

The role of local thyroid hormone perturbation in hippocampal sclerosis dementia – commentary on a multi-modality study

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Dementia is a common condition and its prevalence is expected to increase further in the coming decades due to population ageing. It is estimated that 35.6 million people were living with dementia worldwide in 2010, with numbers expected to rise to 65.7 million in 2030 and 115.4 million in 2050 (1). Dementia affects not only the individuals and families living with the condition but also the social-economy system. The global economic burden is estimated to be more than \$800 billion and expected to rise further still (2). Currently, no effective disease-modifying or preventive measures have been identified. Several stakeholders, including governments of 80 countries, have committed to prioritise research in this area and allocate resources with the aim to reduce the global burden of dementia (3). Alzheimer disease (AD), vascular dementia, dementia with Lewy bodies and frontotemporal dementia are among the most common types of dementia; caused by a complex interplay between genetics, environment and lifestyle (4). AD has a strong genetic component with more than 20 risk alleles being identified and the heritability rate of the different dementia subtypes ranges from 40% to 80% (4).

The hippocampus is a key region involved in cognition, supporting learning and memory, as well as modulating mood and responding to neuronal injury. Thus optimal hippocampal structure and function may be an important factor in the prevention or management of dementia. A recent genome-wide association study (GWAS) of 33,536

individuals discovered that genetic variants associated with decreased hippocampal volume are related to increased risk of AD (5). Hippocampal sclerosis (HS) is a neuropathological condition with substantial loss of neurons and astrogliosis in the hippocampus. HS is a non-specific pathological process and is commonly found on autopsy in older individuals with or without dementia or vascular disease (6). HS affects 5–30% of people older than 90 years, who are often misdiagnosed as having AD (7). TAR-DNA binding protein 43 (TDP-43) is the hallmark disease protein found in some neurodegenerative disease (i.e., frontotemporal lobar degeneration). Brain tissue obtained from older individuals with HS show abnormal hippocampal TDP-43 immunostaining in up to 90% of cases (8). It has been suggested that this dual-neuropathology, termed as cerebral age-related TDP-43 and sclerosis (CARTS), should be treated as a distinct disease to AD, as it seems to preferentially affect people in advanced old age (9).

Thyroid hormones (TH) are critical for brain development and maintenance of normal brain function. Although they are thought to be essential for embryonic and early postnatal brain development, altered mental function and mood changes are observed in adults with overt thyroid disorders. For instance, impaired memory, anxiety, depression and reduced hippocampal size have been observed in adults with hypothyroidism. These features are reversible following treatment, highlighting the active role

of TH in maintaining normal adult brain function. It was conventionally thought that brain neurogenesis does not occur to any significant extent in adult humans. However, recent studies have challenged this view, including some that demonstrated the significant roles of TH in hippocampal neurogenesis, myelination, glial progenitor turnover and survival (10-12). Furthermore, TH have been shown to regulate neural stem cell homeostasis: the active TH triiodothyronine (T3) and its receptor TR α 1 have been shown to repress the master genes involved in neural stem cell pluripotency and hence maintaining the 'stemness' of neural progenitor cells (13). Indeed, experimental adult-onset hypothyroidism in a rat model has been shown to reduce the number of newborn neuroblasts and immature neurons, which is reversed by TH replacement (14). These findings suggest that TH play an essential role in adult hippocampal neurogenesis. Brain-thyroid homeostasis is regulated by a complex molecular network, encompassing various TH transporters, local hormone availability via iodothyronine deiodinases (types 2 and 3) activities and the cross talk between TH and the surrounding paracrine/autocrine signalling pathways. TH are transported through the blood-brain barrier via organic anion transporter proteins (OATP) and the blood-CSF barrier via OATP and monocarboxylate transporter-8 (MCT8) transporters. The predominant TH thyroxine (T4) is converted to the more active T3 by deiodinase 2 in the astrocytes, before being delivered to neurons via MCT8 transporter.

The mechanistic process of how TH may influence dementia is unclear. However, a recent paper published by Nelson and colleagues provides an insight into how neuronal TH transport may play a role in the pathogenesis of HS-related dementia (15). An intronic SNP (rs704180) in the *ABCC9* genomic region (located on chromosome 12p12) has previously been identified as the risk allele for CARTS pathology. The authors investigated the association between other SNPs in the *ABCC9* genomic region, and their associated impact on gene regulatory mechanism relevant to CARTS, using several techniques and multiple independent databases [including genomic, neuroimaging, gene expression profile with single cell sequencing, serum and cerebrospinal fluid (CSF) analysis of TH concentration]. They found that the rs73069071 risk genotype was associated with HS pathology among 2,113 patients, who were found to have rs704180 risk alleles from the National Alzheimer's Coordinating Center/Alzheimer's Disease Genetic Consortium data (n=2,113, including 241 autopsy-confirmed HS cases). Both rs704180 and rs73069071 risk genotypes

were associated with widespread brain atrophy as visualized by MRI imaging, according to the information retrieved from the Alzheimer's Disease Neuroimaging Initiative data (n=1,239). Interestingly, the SNP rs73069071 was also associated with gene expression of an additional 12p12 gene: *SLCO1C1*, which encodes the primary transporter of TH into astrocytes from blood. Both *ABCC9* and *SLCO1C1* were highly expressed in mature astrocytes in the human brain. Genes that had been identified as astrocyte-expressed and enriched after T3 treatment in a mice brain model (16) was strongly correlated with both *ABCC9* and *SLCO1C1* gene variants. These findings are biologically important as the TH regulation in human brain seems to be sensitive towards genetic polymorphism in chromosome 12p12, which is associated with HS-pathology and have an impact on TH-mediated astrocyte gene expression. The authors went on to test TH levels in CSF obtained at autopsy from persons with HS pathology. Total T3 level in CSF was found to be elevated in HS cases, but not in Alzheimer's disease cases, relative to controls. No change was detected in the serum levels of thyroid hormone (T3 or T4) in a subsample of HS cases prior to death.

This is the first publication with genomic evidence that supports the association between TH-dysregulation and dementia. The selected patients from this study were individuals with amnesic dementia in advanced old age, showing CARTS neuropathology, without advanced Alzheimer's-type plaques and tangles in the autopsy. The genetic risk alleles on chromosome 12p12 implicated TH perturbation in CARTS pathology, via genetic variant to TH transporter and TH-mediated astrocyte gene expression. Importantly, the higher T3 level in CSF, but not in the serum, of patients with HS compared to the controls, suggests that local TH transport and cell-uptake has a potential role in CARTS-associated dementia. However, the CSF and serum samples of this published study were taken at a separate time (CSF at autopsy *vs.* stored frozen serum samples during life). There was also lack of biochemical confirmation of thyroid status for each individual and the thyroid status was judged based on participants' medical history and medication list. The authors of this paper also admit that it is possible that their findings may be falsely positive due to the gathering of data and analyses from many different sources.

The exact role of TH in the pathophysiology of AD and CARTS-related dementia remains elusive. Numerous clinical and laboratory studies have given contradicting results with regards to changes in serum or tissue TH concentration among the healthy *vs.* AD participants (17-19). This is largely due to heterogeneity of study

population, different assay methods or study techniques and post-mortem tissue quality. For instance, higher level of total T3 level was found in CSF among participants with HS at autopsy; whereas reduced tissue T3 concentration was seen in the prefrontal cortex of post-mortem AD brain tissue, via radioimmunoassay technique (15,17). On the other hand, both lower and higher thyroid stimulating hormone (TSH) levels have been associated with cognitive impairment. More importantly, the upper and lower limits of the serum TSH reference range broaden with age (20), leading to a wider spread of TSH distribution in older people. Systematic reviews and meta-analysis have consistently demonstrated the association between low serum TSH level (with normal free circulating TH) and cognitive impairment in people above 65 years of age (21,22). Despite the strong association between low TSH in older people and cognitive impairment, the underlying pathophysiology and causative link has yet to be established. Using AD as the disease model, evidence of altered hypothalamus-pituitary-thyroid (HPT) axis was discernible in this type of dementia; including blunted TSH response towards the thyroid-releasing hormone (TRH) stimulation test and lower circulating total T3 level (23).

TH undoubtedly play an important role in brain homeostasis. This paper has provided new insight into the potential role of thyroid dysregulation in non-AD dementia, in which many intriguing questions remain to be answered. Detailed studies into the role of age-associated altered HPT changes in cognitive impairment represents an important field, as subtle thyroid changes are common in older people and might represent an early risk factor for developing dementia in later life. Understanding the pathogenetic and mechanistic profile of age-associated HPT alteration, as well as their impact on cognition, as well as other ageing-associated phenotypes underpins the success in developing essential preventive and curative approach for mild cognitive impairment, AD or CARTS-associated dementia. This could also help to discover a TH-related biomarker that can identify patients at an early stage of a subtype of dementia and facilitate effective treatment.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest

to declare.

References

1. Prince M, Bryce R, Albanese E, et al. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement* 2013;9:63-75.e2.
2. Prince M, Wimo A, Guerchet M, et al. World Alzheimer report 2015: the global impact of dementia [internet]. Alzheimer's Disease International [cited 2017 March 26]. Available online: <https://www.alz.co.uk/research/world-report-2015>
3. Shah H, Albanese E, Duggan C, et al. Research priorities to reduce the global burden of dementia by 2025. *Lancet Neurol* 2016;15:1285-94.
4. van der Flier WM, Scheltens P. Epidemiology and risk factors of dementia. *J Neurol Neurosurg Psychiatry* 2005;76 Suppl 5:v2-7.
5. Hibar DP, Adams HH, Jahanshad N, et al. Novel genetic loci associated with hippocampal volume. *Nat Commun* 2017;8:13624.
6. Dickson DW, Davies P, Bevona C, et al. Hippocampal sclerosis: a common pathological feature of dementia in very old (> or = 80 years of age) humans. *Acta Neuropathol* 1994;88:212-21.
7. Nelson PT, Smith CD, Abner EL, et al. Hippocampal sclerosis of aging, a prevalent and high-morbidity brain disease. *Acta Neuropathol* 2013;126:161-77.
8. Nag S, Yu L, Capuano AW, et al. Hippocampal sclerosis and TDP-43 pathology in aging and Alzheimer disease. *Ann Neurol* 2015;77:942-52.
9. Nelson PT, Trojanowski JQ, Abner EL, et al. "New Old Pathologies": AD, PART, and Cerebral Age-Related TDP-43 With Sclerosis (CARTS). *J Neuropathol Exp Neurol* 2016;75:482-98.
10. Morte B, Bernal J. Thyroid hormone action: astrocyte-neuron communication. *Front Endocrinol (Lausanne)* 2014;5:82.
11. Calzà L, Fernandez M, Giardino L. Cellular approaches to central nervous system remyelination stimulation: thyroid hormone to promote myelin repair via endogenous stem and precursor cells. *J Mol Endocrinol* 2010;44:13-23.
12. Kapoor R, Desouza LA, Nanavaty IN, et al. Thyroid hormone accelerates the differentiation of adult hippocampal progenitors. *J Neuroendocrinol* 2012;24:1259-71.
13. López-Juárez A, Remaud S, Hassani Z, et al. Thyroid hormone signaling acts as a neurogenic Switch by

- repressing Sox2 in the adult neural stem cell niche. *Cell Stem Cell* 2012;10:531-43.
14. Montero-Pedrazuela A, Venero C, Lavado-Autric R, et al. Modulation of adult hippocampal neurogenesis by thyroid hormones: implications in depressive-like behaviour. *Mol Psychiatry* 2006;11:361-71.
 15. Nelson PT, Katsumata Y, Nho K, et al. Genomics and CSF analyses implicate thyroid hormone in hippocampal sclerosis of aging. *Acta Neuropathol* 2016;132:841-58.
 16. Gil-Ibañez P, García-García F, Dopazo J, et al. Global transcriptome analysis of primary cerebrocortical cells: identification of genes regulated by triiodothyronine in specific cell types. *Cereb Cortex* 2017;27:706-17.
 17. Davis JD, Podolanczuk A, Donahue JE, et al. Thyroid hormone levels in the prefrontal cortex of post-mortem brains of Alzheimer's disease patients. *Curr Aging Sci* 2008;1:175-81.
 18. Ganguli M, Burmeister LA, Seaberg EC, et al. Association between dementia and elevated TSH: a community-based study. *Biol Psychiatry* 1996;40:714-25.
 19. van Osch LA, Hogervorst E, Combrinck M, et al. Low thyroid-stimulating hormone as an independent risk factor for Alzheimer disease. *Neurology* 2004;62:1967-71.
 20. Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab* 2002;87:489-99.
 21. Gan EH, Pearce SH. Clinical review: The thyroid in mind: cognitive function and low thyrotropin in older People. *J Clin Endocrinol Metab* 2012;97:3438-49.
 22. Rieben C, Segna D, da Costa BR, et al. Subclinical Thyroid Dysfunction and the Risk of Cognitive Decline: a Meta-Analysis of Prospective Cohort Studies. *J Clin Endocrinol Metab* 2016;101:4945-54.
 23. Thomas DR, Hailwood R, Harris B, et al. Thyroid status in senile dementia of the Alzheimer type (SDAT). *Acta Psychiatr Scand* 1987;76:158-63.

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