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Psychiatric and cognitive manifestations of hypothyroidism

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Abstract

Purpose of review—Overt hypothyroidism has major effects on neuropsychiatric function, but patients with mild hypothyroidism may attribute unrelated neuropsychiatric symptoms to their thyroid condition. This review will summarize data on neuropsychiatric effects of hypothyroidism, and provide guidelines regarding the relationship between hypothyroidism and neuropsychiatric issues, and treatment indications.

Recent findings—Clinical investigations and functional imaging studies confirm that overt hypothyroidism is associated with affective and cognitive decrements, largely reversible with treatment. In contrast, subclinical hypothyroidism is not associated with major neuropsychiatric deficits, although studies utilizing sensitive measures show small deficits in memory and executive function. Neuropsychiatric complaints are more common when patients are aware of their thyroid disease, regardless of their thyroid function at the time of testing.

Summary—Neuropsychiatric dysfunction is common in overt hypothyroidism, and will improve (although perhaps not completely resolve) with therapy. On the other hand, deficits related to thyroid dysfunction are usually mild in subclinical hypothyroidism, and realistic expectations need to be set regarding symptom reversibility with treatment. Patients with mild hypothyroidism and significant distress related to neuropsychiatric symptoms most likely have independent diagnoses that should be evaluated separately.

Keywords

hypothyroid; mood; cognition; levothyroxine

Introduction

The brain is a major target organ for thyroid hormones, and adult-onset hypothyroidism can have significant effects on neuropsychiatric function (1*–3*). On the other hand, patients with mild hypothyroidism may attribute unrelated symptoms to their thyroid condition. This can lead to overtreatment or use of nonstandard thyroid hormone preparations, with attendant risks. In this regard, a recent report from the United Kingdom showed that L-T4 is being prescribed more frequently and for more mild degrees of hypothyroidism (4**). This

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suggests that L-T4 is often prescribed for marginal reasons, which are commonly neuropsychiatric in nature.

This review will summarize data on neuropsychiatric (mood and cognitive) effects of adult-onset hypothyroidism, as well as two related issues: effects of variations in thyroid function within the normal range, and effects of nonstandard thyroid hormone therapies. The major emphasis will be on studies and reviews published in 2013–2014, although pertinent older studies will be summarized.

Hypothyroidism is usually divided into two conditions. *Overt hypothyroidism* is defined as an elevated serum TSH level with a low free T4 (fT4) level, while *mild or "subclinical" hypothyroidism* is defined as an elevated TSH with a normal fT4. In reality, these are part of a continuum of hypothyroidism, but they will be discussed separately. Subclinical hypothyroidism is particularly pertinent, because it is common, especially in the older population with prevalent cognitive issues.

Psychiatric and cognitive effects of overt hypothyroidism

This section will review information on associations between overt hypothyroidism, mood, and cognition.

Mood

Slowing of thought and speech, decreased attentiveness, and apathy often occur in overt hypothyroidism, and the diagnosis may be confused with depression. Rarely, severely hypothyroid patients present with agitation and frank psychosis ("myxedema madness") (5). Objective testing in hypothyroid patients may reveal increased scores on anxiety or depression scales, which largely (but not always completely) reverse with levothyroxine (L-T4) therapy (6–8). A recent nationwide study reported increased psychiatric diagnoses and medication use before and after the diagnosis of hypothyroidism (9). In contrast, a large population-based study failed to find an association between hypothyroidism and anxiety or depression (10). Based on these data, it is likely that individuals vary in their susceptibility to mood alterations in overt hypothyroidism.

Cognition

Overt hypothyroidism can affect a range of cognitive domains (6, 7, 10, 11). Studies report decrements in general intelligence, attention/concentration, memory, perceptual function, language, psychomotor function, and executive function. Memory is the most consistently affected domain (11–16), with specific deficits in verbal memory (11, 12). L-T4 treatment is usually effective in treating these decrements, although there may not be complete reversal (7, 15–18).

Imaging studies provide objective evidence that brain structure and function are altered in hypothyroid patients, with decreased hippocampal volume (19*), cerebral blood flow, and function globally and in regions that mediate attention, visuospatial processing, working memory, and motor speed (20–23). In a recent report, deficits in working memory and

abnormal functional magnetic resonance imaging (fMRI) were no longer present after 6 months of L-T4 therapy (23).

Because overt hypothyroidism may present with mood or cognitive decrements, serum TSH measurement should be performed in patients with affective symptoms or impaired cognitive function. It may be difficult to distinguish thyroid-related neurocognitive decrements from other disease processes. Observation during L-T4 therapy may clarify these issues, as deficits due to hypothyroidism are largely reversible.

Psychiatric and cognitive effects of subclinical hypothyroidism

This section will review information on associations between subclinical hypothyroidism, mood, and cognition. Quality of life and symptoms of fatigue will also be addressed, since they are often present in patients with mood and cognitive symptoms.

Quality of life and fatigue

Many clinic patients complain of poor quality of life and fatigue, which are often associated with psychiatric co-morbidity, and which prompt a screening TSH measurement. If the TSH level is mildly elevated, the patient and provider assume the mild hypothyroidism has caused the symptoms. However, these symptoms often do not resolve with L-T4 treatment, raising the question of whether they were due to the thyroid abnormality in the first place.

Recent studies have demonstrated that a mildly elevated TSH level is not intrinsically associated with poor quality of life or fatigue, but that self-knowledge of a thyroid condition is associated with decrements in these measures, regardless of the TSH level:

1. A population-based survey in the Netherlands measured the intensity of fatigue in almost 6000 subjects aged 18–98 years (24). The prevalence of fatigue in euthyroid subjects with no known thyroid disease was 34%, and was similar in overt or subclinical hypothyroid subjects (who were unaware that they had an abnormal TSH level). In subjects with known thyroid disorders, the rate of fatigue increased to 50%, and was independent of the TSH level.
2. A separate population-based study in the Netherlands administered the SF-36, a widely used validated quality of life scale, to over 9000 subjects aged 18–90 years, who were unaware of their thyroid status (25**). SF-36 scores were indistinguishable between subjects with elevated versus normal TSH levels.

Mood

Depression or anxiety symptoms are reported to be more common in subclinical hypothyroid patients, compared to the general population (reviewed in 1–3). However, this is not a universal finding (10, 26–30). In fact, the largest studies found no differences in depression or anxiety between euthyroid and subclinical hypothyroid subjects (10, 26–28, 31, 32). Strengths of these latter studies include large sample sizes, broad age ranges (large numbers of older subjects), and absence of bias (population based).

The most recent population-based study enrolled over 1200 subjects aged 30–64 years in Baltimore, MD (the Healthy Aging in Neighborhoods of Diversity Across the Life Span, or HANDLS, study) (33*). They found that subclinical hypothyroidism was not associated with increased depression compared to euthyroid controls, regardless of age, gender, or socioeconomic status.

Complementing these population-based studies, there are three randomized, placebo-controlled, blinded studies of L-T4 therapy in subjects with subclinical hypothyroidism, which showed no improvement in depression or psychological distress scores (34–36). In one study, therapy worsened anxiety (35).

Cognition

Subclinical hypothyroidism is not associated with widespread or severe cognitive deficits (reviewed in 1–3). This has been shown in large, rigorous population-based studies that utilized sensitive tests of multiple cognitive domains (26, 27, 37).

The most recent study followed over 5800 participants aged 70–82 years for 3–5 years, who had pre-existing cardiovascular disease or risk factors (38**). There were no baseline or follow-up differences in cognitive measures between subjects with subclinical hypothyroidism versus those with normal thyroid function. This is the largest longitudinal study to date with repeated measures of thyroid function and cognition, and convincingly shows that mild hypothyroidism does not have a major effect on cognitive function, even in elderly subjects with cardiovascular risk factors. Further negative data come from the HANDLS study, where subclinical hypothyroidism was not associated with any differences in a detailed battery of tests covering seven cognitive domains, regardless of age, gender, or socioeconomic status (33*).

In addition to these population-based studies, there are two double-blind, placebo-controlled interventional studies (34, 36), where subjects with subclinical hypothyroidism were randomized to placebo or L-T4 for 12 months. Cognitive testing showed no effect of L-T4. There were some limitations to these studies, including relatively mild degrees of subclinical hypothyroidism, and a high rate of normalization of TSH levels in the placebo group in one study (36). However, these two studies strongly argue against major effects of subclinical hypothyroidism on cognitive function.

In contrast to these negative studies, several small studies employing labor-intensive, sensitive measures report that specific cognitive domains are subtly impaired in subclinical hypothyroidism, although not all studies are consistent (11, 16, 17, 29, 30, 39–42). The most commonly affected cognitive domains are memory and executive function.

Functional neuroimaging provides a neuroanatomical basis for these observed defects. In two recent studies (43, 44*), subjects with subclinical hypothyroidism had impaired verbal and spatial working memory and abnormal fMRI results in frontal brain areas. Some subjects were treated with L-T4 for 6 months, at which point verbal and spatial working memory and fMRI findings normalized. A positron emission tomography (PET) study (45) showed lower regional glucose metabolism in untreated subclinical hypothyroid subjects in

brain areas important for cognition, which was restored after 3 months of L-T4. A likely explanation for the positive results in these experimental studies, compared to population-based studies, is the more sensitive measures of working memory, which can discern smaller differences.

In conclusion, major alterations in quality of life, mood or cognitive function do not occur as a result of subclinical hypothyroidism, and are not reliably improved with L-T4 therapy. However, subtle deficits exist in memory and executive function, documented by functional imaging studies. Sensitive tests are required to delineate these abnormalities, and their clinical significance is likely minor or additive to other cognitive issues. In addition, symptoms are more apparent when subjects are aware of their thyroid status, suggesting that they may be related to the self-knowledge of a thyroid disease process. It is reasonable to initiate treatment for mild hypothyroidism in patients with affective or cognitive complaints, but realistic expectations should be set regarding the likelihood of symptom resolution. Moderate to severe symptoms are unlikely to be due to subclinical hypothyroidism, and need to be evaluated and treated as separate disorders.

Effect of thyroid function variations within the normal range on mood and cognition

In *euthyroid subjects without thyroid disease*fatigue, poor quality of life, mood alterations, and poor memory are common complaints, often prompting subjects to obtain standard or alternative thyroid hormone preparations despite normal thyroid function. This raises the question of whether variations in thyroid function within the reference range are associated with these symptoms.

In the two large Netherlands surveys summarized above, there was no correlation between fatigue or quality of life and variations in thyroid function within the reference range (24, 25). Mood alterations or cognitive deficits have been linked to variations in TSH or fT4 levels within the normal range (26, 27, 32, 33, 46–55). However, the correlations were in different directions depending on the report, and recent large and well conducted studies found no correlations between TSH levels and depression, anxiety, or cognition (10, 26, 27, 32, 55). Most recently, the HANDLS study found complex interactions between variations in normal thyroid function and depression or cognitive measures depending on gender, race, and cognitive domain (33*). It is difficult to draw conclusions from the complex data set, but the magnitude of the differences was generally small. Finally, there is one treatment study, where symptomatic euthyroid subjects with no history of thyroid disease were given L-T4 in a blinded, placebo-controlled fashion, with no improvement in psychological symptoms (56).

Many *hypothyroid patients receiving L-T4 therapy* continue to complain of impaired mood or cognition, despite normal TSH levels. This has been inconsistently supported in the literature (32, 57–61). In the largest study of over 25,000 subjects, there was no correlation between thyroid function and self-reported depression or anxiety overall, but the subgroup with known thyroid disease had an increased risk of both affective disorders, despite normal TSH levels (32). A recent study showed that women receiving replacement or TSH-

suppressive doses of L-T4 had decrements in quality of life and mood, which were more pronounced in those on replacement doses (62*). Both groups had intact cognitive measures. A second recent study found decreased mood but no cognitive deficits or fMRI alterations in L-T4 treated subjects compared to controls (63*). There is one study where L-T4 doses were varied in a blinded fashion within the normal range in hypothyroid subjects, with no changes in cognitive measures (64).

These data suggest that subjects with self-knowledge of a thyroid condition are more likely to report symptoms ("labeling effect"). However, another possible explanation for variations in patients' symptoms may be polymorphisms in the deiodinase 2 or thyroid hormone transporter genes (65, 66). These could theoretically lead to lower intracellular levels of active thyroid hormones. L-T4 treated patients with one such polymorphism had decrements in mood and cognition compared to patients without these polymorphisms (65). These findings require further exploration in controlled studies. In the meantime, persistent affective or cognitive deficits in adequately treated hypothyroid patients require separate evaluation and therapy, and do not indicate a need to increase L-T4 doses or prescribe alternate forms of thyroid hormone.

Impact of nonstandard thyroid hormone therapy on mood and cognition

This section will review information on alternative thyroid hormone preparations and their effects on mood and cognition in hypothyroid patients.

Combination L-T4/L-T3 therapy

Although T4 is the main product of the thyroid gland, T3 is the active thyroid hormone at the cellular level. Most T3 is produced via deiodination of circulating T4 in peripheral tissues, but 20% is produced by the thyroid gland, raising the question of whether patients with continued symptoms might benefit from combined L-T3/L-T4 therapy. Most of the placebo-controlled, blinded interventional studies of this subject failed to find significant improvements in mood or cognitive function with combined therapy (reviewed in 67*, 68*). However, trials are limited by the fact that there is no available sustained release L-T3 preparation that mimics endogenous serum levels.

L-T4 patients with the same polymorphism in the deiodinase 2 gene mentioned above have a better response to combined L-T4/L-T3 therapy compared to L-T4 alone (67, 68). These findings raise the possibility that patients with certain polymorphisms could have relatively lower tissue T3 levels and perhaps derive clinical benefit from T3 therapy. Such a conjecture is currently theoretical, requiring confirmation prior to clinical application.

L-T3 monotherapy

Celi et al recently reported results of a randomized, double-blind experiment in 14 hypothyroid patients (69). Subjects were given L-T4 or L-T3 as sole therapy for 6 weeks to achieve normal TSH levels, and then were crossed over to the other treatment. Subjects lost a small amount of weight on L-T3, but there were no differences in SF-36 or thyroid-specific quality of life questionnaires. There are no studies that investigate mood or

cognitive function in subjects receiving L-T3 as sole therapy, and this regimen is not recommended due to difficulties in maintaining stable thyroid hormone levels.

Desiccated thyroid extract therapy

Hoang et al recently compared desiccated thyroid extract (DTE) (which contains a high L-T3/L-T4 ratio) to L-T4 monotherapy in 70 hypothyroid patients (70**). Subjects were given either DTE or L-T4 for 16 weeks in a randomized, blinded, cross-over fashion. DTE caused modest weight loss, but there were no differences in symptoms, quality of life, depression, or memory. These results suggest that desiccated thyroid extract is not superior to L-T4 for central nervous system function.

Conclusions

Given the variety of findings summarized above, what conclusions can be drawn regarding mood and cognition in hypothyroidism? First, overt hypothyroidism is often associated with clinically significant decrements in mood and cognitive function (especially memory). Second, major affective or cognitive dysfunction is not typical of subclinical hypothyroidism. However, subtle deficits in specific cognitive domains (working memory and executive function) exist in subclinical hypothyroidism.

Therapy for overt hypothyroidism is always indicated, and symptoms of mood or cognitive deficits improve (although perhaps not completely resolve) with therapy. Therapy for subclinical hypothyroidism is more complicated. Since thyroid-related affective or cognitive deficits are subtle in this disorder, realistic expectations need to be set regarding symptom reversibility with L-T4. Currently, there is no role for alternative therapies for hypothyroidism in attempts to reverse mood or cognitive symptoms. Patients with mild hypothyroidism and significant distress related to neuropsychiatric symptoms likely have independent diagnoses that should be evaluated and treated separately.

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Key points

- Overt hypothyroidism is associated with clinically significant neuropsychiatric decrements that are largely reversible with levothyroxine treatment.
- Mild (or subclinical) hypothyroidism is not associated with severe or widespread neuropsychatric decrements, but subtle deficits exist in the specific cognitive domains of memory and executive function.
- Patient with mild hypothyroidism may complain of neuropsychiatric symptoms that are unrelated to their thyroid dysfunction, and these do not reliably reverse with levothyroxine treatment.
- At this time, there is no proven benefit of alternate forms of thyroid hormone therapy on neuropsychatric symptoms in patients with hypothyroidism.