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Subclinical Hypothyroidism, Mood, and Cognition in the Elderly: A Review

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Abstract

Objectives—To perform a critical review of the literature on the mood and cognitive changes associated with subclinical hypothyroidism (SCH), with an emphasis on the elderly. To evaluate these data against the Consensus Statement on management of SCH from the American Association of Clinical Endocrinologists, the American Thyroid Association, and The Endocrine Society.

Method—A comprehensive literature review.

Results—SCH may be associated with an increased risk of mood and cognitive dysfunction, though the strength of this association and the efficacy of replacement hormone therapy requires further investigation.

Conclusion—It remains unclear whether SCH leads to significant mood and cognitive impairments in most elderly patients. More research is required to determine the nature and extent of this association and whether thyroid hormone replacement therapy is appropriate and effective in treating SCH-associated neurobehavioral impairments.

Keywords

Thyroid; Depression; Cognition; Subclinical Hypothyroidism; Dementia

Introduction

The relationship between overt thyroid disease and mood impairment, as well as cognitive dysfunction, has been well described (Whybrow et al, 1969; Rack and Makela, 2000). Overt hypothyroidism is a frequent cause of major depressive disorder, including melancholia, and may lead to a reversible dementia (Rack and Makela, 2000). Recently, more attention has been focused on subclinical hypothyroidism (SCH) and its potential neuropsychiatric and neurocognitive consequences, though, as this review will demonstrate, the specific nature and strength of this association remains unclear. Subclinical hypothyroidism, or “mild hypothyroidism,” is defined as an elevation of thyrotropin (TSH) levels in the presence of normal free circulating thyroid hormones, and is a common abnormality of the thyroid axis (Evered et al, 1973; Woeber, 1997; Surks et al, 2004; Papi et al, 2007). The prevalence of SCH increases with age and is more common in women (Evered et al, 1973; Woeber, 1997;

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Surks et al, 2004; Papi et al, 2007). SCH may affect up to 5–10 percent of adults in the general population. SCH has been found to be associated with vulnerability to adverse medical consequences, including abnormal blood lipids (Pearce, 2004; Papi et al, 2007), increased risk of ischemic heart disease and cardiac mortality (Rolondi et al, 2006; Papi et al, 2007), as well as the well documented progression to overt hypothyroidism (Evered et al, 1973; Woeber, 1997; Surks et al, 2004; Papi et al, 2007). However, there remains some disagreement about these findings (Pearce, 2004; Papi et al, 2007).

There is substantial controversy about the definition of abnormally elevated TSH, the evidence to support adverse medical and psychiatric sequelae, and, most particularly, the potential benefits and risks of treating SCH with thyroid hormone replacement therapy. Given the current state of knowledge and uncertainties about a rational treatment approach, we will focus this review on the cognitive and psychiatric consequences of SCH and the potential benefits of thyroid hormone treatment.

With the elderly population growing substantially as Baby Boomers age, there is a need to increase our understanding of possible causes of morbidity and diminished functioning amongst this age group. The etiology of cognitive and mood disturbance in the elderly is especially critical to understand because of the growing number of older individuals with clinical dementia, mostly caused by Alzheimer's disease (AD) (Alzheimer's Association, 2011). Detecting and treating possible reversible causes of neurobehavioral impairment in the elderly, rather than simply attributing such changes to "normal aging" or to the early stages of AD is critical. SCH is one of those potential contributors to reversible cognitive and mood impairment in the elderly.

Subclinical Hypothyroidism

SCH is defined as an elevated serum TSH in the presence of normal circulating levels of free thyroxine (T4) and triiodothyronine (T3) (Wenzel et al, 1974; Turnbridge et al, 1977). Thyroid antibodies, particularly those against thyroperoxidase (TPO), may be elevated depending on the etiology of the condition, although the most common cause of SCH is chronic autoimmune thyroiditis. In addition to these irreversible causes of SCH, there are reversible causes of elevated TSH levels, such as under-treatment of clinical hypothyroidism and drug treatments such as lithium, amiodarone, and interferon alpha, all of which have some degree of antithyroid effects (Evered et al, 1973). Transient elevations of TSH are also observed in non-thyroidal illness which may be observed in severe medical illness and acute psychiatric disorders. This "sick euthyroid syndrome" is not a disorder of thyroid function and will not be considered further (Warner and Beckett, 2010). SCH can be conceptualized as a mild form of hypothyroidism, which represents a stage on the continuum of normal thyroid function to overt clinical hypothyroidism; although in the past, it has been defined as purely a laboratory abnormality with limited clinical significance (Gharib et al, 2004).

In addition to the common clinical signs and symptoms of clinical hypothyroidism (Papi et al, 2007), psychiatric symptoms, especially depressive and anxiety symptoms and depressive syndromes, are most common (Stern and Prange, 1995; Hennessey and Jackson, 1996), and often lead to initial misdiagnosis. Major depression is a prominent feature of clinical hypothyroidism and often can only be distinguished from the primary psychiatric disorder by thyroid function tests (Stern and Prange, 1995; Hennessey and Jackson, 1996). Cognitive dysfunction, including the clinical features of dementia (i.e., memory and other cognitive impairment severe enough to impact functional independence), are also frequently observed (Stern and Prange, 1995; Hennessey and Jackson, 1996).

Although not as common as in clinical hypothyroidism, a substantial minority of SCH patients -- perhaps up to 30 percent -- will have clinical complaints, many of which are

similar to those reported with clinical hypothyroidism (Cooper et al, 1984; Nystrom et al, 1988; Haggerty et al, 1990; Monzani et al, 1993; Meier et al, 2001; Biondo and Cooper, 2008). In addition to depression, anxiety, and cognitive difficulties, SCH patients frequently report fatigue, hoarseness, constipation, muscle weakness and cramps, cold intolerance, and weight gain (Cooper et al, 1984; Nystrom et al, 1988; Haggerty et al, 1990; Monzani et al, 1993; Meier et al, 2001; Biondo and Cooper, 2008). Most, but not all, studies have found significant differences in physical, mood and cognitive measures between SCH subjects and healthy controls (see below).

Thyroid hormone production and metabolism change with age (Marriotti et al, 1995) with decreased secretion of both total T4 and total T3. However, serum concentrations of T4 and free T4 remain relatively unchanged due to metabolic changes associated with aging, while both T3 and free T3 levels are reduced due to reduced peripheral conversion of T4 (Marriotti et al, 1995). Data regarding changes in TSH levels with aging have been reported as stable, increased, or decreased in healthy adults, and the impact of these changes in the thyroid axis on the aging process are unknown (Marriotti et al, 1995; Surks and Hollowell, 2007; Atzmon et al, 2009). It is clear, however, that there is an age-related increase in SCH and that a significant minority of older adults demonstrates increased TSH levels (Marriotti et al, 1995; Surks and Hollowell, 2007; Atzmon et al, 2009). As already noted, the prevalence estimates for SCH are about 5–10 percent in the general adult population and increase with advancing age, particularly in women (Bagchi et al, 1990; Lindeman et al, 1999; Rivolta et al, 1999; Canaris et al, 2000; Hollowell et al, 2002). Prevalence rates of 26 percent in women over 60 years of age were reported in the Wickham survey of a random sample of 2779 adults in a United Kingdom community (Tunbridge et al, 1977). Gender differences were demonstrated with elevated TSH levels increasing from 2% to 5% across the age spectrum in men and from 4% to 18% in women (Tunbridge et al, 1977). In the Colorado Thyroid Disease Prevalence Study, carried out at health fairs in individuals older than 64 years, the prevalence of SCH was 16% in men and 21% in women (Canaris et al, 2000).

In addition to elevated TSH levels, TPO antibodies are more common in the elderly, with prevalence estimates of 15 to 20 percent (Tunbridge et al, 1977; Hollowell et al, 2002). The prevalence of TPO antibodies is much higher in older adults with SCH, ranging from 40 to 67 percent, in most (Tunbridge et al, 1977; Hawkins et al, 1980; Manciet et al, 1995; Sundbeck et al, 1995; Canaris et al, 2000), but not all studies. (Pinchera et al, 1995). Taken together, these findings suggest that the increased prevalence of thyroid antibodies seen in the elderly is associated with disease rather than normal age-related changes in the thyroid axis (Davis et al, 2003).

SCH and Mood

Several, but not all, studies have suggested a link between SCH and current depressive symptoms, current major depression, and a lifetime history of major depression (Tappy et al, 1987; Joffe and Levitt, 1992; Haggerty et al, 1993; Esposito et al, 1994; Luboshitsky et al, 1996; Roberts et al, 2006; Chuiere et al, 2007). Most studies report a higher frequency and/or severity of current depressive symptoms in young or middle-aged adults with SCH (Tappy et al, 1987; Joffe and Levitt, 1992; Monzani et al, 1993; 16,34,35). There are fewer studies examining the association between depressive symptoms and SCH in the elderly, although some (Chuiere et al, 2007), but not all (Manciet et al, 1995; Roberts et al, 2006), report such an association. These studies do not provide evidence of vulnerability to depression and variations in TSH levels within the normal range (Chueire et al, 2007).

There may also be a higher lifetime prevalence of major depressive disorder in SCH individuals. Haggerty et al. (1993) reported a lifetime prevalence for major depression of 56

percent versus 20 percent in non-elderly women with SCH versus controls; whereas, Esposito and colleagues (1994) found that in 163 SCH subjects older than 65 years in a general medical clinic, 75 percent had a lifetime diagnosis of major depression compared with 18 percent in the euthyroid group. A recent study by Chueire et al. (2007) of 323 subjects over the age of 60 years, also concluded that SCH increases the risk for depression (OR=4.9; 95% CI=2.8–8.6) and that this risk is even greater than it is for clinical hypothyroidism.

These data do not necessarily suggest a direct causal link between SCH and mood disturbance or disorders. However, several studies now suggest that patients with primary major depressive illness may have a reduced rate of antidepressant response and a greater risk of chronicity of depression, if they have co-morbid SCH (Joffe and Levitt, 1992; Chuiere et al, 2007).

SCH and Cognition

There have been various types of studies examining the relationship between mild thyroid failure and cognitive dysfunction. First, several studies have examined cognitive parameters in samples that include subjects with SCH. These studies are summarized in Table 1. Most of these studies are cross-sectional comparisons to euthyroid subjects and few involve longitudinal follow up. Although some include only elderly subjects, others include broad ranges of age, limiting the conclusions that can be drawn from the data. Perhaps the most problematic methodological issue in these studies is the reliance on limited measures of cognitive function, especially the Mini Mental State Examination which provides a very limited assessment of cognition and likely lacks sensitivity to potentially subtle, though clinically meaningful neuropsychological impairments. This may explain why not all studies in both younger and older adults have demonstrated cognitive alterations associated with SCH. Nonetheless, the studies show that in younger adults, mild cognitive abnormalities may occur in individuals with SCH. These are generally identified as difficulties with selective attention and new learning.

A few studies have specifically addressed cognition in older adults with SCH. In one such study, neuropsychological function was assessed in subjects (mean age approximately 69 years) with both clinical and subclinical hypothyroidism and compared to euthyroid controls (Osterweil et al, 1992). This study found that the overall thyroid group (i.e. both clinical and subclinical hypothyroidism) performed worse than controls on various cognitive measures, but differences between the SCH and control group were not significant. They further observed that older adults performed more poorly than younger adults on neuropsychological measures regardless of thyroid status, but there was no interaction observed between age and thyroid status in their study. This study suggests that SCH may be associated with deficits in attention, some aspects of executive functioning, verbal and visual recall, and reaction time, but the degree to which SCH differentially impacts mental status in older individuals, and women in particular, requires additional investigation. Several of the studies in older subjects have not demonstrated significant findings (See Table 1). However, these are predominantly larger population studies with generally limited neuropsychological assessments (Samuels, 2010.) (See Table 1).

In a related set of studies, the relationships between cognitive function and thyroid hormone levels within the normal reference range or across the entire spectrum have been examined. These studies have produced somewhat conflicting findings. Van Boxtel and colleagues (van Boxtel et al, 2004), in the Maastricht Aging Study, reported the predicted inverse relationship between higher TSH levels and poorer cognitive function in a population sample of 120 euthyroid subjects with a mean age of 60.3 years. In contrast, Wahlin (2005)

and collaborators found a direct correlation between TSH levels and cognitive performance in a Swedish sample of 200 subjects, 75 years of age or older. In a third study (Volpato et al, 2002), cognitive performance and thyroid function were assessed in 464 community-dwelling older women who were euthyroid. When the sample was divided into tertiles based on T4 levels, women in the lowest versus the highest tertile had a twofold risk of cognitive decline. There was no association between baseline TSH and cognitive changes. A much larger investigation with the Rancho Bernardo Study examined 1110 men and women (age 42–99) and found that TSH was not associated with cognitive function in both men and women (Kritz-Silverstein et al, 2009). These studies indicate that variation in thyroid function tests within the normal range may be related to cognitive impairment, especially in older women but the directionality of these relationships requires further study.

Another line of research has examined the relationship between thyroid function other than clinical hypothyroidism and vulnerability to dementia especially AD, in the elderly. In a community-based study of 194 individuals age 65 years and older, equally distributed between men and women, a three- to fourfold increase in the probability of definite or possible dementia in subjects with elevated TSH levels was reported (Ganguli et al, 1996). This finding held even after accounting for the effect of age, gender, and years of education. This association was still evident when men and women were separately examined. In contrast to this report, two studies have reported a link between low TSH levels and AD. The Oxford Project to Investigate Memory and Ageing (van Osch et al, 2004), reported low TSH levels as an independent risk factor for AD in a cross sectional study of 178 Alzheimer patients and 291 controls. In the prospective Rotterdam Study (Kalmijn et al, 2000) with average two year follow up, risk for Alzheimer's disease was associated with lower TSH levels and positive thyroid peroxidase antibodies. In a much larger, longitudinal population-based study, the risk of AD based on earlier TSH levels was examined in the original Framingham Study cohort (Tan et al, 2008). In this investigation, 1864 cognitively intact participants (mean age=71) were followed for an average of 12.7 years after an initial TSH measurement. Both low *and* high initial TSH levels were associated with an increased risk of developing AD in women, but not in men. In a cross-sectional investigation of the Sao Paulo Ageing and Health Study (Bensenor et al, 2010), 1276 subjects (age 65 and older) were examined. There was a positive association of subclinical *hyper*thyroidism but not SCH with overall dementia (especially vascular dementia), but only in men.

Taken together, these findings present inconsistent support for an association between SCH and dementia (Bensenor et al, 2010). They also underscore the potential differential sensitivity of the elderly brain to smaller perturbations of the thyroid axis manifesting as cognitive changes.

Treatment Studies of Neurobehavioral Symptoms in SCH

Given the complex relationship between varying degrees of thyroid failure and alterations of mood and cognition, it does not necessarily follow that resolution of the thyroid disorder and mood and cognitive changes occur at the same time. In overt hypothyroidism, the link between thyroid hypofunction and depression is clearly documented. However, although the depression associated with clinical hypothyroidism usually resolves with restoration of normal thyroid function, a substantial minority will require further intervention, usually antidepressants, in order to restore normal mental state.

There have only been a few studies that have assessed the impact of T4 treatment on neurobehavioral symptoms in SCH. These are summarized in Table 2. These studies provide preliminary evidence for the efficacy of T4 treatment of SCH from a mood and cognitive perspective but most are insufficiently powered to detect differences between T4 and

placebo. Some of the larger studies provide some support for the efficacy of T4 (Cooper et al, 1984; Nystrom et al, 1988; Jaeschke et al, 1996; Bono et al, 2004) while the negative studies with larger sample sizes (Volpato et al, 2002; Parle et al, 2010) employed limited psychometric assessments (Kong et al, 2002; Jorde et al, 2006; Parle et al, 2010), fixed T4 doses (Kong et al, 2002) and a very broad age range (Jorde et al, 2006). A critical shortcoming of the largest study to date by Parle and colleagues (2010) was that the neuropsychological test scores in both placebo and T4 groups were within the normal range at baseline so that there were no or limited cognitive impairments to treat. Future studies should focus on the treatment of SCH patients with documented cognitive or mood impairments.

Treatment Recommendations

In general, the potential risk versus benefit of treating SCH has long been a matter of controversy (Surks et al, 2004; Gharib et al, 2004, 2005). As a result, a consensus statement was developed jointly by the American Association of Clinical Endocrinologists, the American Thyroid Association, and The Endocrine Society to provide an evidence-based approach to the management of SCH. The statement notes the absence of good evidence on which to base treatment decisions and, therefore, the need for good clinical judgment and the importance of patient preference in deciding whether to treat SCH. The Consensus Statement underscores the continued need for well designed and adequately powered studies with comprehensive assessments. In general, there are limited data documenting benefit of thyroid replacement except when TSH levels exceed 10 mIU/L, with progression to overt hypothyroidism, at annual conversion rate of approximately 2 to 5%, and higher in those with thyroid auto-antibodies (Surks et al, 2004; Gharib et al, 2004, 2005). There is increasing evidence that SCH may also be associated with increased risk of cardiac disease with increased mortality from this cardiac risk. Moreover, there is also accumulating evidence for abnormal lipid profiles in patients with SCH (Pearce, 2004; Papi et al, 2007). However, there is insufficient data that thyroid hormone replacement therapy significantly reduces risk or mortality of cardiac illness or restores normal blood lipid levels, particularly triglycerides (Pearce, 2004; Papi et al, 2007). Currently, it is increasingly recommended that patients with TSH levels in excess of 10 mIU/L receive thyroxine replacement; whereas, treatment for non-pregnant individuals with TSH levels above the normal range but below 10 mIu/L is still an issue of substantial debate (Surks et al, 2004; Papi et al, 2007; Gharib et al, 2004, 2005).

The potential risks of treatment of SCH include the danger of over-treatment resulting in clinical hyperthyroidism with associated serious medical consequences such as cardiac events, particularly atrial fibrillation, and osteoporosis, especially in the elderly. The cardiac risks are well documented (Pearce, 2004), whereas both cross-sectional and longitudinal studies are inconclusive with regard to the effects of long-term T4 treatment on bone mineral density in postmenopausal women (Ross, 1993; Gyulai et al, 2001; Sheppard et al, 2002 ; Surks et al, 2004). If T4 is to be recommended for treatment of any aspect of SCH, its demonstrated benefit has to exceed the potential risks.

The Consensus Statement highlights the controversy over routine thyroid screening (Gharib et al, 2004, 2005). Although there is support for case finding in subjects with one or two symptoms suggestive of some degree of thyroid failure, applicability to mood and cognitive changes is unknown. This is a particular problem with the potential mood and cognitive benefits of T4 treatment of SCH. The studies in Table 2 are of limited value and the value of the addition of T3, which has been used to treat depression, has not been clearly demonstrated (Sawka et al, 2003).

Conclusions

SCH is a common disorder, particularly in the elderly, and may be associated with clinical symptoms of hypothyroidism as well as associated mood and cognitive deficits. Furthermore, untreated SCH may have significant adverse long-term mental and physical health outcomes that could be ameliorated with treatment.

The pattern and severity of mood and cognitive symptoms in SCH has not been fully delineated, although both depressive symptoms and depressive syndromes may occur with increased frequency. SCH may also be associated with both current cognitive impairment and the future risk of cognitive decline. The efficacy of thyroid hormone treatment in improving the sequelae of SCH has not been rigorously or appropriately tested. Substantial research is required to accumulate data regarding SCH so that, given its considerable potential risks, there is good evidence to allow a rational clinical approach to SCH.

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Key Points

1. Subclinical hypothyroidism is associated with increased depressive symptoms.
2. Subclinical hypothyroidism is associated with increased abnormal measures of cognitive function.
3. The clinical significance of these neuropsychiatric changes require further evaluation.
4. The effect of L-thyroxine treatment for neuropsychiatric changes requires further study.

Table 1

Studies of TSH, SCH, and Cognitive Dysfunction

STUDY	SAMPLE	DESIGN	ASSESSMENT	RESULT
Osterweil et al., 1992	54 hypothyroid, 14 with SCH 30 euthyroid controls	Cross-sectional comparison	Comprehensive neuropsychological	Hypothyroid broad cognitive impairment but no difference between SCH and controls
Monzani et al., 1993	14 SCH young women, 50 euthyroid controls	Cross-sectional comparison	Wechsler Memory Scale	Significant memory impairment in SCH group
Baldini et al., 1997	17 SCH women, 19 euthyroid controls, mean age 52.9yrs	Cross sectional comparison	Neuropsychological tests	SCH impaired memory but no difference in mental control, attention, or visuospatial skills.
del Ser Quijano et al., 2000	15 younger SCH women and 15 euthyroid controls	Cross-sectional comparison	Comprehensive neuropsychological	SCH slowed reaction time, reduced verbal fluency, and impaired visual memory
Gusselkoo et al., 2004	N=558, SCH =30, population based sample of 85 yr old from Leiden 85+ study	Baseline and 2yr follow up	MMSE only	No association between SCH and MMSE
Roberts et al., 2006	N=5865 65yrs or older from primary care registry, SCH N=168	Cross-sectional comparison	MMSE Middlesex Elderly Assessment of Mental State	Statistically significant but clinically limited reduction in MMSE in SCH
Samuels et al., 2007	N=19 women, aged 20–75 yrs, primary hypothyroidism, euthyroid on T4	Double-blind, randomized cross-over study, euthyroid versus experimental SCH	Tests of working and declarative memory and motor learning	In SCH phase reduced working memory
Hogevorst et al., 2008	N=1054 over 64 yrs, including all cases of thyroid dysfunction. MRC Ageing Study	Baseline and 2 year follow up	MMSE only	Association between high TSH and low MMSE score
Ceresini et al., 2009	N=1171, N=918 >65 years. All types of thyroid dysfunction. In Chianti Study	Cross sectional, community based	MMSE only	Only SCH not associated with significant impairment on MMSE
Park et al., 2009	SCH N=164, Controls N=764. All >65 years old. Korean population sample	Cross sectional comparison	Neuropsychological battery	No difference between SCH and euthyroid groups

MMSE= Folstein Mini-Mental Status Exam

Table 2

Treatment Studies of Neurobehavioral Symptoms in SCH

STUDY	SUBJECTS	T4 DOSE AND DURATION	DESIGN	RESULTS
Cooper et al., 1984	N=33 M:F=1:32	Titrated to normalize TSH	Placebo-controlled	T4>Placebo on psychiatric measures
Nystrom et al., 1988	N=34 Women 51–73 years	Fixed dose Six months	Placebo-controlled Cross over	T4>Placebo on psychiatric measures
Monzani et al., 1993	N=14 Women 20–47 years	Fixed dose Six months	Open label	Improvement in obsessionality
Jaeschke et al., 1996	N=37 Men and women >55 years old	Titrated to normalize TSH Six months	Placebo-controlled	T4>Placebo on psychometric but not Quality of Life measures
Baldini et al., 1997	N=19 Women 28–68 years	Titrated to normalize TSH. Three months	Open. Compared to goiter patients	No improvements in mood ratings
Kong et al., 2002	N=40 Women	50–100 micrograms per day Six months	Placebo controlled	Placebo improved more than active treatment.
Bono et al., 2004	N=36 Women 31–70 years	Titrated to normalize TSH. Six months	Open label	Improved Hamilton Depression and Anxiety Scales
Jorde et al., 2005	N=89 M:F=45:44 0–75 years	Titrated to normalize TSH One year	Placebo controlled	T4=Placebo
Correia et al., 2009	N=17 18–65 years	Titrated to normalize TSH Assessments at 3 and 6 months	Open Label	Improvement in memory tasks
Parle et al., 2010	N=94 64–94 years	Titrated to normalize TSH. Twelve months	Placebo Controlled	No improvement, but not selected for deficits at baseline