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Review

Thyroid hormone: Influences on mood and cognition in adults

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ABSTRACT

The association of thyroid dysfunction with alterations in mood and cognition has been recognised since some of the earliest descriptions of thyroid disease. Over the years, researchers have aimed to further define these effects throughout the spectrum of thyroid disorders, to better understand the underlying condition and refine indications for treatment. More recently, attention has turned towards examining the impact of differences in thyroid hormones within the normal reference range, particularly in older adults, providing new insights into the association of thyroid hormone with cognitive decline. This review summarises the evidence assessing the influence of thyroid hormone on mood and cognition in overt and subclinical hypothyroidism, within the reference range, and in subclinical and overt hyperthyroidism. Treatment of overt thyroid dysfunction largely resolves associated disturbances in mood and cognitive dysfunction, however in the setting of overt hypothyroidism subtle detrimental effects on cognition may not be fully reversed. Subclinical hyperthyroidism and higher free thyroxine (FT4) within the normal range have been associated with poorer cognitive outcomes. Future research including randomised controlled trials are required to confirm causality and guide the assessment of benefits vs risks of intervention in the increasing population of older adults with subclinical thyroid disease.

Contents

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1. Introduction

The thyroid, like other endocrine glands of the human body, has wide-ranging effects on multiple organ systems, including the brain and nervous system. Some of the earliest descriptions of thyroid disease noted a link with neuropsychiatric disturbances including mood disorders and cognitive dysfunction. A report by the Committee of the Clinical Society of London in 1888 on myxoedema observed: "Delusions and hallucinations occur in nearly half the cases, mainly where the disease is advanced. Insanity as a complication is noted in about the same proportion as delusions or hallucinations. It takes the form of acute or chronic manias, dementia, or melancholia, with a marked predominance of suspicion and self-accusation" [1]. Similarly, a previous description of thyrotoxicosis in the British Medical Journal noted a significant psychiatric component to this disorder: "One of the commonest areas of diagnostic confusion lies in the distinction between thyrotoxicosis and those anxiety states in which nervous or cardiovascular symptoms predominate. The thyrotoxic patient, often warm and losing weight despite a good appetite, is usually fidgety and hyperkinetic, and her tachycardia is accompanied by a hyperdynamic circulation. . .patients with an anxiety state are seldom hyperkinetic and despite their tachycardia usually have a normodynamic circulation" [2]. The thyroid gland produces the thyroid hormones thyroxine (T4) and liothyronine (T3) under the stimulation of pituitary secretion of thyrotrophin (TSH), and the diagnosis of hyperthyroidism is confirmed by demonstrating elevated free thyroxine (FT4) in conjunction with suppression of TSH via negative feedback to the pituitary [3]. Conversely, hypothyroidism is characterised by reduced FT4 in the setting of elevated TSH. Subclinical thyroid dysfunction is present when thyroid hormone concentrations are in the normal range yet TSH is below normal (subclinical hyperthyroidism) or above normal (subclinical hypothyroidism) [3]. In this review, we describe the relationship between mood and cognitive dysfunction in overt hypothyroidism and overt hyperthyroidism, as well as emerging evidence of corresponding associations throughout the spectrum of subclinical thyroid disorders. The pituitary-thyroid axis evolves with age and this has implications for the increasing numbers of older adults where cognitive impairment is a particular concern.

2. Overt hypothyroidism

2.1. Overt hypothyroidism and mood disorders

Patients presenting with overt hypothyroidism may exhibit significant psychiatric and cognitive disturbance, classically slowness of thought and increased depressive symptoms. The original descriptions of myxoedema madness emphasise psychotic features such as delusions and hallucinations, particularly of the persecutory or suspicious type [1], which can accompany a presentation of florid hypothyroidism. However, the range of neuropsychiatric disturbances encountered in hypothyroid patients is likely to encompass a much broader spectrum. Epidemiological studies have elucidated the association of mood disorders, particularly depression, with hypothyroidism. A selection of recent reports is summarised in Table 1A. Guimaraes et al. [6] showed that high TSH levels in women were associated with an increased risk of developing depression even after adjusting for age, race, smoking and body mass index. Gulseren et al. [5] found that anxiety and depressive symptoms were more severe in patients with hypothyroidism, and that these symptoms improved with thyroxine treatment. In a small case-control study, Mowla et al. [8] compared the characteristics of depression in patients diagnosed with major depressive disorder with and without hypothyroidism. While severity of depression was not significantly worse in those with hypothyroidism, more anxiety symptoms and agitation were present. Conversely, Wu et al. [10] found a higher prevalence and incidence of hypothyroidism in patients with major depressive disorders. There have been several case reports and case series [7,9] describing patients with primary hypothyroidism who have presented with acute mania. In these cases, patients were treated with both psychotropic medication and T4, with gradual improvement in mental state. Heinrich and Grahm [4] presented a case report of a patient presenting with acute psychosis and hypothyroidism who was treated with low-dose T4 and antipsychotic therapy. Within 2–3 weeks of therapy the patient's psychosis had resolved and the antipsychotics were ceased, with no further recurrence of psychiatric symptoms. Therefore overt hypothyroidism is associated with depression, the presence of hypothyroidism can accentuate symptoms such as anxiety and agitation, and treatment with T4 helps improve the disturbance in mood. The wide range of psychiatric presentations ranging from depression to mania reported in overt hypothyroidism emphasises the importance of screening for thyroid dysfunction in patients presenting with an acute psychiatric disturbance [18].

2.2. Overt hypothyroidism and cognitive dysfunction

Cognitive impairment has been regarded as a possible consequence of overt hypothyroidism, although psychiatric disturbances can impact negatively on assessments of cognitive performance [19]. Studies evaluating hypothyroidism and its effects on cognitive function have shown contrasting results, with recent studies summarised in Table 1B. Parsaik et al. [13] performed a cross-sectional study evaluating the association of overt and subclinical hypothyroidism with mild cognitive impairment over a large population based cohort of older adults. They found no significant association between hypothyroidism (overt or subclinical) with mild cognitive impairment after adjusting for possible confounding factors. On the other hand, longitudinal studies evaluating cognition in patients when hypothyroid and after the restoration of euthyroid state show subtle but definable changes in cognition. Schraml et al. [12] assessed neuropsychological outcomes and thyroid function in a group of patients post thyroidectomy, whilst overtly hypothyroid and following adequate thyroid hormone replacement, as compared with controls. Hypothyroid patients performed worse than controls in the domain of working memory, and this improved following thyroid hormone replacement. Smith et al. [14] assessed clinical status, cognitive performance and driving ability in 32 patients undergoing thyroid hormone withdrawal for radioiodine scanning while hypothyroid and following restoration of euthyroid status. They found that transient profound hypothyroidism was characterised by reversible depression, decreased fine motor performance, slowed reaction times and decreased processing speed. These studies support a link between overt hypothyroidism and a degree of reduced cognitive function, although this may be limited to particular domains.

The issue of reversibility of neurocognitive symptoms in treated hypothyroidism has been examined in several studies, summarised in Table 1C. In patients with diagnosed hypothyroidism, residual impairment in cognitive function despite T4 replacement has been reported [15–17]. It is possible that the effects of hypothyroidism on the brain may not be fully reversible, or that exogenous thyroxine replacement falls short of the function of the native pituitary-thyroid axis. It is also plausible that there may be other factors unique to this patient group or their treatment that predisposes them to higher rates of comorbid cognitive disorders. Saravanan e al. [15] surveyed a large group of patients in the UK who had been on T4 for at least 4 months to evaluate their psychological well-being as compared to controls. They found that