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Treated hypothyroidism is associated with cerebrovascular disease but not Alzheimer's disease pathology in older adults

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ABSTRACT

Thyroid hormone disease is common among older adults and is associated with cognitive impairment. However, pathologic correlates are not well understood. We studied pathologic and clinical factors associated with hypothyroidism, the most common manifestation of thyroid disease, in research subjects seen annually for clinical evaluations at U.S. Alzheimer's Disease Centers. Thyroid disease and treatment status were assessed during clinician interviews. Among autopsied subjects, there were 555 participants with treated hypothyroidism and 2146 without known thyroid disease; hypothyroidism was associated with severe atherosclerosis (odds ratio: 1.35; 95% confidence interval: 1.02, 1.79) but not Alzheimer's disease pathologies (amyloid plaques or neurofibrillary tangles). Among participants who did not undergo autopsy (4598 with treated hypothyroidism and 20,945 without known thyroid hormone disease), hypercholesterolemia and cerebrovascular disease (stroke and/or transient ischemic attack) were associated with hypothyroidism, complementing findings in the smaller autopsy sample. This is the first large-scale evaluation of neuropathologic concomitants of hypothyroidism in aged individuals. Clinical hypothyroidism was prevalent (>20% of individuals studied) and was associated with cerebrovascular disease but not Alzheimer's disease–type neuropathology.

1. Introduction

The pathologic sequelae of thyroid hormone (TH) dysregulation in the aged human brain are incompletely understood. Among the elderly, hypothyroidism is reported in up to 30% of research participants and hyperthyroidism in up to 10% (see Canaris et al., 2000; Empson et al., 2007; Sawin et al., 1985; Vanderpump, 2011; Verburg et al., 2017). Both clinical hypothyroidism and hyperthyroidism are associated with substantial morbidity and mortality (Gencer et al., 2013; Grossman et al., 2016; Imaizumi et al., 2004; Tan et al., 2008; Yeap et al., 2013).

TH is an evolutionarily ancient hormone with strong impact on human cellular metabolism, brain development, and cardiovascular health (Boelaert and Franklyn, 2005; Maenhaut et al., 2000). TH dysregulation in advanced age is also associated with risk for dementia (Chaker et al., 2016c; Mafrica and Fodale, 2008; Sampaolo et al., 2005; Tan and Vasan, 2009); a PubMed search using terms "(thyroid or thyroxine) and (Alzheimer's or dementia)" returns >500 published articles. The literature indicates a complicated relationship between TH and dementia risk. Hyperthyroidism is usually more strongly associated with cognitive decline, although some reports indicate that hypothyroidism also is a risk factor for dementia (Akintola et al., 2015; Chaker et al., 2016c; Moon et al., 2014, 2016; Pasqualetti et al., 2015; Rieben et al., 2016; Tan and Vasan, 2009; Wu et al., 2016; Yeap et al., 2012; van Osch et al., 2004). These are important questions, particularly because the elderly population is expanding and pharmacological manipulation of TH levels provides a possible disease-modifying strategy.

Perhaps due to the many relevant covariates that constitute formidable potential experimental confounders, there currently is no consensus as to the mechanism(s) underlying the link(s) between thyroid disease and dementia. In terms of specific disease processes, lack of TH in utero and in early life causes severe cognitive impairment (a component of "cretinism"), with extensive white matter pathology (Rosman, 1972). Some studies suggest that

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hypothyroidism may induce structural changes in the hippocampus (Cooke et al., 2014; Koromilas et al., 2010). However, much is still unknown about how TH dysregulation is correlated with brain pathologies in old age. TH dysregulation has been implicated in or comorbid with cardiovascular disease, stroke, hippocampal sclerosis (HS) of aging/cerebral age-related TAR DNA-binding protein-43 with sclerosis (CARTS), autoimmune disease(s), and, possibly, Alzheimer's disease (AD) (Chaker et al., 2016b, 2017; Collet et al., 2012; de Jong et al., 2009; Frohlich and Wahl, 2017; Mafrica and Fodale, 2008; Nelson et al., 2016a; Squizzato et al., 2005; Tan and Vasan, 2009; Zhang et al., 2017). Prospective studies are few in number and lack pathologic endpoints, and so cohorts that follow patients to autopsy are required to provide needed insights into how thyroid disease affects the aged brain.

The objective of this study was to evaluate associations between common cerebrovascular and neurodegenerative pathologies and clinical hypothyroidism (as operationalized by clinician interview during a clinical examination). We analyzed National Alzheimer's Coordinating Center (NACC) data gathered from U.S. Alzheimer's Disease Centers (ADCs). We focused on treated hypothyroidism because this was by far the most common clinical TH syndrome in this sample. Because hypothyroidism previously has been associated with cardiovascular risk factors (Abreu et al., 2017; Delpont et al., 2016; Imaizumi et al., 2004; Pasqualetti et al., 2015), we hypothesized that hypothyroidism would be associated with cerebrovascular pathology. As a secondary objective, we conducted a separate analysis of the relationship between hypothyroidism and clinical cardiovascular disease and risk factors in a complementary sample of non-autopsied participants.

2. Methods

2.1. Data sources and study populations

Data were obtained from the NACC's Uniform Data Set (UDS) on participants who had been prospectively evaluated at 1 of 34 past and present U.S. ADCs between September 2005 and December 2016. Participants enrolled with any level of cognition from normal to demented. Individual ADCs recruit and enroll participants according to their own protocols. UDS data were collected annually via trained clinicians or interviewers through in-person office visits at each ADC using a standardized clinical protocol (Beekley et al., 2004, 2007). At each visit, subjects received physical and neurological examinations, plus a battery of neuropsychological assessments. Neuropathology data were collected from neuropathologists based on autopsy results for subjects who died and had consented to autopsy evaluation at an ADC. Individual ADCs received institutional review board approval, and written informed consent was obtained from all participants and their study co-participants.

The current analyses focused on 2 samples: (1) UDS participants who had been autopsied (autopsy sample); and (2) UDS participants who were still alive or who had died but had not been autopsied (clinical sample). Participants were excluded from the autopsy sample if they (1) had age of death younger than 55 years (due to small numbers); (2) had rare disease(s) such as Down's syndrome, prion disease, autosomal dominant genetic diseases (i.e., early-onset AD), or frontotemporal lobar degeneration; (3) had reported use of hyperthyroid medication at any visit; or (4) were missing information on thyroid disease, demographics, health history, or common neuropathologies. Participants were excluded from the clinical sample if they (1) had age at baseline younger than 55 years; (2) had reported use of hyperthyroid medication at any visit; or (3) were missing information on thyroid disease, demographics, or health history. Fig. 1 shows the study sample flow and distribution of concurrent thyroid disease and medication use.

Among 2847 autopsied participants who met inclusion criteria, 25% had a history of thyroid disease and/or were taking hypothyroid medications, whereas in the clinical sample, 22% of 26,930 eligible participants had a history of thyroid disease or hypothyroid medication use. Most participants with thyroid disease and hypothyroid treatment reported active thyroid disease (93% in the autopsy sample and 82% in the clinical sample). The majority of

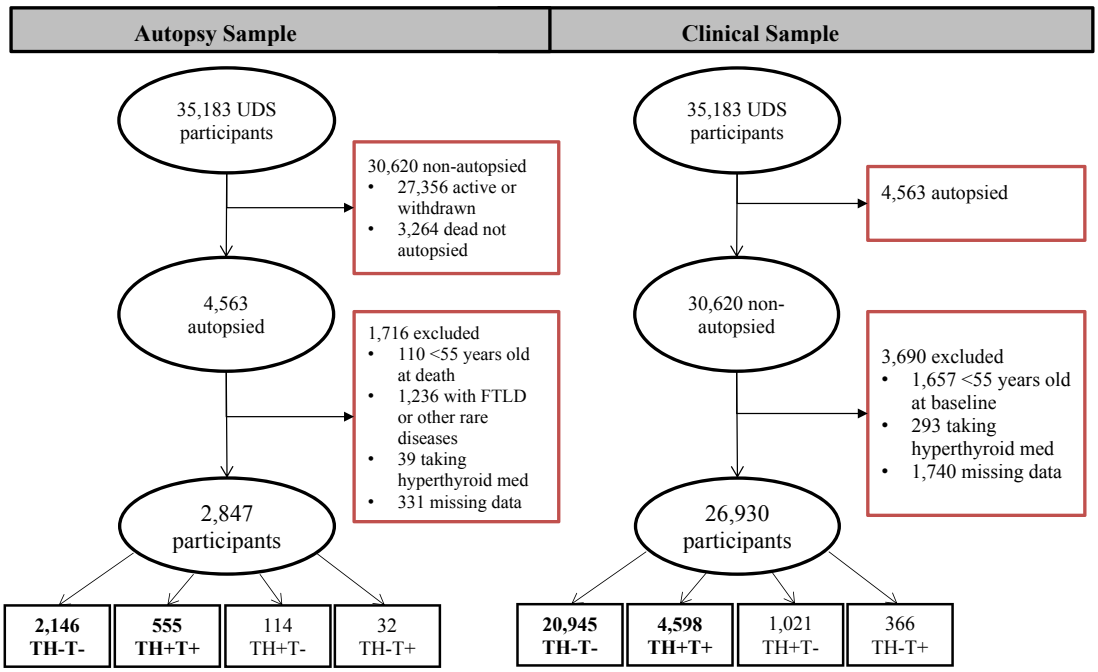

Fig. 1. Study sample flow chart. Primary analyses focus on comparisons between TH−T− and TH+T+ participants. Abbreviations: FTLD, frontotemporal lobar degeneration; NACC, National Alzheimer's Coordinating Center; TH+T+, thyroid disease with hypothyroid treatment; TH+T−, thyroid disease without hypothyroid treatment; TH−T+, thyroid disease not reported but hypothyroid medication reported; TH−T−, no thyroid disease and no treatment; UDS, Uniform Data Set.