Editorial

Cognitive Function in Subclinical Hypothyroidism

Mary H. Samuels

Oregon Health & Science University, Portland, Oregon 97239

Over the past 20 yr, there have been major advances in understanding the neural basis for cognitive processes (1, 2). Cognitive domains include attention and concentration, language, memory, psychomotor function, and executive function. These domains map to neural systems that involve multiple, often overlapping brain regions. There are validated neurocognitive tests to measure these domains, mapped to critical brain regions by lesional studies and functional imaging.

Because thyroid hormone has profound effects on the central nervous system, it is logical to ask how hypothyroidism affects cognition. The consequences of overt hypothyroidism (particularly congenital hypothyroidism) are well known and include widespread cognitive deficits that can affect all the domains listed above (3). In contrast, there is less evidence regarding cognitive effects of subclinical hypothyroidism. This unresolved issue is a problem in clinical practice because subclinical hypothyroidism is prevalent in older patients, many of whom already have some cognitive decline. It is not clear whether these patients should be treated to ameliorate further cognitive dysfunction. Two recent systematic literature reviews did not find enough evidence to recommend treatment of subclinical hypothyroidism based on cognitive effects (4, 5).

The existing literature on subclinical hypothyroidism can be divided into larger cross-sectional or longitudinal studies and smaller interventional [levothyroxine (L-T4) treatment] studies. Many older studies of either type failed to find decrements in cognitive domains, although these were often limited by small sample sizes, heterogeneous subjects, or limited cognitive tests. More recent studies have been larger and/or have used more modern, validated cognitive tests. The most rigorous studies have also controlled for mood alterations, which can occur in thyroid dysfunction and which affect cognitive measures.

Most of the recent cross-sectional or longitudinal natural history studies have failed to find significant cognitive effects of subclinical hypothyroidism at baseline or developing over time (6–11). The largest of these was reported by Roberts *et al.* (7) in 2006. This was a well-conducted, population-based study of almost 6000 subjects, all at least 65 yr old. They underwent an extensive screening battery for cognitive function. No differences were found between subjects with subclinical hypothyroidism and euthyroid subjects. However, the cognitive batteries in this and other large studies were often designed to detect gross impairment in elderly subjects. Therefore, they might not be expected to detect subtle deficits induced by mild thyroid disease. In other cases, more sensitive cognitive tests were used but did not necessarily target the cognitive domains most likely to be affected by subclinical hypothyroidism, based on animal studies of thyroid hormone and its receptor distribution in the brain (12, 13).

There are only a few recent intervention studies that used highly sensitive tests to assess possible effects of L-T4 treatment on cognitive outcomes. The most influential is the study in Tromso, Norway (14). Subjects with subclinical hypothyroidism underwent detailed cognitive testing of multiple domains at baseline and after treatment with placebo or L-T4 for 12 months. There were no baseline differences between subclinical hypothyroid subjects and matched euthyroid controls, and there was no effect of L-T4 treatment on any of the measures. This study concluded that patients with subclinical hypothyroidism have no cognitive deficits, which is well supported by their data. The major limitation was the relatively mild degree of subclinical hypothyroidism, with TSH levels only up to 10 mU/liter.

In a smaller recent intervention study, Correia *et al.* (15) reported that subjects with subclinical hypothyroidism had impaired spatial and verbal memory on detailed cog-

Abbreviations: fMRI, Functional magnetic resonance imaging; L-T4, levothyroxine.

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2010-1242 Received June 2, 2010. Accepted June 11, 2010.

For article see page 3623

nitive testing, which resolved after 6 months of L-T4 therapy. However, this was an open-label, nonrandomized study where all subjects were treated.

An alternate approach was recently reported by our laboratory (16). Subjects with L-T4-treated hypothyroidism were randomized to continue their usual L-T4 dose or to receive a lower dose to induce subclinical hypothyroidism in a crossover design with 12-wk treatment arms. Decrements in working (short-term) memory were seen at the end of the subclinical hypothyroid arm. Note that this study was short-term and involved experimentally inducing subclinical hypothyroidism, which limits its applicability to clinical practice.

A recent study by Zhu *et al.* (17) reported a neuroanatomical basis for this defect in working memory. Subclinical hypothyroid subjects had impaired working memory and abnormal functional magnetic resonance imaging (fMRI) findings in frontal brain areas responsible for executive function. Some of the subclinical hypothyroid subjects were treated with L-T4 for 6 months, at which point working memory and fMRI results normalized. This important study provides the first functional imaging corroboration of a specific deficit in working memory/executive function in subclinical hypothyroidism.

Further objective evidence supporting a functional neurological abnormality is a recent report by Bauer *et al.* (18). Using positron emission tomography, untreated overt and subclinical hypothyroid subjects had lower regional glucose metabolism than controls in specific brain areas important for cognition. Metabolic activity was restored after L-T4 treatment for 3 months.

In sum, the literature on cognitive effects of subclinical hypothyroidism is sparse and inconclusive. Large, cross-sectional or longitudinal studies tend to be negative, although many used global screening measures of cognition rather than sensitive tests for specific domains most likely to be affected in subclinical hypothyroidism. Conversely, some small, interventional studies have shown deficits in executive function or memory, with improvements after L-T4 treatment and with functional imaging correlates. These latter studies used labor-intensive cognitive testing paradigms that are impractical for large population-based studies. This may explain some of the discrepancies among studies, but it leaves open the question of how clinically relevant these highly sensitive research tests are.

With this inconclusive literature as background, the article by Parle *et al.* in this issue of *JCEM* (19) is an important addition to the field. This study combines some of the strengths of previous large-scale, observational studies with those of smaller interventional studies. The authors used their previously published, large cross-sectional study in community-dwelling older subjects (7) to recruit 94 subjects with subclinical hypothyroidism. Subjects were randomized to receive L-T4 or placebo for 12 months, with dose titration to target normal TSH levels in the L-T4 treatment group. Standard tests of cognition were done at baseline and at 6 and 12 months, including two global cognitive assessments [the Mini-Mental Status Examination (MMSE) and the Middlesex Elderly Assessment of Mental State (MEAMS)] and a measure of executive functioning (Trail Making A and B). They appropriately tested for possible mood alterations, which were not present. They found no differences between the L-T4- and placebo-treated groups in any cognitive measures.

There are impressive strengths of this study. Subjects were recruited randomly from the community, eliminating bias due to self-selection or referral. They were at least 65 yr old at entry, representing the most relevant group to study for cognitive effects. It is the largest L-T4 interventional study to date, overcoming difficulties in enrolling significant numbers of subjects. The intervention was randomized, placebo-controlled, blinded, and dose-adjusted. Given the cost and logistical difficulties in completing such a study, we are unlikely to see better designed or conducted studies on this subject.

There are, however, two major limitations to the study. As in previous large-scale studies, the chosen measures cover a broad range of cognitive domains. However, the MMSE and MEAMS are screening tests to detect gross impairment, as the authors point out. The Trail Making Test is a more targeted test of executive function, but it has limited sensitivity compared with other, more intensive tests of this domain. It is possible that subtle defects in specific cognitive domains may have been missed in this study. The valid counter-argument is that such subtle defects may not be clinically significant, at least in otherwise healthy elderly subjects.

The most pertinent limitation to the study is the fate of the placebo-treated group. The study analysis was done on an intention-to-treat basis. However, only 27 of the original 42 placebo-treated subjects completed the study. Of these, 50% normalized their TSH levels by the 12-month study endpoint and cannot be considered a true stable and untreated control group. This finding is not surprising, given the high rate of normalization of mildly elevated TSH levels over time in untreated subclinical hypothyroidism (20). But it leaves only 13 subjects with elevated TSH levels in the placebo group at the end of the study. To compound this problem, 16% of the L-T4-treated subjects failed to normalize their TSH levels at 12 months. These high crossover rates between the two groups limit the conclusions because the groups were not well demarcated by the treatment arms.

Given the inconsistent findings in the published literature and the negative results from the study of Parle *et al.* (19), what conclusions can be drawn regarding cognition in subclinical hypothyroidism? First, global cognitive dysfunction, affecting numerous cognitive domains, does not occur in subclinical hypothyroidism. Second, major decrements in specific cognitive domains are unlikely. Third, subtle deficits in specific cognitive domains (memory and executive function) may exist, based on small intervention studies bolstered by fMRI and positron emission tomography results, which provide direct neuroanatomical correlates. Sensitive and specific tests are required to delineate these abnormalities, and their clinical significance is unclear. Given these conclusions, patients with subclinical hypothyroidism and significant cognitive dysfunction have independent diagnoses that should be evaluated and treated separately.

Acknowledgments

Address all correspondence and requests for reprints to: Mary H. Samuels, M.D., CR107, 3181 SW Sam Jackson Park Road, Portland, Oregon 97239. E-mail samuelsm@ohsu.edu.

Disclosure Summary: The author has nothing to declare.

References

1. **Budson AE, Price BH** 2005 Memory dysfunction. N Engl J Med 352:692–699
2. **Cabeza R, Nyberg L** 2000 Imaging cognition II: an empirical review of 275 PET and fMRI studies. J Cogn Neurosci 12:1–47
3. **Davis JD, Tremont G** 2007 Neuropsychiatric aspects of hypothyroidism and treatment reversibility. Minerva Endocrinol 32:49–65
4. **Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ** 2004 Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA 291:228–238
5. **Helfand M** 2004 Screening for subclinical thyroid dysfunction in nonpregnant adults: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Int Med 140:128–141
6. **Biondi B, Cooper DS** 2008 The clinical significance of subclinical thyroid dysfunction. Endocr Rev 29:76–131
7. **Roberts LM, Pattison H, Roalfe A, Franklyn J, Wilson S, Hobbs FD, Parle JV** 2006 Is subclinical thyroid dysfunction in the elderly associated with depression or cognitive dysfunction? Ann Int Med 145:573–581
8. **Gussekloo J, van Exel E, de Craen AJ, Meinders AE, Frölich M, Westendorp RG** 2004 Thyroid status, disability and cognitive function, and survival in old age. JAMA 292:2591–2599
9. **St John JA, Henderson VW, Gatto NM, McCleary CA, Spencer CA, Hodis HN, Mack WJ** 2009 Mildly elevated TSH and cognition in middle-aged and older adults. Thyroid 19:111–117
10. **Ceresini G, Lauretani F, Maggio M, Ceda GP, Morganti S, Usberti E, Chezzi C, Valcavi R, Bandinelli S, Guralnik JM, Cappola AR, Valenti G, Ferrucci L** 2009 Thyroid function abnormalities and cognitive impairment in elderly people: results of the Invecchiare in Chianti Study. J Am Geriatr Soc 57:89–93
11. **Hogervorst E, Huppert F, Matthews FE, Brayne C** 2008 Thyroid function and cognitive decline in the MRC Cognitive Function and Ageing Study. Psychoneuroendocrinology 33:1013–1022
12. **Broedel O, Eravci M, Fuxius S, Smolarz T, Jeitner A, Grau H, Stoltenburg-Didinger G, Plueckhan H, Meinhold H, Baumgartner A** 2003 Effects of hyper- and hypothyroidism on thyroid hormone concentrations in regions of the rat brain. Am J Physiol Endocrinol Metab 285:E470–E480
13. **Sinha AK, Pickard MR, Kim KD, Ahmed MT, al Yatama F, Evans IM, Elkins RP** 1994 Perturbation of thyroid hormone homeostasis in the adult and brain function. Acta Med Austriaca 21:35–43
14. **Jorde R, Waterloo K, Storhaug H, Nyrnes A, Sundsfjord J, Jenssen TG** 2006 Neuropsychological function and symptoms in subjects with subclinical hypothyroidism and the effect of thyroxine treatment. J Clin Endocrinol Metab 91:145–153
15. **Correia N, Mullally S, Cooke G, Tun TK, Phelan N, Feeney J, Fitzgibbon M, Boran G, O'Mara S, Gibney J** 2009 Evidence for a specific defect in hippocampal memory in overt and subclinical hypothyroidism. J Clin Endocrinol Metab 94:3789–3797
16. **Samuels MH, Schuff KG, Carlson NE, Carello P, Janowsky JS** 2007 Health status, mood, and cognition in experimentally induced subclinical hypothyroidism. J Clin Endocrinol Metab 92:2545–2551
17. **Zhu DF, Wang ZX, Zhang DR, Pan ZL, He S, Hu XP, Chen XC, Zhou JN** 2006 fMRI revealed neural substrate for reversible working memory dysfunction in subclinical hypothyroidism. Brain 129:2923–2930
18. **Bauer M, Silverman DH, Schlagenhauf F, London ED, Geist CL, van Herle K, Rasgon N, Martinez D, Miller K, van Herle A, Berman SM, Phelps ME, Whybrow PC** 2009 Brain glucose metabolism in hypothyroidism: a positron emission tomography study before and after thyroid hormone replacement therapy. J Clin Endocrinol Metab 94:2922–2929
19. **Parle J, Roberts L, Wilson S, Pattison H, Roalfe A, Haque MS, Heath C, Sheppard M, Frankly J, Hobbs FDR** 2010 A randomized controlled trial of the effect of thyroxine replacement on cognitive function in community-living elderly subjects with subclinical hypothyroidism: The Birmingham Elderly Thyroid Study. J Clin Endocrinol Metab 95:3623–3632
20. **Díez JJ, Iglesias P** 2004 Spontaneous subclinical hypothyroidism in patients older than 55 years: an analysis of natural course and risk factors for the development of overt thyroid failure. J Clin Endocrinol Metab 89:4890–4897