

“Thyrotropin Level and Cognitive Performance: Baseline Results From the Elsa-Brazil Study”

Claudia Szlejf^{1,2}

¹Center for clinical and epidemiological research, Hospital Universitario, Univeristy of Sao Paulo, Sao Paulo, Brazil.

²Instituto Nacional de Geriatria, Mexico City, Mexico.

Corresponding Author: Claudia Szlejf . ¹Center for clinical and epidemiological research, Hospital Universitario, Univeristy of Sao Paulo, Sao Paulo, Brazil. ²Instituto Nacional de Geriatria, Mexico City, Mexico Telephone: +52155 36611013 E-mail: claujeru@gmail.com

Received date: January 17,2018; **Accepted date :** February 02, 2018; **Published date:** March 05, 2018.

Cite this Article: Claudia Szlejf (2018) Commentary Thyrotropin level and cognitive performance: Baseline results from the ELSA-Brasil Study and Life Style **Doi:** <http://doi.org/05.2018/1.10002>.

Copyright: © 2018. Claudia Szlejf, This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract:

Dementia Practice guidelines lack recommendations on subtle thyroid function alterations, such as subclinical thyroid disease or thyrotropin (TSH) near the reference limits. Several studies investigated the association of TSH or subclinical thyroid dysfunction with cognitive impairment in older adults. However, neuropathologic alterations begins a long time earlier than cognitive complaints, and little is known about the role of subtle thyroid alterations on cognitive impairment in middle-aged adults. This article comments on the recent work of Szlejf et al. that investigated the association of TSH and subclinical thyroid disease in a large sample of Brazilian middle-aged adults, free of dementia. The study found that lower TSH was associated with poorer performance on executive function.

Keywords TSH, thyroid function, cognition, cognitive test

Introduction

Current guidelines recommend dosing serum thyrotropin (TSH) when evaluating individuals with cognitive complaints because overt thyroid dysfunctions are reversible causes of cognitive decline.¹ However, dementia practice guidelines lack recommendations on subtler thyroid function alterations and practitioners may face uncertainty when dealing with patients with cognitive decline and subclinical thyroid disease or TSH near the reference limits. The better understanding of the role of TSH levels and subclinical thyroid disease on cognitive performance may help improve the management of these patients.

In a recent article, Szlejf et al. demonstrated that low-serum TSH levels were associated with poorer cognitive performance in Brazilian adults without overt thyroid dysfunction.² The aim of the study was to investigate the association of cognitive performance with serum TSH and subclinical thyroid disease in middle-aged adults from a middle-income country. It differed from previous studies in the field, since most of them were conducted in older adults from developed countries. Using baseline data from the ELSA-Brasil study, a cohort of individuals aged 35-74 years at baseline, free of dementia, 10,362 participants were included in this complete case analysis.

The main exclusion criteria were age \geq 65 years, overt thyroid dysfunction, use of medications that can alter thyroid function and that indicate neurologic or psychiatric disease, and previous stroke. Participants with altered baseline TSH were screened for subclinical thyroid disease through free T4 (FT4) measurements. Cognition was evaluated by the CERAD's delayed word recall test, semantic verbal fluency test, and the trail making test version B. Sociodemographic characteristics, cardiovascular risk factors, and depression were considered as possible confounders and used for adjustment in the analysis. Participants in the first TSH tertile had worse performance in the trail making test than participants in the middle TSH tertile. After restricting the analysis for the 9769 participants with TSH within the normal range, the results were similar, with a negative association between the first TSH tertile and performance on the trail making test. Moreover, one-unit increase in TSH had a discrete, although significant, protective effect on performance on the trail making test (OR 0.93, 95% CI 0.87-0.99). When participants were divided according to thyroid function, neither subclinical hypothyroidism nor subclinical hyperthyroidism were associated with performance on the cognitive tests.



The authors mentioned some limitations of the study, mainly the cross-sectional design, and not exploring the association between FT4 and cognitive performance. The authors also comment on possible pathophysiological pathways that could explain the findings, such as: (1) low TSH levels could reflect an excess of thyroid hormones, which have neurotoxic effects,^{3,4} (2) the brain disease that is leading to cognitive decline may also reduce thyrotropin-releasing hormone, leading to a mild central hypothyroidism with lower TSH secretion and reduced thyroid hormone turnover,^{3,4} and (3) a non-causal association between TSH and cognitive impairment, due to non-addressed confounders. It is important to notice that the only significant association was with the trail making test, that evaluates executive function, processing speed, and visuospatial ability.⁵ These cognitive domains may be the first ones to alter in the cognitive decline related to low TSH.

Previous studies, most of them conducted in older adults, have found similar or correlated results with the study of Szlejf et al.² Lower TSH and subclinical hyperthyroidism were associated with higher risk of dementia in a cross-sectional analysis of a cohort of Brazilian older adults, although when restricting the sample to participants with TSH within the normal range, the association was no longer significant.⁶ In the Korean Longitudinal Study of Health and Aging, participants with incident mild cognitive impairment or dementia had lower baseline TSH than participants without these conditions.⁷ Chaker et al. found that higher TSH lowered the dementia risk in the Rotterdam Study, a prospective cohort of middle-aged and older adults.⁸ Higher TSH was also associated with better performance on cognitive tests and better Clinical Dementia Rating scores in community-dwelling older adults.⁹ In a systematic review including 23 studies, 14 cross-sectional and longitudinal well-designed and well-powered studies demonstrated association of low TSH within the reference interval or subclinical hyperthyroidism with dementia or cognitive impairment.⁴ A meta-analysis with cross-sectional and prospective studies did not find an association between subclinical hypothyroidism and cognitive function in older adults.¹⁰ Another recent meta-analysis of prospective studies also did not show that subclinical hypothyroidism was a risk factor for dementia or cognitive decline, although subclinical hyperthyroidism did increase the risk of dementia.¹¹

On the other hand, some works showed results that are notably different. In an analysis of the Framingham original cohort, the lowest and highest tertiles of TSH were associated with dementia risk after a mean follow-up of 12.7 years. However, when restricting the analysis to participants with TSH within the normal range, these associations were no longer significant.¹² A longitudinal study with very old adults from the Netherlands did not find an association between TSH levels and cognitive function at baseline and after 3 years of follow-up.¹³ In another longitudinal Dutch study, TSH level at baseline was not associated with risk of dementia or with brain atrophy on magnetic resonance imaging. However, non-demented subjects with higher FT4 had more hippocampal and amygdalar atrophy.¹⁴ In the Women's Health and Aging Study, a cohort of community-dwelling older women with some degree of disability and TSH within the normal range, baseline TSH was not associated with baseline cognitive performance on the Mini-Mental State Examination and with cognitive decline after 3 years of follow-up. However, participants with total thyroxine in the lowest tertile had a greater decline in cognitive performance.¹⁵ In a cross-sectional analysis of the Healthy Aging Study in England and Wales, participants with higher TSH had lower scores on the Mini-Mental State Examination.¹⁶ Also, Beydoun et al. demonstrated that higher TSH was associated with poorer performance in cognitive tests in cross-sectional analysis of data from two different American cohorts of adults.^{17,18}

Although there are many studies in the field, controversy still remains regarding the association of cognitive performance with TSH and subclinical thyroid disease. The work of Szlejf et al. amplifies the scope of previous studies, since it was conducted in a very large sample of middle-aged adults, free of dementia and overt thyroid disease. As the pathological alterations of dementia precedes the clinical manifestations, it is pivotal to conduct further studies on the influence of thyroid functioning in cognitive impairment in middle-aged adults. Knowing that TSH near the lower limit of the reference range is associated with poorer performance in executive function, processing speed, and visuospatial ability opens a new window of opportunities for future studies.

References

1. Ngo J, Holroyd-Leduc JM. (2015) Systematic review of recent dementia practice guidelines. *Age Ageing*.44(1):25-33. doi:10.1093/ageing/afu143.
2. Szlejf C, Suemoto CK, Santos IS, et al.(October 2017) Thyrotropin level and cognitive performance: baseline results from the ELSA-Brasil Study. *Psychoneuroendocrinology*. doi:10.1016/j.psyneuen.2017.10.017.
3. Annerbo S, Lökk J.(2013) A clinical review of the association of thyroid stimulating hormone and cognitive impairment. *ISRN Endocrinol*.2013:856017. doi:10.1155/2013/856017.
4. Gan EH, Pearce SHS. Clinical review: (2012) The thyroid in mind: cognitive function and low thyrotropin in older people. *J Clin Endocrinol Metab*.97(10):3438-3449. doi:10.1210/jc.2012-2284.
5. Greenlief CL, Margolis RB, Erker GJ. (1985)Application of the Trail Making Test in differentiating neuropsychological impairment of elderly persons. *Percept Mot Skills*.61(3f):1283-1289. doi:10.2466/pms.1985.61.3f.1283.
6. Bens or IM, Lotufo PA, Menezes PR, Scazufca M. (2010)Subclinical hyperthyroidism and dementia: The Sao Paulo ageing & Health study (SPAH). *BMC Public Health*.10. doi:10.1186/1471-2458-10-298.
7. Moon JH, Park YJ, Kim TH, et al.(2014) Lower-but-normal serum TSH level is associated with the development or progression of cognitive impairment in elderly: Korean longitudinal study on health and aging (KLOSHA). *J Clin Endocrinol Metab*.99(2):424-432. doi:10.1210/jc.2013-3385.
8. Chaker L, Wolters FJ, Bos D, et al. (2016) Thyroid function and the risk of dementia: The Rotterdam Study. *Neurology*.87(16):1688-1695..
9. Ojala AK, Schalin-Jäntti C, Pitkälä KH, Tilvis RS, Strandberg TE.(2016) Serum thyroid-stimulating hormone and cognition in older people. *Age Ageing*.45(1):155-157. doi:10.1093/ageing/afv160.
10. Akintola AA, Jansen SW, van Bodegom D, et al. (2015)Subclinical hypothyroidism and cognitive function in people over 60 years: a systematic review and meta-analysis. *Front Aging Neurosci*.7. doi:10.3389/fnagi.2015.00150.
11. Rieben C, Segna D, da Costa BR, et al. (2016) Subclinical Thyroid Dysfunction and the Risk of Cognitive Decline: a Meta-Analysis of Prospective Cohort Studies. *J Clin Endocrinol Metab*.101(December):jc20162129. doi:10.1210/jc.2016-2129.
12. Tan ZS, Beiser A, Vasan RS, et al.(2008)Thyroid function and the risk of Alzheimer disease: The Framingham study. *Arch Intern Med*. 168(14):1514-1520. doi:10.1001/archinte.168.14.1514.
13. Gussekloo J, van Exel E, de Craen AJM, Meinders AE, Frölich M, Westendorp RGJ.et.al (2004) Thyroid status, disability and cognitive function, and survival in old age. *JAMA*.292(21):2591-2599. doi:10.1001/jama.292.21.2591.



14. De Jong FJ, Den Heijer T, Visser TJ, et al. (2006) Thyroid hormones, dementia, and atrophy of the medial temporal lobe. *J Clin Endocrinol Metab.*91(7):2569-2573. doi:10.1210/jc.2006-0449.
15. Volpato S, Guralnik JM, Fried LP, Remaley a T, Cappola a R, Launer LJ.(2002) Serum thyroxine level and cognitive decline in euthyroid older women. *Neurology.*58(7):1055-1061. doi:10.1212/WNL.58.7.1055.
16. Hogervorst E, Huppert F, Matthews FE, Brayne C.(2008) Thyroid function and cognitive decline in the MRC CognitiveFunction and Ageing Study. *Psychoneuroendocrinology.*33(7):1013-1022. doi:10.1016/j.psyneuen.2008.05.008.
17. Beydoun MA, Beydoun HA, Shroff MR, Kitner-Triolo MH, Zonderman AB.(2012) Serum leptin, thyroxine and thyroid-stimulating hormone levels interact to affect cognitive function among US adults: Evidence from a large representative survey. *Neurobiol Aging.* 33(8):1730-1743. doi:10.1016/j.neurobiolaging.2011.05.008.
18. Beydoun MA, Beydoun HA, Kitner-Triolo MH, Kaufman JS, Evans MK, et.al (August2013)Zonderman AB. Thyroid hormones are associated with cognitive function: moderation by sex, race, and depressive symptoms. *J Clin Endocrinol Metab.*98:3470-3481. doi:10.1210/jc.2013-1813.