Cognitive functions and thyroid hormones secretion disorders

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Summary

The functioning of the thyroid gland is of great importance for the formation, maturation and activity of the central nervous system. The association of clinical thyroid dysfunction with mental disorders, including cognitive impairment, seems to be well documented. Abnormal concentrations of thyroid hormones can lead to deterioration of cognitive processes through changes in neurotransmission, intensification of oxidative stress, or impact on β-amyloid transformation and glucose metabolism in the central nervous system. Doubts concern mainly subclinical forms of thyroid dysfunction. According to some data, they are supposed to be related to the state of cognitive functions and to be one of the factors accelerating the mechanisms leading to degeneration of the brain tissue and, consequently, development of dementia. The results of studies on the correlation of thyroid activity with cognitive functions and the possible beneficial effects of hormonal supplementation on cognitive processes, however, bring contradictory results, which may be at least partly due to large methodological problems. One should also not exclude a reverse correlation, where the ongoing neurodegenerative process would affect thyroid function, e.g., by the changed production and secretion of thyroliberin. Despite several decades of intensive research, the explanation of this relationship is still far from conclusive.

Key words: dementia, subclinical hypothyroidism, thyrotropin

Introduction

Thyroid hormones play a key role in the process of cerebral development and maturation, affecting such diverse processes as neuronal growth and integration, cell proliferation, myelination, synaptogenesis and the synthesis of several enzymes essential for the metabolism of neurotransmitters [1]. Any reduction in the availability of these hormones caused by environmental factors, such as iodine deficiency, abnormalities of the maternal thyroid gland during pregnancy or abnormalities in thyroid devel-
opment in the newborn can lead to very serious and usually established neurological deficits and mental disorders, most often in the form of mental retardation. In light of data, especially those from recent years, it seems that while thyroid hormones affect the formation of the entire brain, their special role is related to the development and functioning of areas related to mood regulation and the cognitive sphere [2].

However, the role of thyroid hormones does not end when the brain is shaped. They are necessary for the proper functioning of the central nervous system (CNS) throughout life, being involved in many brain processes and playing a special importance in maintaining the ability to create new synaptic connections, i.e., shaping the so-called brain plasticity [3]. In addition, adequate secretion of thyroid hormones is necessary for the proper functioning of virtually all neurotransmission systems of the brain [4, 5].

Clinical forms of thyroid dysfunction

According to the level of thyroid hormones and thyrotropin (thyroid-stimulating hormone – TSH), the following disorder forms are most often distinguished:

- overt (full-symptom) hypothyroidism – reduced plasma thyroxine (fT\(_4\)) concentration is accompanied by elevated levels of TSH;
- overt hyperthyroidism – high levels of fT\(_4\) and/or triiodothyronine (T\(_3\)) with suppressed TSH secretion;
- subclinical (latent) hypothyroidism – elevated TSH, fT\(_4\) within the normal range;
- subclinical hyperthyroidism – inhibited secretion of TSH with normal levels of fT\(_4\) and T\(_3\).

While there are no major doubts concerning the relationship between the overt illnesses and mental disorders, the views of researchers are divided regarding the subclinical forms.

Subclinical hypothyroidism (SH) is sometimes divided into two subgroups depending on the concentration of TSH. SH of the first stage is recognized when the TSH level is within 0.1-0.4 mU/l and the second when the values are lower than 0.1 mU/l.

The prevalence of SH in the general population is estimated at 5-17%, with a pronounced increase with age: in people over 60, it is estimated at 20% in women and 9.5% in men, while at 74 years of age at, respectively, 21% and 16% [6, 7]. However, it should be stipulated that epidemiological data differ significantly between individual studies. For example, in the publication of Vadiveloo et al. [8] the prevalence was estimated at only 0.63% of the general population. The observation, which does not appear to raise any doubts, is the fact that the prevalence of SH increases with aging.

Attention should be paid to significant methodological difficulties faced by researchers attempting to reliably assess the functioning of the thyroid gland in the elderly. With age, there are changes in both the production and metabolism of thyroid hormones [9]. In healthy people aged 61 – 90 years, both T\(_4\) and T\(_3\) secretion are
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reduced; however, serum levels, especially of $T_4$, may be normal or even somewhat

raised. This is due to the slower rate of $T_4$ decomposition in the body at this age [9].

Some studies question the relationship between aging and progressive impairment

of the functioning of the thyroid gland. Decreased level of TSH and higher level of

$\text{fT}_4$, which are observed at an older age, are explained by a decrease in hepatic clear-

ance of thyroid hormones, which is supposed to result in TSH secretion inhibition and,

consequently, a decrease in serum hormone concentration [10].

**Thyroid hormones and mental disorders**

Due to the importance of thyroid hormones for the proper development and

functioning of the brain, the occurrence of mental disorders in various diseases of the

thyroid gland is understandable. Hyperthyroidism is usually accompanied by anxiety
disorders and mood disorders, including both manic and depressive states. Extreme

hyperactivity of the thyroid gland may even lead to delirium. Hypothyroidism, on

the other hand, is associated with psychomotor retardation, increased drowsiness and
cognitive impairment of varying severity. Particularly the last one is of great interest

with respect to its scope, intensity and further prognosis [11].

A lot of evidence has been collected that, especially in the elderly, the cognitive

sphere is the most often compromised domain in the case of thyroid dysfunction [12],

with cognitive impairment being associated with both hypothyroidism and hyperactivity

of the gland. Cognitive dysfunctions in this case concern mainly memory, visuo-spatial
organization, attention and reaction time [11]. Impairment of cognitive functions due to
hypothyroidism may reach the stage at which it may cause difficulties in differentiation

with dementia due to CNS degeneration. Such conditions, sometimes reversible, have

been called ‘pseudodementia’ and they are one of the reasons for the need to perform

a comprehensive examination before making a diagnosis of dementia.

**Cognitive functions in hypothyroidism and hyperthyroidism**

Cognitive impairment associated with hypothyroidism is usually an element of

a wider psychopathological picture, which also includes concentration disorders, mood

changes and sometimes perceptual disorders. Hyperthyroidism may also cause cognitive
dysfunctions, but of a lower intensity than in the case of hypothyroidism. The distur-
bances that are most frequently observed in studies include: worse performance on
tests of attention and memory as well as disturbances in the rate of synchronization of
visual stimuli with motor activities [13].

In the groups of middle-aged hypothyroid patients, a deterioration in global
cognitive performance, attention deficit, and deterioration in learning, memory and
psychomotor performance were observed. A quite controversial issue, being at the
same time of great clinical significance, is the possibility of recovery from the above
disorders after leveling the thyroid hormone levels. In studies by Wekking et al. [14], it
was indicated that at least some of the cognitive dysfunctions, especially in the area of attention and verbal memory, continued after the substitution treatment with L-thyroxine preparations. Their presence was also confirmed after more than five years since the normalization of thyroid hormone levels. Similarly, in the case of hyperthyroidism, particularly severe, only a partial return of cognitive functions is observed [15].

Compared to the clinical forms of hypo – and hyperactivity, we have far less data on cognitive disorders in subclinical forms of hypothyroidism [16]. This is important because SH is much more common in the elderly and often accompanies the already existing cognitive impairment, while in some studies the relationship between SH and the degree of progression of cognitive impairment is postulated [11]. The presence of such a correlation (or only coincidence, as discussed below) is indicated by a series of longitudinal studies, in which the emergence of cognitive dysfunction leading to dementia was more clearly marked in people with subclinical hypothyroidism [10].

From the clinician’s point of view, the key is to answer the question whether the therapeutic intervention based on substitution treatment in the group of people with SH results in the disappearance of already visible disorders. In the Correia et al. study [17], the administration of L – thyroxine led to the normalization of test results in the field of verbal memory [17]. In this case, however, the therapeutic intervention occurred in people whose cognitive decline was insignificant and did not fulfill criteria for the diagnosis of dementia.

A separate issue is the influence of fluctuations in hormone levels on cognitive processes. Such studies were conducted only in the population of middle-aged people, in whom a positive correlation was found between the degree of concentration fluctuation and cognitive dysfunctions [18]. At the same time, close correlation was observed with other elements of the mental state, especially with mood, which is part of the widely described phenomenon of generating mental disorders in response to changes in the state of the internal environment. The more rapid are the broadly understood changes, whether psychological, social or, as in the discussed case, biological (endocrine), the greater the probability of psychopathological symptoms.

**Parameters for assessing correlation between cognitive dysfunction and thyroid activity**

In studies on the relationship between thyroid gland activity and cognitive functions, there is no consensus on the choice of the best assessment parameter. Some researchers [19] point to the greater importance of TSH, the higher values of which seem to show a stronger correlation with worse cognitive functioning. Others, in turn [20], point to T₄ and fT₄, with high concentration and better cognitive functioning association. One of the studies [21] indicated a faster progression of cognitive disorders in people with lower T₄ levels during the three-year follow-up period in the absence of a similar correlation for TSH.
A reliable link between the assessment of thyroid hormone concentrations and the degree of cognitive impairment is difficult due to several confounding factors, such as mood disorders, which, being associated with the functioning of the thyroid gland, have an influence on cognitive functions. Consideration of these and other factors quite often leads to the negation of the postulated relation of thyroid hormones and cognitive functions, at least in subclinical conditions [22].

On the other hand, quite a frequent objection to this type of research is related to the use of inadequate methods for measuring cognitive functions. It should be remembered that, especially in the case of SH, possible disorders will have a slight severity. The use of tools designed to assess dementia in such studies, which is often the case, may not be appropriate. More detailed neuropsychological examinations show much more often the relationship between thyroid hormone levels and cognitive functioning. An example of this may be the observations of Correia et al. [17], which describe, among others, the deterioration of spatial and verbal memory in people with SH. Interestingly, these disorders normalized after six months of substitution therapy.

Neuropsychological assessment in these studies is supported by neurobiological confirmation. Functional magnetic resonance imaging (fMRI) [23] in people with SH shows reduced brain activity in the frontal lobes responsible for executive functions, which are directly related to the operational memory. After the inclusion of substitution treatment, normalization in the fMRI image was parallel to clinical (neuropsychological) improvement.

Results from studies with fMRI have been confirmed by other neuroimaging techniques. In the positron emission tomography (PET) study [24], both clinical and subclinical forms of hypothyroidism were shown to be associated with reduced glucose metabolism in areas important from the point of view of cognitive functioning. Similar as in the fMRI assessment, re-normalization of metabolism after substitution treatment with L-thyroxine was observed.

**TSH and fT<sub>4</sub> as a risk factor for faster progression of cognitive function disorders**

Mentioned above is the postulated relationship of hypothyroidism with a faster progression of cognitive dysfunction, which in turn may lead to the development of dementia. It is also indicated that a low level of TSH with a high level of thyroxine may be a risk factor for the development of Alzheimer’s disease. The correlation is especially evident in people with mildly impaired cognitive functions (not meeting the criterion for diagnosing dementia), in whom conversion to Alzheimer’s dementia is significantly more common [25]. It should be noted that this applies not only to clinical, but also subclinical forms. At the same time, however, in people with Alzheimer’s dementia, there is no relationship between the level of TSH and T<sub>4</sub> (which are within the reference values) and the severity of cognitive impairment [26].
In some studies, no significant relationship was observed between thyroid hormone levels and the degree of progression of cognitive impairment. Discrepancies in results may result from significant methodological difficulties. Changes in hormone levels may be determined by many factors, which makes the assessment of the test compound difficult because it requires very frequent, preferably constant, monitoring of thyroid peripheral hormone levels, which in practice has been performed in only a small percentage of studies. Research by Wahlin et al. [27] is of great significance, as it presented a relationship between fluctuations in TSH level and the accompanying impairment of verbal fluency and visuo-spatial functions. These fluctuations also predicted a significant deterioration in episodic memory during the six-year observation period.

In another study, attention is focused on the importance of fT4 assessment, where a high value (but maintained within the reference range) was associated with a greater risk of developing cognitive dysfunctions. Hogervorst et al. [28] associate increased fT4 levels with the generation of oxidative processes, the intensity of which increases with age. A possible contribution from oxidative stress will be discussed below. The value of this study is diminished by the fact that the assessment of cognitive functions is based not on a reliable neuropsychological assessment, but only on the results of the Mini-Mental State Examination (MMSE).

Above we have discussed SH as a risk factor for the development of dementia disorders. A similar relationship may also apply to subclinical forms of hyperthyroidism, which by some authors are also recognized as risk factors of Alzheimer’s disease. The relationship seems to be to some extent sex-conditioned and is more pronounced in women [29].

Neurophysiological basis of the observed disorders

Indication of the mechanisms responsible for the postulated relationship of thyroid hormones with the state of cognitive function is not a simple matter. Neurotransmission disorders, oxidative stress, β-amyloid transformation or glucose metabolism, among others, can play a significant role. The involvement of thyroid hormones in fundamental brain functions, including the functioning of neurotransmission systems, seems indisputable. Thyroid hormones regulate, among others, the degree of dopamine receptor density and the activity of key enzymes for catecholaminergic transmission pathways [30].

Hypothyroidism leads to a reduction in the concentration of serotonin in the brain, as well as its precursor, tryptophan (5-HP), whereas chronic supplementation of thyroid hormones raises their level in the CNS [4]. This may indicate a close association with mood regulation, and it should be borne in mind that depressive disorders typically decrease cognitive performance. In addition, there are indications of their correlation (or only coincidence) with the pathogenesis of dementia.

The serotonergic system is not the only neurotransmitter pathway in the brain in which thyroid hormones are involved. They show a connection with practically all
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of the CNS neurotransmission systems, including the noradrenergic system and cholinergic activity [31]. The hormones themselves also behave as neurotransmitters – it was noted that T₃ accumulates in neuronal terminals (reaching high concentration in synaptosomes) from where it is released in a calcium-dependent mechanism [32].

The essence of dementia is degenerative processes of brain tissue, where thyroid hormones may also contribute. It was indicated that a higher level of fT₄ is associated with greater atrophy of temporal structures, including the hippocampus [33]. Attempts have been made to understand the mechanism responsible for triggering the above changes. Oxidative stress generated by fT₄ and leading to neuronal damage is indicated as a possible cause. It is postulated that any increase in fT₄ level, also when still within the normal range, may increase the risk of accelerating degenerative changes by enhancing oxidative processes [34]. Particularly in hyperthyroidism, associated with a general speeding up of metabolism, there is a clear increase in the concentration of free radicals and further activation of lipid peroxidases, which may be associated with a decrease in the activity of antioxidant enzymes [35].

The involvement of fT₄ in neurodegenerative mechanisms is indirectly supported by the results of clinical trials that demonstrated an inverse relationship between fT₄ level and verbal fluency. In addition, at higher concentrations, faster progression of working memory and visuo-spatial functions disorders was observed [12].

What is interesting is the similarity of the CNS image in single-photon emission computed tomography (SPECT) of people with hyperthyroidism with associated cognitive impairment and those with the diagnosis of Alzheimer’s disease. In both states, disturbances in balance between the cholinergic and adrenergic system in the brain were also observed [36]. The association of thyroxine with the intensification of oxidative stress and further destruction of neurons results in some clinicians being cautious with administering this hormone supplementation, especially in the elderly [28].

There are also observations that directly link T₃ to β-amyloid transformations. It is possible that T₃ affects both intracellular and extracellular β-amyloid levels. This means that thyroid hormones can be involved in the pathogenetic mechanisms of Alzheimer’s disease [37]. On the other hand, in some animal studies, thyroid hormones inhibited the expression of a gene responsible for the synthesis of β-amyloid precursor [21].

It is possible that the mechanism of destructive influence of thyroid hormones in abnormal levels on the central nervous system is different in hyperthyroidism and hypothyroidism. Animal studies indicate that hypothyroidism may reduce the number of cells in the dentate gyrus and reduce pyramidal cells and density of dendritic processes in the CA1 region of the hippocampus. This is a crucial region in terms of cognitive processes, especially memory functions. The above changes were associated with a deterioration in the performance of memory functions and spatial orientation abilities [38].

The observed changes can be explained by the fact that a low level of thyroid hormones deprives the brain (probably in a different way in different areas) of sufficient energy supplementation by reducing glucose metabolism. This results, first
and foremost, in neurotransmission disorders, which in the clinical evaluation reveals itself in the form of deterioration of cognitive functions. In the case of chronic low glucose consumption, gradual structural changes may be expected. It is thus not a coincidence that in the study of Reiman et al. [39] in people with Alzheimer’s disease, a faster progression of dementia is associated with low glucose metabolism. It was also shown that glucose metabolism disturbances may precede the clinical onset of dementia even by decades.

Considering the possible mechanisms of the negative impact the thyroid hormones’ abnormal levels have on cognitive functions, the influence of these disorders on the cardiovascular system should not be overlooked. Vascular mechanisms underlie many cases of dementia, not only the vascular dementia (VaD). There are many premises indicating the involvement of these mechanisms also in the pathogenesis of the so-called primary degenerative dementia, including Alzheimer’s disease [40].

Looking at the possible involvement of thyroid hormones in the development of cognitive disorders, and perhaps dementia, one should consider the inverse relationship. Degeneration of the brain tissue affects several areas, including those responsible for regulating the activity of the thyroid gland. An example is the paraventricular nucleus of the hypothalamus containing thyrotropin-releasing hormone (TRH) cells, which is connected by projection routes to many brain regions, including the arcuate nucleus of the hypothalamus and the dorsal nucleus of the hippocampus. It is unlikely that degenerative changes appearing in these structures would have no effect on the secretion of TRH. In addition, the paraventricular nucleus is not the only site for the secretion of TRH. Neurons of the septal nucleus, the pre-ocular region, raphe nuclei, medulla and spinal cord nuclei are also its source and it is understood that each of these areas may be affected in a different way by the dementia process, which significantly changes the potential regulating the secretion of TSH [41].

The correlations observed and described above, although indisputable, can only be coincidental and it cannot be ruled out that the postulated associations of thyroid hormones secretion disorders and cognitive impairment have no direct causal connections.

**Limitations**

Determination of the possible role of thyroid hormones in the pathogenesis of cognitive disorders is difficult. The doubts regarding the selection of the most suitable marker are mentioned above. Assessment of thyroid function, especially in the elderly, is also difficult due to the frequent presence of other diseases that are important for distribution and metabolism of all substances. The importance of pharmacotherapy, including the use of several psychotropic drugs that may influence serum thyroid hormone levels, cannot be overlooked [42].

Administered therapy, but also some other factors, may affect the activity of deiodinases (responsible for reductive elimination of iodine during conversion of T₂ to T₃), especially the 5’D2 form (5’-deiodinase type 2) present in the brain. For example, the
administration of desipramine increases the activity of 5’D2 in most brain regions [43]. This is substantial because the level of T₃ in the CNS depends mainly on the local (brain) resources of T₄. The penetration of T₃ through the blood-brain barrier through active transport seems to play a secondary role [12].

It should be noted here that the 5’D2 activity and consequently the T₃ levels in the brain are affected by a whole range of other factors. The secretion of deiodinase is partially regulated by the circadian rhythm, but this effect decreases with age. This may be related to progressive calcification and, later in life, degenerative changes in the suprachiasmatic nuclei [44]. As a consequence, in older people there is a shift (“acceleration”) of some of the rhythms, including the secretion of TRH. This is another element significantly hindering the reliable assessment of thyroid function [45].

The level of active T₃ in the brain is also influenced by exposure to stressors, during which very strong activation of 5’D2 occurs. It should be noted, however, that the above observation is based solely on the animal model [46].

The activity of 5’D2 also depends on a number of other factors, each of them with the potential to significantly alter T₃ levels in the brain. Sleep disturbances (shortness of sleep), glucose level lowering, several-day reduction in calorie intake are just examples of situations that may affect the concentration of the above-mentioned enzyme [42]. This creates exceptionally great difficulties with correct interpretation of assessed hormone levels (peripheral by necessity) and, in addition, the effect of pharmacotherapy (and other factors) may be different in relation to individual deiodinases. For example, the aforementioned desipramine in the animal model did not have a significant impact on 5’D1, which is important in the process of deionization outside the CNS (mainly in the liver, kidneys, muscles and thyroid).

Finally, a matter often overlooked in studies in which the peripheral concentrations of thyroid hormones are assessed is the problem of referencing the obtained results to their actual level within the brain. The transport of both T₄ and T₃ across the blood-brain barrier is an active, energy-consuming process, dependent on specific transporters – OATP1c1 (organic anion transport polypeptide) for T₄ and MCT8 (monocarboxylate transporter) for T₄ and T₃. In addition, MCT8 transports T₃ of both systemic and brain origins to neurons. It is easy to imagine that, for example, the MCT8 mutation will significantly reduce the T₃ concentration, resulting in isolated neuronal hypoactivity that will, at least at present, be completely beyond the possibilities of research observation [47].

These are just a few examples of how difficult it is to try to explain intra-cerebral mechanisms based on measurements of peripheral parameters. This problem may be partially explained by large discrepancies in the results of studies on the relationship between the functioning of the thyroid gland and cognitive functions.
Summary

It should be clearly emphasized that despite several decades of intensive research, explanation of the relationship between functioning of the thyroid gland and the state of cognitive function is far from conclusive. Despite a certain amount of data indicating a correlation between thyroid function and cognitive processes, there are still many doubts. While in the case of clinical forms of thyroid disorders such an association seems obvious, additionally supported by the experimental model and neurobiological research, the importance of discrete changes in thyroid hormone concentrations in the development of cognitive disorders, and especially in the pathogenesis of dementia processes, is far from being proven. It seems more likely that the degenerative process changes the functioning of the gland, which in turn further intensifies the clinical symptoms of dementia.

Undoubtedly, the situation may vary between individuals. The level of peripheral hormones alone may have a different meaning if only depending on the activity of the allele responsible for synthesis of T4 and T3 transporters across the brain barrier (OATP1c1, MCT8) and enzymes involved in the transformation of T4 to T3, particularly 5’D2 deiodinase.

References


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