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View Point Paper

Mental and Cognitive Disorders in Older People With Subclinical Thyroid Conditions

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Abstract

It is well known that thyroid disorders are associated with impairments in cognitive function and the appearance of symptoms of mental disorders. Thyroid hormone replacement therapy was shown to ameliorate these symptoms. During aging, subtle changes in regulation of the hypothalamus-pituitary-thyroid axis and in serum concentrations of the pituitary thyroid-stimulating hormone

(TSH) can be observed, along with decreased sensitivity of peripheral tissues to thyroid hormones. Since decline in cognitive function is concomitant to aging, there is a question on the influence of these subtle changes in serum thyroid hormone concentrations on age-related cognitive decline. Due to the fact that both, the progression of cognitive function decline, and the appearance of symptoms of mental disorders, in older people, are depended on accumulation of comorbidities during aging, associations of these disorders with subclinical thyroid conditions should be assessed in the context of age and the existing comorbidity patterns.

Abbreviations

TSH: the pituitary thyroid-stimulating hormone
T3: triiodothyronine
T4: thyroxine

Introduction

Thyroid hormones, triiodothyronine (T3) and thyroxine (T4), have a major influence on metabolic processes in the human body. The tight regulation of secretion of thyroid hormones by the hypothalamic-pituitary-thyroid neuro-endocrine axis, and undisturbed responsiveness of peripheral tissues on the action of these hormones, are prerequisites for the optimal function of many organs and systems. The pituitary thyroid-stimulating hormone (TSH) has an essential role in this regulation [1].

Thyroid dysfunctions, in addition to metabolic impairments associated with increased insulin resistance, are the most common endocrine disorders in a population, with the prevalence increasing with age [2]. The most common causes of thyroid dysfunctions refer to the thyroid gland-related pathologies [1]. After introduction of the iodised salt programmes in many regions of the world, and the subsequent reduction of the prevalence of iodine deficiency dependent goiter, thyroid autoimmune disorders, manifested as Graves` disease or Hashimoto`s thyroiditis, have become the main causes of thyroid dysfunctions.

For both, overt hyperthyroidism and hypothyroidism, associations with increased cardiovascular morbidity and mortality have been confirmed [3]. Overt hypothyroidism is well-known as a reversible cause of cognitive impairment and depression [4]. Overt hyperthyroidism is also known to be associated with impairments in concentration, mood changes, and alterations in perception [5].

Symptoms of thyroid disorders are usually non-specific and the diagnosis is based on laboratory testing. In the last decades, due to technological advancements, there has been a dramatic increase in testing serum thyroid hormones. This revealed the subtle deviations in serum TSH and thyroid hormone concentrations, that were found to be particularly frequent in elderly individuals [3-5].

Since there are changes in serum concentrations of thyroid hormones with age, and cognitive impairments are concomitant to aging, the question has raised on whether thyroid dysfunctions in older individuals are causally associated with the decline in cognitive functions [6].

Aging and Cognitive and Mental Disorders

Mild cognitive impairment, defined as a state in the continuum of cognitive decline, ranging from normal cognition to dementia, which can be objectively measured by the available psychological tests, is frequently registered in people of older age [7]. Some aspects of cognitive function are more affected during normal aging than some others. Manifestations of age-related cognitive decline include impairments in working memory, information processing speed and long-term memory [6]. Only a small part of these individuals show a progression towards more advanced stages of cognitive decline and incident dementia [8]. Although factors and mechanisms which drive this progression are not well understood, it is known that behavioural and lifestyle factors and chronic diseases accelerate aging and age-related decline in both, physical and cognitive performances [9]. Some chronic conditions, including diabetes, chronic heart failure, and chronic kidney disease, are particularly associated with increased risk of cognitive decline [10-12]. That these conditions do not increase the risk only of vascular dementia, but also of the neurodegenerative Alzheimer`s disease, the proofs are common cardiovascular risk factors that are known to share between these two types of dementia [13].

Symptoms of mental disorders are frequent in older people but less specific than in people of younger age and often shared between physical and cognitive conditions [14]. These symptoms appear in a wide range of variations, including anxious feeling, dysphoria, apathy, worrying, trouble sleeping, irritability, and fatigue. The risk of the appearance of symptoms of mental disorders increases with the level of comorbidities [15]. The presence of symptoms of mental disorders was found to increase the risk of cognitive impairment and dementia [16].

Aging and Subclinical Thyroid Conditions

Subclinical thyroid conditions, including subclinical hypothyroidism, defined as increased serum TSH concentrations, with normal circulating free T4 and T3, and subclinical hyperthyroidism, defined as serum TSH concentrations below the reference range, with normal free T4 and T3, are more prevalent in older people, than in those of younger age [4-6]. Very mild variations in TSH, that may be observed in older people, are not likely to reflect thyroid dysfunctions, but rather pathophysiology changes associated with aging [4]. Variations in distribution of pathophysiology changes in an older population, is the reason of the significant variations in the upper reference range of TSH (measured at 97.5 percentile), as found in different study groups.

Studies on changes in serum concentrations of thyroid hormones and TSH during aging, are complicated by the presence of a number of confounding factors in older population, such as chronic diseases, multiple medications, nutritional deficiencies, variations in thyroid antibody status, and increased prevalence of non-thyroidal disease (a state of decreased tissue supply of thyroid hormones in the absence of intrinsic thyroid disease) [5,6].

In general, studies indicate the age-dependent decrease in serum concentrations of total and free (biologically active) T3, while concentrations of total and free T4 remain unchanged. In the healthy elderly, thyroid function appears to be well preserved until the eight decade of life, and a reduction of serum free T3 is

observed only in the oldest old (>85). Regarding TSH, some studies show unchanged serum TSH concentrations, while some other show a mild increase of TSH with age. More rarely, there is a mild decrease in serum TSH concentrations. Serum concentrations of reverse T3 (rT3), a metabolite of thyroid hormones, was found to increase with age, in line with the increasing prevalence of non-thyroidal disease (which is characterised with increased rT3, low free T3, and normal or low TSH).

Associations Between Subclinical Thyroid Conditions and Cognitive and Mental Disorders in Older People

There is a number of published studies performed among older people, both cross-sectional and longitudinal, on associations between cognitive performances and thyroid function. Results of these studies are conflicting with respect to questions, such as, which indicator of thyroid function is the most relevant as a marker of cognitive function decline, and for which specific domains of this function. Differences in results are considered to be due to differences in characteristics of individuals in the samples, age range, cognitive tests used for analysis, and due to higher variations in TSH and cognitive functions, known to characterize aging [4-6].

In general, studies show that even variations within the reference ranges of serum TSH and thyroid hormones, in healthy elderly individuals without signs of thyroid disorders, can affect certain aspects of cognitive function. Studies also show that the elderly with subclinical hypothyroidism might be more vulnerable to cognitive impairments than their younger counterparts. This finding is important from the practical perspective, as it indicates the need for systematic screening of elderly individuals on both, different aspects of cognitive function, and serum TSH concentrations. This is even more important when taking into account that subclinical hypothyroidism is rather common in older population, with the prevalence increasing up to 20% in people old 75 years or more [6].

Yet, there is no consensus on recommendations for screening and treatment of older people with higher normal values of TSH or subclinical hypothyroidism. This is because many uncertainties still exist in this area of research and clinical decision making. Studies suggest that there may be a different situation in older individuals aged 60 to 80 years, than in those older than 80-85 years. In the former group, the correlation with decreased cognitive function was found to be stronger for T4 than TSH, which may reflect the direct role of thyroid hormones in regulation of the brain haemodynamics and metabolism. On the contrary, in the oldest population group, positive correlations were found between features of subclinical hypothyroidism (indicated with increasing TSH and decreasing free T4) and preserved cognitive function and better survival, which may indicate the protective adaptive role of decreased thyroid function, as a response to the catabolic processes associated with advanced age.

Studies also show associations between subclinical hyperthyroidism and cognitive decline, but the results are less consistent than in case of subclinical hypothyroidism [5]. It has been emphasized that low serum TSH values, as a part of subclinical hyperthyroidism syndrome, must be considered with a caution, as it can reflect the presence of comorbidities and the associated non-thyroidal disease, or may be due to thyroid medications that are administered to patients with hypothyroidism, or may reflect autoimmune thyroid

disorders. Thus, it is important, in case of a suspicion to subclinical hyperthyroidism, to include information on comorbidities, medications, and thyroid antibodies.

Anxiety in subclinical thyroid disorders has been rarely examined [17]. In the recent meta-analysis, the association was confirmed between subclinical hypothyreoidism and depression [18].

Conclusions

Aging is associated with accumulation of chronic diseases, and higher variations in serum values of TSH and thyroid hormones, cognitive function performances and symptoms of mental disorders. To get more precise answers on the question on whether there are causal relationships between these subtle disorders that are concomitant to aging, these disorders should be considered together, and in the context of age and the comorbidity patterns.

Bibliography

1. Boelaert, K. & Franklyn, J. A. (2005). Thyroid hormone in health and disease. *Review. J Endocrinol., 187,* 1-15.

2. Iwen, K. A., Schröder, E. & Brabant, G. (2013). Thyroid hormones and the metabolic syndrome. *Eur Thyroid J., 2,* 83-92.

3. Barbesion, G. (2019). Thyroid function changes in the elderly and their relationship to cardiovascular health: a mini-review. *Gerontology, 65*(1), 1-8.

4. Leng, O. & Razvi, S. (2019). Hypothyroidism in the older population. *Thyroid Res., 12,* 2.

5. Gan, E. H. & Pearce, S. H. S. (2012). The thyroid in mind: cognitive function and low thyrotropin in older people. *J Clin Endocrinol Metab., 97*(10), 3438-3449.

6. Begin, M. E., Langlois, M. F., Lorrain, D. & Cunnane, S. C. (2008). Thyroid function and cognition during aging. Review. *Curr Gerontol Geriatr Res.,* 474868.

7. Ward, A., Arrighi, H. M., Michels, S. & Cedarbaum, J. M. (2012). Mild cognitive impairment: disparity of incidencia and prevalence estimates. *Alzheimer`s Dementia, 8*(1), 14-21.

8. Kaduszkiewicz, H., Eisele, M., Wiese, B., *et al.* (2014). Prognosis of mild cognitive imapirment in general practice: results of the German AgeCoDe Study. *Ann Fam Med., 12*(2), 158-165.

9. Robertson, D. A., Savva, G. M. & Kenny, R. A. (2013). Frailty and cognitive impairment - a review of the evidence and causal mechanisms. *Ageing Res Rev., 12,* 840-851.

10. Čelutkienė, J., Vaitkevičius, A., Jakštienė, S. & Jatužis, D. (2016). Expert Opinion-Cognitive Decline in Heart Failure: More Attention is Needed. *Cardiac Failure Rev., 2*(2), 106-109.

11. Yaffe, K, Falvey, C., Hamilton, N., *et al.* (2012). Diabetes, glucose control, and 9-year cognitive decline among older adults without dementia. *Arch Neurol., 69*(9), 1170-1175.

12. Bugnicourt, J-M., Godefroy, O., Chillon, J. M., *et al.* (2013). Cognitive disorders and dementia in CKD: The neglected kidney-brain axis. *J Am Soc Nephrol., 24*(3), 353-363.

13. Santos, C. Y., Snyder, P. J., Wu, W. C., *et al.* (2017). Pathophysiologic relationship between Alzheimer's disease, cerebrovascular disease, and cardiovascular risk: A review and synthesis. *Alzheimer's & Dementia (Amsterdam, Netherlands), 7,* 69-87.

14. Valiengo, L. da C., Stella, F. & Forlenza, O. V. (2016). Mood disorders in the elderly: prevalence, functional impact, management and challenges. *Neuropsychatric Dis Treat., 12,* 2105-2114.

15. Barnett, K., Mercer, S. W., Norbury, M., *et al.* (2012). Epidemiology of multimorbidity and implications for health care, research and medical education: A cross-sectional study. *Lancet, 380*(9836), 37-43.

16. Leoutsakos, J. S., Wise, E. A., Lyketsos, C. G. & Smith, G. S. (2019). Trajectories of neuropsychiatric symptoms over time in healthy volunteers and risk of MCI and dementia. *Int J Geriatr Psychiatry., 34*(12), 1865-1873.

17. Gönnen, M. S., Kisakol, G., Cilli, A. S., *et al.* (2004). Assessment of anxiety in subclinical thyroid disorders. *Endocrine J., 51,* 311-315.

18. Loh, H. H., Lim, L. L., Yee, A., *et al.* (2019). Association between subclinical hypothyroidism and depression: an updated systematic review and meta-analysis. *BMC Psychiatry, 19*(1), 12.