, BNT, FAB (similarities go-no-go and lexical fluency), IAT were found statistically significant differences in all groups. Cognitive tests were found to be improved in patients. Although BI was found significant improvement in Group II at 24th week.

Tables 3,4 and 5 shows all differences of cognitive batteries in all groups.

Table 3

The comparison of Group I patients' (fT3 and anti-TPO high, anti-TG normal) cognitive tests at the 1st and 24th week

GROUP II (n = 11)	1st week	24th week	p
Mini Mental State Examination	16.24 ± 4.1	20.6 ± 2.01	0.001
Boston Naming Test	10.31 ± 1.41	14.10 ± 2.12	0.001
Verbal Memory Processes Test			
Immediate Learning	2,76 ± 1,21	3,03 ± 1,34	ns
Delayed Recall	5,31 ± 1,34	5.41 ± 1,14	ns
Total Recall	4,35 ± 1,01	4,75 ± 2.45	ns
Frontal Assessment Battery			
Similarities	1.21 ± 0.10	2.52 ± 1.16	0.001
Go-no go	0.76 ± 1.21	2.02 ± 0.01	0.001
Lexical fluency	1.33 ± 1.10	2.12 ± 0.76	0.001
Barthel Activities of Daily Life Index	79.2 ± 2.02	83.31 ± 4.12	0.001
Ideomotor Apraxia Test	44,02 ± 11,15	47,62 ± 8,63	0.001
ns: p > 0.05			

Table 4

The comparison of Group II patients' (fT3-T4 low, anti-TPO and anti-TG normal) cognitive tests at the 1st and 24th week

GROUP III (n = 4)	1st week	24th week	p
Mini Mental State Examination	21.12 ± 3.21	25.21 ± 2.43	0.001
Boston Naming Test	14.31 ± 2.44	16.10 ± 1.74	0.004
Verbal Memory Processes Test			
Immediate Learning	3,01 ± 1,12	3,11 ± 1,32	ns
Delayed Recall	6.01 ± 1,13	6,04 ± 1,81	ns
Total Recall	5,96 ± 1,20	6.00 ± 2.03	ns
Frontal Assessment Battery			
Similarities	2.11 ± 0.10	2.96 ± 0.02	0.004
Go-no go	0.91 ± 1.26	1.62 ± 1.16	0.012
Lexical fluency	2.11 ± 1.10	2.96 ± 0.01	0.013
Barthel Activities of Daily Life Index	86.2 ± 3.02	88.41 ± 2.26	ns
Ideomotor Apraxia Test	44,01 ± 11,05	49,12 ± 8,13	<.000
ns: p > 0.05			

Table 5

The comparison of Group III patients' (fT3-fT4 low, anti-TPO and anti-TG high) cognitive tests at the 1st and 24th week

GROUP III (n=4)	1 st week	24 th week	p
Mini Mental State Examination	21.12 ± 3.21	25.21 ± 2.43	0.001
Boston Naming Test	14.31 ± 2.44	16.10 ± 1.74	0.004
Verbal Memory Processes Test			
Immediate Learning	3,01 ± 1,12	3,11 ± 1,32	ns
Delayed Recall	6.01 ± 1,13	6,04 ± 1,81	ns
Total Recall	5,96 ± 1,20	6.00 ± 2.03	ns
Frontal Assessment Battery			
Similarities	2.11 ± 0.10	2.96 ± 0.02	0.004
Go-no go	0.91 ± 1.26	1.62 ± 1.16	0.012
Lexical fluency	2.11 ± 1.10	2.96 ± 0.01	0.013
Barthel Activities of Daily Life Index	86.2 ± 3.02	88.41 ± 2.26	ns
Ideomotor Apraxia Test	44,01 ± 11,05	49,12 ± 8,13	< .000
ns: p > 0.05			

In our study, the efficacy of thyroid dysfunction therapy was observed in patients who were previously diagnosed with AD and treated with AD medication, but did not experience cognitive improvement. The most prominent tests of improvement were found in FAB in which the three groups showed significant differences in similarities, go-no go and lexical fluency, MMSE, BNT and IAT.

Discussion

Treatment of dementia depends on its cause. Potentially reversible dementias should be identified and treatment considered. Treatable cognitive disorders have been reported to be between 0–30% in all dementia patients. [8, 9, 10] However, even the types of dementia classified as reversible do not result in complete treatment and complete recovery in cognitive functions.

Thyroid dysfunction is one of the most important causes of cognitive impairment. Cognitive dysfunction due to thyroid disorder can be seen alone or co-morbidity with other types of dementia. Thyroid disorders, which may be seen as hypothyroidism or hyperthyroidism, have been reported to be a risk factor for the progression of irreversible dementia [11].

Thyroid hormones have broad and significant effects in the central nervous system starting from fetal life and continuing throughout adult life [12]. Deficiency of thyroid hormones has been associated with decreased growth, decreased number of cells in the dentate gyrus, and unusual neuronal migration and maturation, which may explain cognitive-behavioral deficiencies. In the thyroid hormone deficiency, cortex cells accumulate smaller and denser than normal; this leads to a reduction in the progression of axon and dendritic processes. Axonal density decreases and the probability of axodendritic interaction decreases approximately 80% [13, 14, 15]. Also, thyroid hormones accelerate the myelin process; it can affect cell migration and controls cell differentiation and maturation of specific neuronal populations.

Thyroid function should be performed while physicians evaluate cognitive functions, but disruptions can be seen in clinical practice. In a retrospective study from Japan's large database, it was found that only 32.6% of 262,279 patients over 65 years of age who newly prescribed anti-dementia medication had thyroid function tests before the initiation of antidementia medication. [16]. This approach should be a result of physicians' assumptions that cognitive dysfunction is caused by primary dementia, such as AD, whose prevalence increases with age [17]. Another point of view is that physicians tend to avoid possible harm that may be caused by unnecessary examinations and treatments in elderly patients. The prevalence of thyroid dysfunction was reported 4.4% in population aged over in elderly patients [18]. These publications have been reported with data from older patients. However, in our study, although thyroid hormone and/or antibody tests were not performed in patients presenting with memory loss under 65 years at the first admission in other clinics. So, unnecessary anti-dementia medication was started instead of thyroid treatment.

Hypothyroidism is more common in the elderly than in young people [19]. One study found an inverse linear relationship between serum fT3 and risk of AD [20]. In our study, 11 patients (20.2%) with hypothyroidism were detected in Group II. There was a statistically significant difference in the first and 24th week cognitive tests with appropriate thyroid treatment.

Although hypothyroidism is more known, hyperthyroidism has important effects on cognitive function. In the Rotterdam study, 9446 people aged 65 years were followed for an average of 8 years and the risk of dementia was reported to be higher in people with high free thyroxine [21]. In our study, 40 (70.2%)

patients with elevated fT3 levels were detected and significant improvement was observed in thyroid therapy and cognitive tests. In the literature, not only hyperthyroidism but also subclinical hyperthyroidism has been reported to be associated with high risk for dementia [22].

When thyroid function tests are performed as fT3, fT4 and TSH, evaluation of anti-TPO and anti-TG antibodies is often overlooked. In our study, 4 (7.1%) patients had normal thyroid hormone levels but high antibodies and cognitive improvement was detected with thyroid treatment. Cognitive impairment should also be considered in the evaluation of thyroid antibodies despite normal thyroid hormone levels [23].

However, AD is the most common type of dementia diagnosed for patients who had memory problems. In clinical practice, we can see that young patients were diagnosed with AD and started to treated with anti-dementia medications quickly. All treatment guidelines recommend to exclude the other causes of dementia that can be treatable reasons in patients with memory loss. Thus, besides the treatment is safe and effective, it can be prevented in the economic burden of unnecessary medications. Our study is a good example of this approach.

In our study, patients who admitted to the clinics with the symptoms of memory problems had an erroneous diagnosis with incomplete diagnostic methods during rapid examinations. Alzheimer's drugs were started to the patients both created an unnecessary and risky treatment for the patients and also created an economic and psychosocial burden for them. The evaluation of patients in our center has been important. The memory problems of our patients were caused by treatable dementia. Also, a cheaper treatment is sufficient for the treatment of dementia.

The most important problem in our study is the question of why we continue the anti-dementia drugs of the patients. The answer to this question may be that we want to see that patients respond well to thyroid therapy. Besides, anti-dementia drugs of the patients seem to be stopped after 24 weeks. Also, cognitive functions of the patients which had no response to AD therapy, had improvement with medical therapy for thyroid dysfunction. However, in recent studies, the fact that thyroid hormones are a risk factor for neurodegenerative diseases may also consider restarting similar drugs in the future.

Worldwide costs of dementia are enormous. The increase in costs arises from increased number of patients with dementia and in increases in per person costs. In 2015, the costs of dementia estimated at United States \$818 billion and increase of 35% since 2010 [24]. In Turkey, minimum cost of anti-dementia drug is \$12.65 (€11.62), maximum cost is \$64.88 (€59.7) for a month. Whereas, costs of thyroid screening blood test and medical treatment for thyroid for a month are \$7.06 (€6.5) in Turkey. Although the certain duration of anti-dementia drugs therapy could not be recorded in our study, the difference between the costs of thyroid screening-medical treatment and unnecessary AD medications for a month is remarkable.

The limitations of our study are the fact that the number of patients was not similar in all groups, that the follow-up of the patients could be recorded retrospectively up to 24 weeks and that dementia treatment/costs ratios could not studied.

Conclusion

If there is a disorder of thyroid hormones and antibodies in patients with memory loss, the treatment of thyroid dysfunction should be planned before onset of anti-dementia medications.

Abbreviations

TFT: Thyroid function tests; AD:Alzheimer disease; MMSE:standardized mini mental state examination; VMPT:Verbal memory process test, BNT:Boston naming test; FAB:Frontal assessment battery; BI:Barthel activities of daily life index; IAT:Ideomotor apraxia test; fT3:free triiodothyronine; fT4:free thyroxine; anti-TPO:anti-thyroid peroxidase antibody; anti-TG:anti-thyroglobulin antibody; TSH:Thyroid stimulating hormone.

Declarations

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Availability of data and materials

The datasets during and / or during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Z.Ö.A, G. U., D. İ. A., A. A. and D. Ö. A and contributed to the study design and concept. Z.Ö.A, G. U., D. İ. A., A. A. and D. Ö. A contributed to analysis and interpretation of data. A. A., and D. Ö. A. were responsible for primary data analysis. Z.Ö.A, G. U., D. İ. A., A. A. and D. Ö. A. contributed to the writing and review. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study complies with the Helsinki Declaration, and approval was obtained from the ethics committee of Eskişehir Osmangazi University. Written informed consent for enrolment was obtained from all patients or their authorized legal representative.

Consent for publication

Consents for publication were obtained from the participants or their legal surrogates.

Competing interests

The authors declare that they have no competing interests.

References

1. Bunevicius R. Thyroid disorders in mental patients. *Current Opinion in Psychiatry*. 2009;22(4):391–5.
2. Ngo J, Holroyd-Leduc JM. Systematic review of recent dementia practice guidelines. *Age Ageing*. 2015;44(1):25–33.
3. Hort J, O'Brien JT, Gainotti G, Pirttila T, Popescu BO, Rektorova I, et al. EFNS guidelines for the diagnosis and management of Alzheimer's disease. *Eur J Neurol*. 2010;17(10):1236–48.
4. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research* 1975;12:189–198.
5. Oktem Tanor O. Oktem Verbal Memory Processes Test in Turkish (Sozel Bellek Surecleri Testi (Oktem-SBST)). 1 ed. Ankara: Turkish Psychologists Society; 2011.
6. Miotto EC, Sato J, Lucia M, Camargo CH, Scaff M. Development of an adapted version of the Boston naming test for portuguese speakers. *Revista Brasileira de Psiquiatria*. 2010;32:279–82.
7. Kertesz A, Ferro JM. Lesion size and location in ideomotor apraxia. *Brain*. 1984;107:921–33.
8. Clarfield AM. The decreasing prevalence of reversible dementias: an updated meta-analysis. *Arch Intern Med*. 2003;163(18):2219–29.
9. Djukic M, Wedekind D, Franz A, Gremke M, Nau R. Frequency of dementia syndromes with a potentially treatable cause in geriatric in-patients: analysis of a 1-year interval. *Eur Arch Psychiatry Clin Neurosci*. 265(5) (2015) 429–438. Harisingani R. Where are the reversible dementias? *J Am Geriatr Soc*. 2005;53(6):1066–1068.
10. Van Osch LADM, Hogervorst E, Combrinck M, Smith AD. Low thyroid-stimulating hormone as an independent risk factor for Alzheimer disease. *Neurology*. 2004;62(11):1967–71.
11. 10.1002/jcp.28198
Bavarsad K, Hosseini M, Hadjzadeh MA, Sahebkar A. The effects of thyroid hormones on memory impairment and Alzheimer's disease. *J Cell Physiol*. Jan 24. (2019)
<https://doi.org/10.1002/jcp.28198>. [Epub ahead of print].
12. Madeira MD, Cadete-Leite A, Andrade JP, Paula-Barbosa MM. Effects of hypothyroidism upon the granular layer of the dentate gyrus in male and female adult rats: A morphometric study. *Journal of Comparative Neurology*. 1991;314(1):171–86.

13. Montero-Pedrazuela A, Venero C, Lavado-Autric R, Fernández-Lamo I, García-Verdugo JM, Bernal J, Guadaño-Ferraz A. Modulation of adult hippocampal neurogenesis by thyroid hormones: Implications in depressive-like behavior. *Mol Psychiatry*. 2006;11(4):361–71.
14. Thompson CC, Potter GB. Thyroid hormone action in neural development. *Cereb Cortex*. 2000;10(10):939–45.
15. Sakata N, Okumura Y. Thyroid function tests before prescribing anti-dementia drugs: a retrospective observational study. *Clin Interv Aging*. 2018;13:1219–23.
16. Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, Brodaty H, et al. Defeating Alzheimer's disease and other dementias: a priority for European science and society. *Lancet Neurol*. 2016;15(5):455–532.
17. Tan ZS, Beiser A, Vasan RS, Rhoda A, Sanford A, Kiel DP, et al. Thyroid function and the risk of Alzheimer disease: the Framingham Study. *Arch Intern Med*. 2008;168(14):1514–20.
18. Bensenor IM, Olmos RD, Lotufo PA. Hypothyroidism in the elderly: diagnosis and management. *Clin Interv Aging*. 2012;7:97–111.
19. Quinlan P, Horvath A, Wallin A, Svensson J. Low serum concentration of free triiodothyronine (FT3) is associated with increased risk of Alzheimer's disease. *Psychoneuroendocrinology* 2019;99:112–119.
20. Chaker L, Wolters FJ, Bos D, Korevaar TI, Hofman A, van der Lugt A, et al. Thyroid function and the risk of dementia: The Rotterdam Study. *Neurology*. 2016;87(16):1688–95.
21. Rieben C, Segna D, da Costa BR, Collet TH, Chaker L, Baumgartner C, et al. Subclinical thyroid dysfunction and the risk of cognitive decline: a meta-analysis of prospective cohort studies. *J Clin Endocrinol Metab*. 2016;101(12):4945–54.
22. Segers K, Braconnier P, Corazza F, Divano L, Mabrouk A, et al. Subacute cognitive deterioration with high serum anti-thyroid peroxidase antibodies: two cases and a plea for pragmatism. *Psychogeriatrics*. 2013;13(3):175–9.
23. Wimo A, Guerchet M, Ali GC, Wu YT, Prina A, Winblad B, et al. The worldwide costs of dementia 2015 and comparison with 2010. *Alzheimers Dement*. 2017;13(1):1–7.