Review

Medicine

Cognitive Dysfunction in Hypothyroidism

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Cognitive function and hypothyroidism are strongly associated, and age-related differences in performance are significant. The association between hypothyroidism and cognitive impairment in adult patients is still debatable, although it is most severe in the fetus and neonatal period, where it is easy to leave lasting sequelae. Current theories postulate that the various age-related manifestations of this cognitive impairment may be linked to the various stages of hypothyroidism during the time-dependent development of the neurological system. Although the precise mechanism is still not entirely understood, it might be connected to immunological factors.

Keywords: Hypothyroidism; Cognitive Function; Correlation; Age

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THYROID hormones are a big part of how the central nervous system grows and develops, and they have a bigger effect on the nervous system than on the rest of the body (1). Studies have shown that thyroid dysfunction is linked to problems with thinking and with the way the nervous system works (2). When a baby is born without enough thyroid hormone, it is often called cretinism (3). When it starts in childhood, it is called juvenile hypothyroidism, and when it starts in adulthood, it is often called adult hypothyroidism. The main signs of cretinism are mental retardation, a decline in cognitive skills, and a slowing of nerve reflexes (4). Even though hypothyroidism in adults can cause brain damage, their performance is very different from that of children. Based on this, this review discusses how hypothyroidism can affect people of different ages in different ways and how that might happen.

Hypothyroidism and Cognitive Impairment in Fetuses, Babies, and Kids

Thyroid hormones are very important for brain development from the time of conception on. If there is not enough thyroid hormone when a baby is still in the womb or when it is young, it will be extremely detrimental to the development of the neurological system (5). When a child is born with hypothyroidism, they are more likely to have primary hypothyroidism than central hypothyroidism (6). High levels of thyroid-stimulating hormone (TSH) and low or normal levels of free thyroxine (FT4) are signs of primary hypothyroidism. Hypothyroidism in the center is different. Most of the time, FT4 lowers the thyroid function, and then the TSH level is either normal or low. Reports showed that the number of babies born with congenital hypothyroidism is getting higher every year (7). Hypothyroidism is one of the main causes of mental retardation in children younger than 2 years old. Hypothyroidism can vary in its severity and duration. Furthermore, variable is the extent to which it damages

a child's brain. The earlier the onset of hypothyroidism, the more difficult it is to treat and the more nerve damage it causes. If a mother does not have enough thyroid hormone in the early stages of pregnancy, the baby may have lifelong problems like mental retardation, cognitive decline, and trouble moving. Hypothyroidism during pregnancy can cause mental and neurological symptoms in the fetus that are similar to cretinism after birth, but the only studies that have been done are observational, and the exact mechanism needs to be figured out (8, 9). The symptoms of childhood hypothyroidism are similar to those of mental retardation, but they are less severe than those of cretinism. Also, the most common symptom in children is growth retardation, not neurological developmental disorders.

In terms of clinical treatment, children with hypothyroidism need to get their thyroid hormone levels back into the normal range as soon as possible to prevent damage to their growth and development. Reasonable thyroid hormone replacement therapy can reduce this damage. However, long-term excessive use of thyroid hormone replacement therapy may cause hyperthyroidism in children (the younger they are, the higher the risk), and the risk of attention deficit increases (10). This means that the dose of thyroid hormone is different, as is the long-term prognosis, but the optimal dose is still unknown (11, 12).

Positive thyroid autoantibodies, such as thyroid peroxidase antibody (TPOAb) or antithyroglobulin antibody, can be a sign of primary hypothyroidism (TgAb). Studies showed that thyroid autoantibodies can affect how the nervous system grows and develops (13). A mother's high TSH level, low FT4, and high TPOAB titer were all independent risk factors for slowing their child's intellectual and motor development (14). Even though it has not been proven that TPOAb can hurt the thyroid function of a fetus, previous studies have shown that TPOAb is an indicator of poor thyroid gland development (15). So, the thyroid works normally during pregnancy, but the TPOAb titer is high, which means the baby is more likely to have nerve damage (16). Cohort studies have shown that even if pregnant women with positive TPOAb titers are given levothyroxine (L-T4) to bring their TSH levels back to normal, their children are still at a much higher risk for ADHD and autism (17). So, immune factors play a significant role in how the nervous system and brain develop in children who don't have enough thyroid hormone.

Hypothyroidism and Cognitive Impairment in Adults

Epidemiological data show that about 0.3% of adults have clinical hypothyroidism, while about 4.3% have subclinical hypothyroidism (18). Hypothyroidism is one of the main reasons why adults' minds get worse. Some researchers thought that a lack of thyroid hormone will cause changes in the neural pathways that the hippocampus controls, which could affect cognitive function (19). Some researchers, on the other hand, thought that the cognitive changes caused by thyroid function depend on how much hypothyroidism a person has. For example, mild emotional problems like anxiety and depression may be accompanied by a decline in cognitive function and memory. These changes do not have much to do with neural pathways (20). With clinical hypothyroidism, slow response and memory loss can be signs of cognitive decline, while the link between subclinical hypothyroidism and cognitive decline in adults is still being debated. Some thought that there is a strong link between subclinical hypothyroidism and cognitive impairment. However, some meta-studies have shown that there is no clear evidence that subclinical hypothyroidism is linked to cognitive impairment (21). Also, researchers are becoming more interested in Alzheimer's disease and Hashimoto's encephalopathy as they relate to cognitive impairment. However, the current research on these two diseases does not give a clear picture of how adult hypothyroidism is linked to cognitive impairment (22).

Most adults with hypothyroidism have autoimmune thyroiditis, which is one of the causes. Such patients have thyroid autoantibodies and organ-specific autoimmune diseases. There are a lot of autoimmune diseases, and they are linked to many psychological and psychiatric diseases, such as attention deficit disorder, attention and memory impairment, psychomotor retardation, depression, anxiety, and delusions of persecution (23). Hashimoto's encephalopathy and myxedema coma can make things worse in severe cases (24). In people with Hashimoto's encephalopathy, cognitive impairment is often caused by an immune inflammatory reaction in the central nervous system, which is different from simple hypothyroidism. This reaction may be combined with cerebral edema. Patient's autoantibody titer is related to how well glucocorticoids work to treat Hashimoto's encephalopathy (25). Studies have shown that L-T4 can help people with treatment-resistant depression respond better to antidepressants while correcting hypothyroidism (26). However, the effect of L-T4 on people with autoimmune thyroiditis and positive autoantibodies is still not clear (27). Autoantibodies are a big part of why these patients' brains do not work as well as they should. As thus, the discovery of TPOAb may help physicians determine how to treat brain autoimmunity by providing them with crucial clinical information.

During treatment, people with central hypothyroidism should make their FT4 value a little bit higher than normal, while people with primary hypothyroidism should keep their serum TSH levels within the normal reference range (28). Studies, however, have shown that cognitive function and mental health problems in adults with hypothyroidism may not be completely fixed by thyroid hormone replacement therapy (29). But animal studies have shown that if mice are without thyroid hormone for a short time, replacement therapy can bring back some brain functions that depend on the hippocampus (30). Some hippocampally dependent functions, like classical conditioning, can be restored with thyroid hormone therapy after a brief period of adult hypothyroidism, but not other hippocampal properties, like the synaptic plasticity elicited during associative learning and during experimentally induced long-term potentiation (31). Some believe that the small improvement in cognitive function after replacement therapy may be due to the fact that thyroid hormone deficiency changes the structure of the brain in a way that cannot be changed back. It may also be due to the fact that exogenous thyroid hormone is not very bioavailable in the central nervous system (32).

Senile Hypothyroidism and Cognitive Impairment

The elderly is more likely to have hypothyroidism (33). Due to less thyroid hormone being made, the brain cells' ability to use oxygen and glucose will slow down. This can make older people feel tired and forgetful. Statistics show that about two-thirds of older people with hypothyroidism have trouble remembering things and paying attention (34). If look closely, there is a difference between how people with hypothyroidism and people with senile dementia act. People with hypothyroidism often have swollen faces, necks, wrists, and ankles; eyelids that are loose and hang down; and a slow heart rate, and it can get better when you take thyroxine tablets (35), but people with senile dementia often have problems with their memory and personality that don't get better when they take thyroxine drugs (36).

Mild cognitive impairment (MCI) is a stage in the decline of brain function between normal and dementia. MCI patients have a much higher chance than the rest of the population of getting dementia in the next few years (37). Even though this study did not find a link between hypothyroidism and cognitive decline before dementia, the fact that it was a cross-sectional study does not mean that hypothyroidism can't be used to predict the progression of MCI to clinical dementia (38).

Potential Mechanism of Cognitive Impairment in Hypothyroidism

The amount of cognitive impairment in people with hypothyroidism is related to how long they did not have enough thyroid hormone while their nervous systems were developing. This effect is time- and dose-dependent. During the development of the nervous system, especially in the first trimester, the fetal nervous system needs thyroid hormone, which comes from the mother until the fetal thyroid matures and can make enough of its own. Thyroid hormones help the nervous system develop by taking part in the growth and movement of neurons, the differentiation of neurons and glial cells, and the creation of new connections between neurons (39). A lack of thyroid hormone can also change the brain's chemical structure and properties. Studies have confirmed that a lack of thyroid hormones in the brain microenvironment can cause a drop in monoamines like epinephrine and norepinephrine (40), and an increase in γ -aminobutyric acid (41). Furthermore, metabolites of thyroid hormones, like 3′ -iodothyronine (T1AM), can also have important effects on the central nervous system (42). In a dose-dependent way, T1AM can stop thyroid hormones from moving through the blood-brain barrier by organic anion-transporting polypeptide 1C1 (OATP1C1) and monocarboxylate transporter 8 (MCT8), which changes the way thyroid hormones work in the central nervous system (43). Studies on animals have shown that T1AM can help coordinate how the brain sends and receives signals and how it learns and remembers things. It does this by activating mitochondrial ATP synthase and the trace amine-associated receptor 1 (TAAR1) (44, 45). Also, thyroid hormones can change the way myelin proteins are made, so they are essential to the formation of myelin (46).

In the early stages of embryonic development, thyroid hormones can affect not only brain molecules and functional pathways but also structures like the cerebral cortex, hippocampus, and cerebellum (2). If the lack of thyroid hormone is not fixed after the baby is born, it will cause damage to the nervous system that cannot be fixed. The symptoms of hypothyroidism in adults are not severe. Some feel that the memory loss induced by hypothyroidism in adults is primarily due to hypoxia, or decreased blood flow to the brain (47). Patients in this age group may have a decline in all of their cognitive functions, such as language function, logical ability, memory, and some may also feel tired. If the person is old, it could be mistakenly thought that they have Alzheimer's disease. At the same time, adults are more likely than children to have emotional problems, which usually show up as depression, paranoia, or excitement. It has been said that there is a strong link between hypothyroidism in adults and Alzheimer's disease (48). As people get older, they are more likely to get hypothyroidism, and their risk of getting Alzheimer's disease also goes up a lot. Reserchers in the field have proposed a possible explanation, which is that thyroid hormone can regulate the expression of the amyloid gene and alter how brain tissue functions. But some researchers think that hypothyroidism does not have much to do with cognitive function or Alzheimer's disease (49). So, the link between hypothyroidism in adults and Alzheimer's disease is still up for debate.

Most studies on cognitive decline in people with hypothyroidism caused by immune factors have been done on adults, and there are not many studies on fetal, infant, or child patients. Studies have shown that the effect of high titers of TPOAb on cognition in the fetus may be related to the change in gray matter volume (50), but there is still no solid evidence, and more studies are needed right away to prove the link between brain function and structural changes and immune-related factors in children with hypothyroidism. Some believed that high titers of TPOAB in adults with thyroiditis can cause T cells to make more helper T cells or cytotoxic T cell 1 cytokines (51). This change in the immune system can affect how neurotransmitters like serotonin, dopamine, and glutamate are made, released, and taken back up. These cytokines take tryptophan, an amino acid that helps make serotonin, and turn it into neuroactive metabolites that have a big effect on how dopamine and glutamate are regulated. People with positive thyroid autoantibodies have an uneven flow of blood to the parietal lobe compared to people with negative autoantibodies. This uneven flow can cause mental decline and emotional problems (52).

Moreover, people with pituitary stalk interruption syndrome (PSIS) can get central hypothyroidism early in life, but they usually have slow growth and/or low sexual development, and their cognitive function is not significantly affected (53, 54). This means that mental decline like cretinism does not happen very often. So far, no studies have found a link between hypothyroidism and how well PSIS patients think. Patients with PSIS may have hypofunction of all or part of the pituitary axis, which is different from patients with simple congenital hypothyroidism, and there are more different types of symptoms. Patients with PSIS are less likely to have autoimmune diseases at the same time as people with chronic lymphocytic thyroiditis. This means that hypothyroidism and autoimmune diseases are not usually linked. As thus, some of the reasons why people with PSIS have less severe cognitive function problems than people with autoimmune-mediated hypothyroidism may be: (i) When damage to the pituitary axis is added to other types of damage to the pituitary axis, the body can't grow and develop normally and keep

the brain working normally. There is a corresponding drop in the need for thyroid hormones, which may be caused by the complicated way that hormones in the body work together. When there is a lack of growth hormone at the same time, the signs of hypothyroidism are often hard to see; when growth hormone is added to the body in a natural way, hypothyroidism symptoms will show up. (ii) Hypothyroidism in PSIS patients is mostly caused by mechanical damage to the pituitary stalk. Its cause is not an autoimmune disease, and more research is needed to figure out how it happens.

Conclusion

The development of the central nervous system depends on thyroid hormones, so thyroid function is closely linked to cognitive function. Hypothyroidism, on the other hand, can cause different levels of brain damage and physical symptoms in people of different ages. Patients who are still in the womb or just born may have irreversible cognitive impairment if they don't get thyroid hormone supplementation right away, but the opposite is true for adults. Different age groups have different levels of impairment in cognitive function, and the thyroid function is closely linked to cognitive function. Hypothyroidism, on the other hand, can cause different levels of brain damage and physical symptoms in people of different ages. Patients who are still in the womb or just born may have irreversible cognitive impairment if they do not get thyroid hormone supplementation right away, but the opposite is true for adults. Different age groups have different levels of impairment in cognitive function. This has to do with how long they were without enough thyroid hormone and is closely linked to immune factors. Some studies suggest that the presence of TPOAB in people with hypothyroidism may be an important sign of damage to the nervous system. Hypothyroidism doesn't usually cause obvious mental retardation in PSIS patients, but there is no research report on this, and its mechanism still needs more basic research and/or large-sample, multi-center clinical research to prove it.■

References

1. Shahid MA, Ashraf MA, Sharma S. Physiology, Thyroid Hormone. [Updated 2022 May 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan. Available at: https://www.ncbi.nlm.nih.gov/books/NBK500006/
2. Bernal J. Thyroid Hormones in Brain Development and Function. [Updated 2022 Jan 14]. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000. Available at: https://www.ncbi.nlm.nih.gov/books/NBK285549/
3. Srivastav A, Maisnam I, Dutta D, Ghosh S, Mukhopadhyay S, Chowdhury S. Cretinism revisited. Indian J Endocrinol Metab 2012; 16(Suppl 2):S336-S337. DOI: https://doi.org/10.4103/2230-8210.104081
4. Segni M. Disorders of the Thyroid Gland in Infancy, Childhood and Adolescence. [Updated 2017 Mar 18]. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000. Available at: https://www.ncbi.nlm.nih.gov/books/NBK279032/
5. Moog NK, Entringer S, Heim C, Wadhwa PD, Kathmann N, Buss C. Influence of maternal thyroid hormones during gestation on fetal brain development. Neuroscience 2017; 342:68-100. DOI: https://doi.org/10.1016/j.neuroscience.2015.09.070
6. Bowden SA, Goldis M. Congenital Hypothyroidism. [Updated 2022 Jun 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan. Available at: https://www.ncbi.nlm.nih.gov/books/NBK558913/
7. Taheri Soodejani M, Tabatabaei SM, Shoraka HR, Fallahzadeh H, Ghaderi A. Trend of congenital hypothyroidism incidence and its affecting factors in Shahr-e-Kord, Western Iran. Iran J Public Health 2020; 49(5):989-994.
8. Smallridge RC, Ladenson PW. Hypothyroidism in pregnancy: Consequences to neonatal health. J Clin Endocrinol Metab. 2001; 86(6):2349-2353. DOI: https://doi.org/10.1210/jcem.86.6.7577
9. Tudosa R, Vartej P, Horhoianu I, Ghica C, Mateescu S, Dumitrache I. Maternal and fetal complications of the hypothyroidism-related pregnancy. Maedica (Bucur) 2010; 5(2):116-123.
10. Léger J, Carel JC. Hyperthyroidism in childhood: Causes, when and how to treat. J Clin Res Pediatr Endocrinol 2013; 5 Suppl 1(Suppl 1):50-56. DOI: https://doi.org/10.4274/jcrpe.854
11. Rotondi M, Cappelli C, Pirali B, Pirola I, Magri F, Fonte R, Castellano M, Rosei EA, Chiovato L. The effect of pregnancy on subsequent relapse from Graves' disease after a successful course of antithyroid drug therapy. J Clin Endocrinol Metab 2008; 93(10):3985-3988. DOI: https://doi.org/10.1210/jc.2008-0966
12. Sjölin G, Holmberg M, Törring O, Byström K, Khamisi S, de Laval D, Abraham-Nordling M, Calissendorff J, Lantz M, Hallengren B, Filipsson Nyström H, Wallin G. The long-term outcome of treatment for Graves' hyperthyroidism. Thyroid 2019; 29(11):1545-1557. DOI: https://doi.org/10.1089/thy.2019.0085
13. Franco JS, Amaya-Amaya J, Anaya JM. Thyroid disease and autoimmune diseases. In: Anaya JM, Shoenfeld Y, Rojas-Villarraga A, et al., editors. Autoimmunity: From Bench to Bedside [Internet]. Bogota (Colombia): El Rosario University Press; 2013 Jul 18. Chapter 30. Available at:

https://www.ncbi.nlm.nih.gov/books/NBK459466/

14. Wang Q, Jiang Y, Lv H, Lu Q, Tao S, Qin R, Huang L, Liu C, Xu X, Lv S, Li M, Li Z, Du J, Lin Y, Ma H, Chi X, Hu Z, Jiang T, Zhang G. Association of maternal mild hypothyroidism with offspring neurodevelopment in TPOAb-negative women: A prospective cohort study. Front Endocrinol (Lausanne) 2022; 13:884851. DOI: https://doi.org/10.3389/fendo.2022.884851
15. Wang C, Niu Q, Lv H, Li Q, Ma Y, Tan J, Liu C. Elevated TPOAb is a strong predictor of autoimmune development in patients of type 2 diabetes mellitus and non-alcoholic fatty liver disease: A case-control study. Diabetes Metab Syndr Obes 2020; 13:4369-4378. DOI: https://doi.org/10.2147/DMSO.S280231
16. Ghassabian A, Bongers-Schokking JJ, de Rijke YB, van Mil N, Jaddoe VW, de Muinck Keizer-Schrama SM, Hooijkaas H, Hofman A, Visser W, Roman GC, Visser TJ, Verhulst FC, Tiemeier H. Maternal thyroid autoimmunity during pregnancy and the risk of attention deficit/hyperactivity problems in children: The Generation R Study. Thyroid 2012; 22(2):178-86. DOI: https://doi.org/10.1089/thy.2011.0318
17. Lazarus J. Thyroid Regulation and Dysfunction in the Pregnant Patient. [Updated 2016 Jul 21]. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000. Available at: https://www.ncbi.nlm.nih.gov/books/NBK279059/
18. Strikić Đula I, Pleić N, Babić Leko M, Gunjača I, Torlak V, Brdar D, Punda A, Polašek O, Hayward C, Zemunik T. Epidemiology of hypothyroidism, hyperthyroidism and positive thyroid antibodies in the Croatian population. Biology (Basel) 2022; 11(3):394. DOI: https://doi.org/10.3390/biology11030394
19. Grigorova M, Sherwin BB. Thyroid hormones and cognitive functioning in healthy, euthyroid women: A correlational study. Horm Behav 2012; 61(4):617-22. DOI: https://doi.org/10.1016/j.yhbeh.2012.02.014
20. Samuels MH. Psychiatric and cognitive manifestations of hypothyroidism. Curr Opin Endocrinol Diabetes Obes 2014; 21(5):377-383. DOI: https://doi.org/10.1097/MED.0000000000000089
21. Akintola AA, Jansen SW, van Bodegom D, van der Grond J, Westendorp RG, de Craen AJ, van Heemst D. Subclinical hypothyroidism and cognitive function in people over 60 years: A systematic review and meta-analysis. Front Aging Neurosci 2015; 7:150. DOI: https://doi.org/10.3389/fnagi.2015.00150
22. Waliszewska-Prosół M, Ejma M. Hashimoto encephalopathy-still more questions than answers. Cells 2022; 11(18):2873. DOI: https://doi.org/10.3390/cells11182873
23. Ravan JR, Chatterjee S, Singh P, Maikap D, Padhan P. Autoimmune rheumatic diseases masquerading as psychiatric disorders: A case series. Mediterr J Rheumatol 2021; 32(2):164-167. DOI: https://doi.org/10.31138/mjr.32.2.164
24. Payer J, Petrovic T, Lisy L, Langer P. Hashimoto encephalopathy: A rare intricate syndrome. Int J Endocrinol Metab 2012; 10(2):506-514. DOI: https://doi.org/10.5812/ijem.4174
25. Li J, Li F. Hashimoto's encephalopathy and seizure disorders. Front Neurol 2019; 10:440. DOI: https://doi.org/10.3389/fneur.2019.00440
26. Joffe RT. Should thyroid replacement therapy be considered for patients with treatment-refractory depression? J Psychiatry Neurosci 2002; 27(1):80.
27. Bauer M, Whybrow PC. Role of thyroid hormone therapy in depressive disorders. J Endocrinol Invest 2021; 44(11):2341-2347. DOI: https://doi.org/10.1007/s40618-021-01600-w
28. Sheehan MT. Biochemical testing of the thyroid: TSH is the best and, oftentimes, only test needed - A review for primary care. Clin Med Res 2016; 14(2):83-92. DOI: https://doi.org/10.3121/cmr.2016.1309
29. van Vliet NA, van Heemst D, Almeida OP, Åsvold BO, Aubert CE, Bae JB, Barnes LE, Bauer DC, Blauw GJ, Brayne C, Cappola AR, Ceresini G, Comijs HC, Dartigues JF, Degryse JM, Dullaart RPF, van Eersel MEA, den Elzen WPJ, Ferrucci L, Fink HA, Flicker L, Grabe HJ, Han JW, Helmer C, Huisman M, Ikram MA, Imaizumi M, de Jongh RT, Jukema JW, Kim KW, Kuller LH, Lopez OL, Mooijaart SP, Moon JH, Moutzouri E, Nauck M, Parle J, Peeters RP, Samuels MH, Schmidt CO, Schminke U, Slagboom PE, Stordal E, Vaes B, Völzke H, Westendorp RGJ, Yamada M, Yeap BB, Rodondi N, Gussekloo J, Trompet S; Thyroid studies collaboration. association of thyroid dysfunction with cognitive function: An individual participant data analysis. JAMA Intern Med 2021; 181(11):1440-1450. DOI: https://doi.org/10.1001/jamainternmed.2021.5078
30. Fu A, Zhou R, Xu X. The synthetic thyroid hormone, levothyroxine, protects cholinergic neurons in the hippocampus of naturally aged mice. Neural Regen Res 2014; 9(8):864-71. DOI: https://doi.org/10.4103/1673-5374.131602
31. Fernández-Lamo I, Montero-Pedrazuela A, Delgado-García JM, Guadaño-Ferraz A, Gruart A. Effects of thyroid hormone replacement on associative learning and hippocampal synaptic plasticity in adult hypothyroid rats. Eur J Neurosci 2009; 30(4):679-692. DOI: https://doi.org/10.1111/j.1460-9568.2009.06862.x
32. Idrose AM. Acute and emergency care for thyrotoxicosis and thyroid storm. Acute Med Surg 2015; 2(3):147-157. DOI: https://doi.org/10.1002/ams2.104
33. Kim MI. Hypothyroidism in Older Adults. [Updated 2020 Jul 14]. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available at: https://www.ncbi.nlm.nih.gov/books/NBK279005/
34. Bégin ME, Langlois MF, Lorrain D, Cunnane SC. Thyroid function and cognition during aging. Curr Gerontol Geriatr Res 2008; 2008:474868. DOI: https://doi.org/10.1155/2008/474868
35. Wortsman J, Wavak P. Palpebral redundancy from hypothyroidism. Plast Reconstr Surg. 1980 Jan;65(1):1-3. DOI: https://doi.org/10.1097/00006534-198001000-00001
36. de Jong FJ, Masaki K, Chen H, Remaley AT, Breteler MM, Petrovitch H, White LR, Launer LJ. Thyroid

function, the risk of dementia and neuropathologic changes: The Honolulu-Asia aging study. Neurobiol Aging 2009; 30(4):600-606. DOI: https://doi.org/10.1016/j.neurobiolaging.2007.07.019

37. Campbell NL, Unverzagt F, LaMantia MA, Khan BA, Boustani MA. Risk factors for the progression of mild cognitive impairment to dementia. Clin Geriatr Med 2013; 29(4):873-893. DOI: https://doi.org/10.1016/j.cger.2013.07.009
38. Parsaik AK1, Singh B2, Roberts RO3, Pankratz S4, Edwards KK4, Geda YE5, Gharib H6, Boeve BF7, Knopman DS7, Petersen RC7. Hypothyroidism and risk of mild cognitive impairment in elderly persons: A population-based study. JAMA Neurol 2014; 7:201-207. DOI: https://doi.org/10.1001/jamaneurol.2013.5402
39. Noda M. Thyroid Hormone in the CNS: Contribution of Neuron-Glia Interaction. Vitam Horm 2018; 106:313-331. DOI: https://doi.org/10.1016/bs.vh.2017.05.005
40. Swann AC. Thyroid hormone and norepinephrine: Effects on alpha-2, beta, and reuptake sites in cerebral cortex and heart. J Neural Transm 1988; 71(3):195-205. DOI: https://doi.org/10.1007/BF01245713
41. Wiens SC, Trudeau VL. Thyroid hormone and gamma-aminobutyric acid (GABA) interactions in neuroendocrine systems. Comp Biochem Physiol A Mol Integr Physiol 2006; 144(3):332-344. DOI: https://doi.org/10.1016/j.cbpa.2006.01.033
42. Zucchi R, Accorroni A, Chiellini G. Update on 3-iodothyronamine and its neurological and metabolic actions. Front Physiol 2014; 5:402. DOI: https://doi.org/10.3389/fphys.2014.00402
43. Ceballos A, Belinchon MM, Sanchez-Mendoza E, Grijota-Martinez C, Dumitrescu AM, Refetoff S, Morte B, Bernal J. Importance of monocarboxylate transporter 8 for the blood-brain barrier-dependent availability of 3,5,3'-triiodo-L-thyronine. Endocrinology. 2009; 150(5):2491-2496. DOI: https://doi.org/10.1210/en.2008-1616
44. Miller GM. The emerging role of trace amine-associated receptor 1 in the functional regulation of monoamine transporters and dopaminergic activity. J Neurochem 2011; 116(2):164-176. DOI: https://doi.org/10.1111/j.1471-4159.2010.07109.x
45. Dinter J, Mühlhaus J, Wienchol CL, Yi CX, Nürnberg D, Morin S, Grüters A, Köhrle J, Schöneberg T, Tschöp M, Krude H, Kleinau G, Biebermann H. Inverse agonistic action of 3-iodothyronamine at the human trace amine-associated receptor 5. PLoS One 2015; 10(2):e0117774. DOI: https://doi.org/10.1371/journal.pone.0117774
46. Valcana T, Einstein ER, Csejtey J, Dalal KB, Timiras PS. Influence of thyroid hormones on myelin proteins in the developing rat brain. J Neurol Sci 1975; 25(1):19-27. DOI: https://doi.org/10.1016/0022-510x(75)90183-5
47. Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism. Lancet 2017; 390(10101):1550-1562. DOI: https://doi.org/10.1016/S0140-6736(17)30703-1
48. Kim JH, Lee HS, Kim YH, Kwon MJ, Kim JH, Min CY, Yoo DM, Choi HG. The association between thyroid diseases and Alzheimer's disease in a national health screening cohort in Korea. Front Endocrinol (Lausanne) 2022; 13:815063. DOI: https://doi.org/10.3389/fendo.2022.815063
49. Przybylak M, Grabowski J, Bidzan L. Cognitive functions and thyroid hormones secretion disorders. Psychiatr Pol 2021; 55(2):309-321. English, Polish. DOI: https://doi.org/10.12740/PP/112470
50. Tingi E, Syed AA, Kyriacou A, Mastorakos G, Kyriacou A. Benign thyroid disease in pregnancy: A state of the art review. J Clin Transl Endocrinol 2016; 6:37-49. DOI: https://doi.org/10.1016/j.jcte.2016.11.001
51. Guo Y, Zynat J, Xing S, Xin L, Li S, Mammat N, Chen Y, Zhao L, Zhao H, Wang X. Immunological changes of T helper cells in flow cytometer-sorted CD4+ T cells from patients with Hashimoto's thyroiditis. Exp Ther Med 2018; 15(4):3596-3602. DOI: https://doi.org/10.3892/etm.2018.5825
52. Twito O, Shapiro Y, Golan-Cohen A, Dickstein Y, Ness-Abramof R, Shapiro M. Anti-thyroid antibodies, parietal cell antibodies and tissue transglutaminase antibodies in patients with autoimmune thyroid disease. Arch Med Sci 2018; 14(3):516-520. DOI: https://doi.org/10.5114/aoms.2016.58743
53. Zhang W, Qian F, Lu G, Wu Y, Li R, Xia L, Zhao R, Lin Y, Gu M, Chen W. Pituitary stalk interruption syndrome: A rare case report and literature review. Medicine (Baltimore) 2020; 99(50):e23266. DOI: https://doi.org/10.1097/MD.0000000000023266
54. Persani L, Cangiano B, Bonomi M. The diagnosis and management of central hypothyroidism in 2018. Endocr Connect 2019; 8(2):R44-R54. DOI: https://doi.org/10.1530/EC-18-0515

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