Neurobehavioral Functioning in Thyroid Disorders

Geoffrey Tremont, PhD, Robert A. Stern, PhD, Holly James Westervelt, PhD, Catherine Lee Bishop, PsyD, and Jennifer Duncan Davis, PhD

This paper reviews the neuropsychological findings and psychiatric symptoms associated with overt hyperthyroidism, overt hypothyroidism, and subclinical or mild hypothyroidism, emphasizing the specific neuropsychological findings and psychiatric symptoms associated with each of these conditions. Although there is a history of anecdotal clinical reports and speculation regarding the effects of thyroid disorders on brain and behavior, there has been relatively recent empirical evidence supporting cognitive, behavioral, and emotional changes in thyroid disorders, as well as further support by recent functional neuroimaging studies of altered CNS functioning in thyroid disorder. We present data from a recent investigation of the neuropsychological consequences of Graves' disease, as well as an ongoing functional neuroimaging study. Finally, we describe how neurobehavioral aspects of thyroid disease are of particular importance in the elderly.

Hyperthyroidism and Graves' Disease

Psychiatric Symptoms of Hyperthyroidism

Diagnosing Graves' disease is complicated by the behavioral nature of the symptoms. There is considerable overlap between the phenomenology of primary anxiety (e.g., Generalized Anxiety Disorder) and hyperthyroidism. (Table 1). Because Graves' disease most commonly presents in young women who are otherwise healthy and who may be managing careers and family responsibilities, the condition is frequently misdiagnosed as stress-related. Therefore, many of these patients initially present to psychiatrists, psychologists, or other mental health professionals.

The majority of hyperthyroid individuals meet formal diagnostic criteria for anxiety disorders or major depressive episodes.[1,2,3] Some of the psychiatric symptoms associated with Graves' disease may be due to increased peripheral sympathetic tone that can frequently be relieved by beta-blockers. A large survey of members of the National Graves' Disease Foundation conducted by our research group found that over 60% of respondents reported irritability, visible shakiness, anxiety, sleep difficulties, fatigue, and weakness while they were hyperthyroid.[4] Furthermore, 35% of subjects did not seek treatment for 6 months or more after symptom onset, and 35% were not diagnosed with Graves disease until 3 months or more after seeking treatment, indicating that a significant percentage of patients suffer with symptoms for an extended period, possibly because of difficulties with differential diagnosis. There is also evidence that the neurobehavioral effects of hyperthyroidism can persist for some time following the onset of treatment. Overall, research into psychiatric features of hyperthyroidism has been limited by methodological shortcomings, such as including mixed groups of hyperthyroid patients (i.e., not only Graves' patients), inadequate control of premorbid conditions, inclusion of older patients and males who may present with different symptoms, or reliance on retrospective self-report data.

Neuropsychological and Neuroimaging Correlates

Individuals with hyperthyroidism can exhibit neuropsychological deficits. The most common neuropsychological difficulties observed in Graves' disease include decreased concentration, slowed reaction time, decreased complex visual processing and spatial organization abilities, and poor conceptual skills.[1] These deficits have been consistently observed and are not necessarily attributable to psychiatric symptomatology. Based on these findings, Stern and Prange[5] proposed that the cognitive deficits seen in hyperthyroidism/Graves disease reflect frontal systems dysfunction (i.e., frontal cortex and associated subcortical structures). Based in part on this observation, Bhatara and colleagues[6] conducted a preliminary study using magnetic resonance spectroscopy, selecting the right frontal lobe as the area of study. Their results indicated re-

Table 1
Signs and Symptoms Common to Both Hyperthyroidism and Anxiety

Hyperthyroidism Only	Anxiety Only	Hyperthyroidism & Anxiety
Goiter	Anxious or dysphoric mood	Shakiness
Exophthalmos	Fear of dying	Heart palpitations
Heat intolerance	Dizziness	Sweating
Warm, moist skin	Sense of unreality	Shortness of breath
Increased appetite	Chest pain	Fatigue
Weight loss	Faintness	Decreased sleep
Amenorrhea or impotence		Nervousness
Hyperactive reflexes		Irritability
Muscle wasting		Diminished concentration
Onycholysis		

duced cerebral metabolism in the right frontal lobes of thyrotoxic Graves' patients compared to healthy controls, which appears to normalize after patients are euthyroid. As with psychiatric symptoms, preliminary clinical data suggest that cognitive deficits can persist once a patient is euthyroid.[4]

To more clearly address the possibility of frontal systems dysfunction in Graves' disease, our group recently conducted a study of 20 patients (19 females, 1 male) with Graves' disease who were acutely hyperthyroid and compared their neuropsychological test performance to 20 healthy controls matched for age (Graves' M = 33.1, SD = 7.5; Controls M = 31.7, SD = 13.2) and years of education (Graves' M = 13.5, SD = 2.4; Controls M = 13.7, SD = 1.7). Diagnosis was established by clinical exam, laboratory testing, and when needed, thyroid uptake scans. All subjects were carefully screened to rule out other illnesses that could affect central nervous system functioning. All participants were administered the Rey-Osterrieth Complex Figure, a visuoconstructional and memory task that is also sensitive to frontal systems functioning.[7] Results showed that patients with Graves' disease performed significantly poorer on measures sensitive to executive functioning, including planning, vertical and horizontal expansion of the design, and attention to details. There were no significant differences between the groups for immediate or delayed retention of the figure, arguing against any significant memory problems. A subset of patients with Graves' disease (n = 15) and healthy controls (n = 8) completed other neuropsychological tests, including measures of verbal fluency, verbal list learning, manual dexterity, information processing speed, psychomotor speed, response set maintenance, conceptualization, and selective attention. Results from this analysis showed that Graves' patients performed significantly worse on a visuospatial conceptualization task compared to healthy controls, with no differences between the groups on any other measures. Overall, results suggest that executive and attentional functioning may be particularly affected in Graves' hyperthyroidism, supporting the recent functional neuroimaging study implicating involvement of the frontal systems.

To further examine the relationship between Graves' hyperthyroidism and frontal systems dysfunction, our group is currently conducting a longitudinal study using **Single Photon Emission Computed Tomography (SPECT)** combined with measures of neuropsychologic and psychiatric functioning. The goal of the study is to determine patterns of cerebral perfusion and neurobehavioral functioning while Graves' patients are thyrotoxic and again when they are euthyroid. Preliminary data suggest that Graves' disease patients who have abnormal SPECT results show consistently impaired verbal list learning, planning and organization, and visuospatial skills, as well as greater perseveration and mild to moderate depressive symptoms. In contrast, Graves' patients with normal SPECT studies have shown less pronounced cognitive deficits, including mild attention problems, slowed psychomotor speed, and mild depression. The variability of SPECT findings and cognitive symptoms in these patients is similar to the variability seen in other autoimmune disorders, such as multiple sclerosis, suggesting that there may be an autoimmune component of the disease that is directed at the brain in some patients.

Table 2
Signs and Symptoms Common to Both Hypothyroidism and Depression

Hypothyroidism Only	Depression Only	Hypothyroidism & Depression
Cold intolerance	Weight loss	Depressed mood
Hyperlipidemia	Sleep disturbance	Apathy
Brittle, dry hair	Appetite decrease	Emotional lability
Eyebrow hair loss		Weight gain
Dry, thickened skin		Appetite decrease
Bradycardia		Sleep increase
Delayed reflexes		Fatigue, anergia
Myxedema		Poor concentration
Reduced basal metabolic rate		Memory complaints
Anemia		Mental slowing
Mennorrhagia		Diminished libido
Goiter		Suicidal ideation
		Delusions

Hypothyroidism

Psychiatric Symptoms of Hypothyroidism

As in hyperthyroidism, differential diagnosis in hypothyroidism is complicated by the symptom overlap with psychiatric disorders. Psychiatric symptoms are often the presenting complaint, and hypothyroidism is frequently associated with dysphoric mood and may be misdiagnosed as depression. (Table 2). As such, laboratory data are essential to avoid misdiagnosis.

The relationship between depression and hypothyroidism is complex. However, they are not necessarily mutually exclusive disorders; hypothyroidism may cause depressive symptoms, and patients with primary depression who are considered euthyroid may have mild alterations in their thyroid function.[8]

Neuropsychological Correlates

Patients with hypothyroidism may also present with cognitive difficulties. The most common neuropsychological deficits observed in hypothyroidism include mental slowing and long response latencies, diminished attention and concentration, impairments in learning and memory, executive dysfunction, and global cognitive deficits (i.e., dementia). In contrast, language and motor skills are generally unaffected. Despite the widely held belief that significant cognitive disturbance is associated with hypothyroidism (i.e., a common cause of reversible dementia), few comprehensive neuropsychological investigations of large groups of hypothyroid patients have been conducted. Therefore, a clear neuropsychological profile and description of specific, associated neurological substrates/systems are relatively undefined at this time. However, there is preliminary evidence to suggest that hypothyroidism, like hyperthyroidism, may be associated with frontal systems dysfunction.

Neuroimaging Findings

The etiology of cognitive deficits in hypothyroidism is not clear. Neuroimaging studies have provided some insight into possible changes in brain metabolism in hypothyroidism. A recent study examined cerebral metabolism by using positron emission tomography in patients who were euthyroid and then became hypothyroid after thyroid hormone withdrawal. While hypothyroid, patients showed generalized decrease in regional cerebral blood flow and in cerebral glucose metabolism. There were no specific localized defects, suggesting globally reduced brain activity.[9] Similarly, SPECT imaging in a patient with iatrogenic hypothyroid dementia showed diffuse cerebral hypoperfusion during the dementia. Once euthyroid, the SPECT normalized and cognitive impairment, as measured by the Mini Mental State Exam, resolved.[10] Finally, a study using MRS showed specific changes in frontal metabolism in hypothyroid patients, which normalized following T4 treatment.[11] Taken together, these studies suggest that hypothyroidism is associated with alternations in cerebral metabolism, with possible localization to the frontal lobes.

Treatment

Thyroid replacement therapy with synthetic T4 (levothyroxine) is generally the treatment of choice for hypothyroidism. Serum thyroid levels and may take up to three months to normalize, though there is *no* consistent pattern of recovery of neurobehavioral symptoms following treatment. Furthermore, there are no prospective, objective research studies to clearly address *reversibility* of cognitive and/or psychiatric symptoms.

T4 and T3

It is not uncommon for patients who were previously hypothyroid to complain of persistent physical, emotional, and cognitive symptoms, despite being euthyroid. One possible explanation of these ongoing symptoms may be that peripheral euthyroidism (as achieved by treatment with T4) does not necessarily reflect euthyroidism in all organs of the body (particularly in the brain). One study has supported this notion by demonstrating differential effects of T4 versus a combination of T3 and T4 on treatment outcome. Bunevicius and colleagues[12] examined 33 hypothyroid patients in a randomized, double-blind clinical trial over two 5-week periods. Within each treatment session, patients were either treated with a standard 50 mg dose of levothyroxine (T4) alone or a combination of 37.5 mg T4 and 12.5 mg triiodothyronine (liothyronine, T3). Compared to T4 alone, T4 plus T3 resulted in improved cognition and mood state, as well as improved subjective report of physical symptoms, with no measurable change in TSH. These findings, if replicated, argue for the possibility that exogenous T3 may play an important role in normalizing cerebral functioning in hypothyroid patients.

Subclinical Hypothyroidism

Subclinical hypothyroidism (SCH) is defined by an elevated serum TSH in the presence of normal serum thyroid hormone levels. SCH was first defined by Wenzel[13] and Evered[14] and was generally considered an asymptomatic laboratory condition. However, there is now considerable evidence indicating that SCH is a relatively common disorder that may be associated with mild cognitive and neuropsychiatric dysfunction that responds to thyroid replacement therapy.[15]

The prevalence of SCH is 5% in the general population, and nearly 20% in women over the age of 60.[16] Although the majority of patients with subclinical hypothyroidism have few or no overt clinical symptoms, some patients complain of mild symptoms of hypothyroidism, such as anergia, malaise, and abulia.[17, 18] Although these complaints are somewhat diffuse and relatively common in the general population, a large, population-based study reported greater complaints of dry skin, cold intolerance, and easy fatigue in patients with subclinical hypothyroidism compared to healthy controls.[16]

Perhaps the best evidence for objective neurobehavioral changes in subclinical hypothyroidism comes from neuropsychological studies that have identified subtle, though clinically significant, neuropsychological deficits and mood disturbance. Neuropsychological deficits include diminished speed of information processing and reaction time, impaired selective attention, poor working memory capacity, difficulty learning/encoding new information, and reduced verbal fluency.[15, 19, 20] Results of treatment studies have also shown that these neuropsychological deficits improve following levothyroxine treatment.[19]

Given that not all patients have somatic complaints and that neuropsychological and cognitive changes may be mild, there remains much controversy around whether subclinical hypothyroidism should be treated. However, there is some indication that untreated subclinical hypothyroidism

may have negative medical consequences. One of the major risks associated with subclinical hypothyroidism is conversion to overt thyroidism, particularly in women with elevated serum TSH levels and antithyroid antibodies.[21] Individuals with untreated subclinical hypothyroidism also have an increased risk of hyperlipidemia, atherosclerosis, and cardiac difficulties (including myocardial infarction in older women). There is also evidence that patients with subclinical hypothyroidism are at increased lifetime risk for depression relative to euthyroid controls.[22] Finally, more recent data suggest a relationship between cognitive decline and thyroid status in older women. In a longitudinal study of community dwelling older women, women with lower serum free T4 concentrations demonstrated a two-fold increased risk of cognitive decline compared to women with T4 concentrations in the highest tertile.[23]

Although these studies provide strong support for cognitive dysfunction in patients with subclinical hypothyroidism, treatment remains controversial. Clearly, additional research is necessary to determine both the severity and pattern of cognitive and neuropsychiatric deficits and treatment responsiveness in patients with subclinical hypothyroidsm.

Thyroid Disease in the Elderly

With advancing age, there are notable alterations in hormone production, metabolism, and action during a time of reduced adaptability to metabolic perturbation.[24] Laboratory findings in the healthy elderly typically demonstrate that thyroid secretion is reduced with age. T4 serum concentrations are generally unchanged because T4 degradation is also reduced, though serum T3 concentrations are diminished, most likely due to reduced peripheral conversion of T4 to T3.

Hypothyroidism

Although TSH concentrations are generally normal in the elderly, a significant minority of elderly adults demonstrate increased levels. The most common cause of hypothyroidism in the elderly is autoimmune thyroiditis, though iatrogenic thyroid failure can also occur as a late consequence of treatment for Graves' disease, toxic adenoma, or multinodular goiter, or as a result of treatment with certain drugs (e.g., lithium) or excessive iodine intake. The clinical features of hypothyroidism tend to be nonspecific in the elderly and, hence, may not raise suspicion of thyroid dysfunction. For example, in an investigation which screened 3417 elderly patients, a clinical diagnosis of hypothyroidism was made in only 10% of patients with clinically elevated TSH levels.[25] This was likely due to the often insidious onset and ambiguity of symptoms which may be subtle and misattributed to aging or other disease states (e.g., fatigue, depression, decline in mental status, dry skin, hair loss, constipation, poor appetite, hearing loss, cardiomegaly, congestive heart failure). Neurologic signs such as syncope, seizures, and impaired cerebellar function may also be seen, as may vague arthritic complaints.

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Cognitive impairment associated with hypothyroidism in the elderly may include deficits in learning and memory, executive function, semantic verbal fluency, complex construction, and psychomotor speed, with a subset of patients showing global deficits. Although relatively uncommon, the degree of cognitive decline may be severe enough to mimic a degenerative dementia. Therefore, it is typical clinical practice to examine thyroid function in elderly patients with memory problems to rule out this potentially reversible dementia. Treatment with replacement hormone can result in improved cognition, although complete recovery is not consistently achieved. The degree of cognitive impairment tends to be associated with the degree of hormone abnormality in hypothyroid patients, particularly T4 levels. Older adult patients with subclinical hypothyroidism have also shown improved cognitive functioning with hormone replacement, and, interestingly, *euthyroid* elderly patients show a strong relationship between T4 level and performance on a host of cognitive tasks.[26, 27]

Hyperthyroidism

The prevalence of hyperthyroidism is likely increased in adults over the age of 60. As with younger individuals, Graves' disease is the most common cause of hyperthyroidism in the elderly in the US, followed by multinodular goiter, with their relative proportion varying by region in relation to iodine intake. Thyroid cancer is a less frequent but notable cause of hyperthyroidism, and some forms may be more invasive in this age group (as with differentiated thyroid carcinoma) or almost exclusively seen in older adults (as with anaplastic carcinoma and lymphoma). Subclinical hyperthyroidism may be fairly common in the elderly, with one UK study showing a prevalence of 6.3% in women and 5.5% of men, though the significance of these findings is unclear, as TSH levels normalized after one year in the majority of cases.[28]

Elderly patients show fewer signs and symptoms of hyperthyroidism than do younger patients. Apathy may be the primary symptom, and indeed, the disease has been referred to as "apathetic thyrotoxicosis." Often, elderly patients lack symptoms such as tremor, ocular signs, heat intolerance, or anxiety/nervousness. Rather, these patients may present with cardiac complications, unexplained weight loss associated with gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea, constipation) and loss of appetite. Depression, often with notable anhedonia, may be present, as may symptoms of-

ten associated with mania. As with hypothyroidism, cognitive impairment severe enough to warrant a diagnosis of dementia can occur, and in some cases, the cognitive deficits are not entirely reversible with treatment.

Conclusions

Historically, the relationship between alteration of the hypothalamic pituitary thyroid axis and cognition and behavior had been supported predominantly by single case reports or anectdotal descriptions. However, over the past twenty years, there has been growing, converging evidence that thyroid disorders are associated with physical, behavioral, and cognitive symptoms that can significantly impact an individual's day-to-day functioning. In addition, these disorders can mimic psychiatric and cognitive disorders, leading to misdiagnosis and inappropriate treatment. Complete return to baseline functioning may not be achieved in individuals with thyroid disorders, particularly in those disorders involving autoimmune mechanisms. Longitudinal studies are needed to more clearly address the cognitive and emotional functioning at each stage of the disorders and following treatment. Elderly individuals can exhibit atypical physical and behavioral symptoms of thyroid disorders that can be misdiagnosed, and that may result in significant cognitive impairment.

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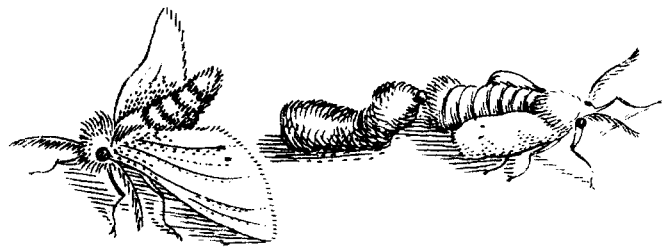

Geoffrey Tremont, PhD, is Associate Director, Neuropsychology Program, Department of Psychiatry at Rhode Island Hospital, and Clinical Assistant Professor, Department of Psychiatry and Human Behavior, Brown Medical School.

Robert A. Stern, PhD, is Director, Neuropsychology Program, Department of Psychiatry at Rhode Island Hospital, and Associate Professor, Department of Psychiatry and Human Behavior, Brown Medical School.

Holly James Westervelt, PhD, is Staff Neuropsychologist, Neuropsychology Program, Department of Psychiatry at Rhode Island Hospital, and Clinical Assistant Professor, Department of Psychiatry and Human Behavior, Brown Medical School.

Catherine Lee Bishop, PsyD, is a Post-Doctoral Fellow, Neuropsychology Program, Department of Psychiatry at Rhode Island Hospital & Department of Psychiatry and Human Behavior, Brown Medical School.

Jennifer Duncan Davis, PhD, is a Post-Doctoral Fellow, Neuropsychology Program, Department of Psychiatry at Rhode Island Hospital & Department of Psychiatry and Human Behavior, Brown Medical School.

Correspondence:
Geoffrey Tremont, PhD
Neuropsychology Program
Rhode Island Hospital
Physicians Office Building
596 Eddy Street
Providence, RI 02903
Phone: (401) 444-4500
e-mail: gtremont@lifespan.org