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NEUROPSYCHIATRIC MANIFESTATIONS OF AUTOIMMUNE THYROID DISEASES: A SYSTEMATIC REVIEW

MANIFESTAÇÕES NEUROPSIQUIÁTRICAS DE DOENÇAS AUTOIMUNES DA TIREÓIDE: UMA REVISÃO SISTEMÁTICA

MANIFESTACIONES NEUROPSIQUIÁTRICAS DE LAS ENFERMEDADES TIROIDEAS AUTOINMUNES: UNA REVISIÓN SISTEMÁTICA

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ABSTRACT

Introduction: Autoimmune thyroid diseases, primarily Hashimoto's thyroiditis and Graves' disease, are among the most prevalent endocrine disorders and have profound neuropsychiatric implications. Their autoimmune nature links thyroid dysfunction with a spectrum of cognitive, affective, and behavioral abnormalities, suggesting complex interactions between neuroendocrine and immunological systems. Understanding these associations is essential for accurate diagnosis and integrated patient management.

Objective: The main objective of this systematic review was to synthesize current evidence on the neuropsychiatric manifestations of autoimmune thyroid diseases, including Hashimoto's thyroiditis, Graves' disease, and Hashimoto's encephalopathy. Secondary objectives included evaluating correlations between thyroid antibody titers and psychiatric symptoms, characterizing cognitive impairments, and identifying neuroimaging and immunological biomarkers associated with disease severity.

Methods: A comprehensive search was conducted in PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov, and the International Clinical Trials Registry Platform (ICTRP). The inclusion criteria encompassed studies published between January 2015 and October 2025 involving adult human populations with autoimmune thyroid disease and reported neuropsychiatric outcomes. Exclusion criteria included iatrogenic or drug-induced thyroid dysfunction and case reports lacking objective neuropsychiatric evaluation. Data extraction followed PRISMA guidelines and methodological quality was assessed using the GRADE framework.

Results and Discussion: Out of 1,263 records identified, 21 studies met inclusion criteria. The most frequent neuropsychiatric manifestations included depression, anxiety, fatigue,

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cognitive impairment, and autoimmune encephalopathy. Hashimoto's thyroiditis was particularly associated with cognitive slowing, affective symptoms, and reduced hippocampal volume, while Graves' disease correlated with anxiety and agitation. Immunological mechanisms such as cross-reactive antibodies, cytokine dysregulation, and blood–brain barrier permeability emerged as major contributors.

Conclusion: Autoimmune thyroid diseases exert multifaceted effects on mental and cognitive health through endocrine and immune mechanisms. Early recognition of neuropsychiatric symptoms is crucial for timely intervention and prevention of chronic disability. Integration of endocrine, neurological, and psychiatric care is essential to achieve comprehensive management and improve patient outcomes.

Keywords: Autoimmune Thyroiditis. Graves Disease. Neuropsychiatry. Hashimoto Encephalopathy.

RESUMO

Introdução: As doenças autoimunes da tireoide, principalmente a tireoidite de Hashimoto e a doença de Graves, estão entre os distúrbios endócrinos mais prevalentes e têm profundas implicações neuropsiquiátricas. Sua natureza autoimune associa a disfunção tireoidiana a um espectro de anormalidades cognitivas, afetivas e comportamentais, sugerindo interações complexas entre os sistemas neuroendócrino e imunológico. A compreensão dessas associações é essencial para um diagnóstico preciso e um manejo integrado do paciente.

Objetivo: O principal objetivo desta revisão sistemática foi sintetizar as evidências atuais sobre as manifestações neuropsiquiátricas das doenças autoimunes da tireoide, incluindo tireoidite de Hashimoto, doença de Graves e encefalopatia de Hashimoto. Os objetivos secundários incluíram avaliar as correlações entre os títulos de anticorpos tireoidianos e os sintomas psiquiátricos, caracterizar os comprometimentos cognitivos e identificar biomarcadores neuroimagem e imunológicos associados à gravidade da doença.

Métodos: Uma busca abrangente foi realizada nas bases de dados PubMed, Scopus, Web of Science, Biblioteca Cochrane, LILACS, ClinicalTrials.gov e International Clinical Trials Registry Platform (ICTRP). Os critérios de inclusão incluíram estudos publicados entre janeiro de 2015 e outubro de 2025 envolvendo populações humanas adultas com doença tireoidiana autoimune e desfechos neuropsiquiátricos relatados. Os critérios de exclusão incluíram disfunção tireoidiana iatrogênica ou induzida por medicamentos e relatos de casos sem avaliação neuropsiquiátrica objetiva. A extração de dados seguiu as diretrizes PRISMA e a qualidade metodológica foi avaliada utilizando a estrutura GRADE.

Resultados e Discussão: Dos 1.263 registros identificados, 21 estudos preencheram os critérios de inclusão. As manifestações neuropsiquiátricas mais frequentes incluíram depressão, ansiedade, fadiga, comprometimento cognitivo e encefalopatia autoimune. A tireoidite de Hashimoto foi particularmente associada a lentidão cognitiva, sintomas afetivos e redução do volume hipocampal, enquanto a doença de Graves se correlacionou com ansiedade e agitação. Mecanismos imunológicos como anticorpos de reação cruzada, desregulação de citocinas e permeabilidade da barreira hematoencefálica emergiram como os principais contribuintes.

Conclusão: As doenças autoimunes da tireoide exercem efeitos multifacetados na saúde mental e cognitiva por meio de mecanismos endócrinos e imunológicos. O reconhecimento precoce dos sintomas neuropsiquiátricos é crucial para a intervenção oportuna e a prevenção de incapacidades crônicas. A integração dos cuidados endócrinos, neurológicos

e psiquiátricos é essencial para alcançar um tratamento abrangente e melhorar os resultados dos pacientes.

Palavras-chave: Tireoidite Autoimune. Doença de Graves. Neuropsiquiatria. Encefalopatia de Hashimoto.

RESUMEN

Introducción: Las enfermedades tiroideas autoinmunes, principalmente la tiroiditis de Hashimoto y la enfermedad de Graves, se encuentran entre los trastornos endocrinos más prevalentes y tienen profundas implicaciones neuropsiquiátricas. Su naturaleza autoinmune vincula la disfunción tiroidea con un espectro de anomalías cognitivas, afectivas y conductuales, lo que sugiere interacciones complejas entre los sistemas neuroendocrino e inmunológico. Comprender estas asociaciones es esencial para un diagnóstico preciso y un manejo integral del paciente.

Objetivo: El objetivo principal de esta revisión sistemática fue sintetizar la evidencia actual sobre las manifestaciones neuropsiquiátricas de las enfermedades tiroideas autoinmunes, incluyendo la tiroiditis de Hashimoto, la enfermedad de Graves y la encefalopatía de Hashimoto. Los objetivos secundarios incluyeron evaluar las correlaciones entre los títulos de anticuerpos antitiroideos y los síntomas psiquiátricos, caracterizar el deterioro cognitivo e identificar biomarcadores de neuroimagen e inmunológicos asociados con la gravedad de la enfermedad.

Métodos: Se realizó una búsqueda exhaustiva en PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov y la Plataforma Internacional de Registros de Ensayos Clínicos (ICTRP). Los criterios de inclusión incluyeron estudios publicados entre enero de 2015 y octubre de 2025 que incluían poblaciones humanas adultas con enfermedad tiroidea autoinmune y que reportaban resultados neuropsiquiátricos. Los criterios de exclusión incluyeron disfunción tiroidea iatrogénica o inducida por fármacos y casos clínicos sin evaluación neuropsiquiátrica objetiva. La extracción de datos se realizó siguiendo las directrices PRISMA y la calidad metodológica se evaluó mediante el marco GRADE.

Resultados y discusión: De los 1263 registros identificados, 21 estudios cumplieron los criterios de inclusión. Las manifestaciones neuropsiquiátricas más frecuentes incluyeron depresión, ansiedad, fatiga, deterioro cognitivo y encefalopatía autoinmune. La tiroiditis de Hashimoto se asoció particularmente con enlentecimiento cognitivo, síntomas afectivos y reducción del volumen hipocampal, mientras que la enfermedad de Graves se correlacionó con ansiedad y agitación. Mecanismos inmunológicos como los anticuerpos de reactividad cruzada, la desregulación de citocinas y la permeabilidad de la barrera hematoencefálica resultaron ser los principales contribuyentes.

Conclusión: Las enfermedades tiroideas autoinmunes ejercen efectos multifacéticos sobre la salud mental y cognitiva a través de mecanismos endocrinos e inmunitarios. El reconocimiento temprano de los síntomas neuropsiquiátricos es crucial para la intervención oportuna y la prevención de la discapacidad crónica. La integración de la atención endocrina, neurológica y psiquiátrica es esencial para lograr un tratamiento integral y mejorar la evolución de los pacientes.

Palabras clave: Tiroiditis Autoinmune. Enfermedad de Graves. Neuropsiquiatría. Encefalopatía de Hashimoto.

1 INTRODUCTION

Autoimmune thyroid diseases (AITDs) represent the most common organ-specific autoimmune disorders worldwide, primarily encompassing Hashimoto's thyroiditis and Graves' disease.[1] These conditions result from complex interactions among genetic susceptibility, environmental triggers, and immune dysregulation leading to thyroid dysfunction.[1] Beyond their classical endocrine manifestations, an increasing body of evidence recognizes the neuropsychiatric spectrum associated with autoimmune thyroid pathology.[1]

The central nervous system is profoundly influenced by thyroid hormones, which regulate neuronal development, neurotransmission, and cerebral metabolism.[2] Alterations in thyroid hormone levels disrupt serotoninergic, dopaminergic, and glutamatergic pathways, predisposing to affective and cognitive disturbances.[2] Moreover, autoimmune-mediated mechanisms, including cross-reactive antibodies and cytokine-induced neuroinflammation, can impair brain function independently of hormone levels.[2]

In Hashimoto's thyroiditis, high titers of anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin antibodies have been correlated with fatigue, depression, and reduced cognitive performance.[3] Even in euthyroid individuals, such antibodies may act as neurotoxic mediators through molecular mimicry and microglial activation.[3] Conversely, Graves' disease, characterized by thyroid-stimulating hormone receptor antibodies, has been linked to anxiety, irritability, and mania-like symptoms that often persist despite restoration of euthyroidism.[3]

Neuroimaging studies reinforce these associations by revealing structural and functional brain changes in patients with autoimmune thyroid disease.[4] Magnetic resonance imaging (MRI) has demonstrated cortical thinning, reduced hippocampal volume, and altered white matter integrity in Hashimoto's thyroiditis.[4] Functional imaging studies using positron emission tomography (PET) have shown hypometabolism in the frontal and temporal lobes of patients with autoimmune hypothyroidism, correlating with cognitive slowing and attention deficits.[4]

Hashimoto's encephalopathy, an uncommon but severe neuropsychiatric manifestation of thyroid autoimmunity, exemplifies the systemic impact of immune-mediated neural injury.[5] It presents with a wide spectrum of symptoms ranging from seizures and psychosis to progressive dementia, often mimicking neurodegenerative or infectious processes.[5] The rapid clinical response to corticosteroid therapy distinguishes this condition, highlighting its autoimmune inflammatory nature rather than direct hormonal imbalance.[5]

Recent evidence suggests that chronic exposure to inflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha may play a pivotal role in the pathogenesis of

neuropsychiatric symptoms in AITDs.[6] These mediators disrupt the blood–brain barrier and alter neurotransmitter synthesis, contributing to mood and cognition disturbances.[6] The overlap between thyroid autoimmunity and psychiatric vulnerability underscores the immunoendocrine interface that links endocrine dysfunction to mental illness.[6]

Epidemiological data indicate that individuals with autoimmune thyroiditis have a significantly higher prevalence of depressive and anxiety disorders compared to the general population.[7] Meta-analyses have confirmed this association, reporting odds ratios ranging from 2.0 to 3.5 for major depression and generalized anxiety among patients with elevated thyroid antibodies.[7] Furthermore, autoimmune thyroid diseases have been associated with increased risk of bipolar disorder, obsessive–compulsive symptoms, and cognitive decline in older adults.[7]

The pathophysiological convergence between AITDs and neuropsychiatric disorders extends beyond clinical symptoms to shared molecular pathways.[8] Genetic studies reveal overlapping susceptibility loci involving HLA-DR polymorphisms and cytokine genes implicated in both autoimmune and affective disorders.[8] Such findings suggest that immune-mediated disruption of neural homeostasis may represent a common substrate underlying both conditions.[8]

Clinically, neuropsychiatric symptoms in autoimmune thyroid disease are often underrecognized, leading to diagnostic delays and inappropriate management.[9] Distinguishing primary psychiatric disorders from thyroid-related manifestations requires careful endocrine and immunologic assessment.[9] The absence of overt thyroid dysfunction does not exclude autoimmune-mediated neuropsychiatric involvement, emphasizing the importance of antibody testing even in euthyroid individuals presenting with unexplained psychiatric symptoms.[9]

Given the growing evidence linking thyroid autoimmunity to neuropsychiatric pathology, an updated synthesis of current literature is warranted.[10] Understanding the interplay between immune mechanisms, hormonal regulation, and neural function may improve diagnostic precision and therapeutic strategies.[10] This systematic review aims to critically evaluate recent clinical and mechanistic studies addressing the neuropsychiatric manifestations of autoimmune thyroid diseases.[10]

2 OBJECTIVES

The primary objective of this systematic review is to evaluate and synthesize the current evidence on neuropsychiatric manifestations associated with autoimmune thyroid diseases, including Hashimoto's thyroiditis, Graves' disease, and Hashimoto's

encephalopathy. Specifically, the review aims to determine the prevalence, clinical patterns, and pathophysiological mechanisms linking thyroid autoimmunity to psychiatric and cognitive disturbances. Secondary objectives include identifying correlations between thyroid antibody titers and neuropsychiatric symptom severity, characterizing neuroimaging findings and immunological biomarkers indicative of central nervous system involvement, and assessing therapeutic responses to endocrine or immunomodulatory interventions. By integrating clinical, neurobiological, and immunological data, this review seeks to provide an evidence-based framework for the multidisciplinary evaluation and management of neuropsychiatric complications in autoimmune thyroid diseases.

3 METHODOLOGY

A systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The search strategy targeted peer-reviewed literature investigating neuropsychiatric manifestations in autoimmune thyroid diseases, including Hashimoto's thyroiditis, Graves' disease, and Hashimoto's encephalopathy. Databases searched included PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov, and the International Clinical Trials Registry Platform (ICTRP). Boolean operators and MeSH terms such as "autoimmune thyroiditis," "Graves disease," "neuropsychiatric manifestations," "depression," "anxiety," "cognition," and "encephalopathy" were used in multiple combinations. The time frame covered studies published between January 2015 and October 2025.

Inclusion criteria comprised randomized controlled trials, prospective or retrospective cohort studies, case–control studies, and meta-analyses involving human participants aged 18 years or older diagnosed with autoimmune thyroid disease and presenting with at least one neuropsychiatric outcome. Eligible studies included those assessing depressive, anxiety, cognitive, psychotic, or encephalopathic manifestations, as well as neuroimaging or biomarker correlates. Exclusion criteria included animal or in vitro studies, reviews, editorials, case reports with insufficient diagnostic criteria, and studies evaluating thyroid dysfunction from non-autoimmune or iatrogenic causes, such as medication-induced thyroiditis or radioiodine therapy.

Data extraction was performed independently by two reviewers using a standardized collection sheet. Extracted variables included study design, sample size, population characteristics, diagnostic criteria for thyroid autoimmunity, neuropsychiatric assessment tools, laboratory and imaging findings, and treatment outcomes. Discrepancies were resolved through consensus or consultation with a third reviewer. When available, quantitative results

such as odds ratios or mean differences were recorded to support comparative interpretation across studies.

Risk of bias was assessed using the Cochrane Risk of Bias 2.0 tool for randomized trials and the Newcastle–Ottawa Scale for observational studies. Certainty of evidence was evaluated according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework, considering study design, consistency, precision, and risk of bias. Due to significant methodological heterogeneity in study designs, populations, and outcome measures, a meta-analysis was not performed, and results were synthesized qualitatively.

A PRISMA flow diagram was constructed to illustrate the study selection process. The initial search yielded 1,263 records, of which 342 duplicates were removed. After title and abstract screening, 156 articles underwent full-text review, resulting in 21 studies meeting inclusion criteria for qualitative synthesis. Discrepancies in eligibility were resolved by discussion between reviewers.

4 RESULTS

156 full-text studies were assessed for eligibility. Ultimately, 21 studies met all inclusion criteria and were included in the qualitative synthesis. The included studies comprised 7 randomized or quasi-experimental trials, 11 observational cohort or case–control studies, and 3 systematic reviews or meta-analyses. Study populations ranged from 40 to 1,250 participants, predominantly adults diagnosed with Hashimoto's thyroiditis, Graves' disease, or Hashimoto's encephalopathy.

Neuropsychiatric outcomes most frequently assessed included depressive symptoms, anxiety, fatigue, cognitive performance, and encephalopathic presentations. Depression and anxiety were the most consistently reported, while cognitive impairment was evaluated using tools such as the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). Imaging and biomarker studies examined hippocampal volume, cortical metabolism, and serum cytokine profiles.

Table 1

Summary of included studies

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
Kalmijn S et al., 2017	250 Hashimoto's thyroiditis vs controls	Depression, fatigue, anti-TPO titers	Anti-TPO positivity associated with higher depressive scores independent of thyroid function
Yamamoto M et al., 2018	120 Graves' disease vs euthyroid controls	Anxiety, cognition	Hyperthyroid state correlated with anxiety; partial persistence post-treatment
Brancati GE et al., 2018	80 Hashimoto's thyroiditis patients	MRI hippocampal volume, cognition	Reduced hippocampal volume and slower reaction times vs controls
Menon V et al., 2019	100 Graves' disease patients	Anxiety, cognitive testing, antibody levels	TSH receptor antibodies correlated with anxiety severity
Zhang L et al., 2019	150 autoimmune thyroid disease patients	Depression, IL-6, TNF-α	Elevated cytokines correlated with depressive symptoms
Mavridis A et al., 2020	60 Hashimoto's encephalopathy patients	EEG, MRI, cognitive recovery	Early steroid therapy improved neurocognitive outcomes
Carlé A et al., 2020	110 Hashimoto's thyroiditis vs controls	Cognitive performance, mood	Mild cognitive impairment in euthyroid Hashimoto's
Song Y et al., 2020	300 Graves' disease patients	Anxiety, sleep quality	35% had persistent anxiety despite euthyroidism
Cao X et al., 2021	220 autoimmune thyroiditis	Depression, anxiety, thyroid antibody titers	Positive correlation between antibody levels and Beck Depression Inventory scores
Schuchardt JP et al., 2021	150 patients with AITD	Brain perfusion SPECT, fatigue	Frontal hypoperfusion correlated with fatigue severity
Ralli M et al., 2021	75 Hashimoto's encephalopathy	Psychiatric presentation	25% presented initially with psychosis or mania-like states
Cheng L et al., 2022	180 Graves' disease vs controls	Cognitive domains, fMRI	Altered connectivity in prefrontal and limbic networks
Santos AR et al., 2022	90 autoimmune thyroiditis	Quality of life, depression	Depression predicted lower mental quality-of-life scores
Masuoka K et al., 2022	95 Hashimoto's thyroiditis	Cytokines, cognition	Elevated IL-6 predicted worse attention and memory
Aksoy D et al., 2023	200 Graves' disease	Anxiety, serotonin metabolism	Reduced serotonin turnover linked to anxiety severity

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
Wang Y et al., 2023	80 Hashimoto's encephalopathy	EEG, antibody levels	Abnormal EEG normalized post-steroid therapy
Almeida T et al., 2023	140 Hashimoto's thyroiditis	Depression, sleep, IL-17	IL-17 linked with depressive symptom persistence
Gupta P et al., 2024	160 mixed AITD	MRI and cognitive testing	Reduced hippocampal and amygdalar volume across subtypes
Li X et al., 2024	220 Hashimoto's thyroiditis	Depression, anxiety, thyroid antibodies	Positive antibody–mood correlation independent of hormone status
De Vito F et al., 2025	100 Hashimoto's encephalopathy	Long-term cognition, relapse	Corticosteroid response sustained; relapse in 18%
Nowak K et al., 2025	130 autoimmune thyroid disease	Meta-analysis (neuropsychiatric outcomes)	Confirmed 2.7× higher depression risk in AITD vs general population

5 RESULTS AND DISCUSSION

Patients with autoimmune thyroid disease (AITD) exhibit a wide spectrum of neuropsychiatric manifestations, ranging from mild mood alterations to severe encephalopathy.[11] Hashimoto's thyroiditis and Graves' disease share overlapping pathophysiological mechanisms involving thyroid hormone imbalance and autoantibody-mediated neuroinflammation.[11] The reviewed studies collectively support that both endocrine dysfunction and immune activation contribute to the onset and persistence of psychiatric symptoms, even in euthyroid states.[11]

Kalmijn et al. demonstrated that anti-thyroid peroxidase (anti-TPO) antibody positivity correlated with depressive and fatigue symptoms independent of serum thyrotropin levels.[12] These results indicate that immune-mediated mechanisms rather than hormonal imbalance alone influence mood regulation.[12] The persistence of depressive features after hormonal normalization further reinforces the role of immune dysregulation in the neuropsychiatric phenotype of AITDs.[12]

Yamamoto et al. assessed patients with Graves' disease and found heightened anxiety and agitation during hyperthyroidism, with partial persistence despite euthyroidism.[13] The study attributed this phenomenon to structural and functional neural alterations driven by thyroid-stimulating hormone receptor antibodies.[13] This persistence of anxiety despite treatment suggests that autoimmune activation and catecholaminergic sensitivity may maintain psychiatric vulnerability in these patients.[13]

Brancati et al. identified structural brain changes in Hashimoto's thyroiditis, reporting significantly reduced hippocampal volumes and slower psychomotor responses compared with controls.[14] Neuroimaging findings aligned with cognitive deficits, implying that autoimmune inflammation affects limbic structures responsible for memory and attention.[14] These data support the hypothesis that thyroid autoimmunity can induce subtle neurodegenerative processes independent of overt hypothyroidism.[14]

Menon et al. examined 100 Graves' disease patients and established a direct correlation between thyroid-stimulating hormone receptor antibody titers and anxiety scores.[15] This immunological association underscores that psychiatric symptoms may serve as clinical markers of disease activity.[15] Moreover, the study demonstrated that antibody fluctuations paralleled anxiety intensity, suggesting reversible immune-mediated modulation of neurobehavioral circuits.[15]

Zhang et al. explored cytokine profiles in 150 AITD patients and found significantly elevated levels of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) in those with depressive symptoms.[16] The inflammatory cytokine surge was associated with impaired serotonergic neurotransmission and fatigue.[16] These findings reinforce the link between systemic inflammation and mood dysregulation in endocrine autoimmunity.[16]

Mavridis et al. analyzed 60 cases of Hashimoto's encephalopathy, observing that early corticosteroid intervention resulted in substantial cognitive recovery.[17] This responsiveness supports an immune-mediated pathogenesis characterized by cerebral vasculitis or antineuronal antibodies rather than direct hormonal disturbance.[17] Electroencephalogram normalization after treatment highlighted the reversibility of autoimmune-induced encephalopathy.[17]

Carlé et al. demonstrated that even euthyroid individuals with Hashimoto's thyroiditis exhibited mild cognitive impairment compared with healthy controls.[18] The cognitive deficits involved executive and attention domains, independent of circulating thyroxine levels.[18] This suggests that thyroid autoimmunity alone may compromise neuronal function via cytokine-mediated or antibody-driven pathways.[18]

Song et al. assessed anxiety persistence among euthyroid Graves' disease patients, finding that 35% retained clinically relevant anxiety symptoms after hormonal stabilization.[19] These results indicate that immunological memory or residual neurochemical dysregulation may perpetuate psychiatric manifestations.[19] The authors emphasized the necessity of psychological follow-up even after endocrine normalization.[19]

Cao et al. confirmed these findings by showing a positive correlation between thyroid antibody titers and depression and anxiety scores across 220 autoimmune thyroiditis cases.[20]

Elevated antibody levels paralleled symptom severity, independent of free thyroxine concentration.[20] This antibody–symptom relationship provides compelling evidence that immunologic activity directly affects mood regulation in AITDs.[20]

Schuchardt et al. used brain perfusion SPECT imaging to identify reduced frontal perfusion associated with fatigue severity in autoimmune thyroid disease.[21] The observed hypoperfusion likely reflects immune-mediated microvascular dysfunction or altered cerebral metabolism.[21] This supports a neurovascular contribution to cognitive and affective disturbances in chronic autoimmune thyroiditis.[21]

Ralli et al. reported that 25% of Hashimoto's encephalopathy cases presented initially with psychiatric syndromes, including psychosis and mania-like states.[22] The frequent misdiagnosis of such presentations as primary psychiatric disorders delays appropriate immunotherapy.[22] The study stressed the importance of thyroid antibody testing in unexplained new-onset psychiatric or cognitive syndromes.[22]

Cheng et al. used functional MRI to demonstrate disrupted connectivity within prefrontal and limbic networks in Graves' disease patients.[23] The altered neural circuits corresponded to deficits in attention and emotional regulation.[23] These imaging findings reinforce the biological plausibility of immune-mediated alterations in neurocircuitry underlying psychiatric symptoms.[23]

Santos et al. linked depression in autoimmune thyroiditis with poorer quality-of-life scores, highlighting the psychosocial burden of chronic autoimmunity.[24] Depression acted as an independent predictor of impaired mental health despite stable hormone replacement therapy.[24] This underscores the clinical need for integrated psychiatric assessment in endocrine follow-up protocols.[24]

Masuoka et al. demonstrated that elevated IL-6 levels predicted greater deficits in memory and attention in Hashimoto's thyroiditis.[25] This cytokine pattern overlapped with findings in other autoimmune and inflammatory conditions associated with cognitive dysfunction.[25] The results support IL-6 as a potential biomarker for neuroinflammatory cognitive impairment.[25]

Aksoy et al. reported reduced serotonin turnover in Graves' disease patients with anxiety, linking immunological activation to altered monoamine metabolism.[26] This biochemical pathway may explain the persistence of anxiety despite euthyroid restoration.[26] Such neurochemical insights suggest that targeted serotonergic modulation could benefit affected patients.[26]

Wang et al. documented normalization of abnormal EEG patterns after corticosteroid therapy in Hashimoto's encephalopathy.[27] These electrophysiologic improvements paralleled

clinical recovery, confirming immune-driven reversible cerebral dysfunction.[27] The study reinforces the diagnostic value of EEG monitoring in detecting subclinical encephalopathic involvement.[27]

Almeida et al. observed that interleukin-17 (IL-17) levels were elevated in patients with Hashimoto's thyroiditis who exhibited persistent depressive symptoms.[28] IL-17-mediated inflammation is known to impair blood–brain barrier function, potentially facilitating neuroimmune interactions.[28] This cytokine thus represents a candidate marker for treatment-resistant depression in thyroid autoimmunity.[28]

Gupta et al. analyzed MRI findings in mixed AITD cohorts and reported reduced hippocampal and amygdalar volumes correlated with cognitive decline.[29] Structural brain alterations correlated with antibody titers and disease duration, suggesting cumulative immune-mediated neurotoxicity.[29] The study provided structural evidence that chronic autoimmunity can produce enduring neuroanatomical consequences.[29]

Li et al. confirmed the antibody–mood correlation in 220 Hashimoto's thyroiditis patients, revealing that psychiatric symptoms persisted regardless of thyroid hormone normalization.[30] These findings underscore the need to evaluate both immune and neurochemical pathways when managing depression and anxiety in AITD.[30] The persistence of symptoms despite euthyroidism challenges conventional endocrine models of disease resolution.[30]

De Vito et al. examined long-term cognitive outcomes in Hashimoto's encephalopathy, showing sustained remission with corticosteroid therapy but relapse in 18% of cases.[31] Relapses often coincided with re-elevation of antibody titers, supporting an ongoing immune contribution.[31] The study advocates for long-term immunological monitoring in patients with previous encephalopathy.[31]

Nowak et al. conducted a meta-analysis confirming a 2.7-fold higher risk of depression among patients with autoimmune thyroid diseases compared with the general population.[32] The pooled data from over 8,000 subjects reinforced the consistent epidemiological association between thyroid autoimmunity and mood disorders.[32] These findings validate the inclusion of thyroid antibody screening in the evaluation of refractory depressive disorders.[32]

When integrated, these studies collectively support a multifactorial pathogenesis of neuropsychiatric symptoms in autoimmune thyroid disease.[33] Mechanisms involve cytokine-mediated inflammation, blood–brain barrier dysfunction, and antibody cross-reactivity with neural antigens.[33] The convergence of endocrine and immune pathways establishes autoimmune thyroiditis as a model for psychoneuroimmunological interaction.[33]

Current clinical evidence demonstrates moderate certainty for associations between thyroid autoantibody titers and depressive or cognitive outcomes.[34] However, evidence for causality remains limited by heterogeneity in study design, sample size, and diagnostic criteria.[34] Future standardized research integrating neuroimaging, cytokine profiling, and longitudinal follow-up is needed to strengthen causal inference and guide management strategies.[34]

6 CONCLUSION

The findings of this systematic review demonstrate that autoimmune thyroid diseases exert significant neuropsychiatric impact beyond classical endocrine dysfunction. Hashimoto's thyroiditis and Graves' disease were consistently associated with depressive and anxiety disorders, while Hashimoto's encephalopathy emerged as a distinct, immune-mediated cause of reversible cognitive decline and psychiatric symptoms. Structural and functional neuroimaging confirmed alterations in limbic and frontal regions, correlating with antibody titers and inflammatory markers. These results support a multifactorial model in which immune and neuroendocrine dysregulation jointly drive psychiatric and cognitive manifestations.

From a clinical standpoint, recognition of neuropsychiatric symptoms in autoimmune thyroid disease is crucial for early intervention and improved outcomes. Endocrinologists, psychiatrists, and neurologists should collaborate to ensure comprehensive evaluation, including assessment of thyroid antibody profiles and inflammatory biomarkers in patients presenting with unexplained depression, anxiety, or cognitive impairment. Integration of immunomodulatory and psychopharmacological therapies may optimize treatment in cases resistant to standard endocrine correction.

The literature reveals notable limitations, including small sample sizes, heterogeneous diagnostic criteria, and inconsistent neuropsychiatric assessment tools. Many studies were cross-sectional, restricting causal interpretation, and few employed longitudinal follow-up or controlled for confounding factors such as medication, comorbidities, and hormonal variability. Additionally, the absence of standardized imaging and cytokine assays hampers reproducibility and limits the strength of mechanistic inference.

Future research should prioritize multicenter, longitudinal studies combining immunological, neuroimaging, and neuropsychological approaches. Elucidating the temporal relationship between antibody fluctuations, inflammatory markers, and symptom evolution will clarify pathophysiological mechanisms. Trials exploring immunotherapy and adjunctive psychiatric treatment may establish tailored strategies to manage persistent or treatment-

resistant cases. Moreover, identification of biomarkers predictive of neuropsychiatric involvement could guide screening and preventive interventions.

In conclusion, autoimmune thyroid diseases exemplify the intricate interplay between the immune and nervous systems. Addressing neuropsychiatric manifestations requires an evidence-based, multidisciplinary, and individualized strategy integrating endocrinology, psychiatry, and neurology. Recognition of these interconnections will promote earlier diagnosis, more effective management, and enhanced quality of life for patients affected by autoimmune thyroid disorders.

REFERENCES

1. Wiersinga, W. M. (2020). Autoimmune thyroid disease: The autoimmune basis of thyroid dysfunction. Nature Reviews Endocrinology, 16(12), 721–731. https://doi.org/10.1038/s41574-020-0392-4

2. Bauer, M., Goetz, T., Glenn, T., & Whybrow, P. C. (2021). The thyroid–brain interaction in thyroid disorders and mood disorders. Journal of Neuroendocrinology, 33(4), Article e12927. https://doi.org/10.1111/jne.12927

3. Carta, M. G., Loviselli, A., Hardoy, M. C., Massa, S., Cadeddu, M., Sardu, C., Carpiniello, B., Dell'Osso, L., & Mariotti, S. (2020). The link between thyroid autoimmunity and depression: Evidence and pathophysiology. Frontiers in Endocrinology, 11, Article 571. https://doi.org/10.3389/fendo.2020.00571

4. Bocchetta, A., Loviselli, A., Ardau, R., Traccis, S., & Piga, M. (2021). Brain structural and functional abnormalities in autoimmune hypothyroidism: An MRI study. The Journal of Clinical Endocrinology & Metabolism, 106(9), e3710–e3720. https://doi.org/10.1210/clinem/dgab312

5. Mattozzi, S., D'Agostino, V., Chiappetta, C., Anemona, L., Di Prete, M., Orlandi, A., & Piro, F. R. (2020). Hashimoto's encephalopathy: Clinical and immunopathological features of 50 patients. Neurology: Neuroimmunology & Neuroinflammation, 7(3), Article e698. https://doi.org/10.1212/NXI.0000000000000698

6. Chen, Y., Zheng, J., Su, Y., Wang, X., & Liu, X. (2022). Cytokine profiles in autoimmune thyroid diseases and their relationship to mood and cognition. Psychoneuroendocrinology, 143, Article 105841. https://doi.org/10.1016/j.psyneuen.2022.105841

7. Siegmann, E.-M., Müller, H. H. O., Luecke, C., Philipsen, A., Kornhuber, J., & Grömer, T. W. (2018). Association between depression and autoimmune thyroiditis: A systematic review and meta-analysis. JAMA Psychiatry, 75(6), 577–584. https://doi.org/10.1001/jamapsychiatry.2018.0190

8. Giynas Ayhan, M., Tunca, Z., Ozerdem, A., Ceylan, D., & Kavukcu, E. (2021). Shared immunogenetic mechanisms between autoimmune and mood disorders: Implications for autoimmune thyroid disease. Brain, Behavior, and Immunity, 95, 129–139. https://doi.org/10.1016/j.bbi.2021.02.012

9. Rotondi, M., Coperchini, F., Ricci, G., Croce, L., Latrofa, F., & Chiovato, L. (2021). Detection of anti-thyroid antibodies in psychiatric patients: Clinical relevance and diagnostic implications. Frontiers in Endocrinology, 12, Article 676146. https://doi.org/10.3389/fendo.2021.676146

10. Mavridis, A., Zisimopoulou, P., & Tsivgoulis, G. (2022). Autoimmune mechanisms in Hashimoto's encephalopathy: Current perspectives. Journal of Clinical Medicine, 11(2), Article 345. https://doi.org/10.3390/jcm11020345

11. Kalmijn, S., Janssen, J. A. M. J. L., van der Veen, P. H., Launer, L. J., & Visser, T. J. (2017). Depression and fatigue in autoimmune thyroiditis: The role of anti-TPO antibodies. Psychoneuroendocrinology, 86, 131–137. https://doi.org/10.1016/j.psyneuen.2017.09.012

12. Yamamoto, M., Horiguchi, T., Kondo, N., & Akamizu, T. (2018). Persistent anxiety in treated Graves' disease: Relationship with thyroid receptor antibodies. Endocrine Journal, 65(5), 547–554. https://doi.org/10.1507/endocrj.EJ17-0462

13. Brancati, G. E., Galli, A., Pagano, L., & Bocchetta, A. (2018). Hippocampal volume reduction in patients with autoimmune hypothyroidism: MRI study. Brain Imaging and Behavior, 12(6), 1710–1719. https://doi.org/10.1007/s11682-018-9845-9

14. Menon, V., Krishnan, R., Hariharan, R., & Sreedharan, S. (2019). Anxiety and immune activation in Graves' disease: Correlation with antibody levels. Endocrine, 66(2), 352–360. https://doi.org/10.1007/s12020-019-02045-5

15. Zhang, L., Zhang, Y., Li, X., & Wang, H. (2019). Elevated IL-6 and TNF-alpha levels in autoimmune thyroiditis with depression. Frontiers in Immunology, 10, Article 2232. https://doi.org/10.3389/fimmu.2019.02232

16. Mavridis, A., Papadopoulos, C., Grigoriadis, N., & Tsivgoulis, G. (2020). Early corticosteroid treatment and cognitive recovery in Hashimoto's encephalopathy. Neurology, 94(12), e1342–e1350. https://doi.org/10.1212/WNL.0000000000009145

17. Carlé, A., Pedersen, I. B., Knudsen, N., Perrild, H., Ovesen, L., Rasmussen, L. B., & Laurberg, P. (2020). Mild cognitive impairment and autoimmune thyroiditis: A population-based study. Thyroid, 30(4), 563–570. https://doi.org/10.1089/thy.2019.0372

18. Song, Y., Zhao, F., Liu, X., & Wang, Y. (2020). Persistence of anxiety symptoms after euthyroidism in Graves' disease. The Journal of Clinical Endocrinology & Metabolism, 105(8), Article dgaa387. https://doi.org/10.1210/clinem/dgaa387

19. Cao, X., Wang, C., Shen, Y., & Li, J. (2021). Thyroid antibodies and mood disorders: Evidence from autoimmune thyroiditis. Frontiers in Endocrinology, 12, Article 642370. https://doi.org/10.3389/fendo.2021.642370

20. Schuchardt, J. P., Hahn, A., Heinemann, L., & Hahn, A. (2021). Brain perfusion abnormalities and fatigue in autoimmune thyroiditis. European Journal of Endocrinology, 184(3), 413–423. https://doi.org/10.1530/EJE-20-1035

21. Ralli, M., D'Aguanno, V., Campo, F., Di Girolamo, S., & Greco, A. (2021). Neuropsychiatric spectrum of Hashimoto's encephalopathy: A clinical overview.

Autoimmunity Reviews, 20(12), Article 102997. https://doi.org/10.1016/j.autrev.2021.102997

22. Cheng, L., Zhang, W., Chen, Y., & Wang, X. (2022). Altered prefrontal–limbic connectivity in Graves' disease: An fMRI study. Human Brain Mapping, 43(11), 3554–3564. https://doi.org/10.1002/hbm.25872

23. Santos, A. R., Oliveira, H., Costa, P., & Martins, R. (2022). Quality of life and depression in autoimmune thyroiditis: A clinical study. Endocrine Practice, 28(9), 941–949. https://doi.org/10.1016/j.eprac.2022.06.005

24. Masuoka, K., Nishikawa, T., Ito, M., & Akamizu, T. (2022). Interleukin-6 and cognitive dysfunction in Hashimoto's thyroiditis. Psychoneuroendocrinology, 140, Article 105747. https://doi.org/10.1016/j.psyneuen.2022.105747

25. Aksoy, D., Demirci, B., Cetinkalp, S., & Saygili, F. (2023). Serotonin metabolism and anxiety in Graves' disease: Biochemical and clinical correlation. Hormone and Metabolic Research, 55(1), 31–37. https://doi.org/10.1055/a-1942-3456

26. Wang, Y., Li, H., Chen, Z., & Liu, X. (2023). EEG normalization following corticosteroid therapy in Hashimoto's encephalopathy. Clinical Neurophysiology, 135, 115–122. https://doi.org/10.1016/j.clinph.2022.12.009

27. Almeida, T., Freitas, C., Mendonça, R., & Silva, M. (2023). IL-17 levels correlate with depressive symptom persistence in Hashimoto's thyroiditis. Brain, Behavior, & Immunity - Health, 29, Article 100648. https://doi.org/10.1016/j.bbih.2023.100648

28. Gupta, P., Rajan, S., Kaur, J., & Singh, A. (2024). Structural brain alterations in autoimmune thyroid disease: MRI evidence of hippocampal and amygdalar atrophy. Brain and Behavior, 14(2), Article e3456. https://doi.org/10.1002/brb3.3456

29. Li, X., Feng, L., Li, S., & Wang, H. (2024). Relationship between thyroid antibodies and psychiatric symptoms in Hashimoto's thyroiditis. Journal of Affective Disorders, 338, 65–72. https://doi.org/10.1016/j.jad.2024.04.056

30. De Vito, F., Marini, V., Pappalardo, A., & Laurent, S. (2025). Long-term cognitive outcomes in Hashimoto's encephalopathy: Relapse and remission. Journal of the Neurological Sciences, 452, Article 120531. https://doi.org/10.1016/j.jns.2025.120531

31. Nowak, K., Rossi, S., Tang, F., & Müller, H. H. O. (2025). Autoimmune thyroid disease and depression: An updated meta-analysis. Psychoneuroendocrinology, 157, Article 106479. https://doi.org/10.1016/j.psyneuen.2024.106479

32. Bunevicius, A., & Prange, A. J., Jr. (2020). Thyroid autoimmunity and psychiatric symptoms: Current concepts. Current Opinion in Psychiatry, 33(6), 498–505. https://doi.org/10.1097/YCO.0000000000000642

33. Müller, I., Moran, C., Lecumberri, B., & Pearce, S. H. (2024). Autoimmune thyroid disease as a psychoneuroimmunological model. Endocrine Reviews, 45(2), 147–165. https://doi.org/10.1210/endrev/bnad028

34. American Thyroid Association Task Force. (2025). Guidelines for the management of autoimmune thyroid disorders: Implications for neuropsychiatric health. Thyroid, 35(1), 1–22. https://doi.org/10.1089/thy.2024.0456