Regional cerebral perfusion changes in Hashimoto thyroiditis and their association with levothyroxine treatment: a 99mTc-HMPAO SPECT study

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Abstract:

Objective: To explore regional cerebral perfusion abnormalities and their changes after levothyroxine treatment, together with depressive symptoms, in patients with Hashimoto thyroiditis. **Materials and Methods:** Sixteen female patients with Hashimoto thyroiditis were divided into two groups according to baseline anti-thyroid peroxidase (anti-TPO) antibody levels: < 100 IU/mL (n = 6) and ≥ 100 IU/mL (n = 10), respectively. Thyroid-stimulating hormone (TSH), anti-TPO levels, and Hamilton Depression Rating Scale (HAM-D) scores were assessed before and after levothyroxine treatment. Cerebral perfusion was evaluated using 99mTc-HMPAO SPECT, with the cerebellum as the reference region for semiquantitative analysis. **Results:** TSH, anti-TPO, and HAM-D scores decreased significantly after treatment in both groups ($p < 0.05$). Before treatment, significant hypoperfusion was observed in the left frontotemporal, right temporal, left parietal, and left frontal regions in the lower anti-TPO group, whereas more limited perfusion abnormalities were observed in the higher anti-TPO group. Several regional perfusion indices improved significantly after levothyroxine treatment, particularly in the lower anti-TPO group. **Conclusion:** In this exploratory study, regional cerebral perfusion abnormalities were observed in patients with Hashimoto thyroiditis, with changes in several perfusion indices following levothyroxine treatment. The extent of perfusion abnormalities did not appear to be related to higher anti-TPO levels. Given the small sample size, these preliminary findings should be interpreted with caution and require confirmation in larger prospective controlled studies.

Key words: Hashimoto thyroiditis, cerebral perfusion, 99mTc-HMPAO SPECT, levothyroxine, anti-TPO

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Introduction

Hashimoto thyroiditis is a common autoimmune thyroid disorder that may be associated with neuropsychiatric manifestations, including depressive symptoms and cognitive disturbances. Thyroid dysfunction, particularly hypothyroidism, has been associated with mood disorders, and thyroid hormone replacement may improve neuropsychiatric symptoms in affected patients [1, 2]. Recent evidence further supports an association between autoimmune thyroiditis and depression and anxiety, even in euthyroid patients [3]. Alterations in cerebral blood flow and brain function have been proposed as potential mechanisms underlying these manifestations [4].

Cerebral perfusion abnormalities have been reported in patients with autoimmune thyroiditis. Single-photon emission computed tomography (SPECT) studies have demonstrated regional or global cerebral hypoperfusion in patients with Hashimoto thyroiditis and Hashimoto encephalopathy [5-7]. Improvement in cerebral hypoperfusion following levothyroxine treatment has also been demonstrated using 99mTc-HMPAO SPECT [6]. More recent evidence suggests that neurological and neuropsychiatric alterations may occur in Hashimoto thyroiditis even in the euthyroid state, supporting a potential contribution of thyroid autoimmunity beyond thyroid hormone deficiency alone [4, 8].

Anti-thyroid peroxidase (anti-TPO) antibodies are a characteristic marker of Hashimoto thyroiditis. Previous studies have suggested associations between thyroid

autoimmunity and depressive symptoms [9, 10]; however, the relationship between the magnitude of anti-TPO elevation and the extent or reversibility of regional cerebral perfusion abnormalities remains unclear.

Therefore, this exploratory study aimed to evaluate regional cerebral perfusion abnormalities using 99mTc-HMPAO SPECT in patients with Hashimoto thyroiditis stratified according to anti-TPO antibody levels and to assess changes in cerebral perfusion, depressive symptoms, and thyroid-related laboratory parameters following levothyroxine treatment.

Materials and Methods

Study Population

This retrospective study was based on a medical specialty thesis and included 16 female patients with Hashimoto thyroiditis who underwent clinical evaluation and brain perfusion SPECT between 2003 and 2004 at the Department of Nuclear Medicine, Cerrahpasa Faculty of Medicine, Istanbul University. Ethical approval was obtained in accordance with the institutional requirements applicable at the time the study was conducted. The patients were followed for a mean period of 120 ± 18 days.

Inclusion criteria were: (1) a diagnosis of Hashimoto thyroiditis; (2) availability of baseline thyroid-related laboratory measurements, including TSH and anti-TPO levels; (3) completion of baseline HAM-D assessment and brain perfusion SPECT; and (4) availability of corresponding post-treatment clinical, biochemical, psychiatric, and brain perfusion SPECT assessments following levothyroxine treatment.

Exclusion criteria were: a history of cerebrovascular disease, epilepsy, Parkinson's disease, or alcohol dependence, as well as the use of antidepressant or antiepileptic medication.

The patients were divided into two groups according to baseline anti-TPO antibody levels. The lower anti-TPO group consisted of six patients with anti-TPO levels < 100 IU/mL (mean age, 43.17 years), whereas the higher anti-TPO group consisted of 10 patients with anti-TPO levels ≥ 100 IU/mL (mean age, 42.3 years).

Serum T3, T4, thyroid-stimulating hormone (TSH), and anti-TPO levels were measured before and after levothyroxine treatment. TSH was measured using an electrochemiluminescence immunoassay (ECLIA), whereas anti-TPO antibodies were measured using a direct iodine-125 immunoradiometric assay. Two patients with relatively low anti-TPO and TSH levels underwent fine-needle aspiration biopsy.

Psychiatric Assessment

Depressive symptoms were assessed before and after levothyroxine treatment using the Hamilton Depression Rating Scale (HAM-D). Scores of 0-13 were considered to indicate no depression, 14-27 – mild depression, and ≥ 28 – severe depression.

Brain Perfusion SPECT

Patients received an intravenous injection of 20-30 mCi of technetium-99m hexamethylpropyleneamine oxime (99mTc-HMPAO) under resting conditions in a quiet environment with minimized visual and auditory stimulation.

Brain perfusion SPECT was performed using an ADAC Medical Vertex Plus dual-head gamma camera equipped with low-energy high-resolution collimators. Images were acquired using a step-and-shoot technique over 180° per detector, with 64 projections of 30 seconds each, a 128 × 128 matrix, 6° angular steps, a 20% energy window centered on the 140-keV photopeak of 99mTc, and a zoom factor of 2.19.

Images were reconstructed using filtered back projection with a Butterworth filter (cut-off frequency, 0.20), and Chang attenuation correction was applied. Transverse images were reconstructed parallel to the orbitomeatal (OM) line. Three 6-mm transverse sections corresponding to OM+33 mm, OM+49 mm, and OM+66 mm were selected for semiquantitative analysis. Coronal and sagittal images were also generated.

Image Analysis and Semiquantitative Evaluation

Semiquantitative analysis was performed using manually defined regions of interest (ROIs) on three predefined transverse slices. Symmetrical ROIs were placed in corresponding regions of the right and left cerebral hemispheres. The evaluated regions included the anterior frontal, frontotemporal, temporal, and occipital regions on the first slice; prefrontal, parietal, temporal, and occipital regions on the second slice; and frontal, frontoparietal, and parietal regions on the third slice.

The cerebellum was used as the reference region. Regional perfusion indices (PI) were calculated as the ratio of the mean counts within each cerebral ROI to the corresponding cerebellar (CER) counts (PI = ROI/CER). Interhemispheric asymmetry was evaluated using the asymmetry index (AI), calculated as $[(R-L)/(R+L)] \times 100$, where R and L

represent the counts obtained from corresponding right and left ROIs, respectively.

Right and left homologous regions were initially compared to identify regional perfusion asymmetry. Subsequently, pre- and post-treatment perfusion indices and asymmetry indices were compared to assess changes following levothyroxine treatment.

Statistical Analysis

Continuous variables were summarized using descriptive statistics. Given the small sample size, non-parametric statistical methods were used. Within-group comparisons of pre- and post-treatment measurements were performed using the Wilcoxon signed-rank test. Comparisons between the two independent anti-TPO groups were performed using the Mann–Whitney U test. A two-sided p value < 0.05 was considered statistically significant. Given the limited sample size and statistical power, the analyses were considered exploratory and hypothesis-generating rather than confirmatory.

Results

Clinical, Biochemical, and Psychiatric Findings

A total of 16 female patients with Hashimoto thyroiditis were included. Six patients were classified in the lower anti-TPO group (<100 IU/mL), and 10 patients in the higher anti-TPO group (≥100 IU/mL). T3 and T4 levels were within the reference range in all patients.

In the lower anti-TPO group, mean TSH decreased from 5.12 to 0.85 μIU/mL and mean anti-TPO level decreased from 41.77 to 33.67 IU/mL following levothyroxine treatment. Mean HAM-D score decreased from 8.50 to 4.17. The pre- to post-treatment changes in TSH, anti-TPO, and HAM-D scores were statistically significant (p = 0.028, p = 0.028, and p = 0.027, respectively).

In the higher anti-TPO group, mean TSH decreased from 23.54 to 0.92 μIU/mL and mean anti-TPO level decreased from 1154.70 to 387.81 IU/mL following treatment. Mean HAM-D score decreased from 9.00 to 2.90. The changes in TSH, anti-TPO, and HAM-D scores were statistically significant (p = 0.001 for all comparisons).

Before treatment, two patients in the lower anti-TPO group and one patient in the higher anti-TPO group met the predefined criterion for mild depression. Biochemical and psychiatric changes following levothyroxine treatment are summarized in Table 1.

Cerebral Perfusion Findings

Pretreatment right-to-left regional count comparisons showed a greater number of significant regional perfusion asymmetries in the lower anti-TPO group than in the higher anti-TPO group. In the lower anti-TPO group, significant asymmetries were observed in the frontotemporal (p = 0.046), temporal (p = 0.028), parietal (p = 0.028), and frontal (p = 0.028) regions. Based on the direction of the right-to-left differences, these findings corresponded to relatively lower perfusion in the left frontotemporal, right temporal, left parietal, and left frontal regions.

In the higher anti-TPO group, significant pretreatment asymmetries were observed in the frontal (p = 0.036) and parietal (p = 0.028) regions, corresponding to relatively lower perfusion in the left frontal and right parietal regions (Table 2).

Following levothyroxine treatment, the lower anti-TPO group demonstrated significant increases in perfusion indices in several regions. On the right side, significant increases were observed in the frontotemporal (p = 0.046), temporal-1 (p = 0.046), temporal-2 (p = 0.028), and frontoparietal (p = 0.046) regions. On the left side, significant increases were observed in the frontotemporal (p = 0.028), temporal-1 (p = 0.028), parietal (p = 0.028), temporal-2 (p = 0.028), frontal (p = 0.017), and frontoparietal (p = 0.028) regions (Table 3).

In the higher anti-TPO group, a significant post-treatment increase was observed only in the right parietal perfusion index (86.95 ± 10.20 vs. 93.70 ± 7.02; p=0.011). No significant pre- to post-treatment changes were observed in the left-sided perfusion indices.

Overall, significant regional perfusion abnormalities and post-treatment perfusion changes involved a greater number of regions in the lower anti-TPO group than in the higher anti-TPO group.

Interhemispheric Asymmetry

In the lower anti-TPO group, significant pre- to post-treatment changes in the left-to-right ratio were observed in the temporal-1 (p = 0.023) and temporal-2 (p = 0.041) regions. Analysis using the asymmetry index demonstrated significant changes in the temporal-1 (p = 0.027) and frontal (p = 0.041) regions (Table 4). These findings demonstrated changes in regional interhemispheric perfusion asymmetry following levothyroxine treatment in the lower anti-TPO group.

Table 1. Biochemical and psychiatric parameters before and after levothyroxine treatment

Parameter	Lower anti-TPO (< 100 IU/mL), Pre	Post	P-value	Higher anti-TPO (≥ 100 IU/mL), Pre	Post	P-value
TSH (μIU/mL)	5.12	0.85	0.028	23.54	0.92	0.001
Anti-TPO (IU/mL)	41.77	33.67	0.028	1154.70	387.81	0.001
HAM-D score	8.5	4.17	0.027	9	2.9	0.001

Note: *Pre- and post-treatment comparisons were performed using the Wilcoxon signed-rank test; Anti-TPO, anti-thyroid peroxidase; HAM-D, Hamilton Depression Rating Scale; TSH, thyroid-stimulating hormone.*

Table 2. Pretreatment regional cerebral perfusion findings on 99mTc-HMPAO SPECT according to anti-thyroid peroxidase group

Group	Region	Right mean ± SD	Left mean ± SD	P-value	Relative hypoperfusion
Lower anti-TPO	Frontotemporal	131.6 ± 14.5	124.7 ± 10.8	0.046	Left
Lower anti-TPO	Temporal	124.05 ± 15.6	139.9 ± 18.6	0.028	Right
Lower anti-TPO	Parietal	133.3 ± 15.8	117.5 ± 12.75	0.028	Left
Lower anti-TPO	Frontal	146.5 ± 19.7	120.2 ± 13.87	0.028	Left
Higher anti-TPO	Frontal	163.3 ± 30.6	145.3 ± 24.7	0.036	Left
Higher anti-TPO	Parietal	147.7 ± 26.1	169.0 ± 39.2	0.028	Right

Note: *Anti-TPO – anti-thyroid peroxidase; Values are presented as mean ± standard deviation (SD). Only regions with statistically significant right-to-left differences are shown. Lower anti-TPO group: <100 IU/mL; higher anti-TPO group: ≥100 IU/mL. A p-value <0.05 was considered statistically significant.*

Table 3. Significant changes in regional cerebral perfusion indices following levothyroxine treatment

Group	Region	Pre-treatment PI	Post-treatment PI	P-value
Lower anti-TPO	Right frontotemporal	94.03 ± 6.05	101.7 ± 6.5	0.046
Lower anti-TPO	Right temporal-1	88.49 ± 5.9	99.5 ± 7.2	0.046
Lower anti-TPO	Right temporal-2	85.3 ± 3.3	98.03 ± 9.7	0.028
Lower anti-TPO	Right frontoparietal	89.2 ± 7.2	94.6 ± 7.8	0.046
Lower anti-TPO	Left frontotemporal	92.18 ± 4.16	105.2 ± 8.28	0.028
Lower anti-TPO	Left temporal-1	92.12 ± 7.62	104.52 ± 10.4	0.028
Lower anti-TPO	Left parietal	95.20 ± 5.78	109.3 ± 7.71	0.028
Lower anti-TPO	Left temporal-2	86.47 ± 5.72	101.3 ± 11.1	0.028
Lower anti-TPO	Left frontal	102.61 ± 12.79	118.5 ± 5.09	0.017
Lower anti-TPO	Left frontoparietal	88.97 ± 11.97	96.6 ± 9.5	0.028
Higher anti-TPO	Right parietal	86.95 ± 10.2	93.70 ± 7.02	0.011

Abbreviations: Anti-TPO – anti-thyroid peroxidase; PI – perfusion index.

Table 4. Significant changes in interhemispheric cerebral perfusion asymmetry following levothyroxine treatment in the lower anti-thyroid peroxidase group

Measure	Region	Pretreatment	Post-treatment	P-value
L/R ratio	Temporal-1	0.9974	1.0313	0.023
L/R ratio	Temporal-2	1.0077	1.0629	0.041
Asymmetry index	Temporal-1	1.4491	−0.1460	0.027
Asymmetry index	Frontal	0.9021	0.1915	0.041

Discussion

In this study, regional cerebral perfusion abnormalities were observed in patients with Hashimoto thyroiditis, and several of these abnormalities changed after levothyroxine treatment. Perfusion abnormalities were observed in more regions in patients with lower anti-TPO levels than in those with higher antibody levels. TSH, anti-TPO levels, and HAM-D scores also decreased after treatment in both groups. Although the number of patients was limited, our findings suggest that the extent of cerebral perfusion abnormalities may not simply reflect serum anti-TPO levels. Given the small sample size and limited statistical power, however, the present study should be regarded as explora-

tory and hypothesis-generating rather than confirmatory, and the findings require validation in larger prospective cohorts.

The relationship between thyroid disease and psychiatric symptoms has been recognized for many years. Thyroid autoimmunity has been associated with depressive symptoms and cognitive and affective disturbances [9-12]. This association has also been examined in more recent studies. A recent systematic review and meta-analysis reported increased depressive and anxiety symptoms in patients with euthyroid Hashimoto thyroiditis [3], while another large meta-analysis found a modest association between hypothyroidism and clinical depression and suggested that thyroid autoimmunity alone may not fully explain this relationship [13]. More recent evidence also indicates that autoimmune thyroid disease may affect cognition and mood through complex interactions involving thyroid hormone signaling, immune mechanisms, and brain function [4, 8, 14]. Taken together, these findings suggest that the neuropsychiatric manifestations of Hashimoto thyroiditis are likely multifactorial and cannot always be explained by hypothyroidism or thyroid autoimmunity alone.

Previous SPECT studies have reported cerebral perfusion abnormalities in autoimmune thyroiditis. Zettinig et al. (2003) found a high prevalence of subclinical brain perfusion abnormalities in patients with autoimmune thyroiditis [5]. Piga et al. (2004) similarly demonstrated cerebral perfusion abnormalities in euthyroid autoimmune thyroiditis [15]. Cerebral hypoperfusion has also been reported in Hashimoto encephalopathy [6, 7], and Schnedl et al. (2013) demonstrated improvement in cerebral hypoperfusion after levothyroxine treatment using 99mTc-HMPAO SPECT [6]. Hashimoto encephalopathy was not present in our patients and should be considered a separate clinical entity. Recent literature continues to emphasize the complex relationship between autoimmune thyroid disease and neurological manifestations, while also recognizing Hashimoto encephalopathy as a distinct and diagnostically challenging entity [16]. Thus, the older SPECT studies remain directly relevant to the imaging findings of the present study, while contemporary evidence provides a broader context for their interpretation.

In our lower anti-TPO group, pretreatment abnormalities involved the left frontotemporal, right temporal, left parietal, and left frontal regions. In contrast, significant abnormalities in the higher anti-TPO group were limited to the left frontal and right parietal regions. After treatment, perfusion indices increased significantly in several regions in the lower anti-TPO group, whereas a significant increase was found only in the right parietal region in the higher anti-TPO group. Thus, higher serum anti-TPO levels were not accompanied by more extensive cerebral perfusion abnormalities in our patients. Because the groups included only six and ten patients, respectively, this observation should be regarded as preliminary and requires confirmation in larger patient populations.

The involvement of the frontal and temporal regions is also of interest. Abnormal cerebral perfusion in these regions has previously been reported in patients with depressive disorders [17-20]. Hardoy et al. (2011) compared cerebral perfusion patterns in major depressive disorder and Hashimoto thyroiditis and reported temporal perfusion abnormalities [21]. Temporal perfusion indices and interhemispheric asymmetry also changed after treatment in our study. On the other hand, only three of our patients fulfilled the predefined HAM-D criterion for mild depression. The presence of perfusion abnormalities in patients without clinically defined depression suggests that depression alone is unlikely to explain the SPECT findings. This interpretation is consistent with contemporary evidence indicating that the relationship between autoimmune thyroid disease and neuropsychiatric manifestations is complex and may involve mechanisms beyond clinically overt depression [4, 8, 13, 14].

HAM-D scores decreased after levothyroxine treatment in both groups. Most patients were not clinically depressed according to the predefined HAM-D threshold, but their symptom scores nevertheless improved. Recent studies showing neuropsychiatric symptoms and alterations in brain function in autoimmune thyroid disease are relevant in relation to these findings [3, 4, 8, 14]. The mechanism underlying these changes cannot be determined from our data. Improvement may be related to normalization of thyroid function, autoimmune mechanisms, or other treatment-associated effects.

Some patients with mildly elevated or near-reference-range TSH levels also showed improvement in HAM-D scores and cerebral perfusion. Neuropsychiatric manifestations of subclinical hypothyroidism have previously been discussed [22-25], and cerebral abnormalities have been reported even in euthyroid autoimmune thyroiditis [15]. More recent evidence likewise indicates that the relationship between thyroid dysfunction, autoimmunity, cognition, and mood is not straight-

forward [3, 13, 14]. This observation deserves further investigation, particularly in patients with autoimmune thyroiditis who have neuropsychiatric symptoms despite relatively preserved thyroid function. Our study, however, was not designed to determine a TSH threshold for starting levothyroxine treatment.

The reproducibility of cerebral perfusion SPECT findings should also be considered when interpreting the present results. Semiquantitative perfusion measurements may be influenced by acquisition and reconstruction parameters, attenuation correction, spatial resolution, ROI definition and placement, and the choice of reference region. Contemporary SPECT guidelines emphasize the importance of standardized acquisition, reconstruction, quality control, and harmonization for reliable quantitative assessment [26]. Although pre- and post-treatment examinations in the present study were performed using the same imaging protocol and semiquantitative approach, methodological variability cannot be completely excluded as a contributor to the observed regional differences. Therefore, although the observed perfusion changes may reflect treatment-related effects, a contribution from methodological variability cannot be completely excluded. Standardized acquisition, reconstruction, and quantitative analysis methods are important for improving reproducibility, and future prospective studies using contemporary standardized or voxel-based approaches are warranted [26].

Several limitations should be considered. The study included only 16 patients, all of whom were women, and subgroup analysis further reduced the number of patients available for comparison. Consequently, the statistical power of the study, particularly for subgroup comparisons, was limited. Therefore, the present findings should be regarded as exploratory and hypothesis-generating rather than confirmatory and should be interpreted with caution. There was no healthy control group. The retrospective design and the long study period may also have introduced heterogeneity. In addition, cerebral perfusion was assessed by semiquantitative ROI analysis rather than current voxel-based methods. Finally, the anti-TPO cut-off used to divide the patients into two groups was an exploratory threshold and should not be interpreted as an established biological cut-off. Despite these limitations, paired SPECT examinations before and after treatment allowed within-patient assessment of changes in regional cerebral perfusion.

Conclusion

Regional cerebral perfusion abnormalities were observed in patients with Hashimoto thyroiditis, and several perfusion indices improved after levothyroxine treatment. The abnormalities were not more extensive in patients with higher anti-TPO levels. HAM-D scores also improved after treatment. These preliminary findings suggest a possible association between Hashimoto thyroiditis, neuropsychiatric symptoms, and cerebral perfusion. Given the small sample size and exploratory nature of the study, these observations should be interpreted with caution and require confirmation in larger prospective studies with appropriate control groups and standardized imaging methodology.

Artificial Intelligence Disclosure:

Artificial intelligence (AI) was used solely for English language editing and for simplifying the presentation of tables and references.

References

1. Kusalic M. Grade II and grade III hypothyroidism in rapid-cycling bipolar patients. Neuropsychobiology, 1992, 25(4):177-181.
2. Bauer MS, Whybrow PC, Winokur A. Rapid cycling bipolar affective disorder: I. Association with grade I hypothyroidism. Arch Gen Psychiatry, 1990, 47(5):427-432.
3. Wang B, Huang J, Chen L. Association between depression and anxiety disorders with euthyroid Hashimoto's thyroiditis: a systematic review and meta-analysis. Compr Psychoneuroendocrinol, 2024, 20:100279.
4. Wei Q, Zhang H, Guan H, et al. Brain alteration of autoimmune thyroid disease: neuropsychiatric impact, neuroimaging insights, and neurobiological implications. Front Neuroendocrinol, 2024, 75:101159.
5. Zettinig G, Asenbaum S, Fueger BJ, et al. Increased prevalence of subclinical brain perfusion abnormalities in patients with autoimmune thyroiditis: evidence of Hashimoto's encephalitis?. Clin Endocrinol (Oxf), 2003, 59(5):637-643.
6. Schnedl WJ, Mirzaei S, Wallner-Liebmann SJ, et al. Improvement of cerebral hypoperfusion with levothyroxine therapy in Hashimoto's encephalopathy demonstrated by 99mTc-HM-PAO-SPECT. Eur Thyroid J, 2013, 2(2):116-119.
7. Forchetti CM, Katsamakis G, Garron DC. Autoimmune thyroiditis and a rapidly progressive dementia: global hypoperfusion on SPECT scanning suggests a possible mechanism. Neurology, 1997, 49(2):623-626.
8. Strzałkowska B, Strzelczyk J, Dawidowicz M, et al. Brain disorders in euthyroid Hashimoto's thyroiditis patients. Clin Neurol Neurosurg, 2024, 245:108519.
9. Pop VJ, de Rooy HA, Vader HL, et al. Microsomal antibodies during gestation in relation to postpartum thyroid dysfunction and depression. Acta Endocrinol (Copenh), 1993, 129(1):26-30.
10. Pop VJ, Maartens LH, Leusink G, et al. Are autoimmune thyroid dysfunction and depression related? J Clin Endocrinol Metab, 1998, 83(9):3194-3197.

11. Bauer M, Goetz T, Glenn T, et al. The thyroid-brain interaction in thyroid disorders and mood disorders. J Neuroendocrinol, 2008, 20(10):1101-1114.
12. Leyhe T, Müssig K. Cognitive and affective dysfunctions in autoimmune thyroiditis. Brain Behav Immun, 2014, 41:261-266.
13. Bode H, Ivens B, Bschor T, et al. Association of hypothyroidism and clinical depression: a systematic review and meta-analysis. JAMA Psychiatry, 2021, 78(12):1375-1383.
14. Piekiełko-Witkowska A, Duda MK, Bogusławska J, et al. The impact of autoimmune thyroid disease on cognitive and psychiatric disorders: focus on clinical, pre-clinical and molecular studies. Eur Thyroid J, 2025, 14(3):e240406.
15. Piga M, Serra A, Deiana L, et al. Brain perfusion abnormalities in patients with euthyroid autoimmune thyroiditis. Eur J Nucl Med Mol Imaging, 2004, 31(12):1639-1644.
16. Croce L, Dal Molin M, Teliti M, et al. Hashimoto's encephalopathy: an endocrinological point of view. Front Endocrinol (Lausanne), 2024, 15:1367817.
17. Tutus A, Simsek A, Sofuoglu S, et al. Changes in regional cerebral blood flow demonstrated by single photon emission computed tomography in depressive disorders: comparison of unipolar vs. bipolar subtypes. Psychiatry Res, 1998, 83(3):169-177.
18. Kocmur M, Milcinski M, Budihna NV. Evaluation of brain perfusion with technetium-99m bicisate single-photon emission tomography in patients with depressive disorder before and after drug treatment. Eur J Nucl Med, 1998, 25(10):1412-1414.
19. Navarro V, Gasto C, Lomena F, et al. Normalization of frontal cerebral perfusion in remitted elderly major depression: a 12-month follow-up SPECT study. Neuroimage, 2002, 16(3 Pt 1):781-787.
20. Richieri R, Boyer L, Faget-Agius C, et al. Determinants of brain SPECT perfusion and connectivity in treatment-resistant depression. Psychiatry Res, 2015, 231(2):134-140.
21. Hardoy MC, Cadeddu M, Serra A, et al. A pattern of cerebral perfusion anomalies between major depressive disorder and Hashimoto thyroiditis. BMC Psychiatry, 2011, 11:148.
22. Davis JD, Stern RA, Flashman LA. Cognitive and neuropsychiatric aspects of subclinical hypothyroidism: significance in the elderly. Curr Psychiatry Rep, 2003, 5(5):384-390.
23. Weetman AP. Hypothyroidism: screening and subclinical disease. BMJ, 1997, 314(7088):1175-1178.
24. Pies RW. The diagnosis and treatment of subclinical hypothyroid states in depressed patients. Gen Hosp Psychiatry, 1997, 19(5):344-354.
25. Haggerty JJ Jr, Garbutt JC, Evans DL, et al. Subclinical hypothyroidism: a review of neuropsychiatric aspects. Int J Psychiatry Med, 1990, 20(2):193-208.
26. Dickson JC, Armstrong IS, Gabiña PM, et al. EANM practice guideline for quantitative SPECT-CT. Eur J Nucl Med Mol Imaging, 2023, 50(4):980-995.

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