

Hashimoto's Thyroiditis and Encephalopathy

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Abstract

Although very rare, the literature describes cases of Hashimoto encephalopathy attesting to its occurrence. Affected patients present with seizures, stroke-like episodes, transient focal and global neurological deficits, and a variety of neuropsychiatric disturbance from dementia to hallucinations and psychosis. The encephalopathy evolves with concomitantly elevated anti-thyroid peroxidase antibodies, independent from hormonal thyroid function setting it apart from thyrotoxicosis and myxedema. A new patient reported with Hashimoto's encephalopathy, in whom neurocognitive impairment and stroke-like onset of hemiparesis and hemiparkinsonism correlated with brain magnetic resonance imaging fused with positron emission tomography.

Keywords

Autoimmune, Encephalitis, Hashimoto, Thyroiditis, Encephalopathy

1. Introduction

Hashimoto thyroiditis and Hashimoto encephalopathy are well-described clinical and pathologic entities [1]. However, neuropathological data are lacking due to the effectiveness of corticosteroids therapy [1]. An autoimmune pathogenesis targeting the central nervous system is suggested [2] [3]. This chapter reviews the historical background, epidemiology, clinical presentation, histopathologic findings, etiologic basis, diagnosis and treatment of Hashimoto's thyroiditis and encephalopathy. The promising utility of brain magnetic resonance imaging fused with positron emission tomography are illustrated in a patient with Hashimoto's thyroiditis and encephalopathy who presented neurocognitive deficits in association with hemiparesis and hemiparkinsonism.

2. Hashimoto Thyroiditis

2.1. Historical Background

Sawin [4] reviewed the history of Hashimoto thyroiditis. In 1912, Hakaru Ha-

shimoto [5] published a description of four women, all over age 40, who showed a preponderance of lymphoid follicles, with parenchymal and interstitial changes, one of whom was hypothyroid. He recognized the similarities of the histology of the histology to Grave's disease but ruled it out clinically [6] and Riedel's (fibrous) thyroiditis [7] with a different pathology [8]. He speculated there was a factor that caused the lymphocytic expansion of the thyroid size, naming it after its histologic characteristics, lymphomatous goiter, in the absence of a known cause. The medical community ignored goitrous lymphocytic thyroiditis until the 1930s when Hashimoto's name attached to the disease in American [9] and British surgical texts [10]. McClintock and Wright [11] reviewed the world's literature in 1937 and found only 50 cases of Hashimoto thyroiditis. Between 1956 and 1958, two teams of investigators [12] [13] [14] each employing different techniques, described circulating thyroglobulin (Tg) antibodies (Ab) in auto-immunized animals using tanned red cells coated with Tg [12] [13] or immunoprecipitation in Hashimoto thyroiditis patients with goiters undergoing thyroidectomy [14]. With recognition of the pathologic entity and immune pathogenesis, there was a marked increase in the incidence of newly reported cases [15], and the entity became well entrenched in the endocrinology literature [16] [17], and synonymous with the commonest form of autoimmune thyroid disease (AITD) [18].

Antibodies to thyroid microsomal (cytoplasmic) antigens, more commonly termed thyroid peroxidase (TPO) distinct from Tg were later demonstrated using complement-fixation of human thyrotoxic extracts of postmortem or biopsy tissue [19]; and later by a more sensitive indirect immunofluorescence technique using fresh thyrotoxic tissue as substrate [20]. Although anti-thyroid antibodies relate to both goiter and thyroid atrophy, it was uncertain then as it is now, why some patients with Hashimoto thyroiditis fail to develop a goiter.

2.2. Epidemiology

Hashimoto's thyroiditis affects up to 2% of the general population [21], and afflicts women ten-fold more than in men. The National Health and Nutrition Examination Survey III estimated the prevalence of subclinical and clinical hypothyroidism to be 4.6% and 0.3% respectively [22]. The Whickham survey [23] estimated the prevalence of spontaneous hypothyroidism at 1.5% in women and <0.1% in men. Subclinical hypothyroidism, characterized by an increase in serum thyrotropin (TSH) while serum levels of thyroxine (T4) and triiodothyronine (T3) remain normal in 8% of women and 3% of men [24]. Furszyfer and colleagues [25] estimated that the incidence of clinical evident Hashimoto thyroiditis at 69 per 100,000 in Rochester, Minnesota. However, this figure greatly underestimated the actual incidence since histologic evidence of the disease, which variably included infiltration of the thyroid by lymphocytes and gradual destruction of the gland, in 2% of unselected Caucasian females at autopsy [26].

Hashimoto thyroiditis is the third most prevalent autoimmune disease in the

U.S., and the commonest form of AITD [27]. It leads to a dramatic loss of thyroid follicular cells, with concomitant hypothyroidism, goiter formation, and circulating autoantibodies, notably to the primary thyroid-specific antigens, Tg and TPO. Thyroglobulin is the main protein synthesized in the thyroid gland and serves both in the synthesis and in the storage of thyroid hormone. Its synthesis and iodine content play an important role in epitope recognition and antigenicity. Thyroid peroxidase, the other significant autoantigen in Hashimoto thyroiditis, catalyzes the oxidation of iodine to an iodinating species. Antibodies to TPO are heterogeneous with almost 180 forms cloned and sequenced. Both antibodies occur in patients with AITD and are more prevalent in women and with increasing age [28]. In one-third of population sera, both antibodies are present in concentrations that are generally higher than in sera of those with only one antibody type.

Abundant epidemiologic and genome-wide association study data and animal models of AITD suggest a strong genetic basis for Hashimoto thyroiditis, with contributions from polymorphisms in major histocompatibility complex and class I to III human leukocyte antigen (HLA) genes, immune modulatory genes, with epigenetic influences. Hashimoto thyroiditis occurs with other autoimmune diseases such as type-1 diabetes, Celiac disease, rheumatoid arthritis, multiple sclerosis, and vitiligo [29]. It can be part of the autoimmune poly-endocrine syndrome type-2. Autoantibodies to TPO and Tg are inherited as a dominant Mendelian trait in women with reduced penetrance in men [30]. Thyroid abnormalities occur in one-third of offspring of patients with Hashimoto thyroiditis [31] with a sibling risk ratio that supports a strong case for genetic influence on disease development [32].

Recent interest has focused on the candidate role of the HLA polymorphisms and cytotoxic T-cell -associated 4 (*CTLA4*) gene as primary determinants of the risk of developing Hashimoto thyroiditis [33]. Genome-wide association studies showed associations with HLA-DR4 in 56 multiplex families of 354 individuals with AITD [34], as well as with HLA DR5 in goitrous Hashimoto thyroiditis, and DR3 in atrophic Hashimoto thyroiditis [35]. The mechanism of *CTLA4* gene susceptibility to autoimmune disease including Hashimoto's thyroiditis results from a failure to establish and maintain immunologic non-responsiveness or tolerance to self-antigens [36]. In humans, disease susceptibility in Hashimoto thyroiditis maps to a noncoding 6.1-kb 3-prime region of the *CTLA4* gene, the common allelic variation of which correlated with lower mRNA levels of the soluble alternative splice form of CTLA4. Several case-controlled studies have established an important role for the *CTLA4* gene in the development of Hashimoto's thyroiditis [37] [38] [39].

The influence of environmental factors that interact with susceptibility genes to produce a synergistic effect in triggering autoimmune thyroid disease through epigenetic modulation [40], that is, in regulating gene expression and phenotypes without alterations of the genetic code in deoxyribonucleic acid, do so through methylation, histone modifications, and non-coding ribonucleic acids.

Deoxyribonucleic acid (DNA) methylation mainly results in transcriptional repression especially when it occurs in the region of 5' promoter regions with high density, as occurs in the *CTLA4* gene in AITD [41]. Polymorphisms in histone modifier genes, which have key roles in the compaction of DNA to form tightly compacted chromatin, can lead to susceptibility to AITD and higher levels of thyroid autoantibodies [42]. Micro ribonucleic acid (RNA) (miRNA) are small non-coding RNA molecules that contain about 22 nucleotides and function as silencers and regulators of messenger RNA that conveys genetic information from DNA, to specify the amino acid sequence of the protein products of gene expression through the process known as post-transcription gene regulation. Recent studies [43] reveal that some miRNA are also involved in the development of AITD in modulating the differentiation or activation of immune cells and immune responsiveness.

2.3. Clinical Presentation

Patients with Hashimoto thyroiditis may present with hypothyroidism, goiter, or both. According to the Whickman survey [23], affected patients are typically <45 years of age, with the risk of a goiter increasing with age and one-half of those with goiter between age 45 and 64 years. Autoimmune thyroid disease may account for up to 40% of goiters in adolescents. Common presenting symptoms of Hashimoto thyroiditis include fatigue, weight gain, pale or puffy face, feeling cold, joint and muscle pain, constipation, dry and thinning hair, heavy menstrual flow or irregular periods, depression, panic disorder, bradycardia, and difficulty becoming pregnant or maintaining pregnancy. Joint stiffness, aching pain, arthralgia, myalgia, fatigue, shoulder and pelvic girdle pain and disturbed sleep were reported symptoms among 23.5% cases seen at the Mayo Clinic in a seminal study that noted inordinately increased prevalence of rheumatoid arthritis, spondylitis, scleroderma, lupus erythematosus, and other connective tissue disorder [44].

2.4. Laboratory Investigation

Patients with multinodular goiter and thyroid cancer can harbor low serum titers of Tg and TPO antibodies, but titers >1:6400 or >200 IU/ml respectively strongly AITD including Hashimoto thyroiditis. In areas with sufficient iodine, an increased serum thyrotropin level is evidence of AITD. Histologically, a goitrous thyroid gland diffusely enlarges with firm consistency and irregular surface. There can be extensive fibrosis results in a hard mass that may be confused with malignant disease [45] [46]. Affected patients rarely complain of laryngeal or esophageal pain, tightness in the neck, focal glandular pain or palpable tenderness. Goiters may be asymmetric and mistaken for a solitary nodule or multinodular goiter in euthyroid patients however; those with atrophic AITD do not have a goiter. Thyroid-associated ophthalmopathy is far more common in Graves' disease than Hashimoto thyroiditis. Subclinical hypothyroidism develops into overt hypothyroidism at a rate of 4% cases per year.

Thyroid peroxidase is the major and possibly only auto-antigenic component of thyroid microsomes. Mariotti and coworkers [47] described a radioimmunoassay (RIA) for anti-TPO Ab based on competitive inhibition of radio-iodinated TPO to an anti-TPO monoclonal antibody in a large series of sera from normal controls and patients with or without different thyroid diseases that was more accurate than standard anti-microsomal Ab determinations. In community surveys, 50% to 75% of individuals with circulating anti-thyroid antibodies are euthyroid, however up to one-half may have subclinical hypothyroidism, and up to 10% may be overtly hypothyroid. In addition to thyroid function tests and available thyroid autoantibodies, patients with Hashimoto thyroiditis should undergo screening chemistries, erythrocyte sedimentation rate, hemoglobin A1c, serum protein electrophoresis, immunofixation, and screening antinuclear antibodies to search for associated multiple endocrine neoplasia type II, and the POEMS syndrome of polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes.

Patients with suspected Hashimoto thyroiditis should undergo ultrasonography for an enlarged thyroid gland that typically shows diffuse hypoechoogenicity in three-quarters of cases, even though it is typically nonspecific. Radionuclear scanning is generally unnecessary and can be misleading. The uptake of radio-nuclide is characteristically normal or elevated in patients with goitrous Hashimoto thyroiditis, even in the presence of hypothyroidism, whereas in those with subacute or silent thyroiditis, the uptake is low. Fine-needle aspiration of the gland is the only way to demonstrate the expected histology, and to examine clinically suspicious areas in those with enlarged goitrous nodular glands. Whereas high-grade lymphoma poses little difficulty, lower grades on biopsy pathology may be suspected based on the presence of monomorphic lymphocytes and appropriate immunohistochemical studies.

2.5. Immunopathogenesis

In individuals genetically predisposed to AITD, non-genetic or environmental triggers set in motion the initial steps that break down immune tolerance leading to glandular inflammation, goiter formation, and thyroid hypofunction. In the initial stages, main histocompatibility class II-positive dendritic and macrophage antigen presenting cells infiltrate the gland leading to thyrocyte insult and release of host-specific antigens. These peptides, presented on the surface of antigen presenting cells to naïve T-cells, cause activation and clonal expansion of autoreactive CD4+ T-cells, CD8+ cytotoxic T-cells and immunoglobulin (Ig)-G autoantibodies in draining lymph nodes. Lymphoid tissue later develops directly in the gland itself with distinct cords of antibody producing plasma cells, and occasional multinuclear giant cells with enlarged epithelial cells and a distinctive eosinophilic cytoplasm, owing to increased number of mitochondria [48]. The process itself, mediated by T helper type-1 (T_{H1}) cells, is associated with secretion of interleukin-12, interferon- α , and tumor necrosis factor- γ . In the final stages of HT, autoreactive T-cells, B-cells, and antibody cause a massive deple-

tion of thyrocytes via antibody-, cellular-, and cytokine-mediated, and apoptotic mechanisms of cytotoxicity that lead to hypothyroidism and progressive glandular atrophy [49].

The immunopathologic potential for Hashimoto thyroiditis resides in the cellular elements of the thyroid gland [50]. Thyrocytes from Hashimoto thyroiditis glands, but not from non-autoimmune thyroids, express tumor necrosis factor receptor superfamily, member 6 (Fas), and its ligand FasL, which regulates cellular apoptosis. Interleukin-1- β , abundantly produced in HT glands, induces Fas expression in normal thyrocytes. Cross-linking of Fas results in massive thyrocyte apoptosis. Exposure to interleukin-1- β -induced thyrocyte apoptosis, and prevented by antibodies that block Fas, suggest that interleukin-1- β -induced Fas expression may be an important limiting factor for thyrocyte destruction.

Notwithstanding, a tendency for systemic autoimmunity in Hashimoto thyroiditis was recognized by Becker and coworkers a half century ago [44] in an analysis of 506 cases seen at the Mayo Clinic in which 119 (23.5%) were found to have systemic concomitant connective tissue diseases with varying degrees of vascular involvement and autoimmune hypersensitivity reactions. Later reports of two children with nephrotic syndrome, both with glomerular staining for TPO and Tg antigens and either hyperthyroid [51] or hypothyroid [52] AITD, and others with vasculitic neuropathy [53] or giant-cell arteritis [54] showed that patients with Hashimoto thyroiditis may have widespread extra-thyroid abnormal autoimmune activity including an association with systemic vasculitis. Like those with Hashimoto thyroiditis, patients with anti-neutrophil cytoplasmic autoantibody vasculitis show a genetic predisposition for disease susceptibility manifesting both single nucleotide polymorphisms in the *CTLA4* gene [55], and aberrant expression of anti-neutrophil cytoplasmic autoantigen proteinase-3 and its endogenous inhibitor, alpha-1-antitrypsin, as well as, pathogenic expression of myeloperoxidase epitopes in circulating neutrophils. Although encoded on different chromosomes, their expression is highly coordinated and subjected to epigenetic mechanisms and faulty gene silencing which contribute to aberrant chromatin transcription errors in mature monocytes and neutrophils.

2.6. Treatment

Patients with overt hypothyroidism receive thyroxine at a dosage that normalizes the TSH level. The role of thyroxine in patients with subclinical hypothyroidism is more controversial. In placebo-controlled trial of 33 cases randomly assigned to receive placebo or L-thyroxine therapy and followed for 1 year with thyroid function tests and other metabolic determinants [56], symptoms were significantly improved in the treatment group ($P < 0.05$). Treatment is generally recommended in patients with any symptoms potentially attributable to hypothyroidism especially if the TSH level is >10 mU per liter, and the patient is at high risk for progressing to overt hypothyroidism because of strongly positive TPO antibodies, age > 45 years, and male sex. Up to a quarter of patients with

hypothyroidism due to AITD treated with thyroxine for >1 year experience a spontaneous recovery with disappearance of autoantibodies [57] suggesting that hypothyroidism due to thyrotropin-blocking antibodies can be the cause of transient as well as permanent hypothyroidism. Concomitant with a gradual increase in serum free T4 and T3 levels, and a fall in TSH levels, there was a gradual decrease in thyroid volume of 32% in 13 women with Hashimoto thyroiditis, all with initially high TPO antibody titers [58].

3. Hashimoto Encephalopathy

3.1. Historical Background

In 1966, Lord Brain and colleagues [59] described the entity of Hashimoto's disease and encephalopathy in a 40-year-old man with 12 ictal and stroke-like episodes of confusion and agitation one year after onset of treated hypothyroidism. The cerebral disorder remitted completely after 19 months commensurate with a decline in high serum thyroid-antibody levels. Treatment with prednisone and an anticoagulant for 3 months was ineffective. His neurologic symptoms remitted while he was taking only levothyroxine. Brain and colleagues [59] concluded that the likeliest explanation for this protracted and stuttering brain disorder was localized cerebral edema due to antibody-mediated autoimmunity, and that antibody studies in future cases of unexplained encephalopathy would show whether their findings constituted a syndrome or coincidence. Jellinek and Ball [60] extended the results of Brain and colleagues [59] describing their original patient, who at age 62 died 12 years later of other causes. Postmortem examination showed virtually no remaining thyroid tissue and atheromatous cerebrovascular changes with splenic atrophy. The authors postulated that underlying autoimmunity was the cause Hashimoto's thyroiditis and encephalopathy, and splenic atrophy.

Hashimoto encephalopathy is a rare disorder and there are no epidemiologic studies of its population incidence or prevalence. Rowland and coworkers [61] characterized the clinic-pathologic findings of literature cases of Hashimoto's encephalopathy, beginning with the patient described by Brain and colleagues [59] through 2002, and adding their own patient. The diagnosis of Hashimoto's encephalopathy, as described by Brain and colleagues [58], and later by Rowland and coworkers [61], which rests on the histologic presence of thyroiditis and a high serum concentration of anti-thyroid antibodies, stands as the standard for case selection. However then as now, it remains unknown whether anti-thyroid antibodies and concomitant thyroid dysfunction contribute to the pathogenesis of Hashimoto's encephalopathy.

3.2. Selection of Cases

New York University Langone Medical Center, New York.

3.3. Patient Report

The author found a patient from his recent files who met the criteria for Hashi-

moto's encephalopathy as described by Brain and colleagues [59].

In January 2015, a 57-year-old right-handed woman developed subacute right arm and leg weakness and shaking of the right hand at rest with handwriting difficulty. She later developed gait imbalance and clumsiness followed by lack of mental focus. There was a history of intermittent bronchial asthma. Generalized fatigue, temperature sensitivity, and arthralgia led to a suspicion of hypothyroidism but routine thyroid function tests in the year prior to evaluation were normal. She drank alcohol socially but did not smoke cigarettes or abuse drugs. She did not complain of food allergies, bloating, or abdominal pain. She was postmenopausal and married with two children, and self-employed in public relations. She took no prescription medications.

General examination in July 2017 showed normal vital signs, heart, lungs, abdomen and limbs. Neurological examination showed a 4 to 6 Hz pill rolling like tremor of the right hand at rest with cogwheel rigidity. Strength was graded 4/5 in the right side with weakness predominating in anti-gravity muscles of the proximal and distal arm and leg. There was mild loss of check in the erect stance. She walked with a forward-flexed Trendelenburg gait, tilting to the right side because of ipsilateral weakness without significant shuffling. Tendon reflexes were active throughout without Hoffman, exaggerated finger flexor responses, Babinski signs or ankle clonus.

Laboratory studies showed an anti-Tg antibody level of 89.8 IU/ml (Reference range, 0 - 5 IU/ml), anti-TPO antibody 790.9 IU/ml (Reference range, 0 - 5.5 IU/ml), and TSH 5.680 mIU/L (Reference range, 0.4 - 4 mIU/L). The blood was normal or negative for serum anti-neutrophil cytoplasmic autoantibody, proteinase-3, myeloperoxidase, rheumatoid factor, ribonucleoprotein, Smith antigen, Sjogren's serology, creatine kinase, cortisol, T-cell subsets, quantitative immunoglobulins, antinuclear antibody; viral and retroviral serology, and bacterial cultures.

Thyroid ultrasound showed a heterogeneous and mildly hyperemic gland with a sub-centimeter colloid cyst. Using sonographic guidance, fine needle aspiration of a defined area of decreased echogenicity in the mid right thyroid lobe was performed that showed abundant colloid and sheets and clusters of follicular cells, with rare Hürthle cell changes of abundant eosinophilic granular cytoplasm, in a background of predominantly mature lymphocytes (**Figure 1**). Cerebrospinal fluid showed normal cell count, protein content, IgG levels and absent oligoclonal bands, with negative viral and bacterial culture studies. Brain ¹⁸Fluoro-D-glucose-positron emission tomography (FDG-PET) metabolic imaging (**Figure 2**) showed severe hypometabolism within the posterior aspect of the left putamen suggesting focal vascular injury, and mild left temporal and left parietal hypometabolism and mild volume loss relative to the rest of the brain. Magnetic resonance angiogram of the head and neck, and MRI of the total spinal cord were all normal. The clinicopathologic and serologic findings were consistent with Hashimoto's thyroiditis and encephalopathy, and hypothyroidism in association with subacute right hemiparesis and hemi-parkinsonism.

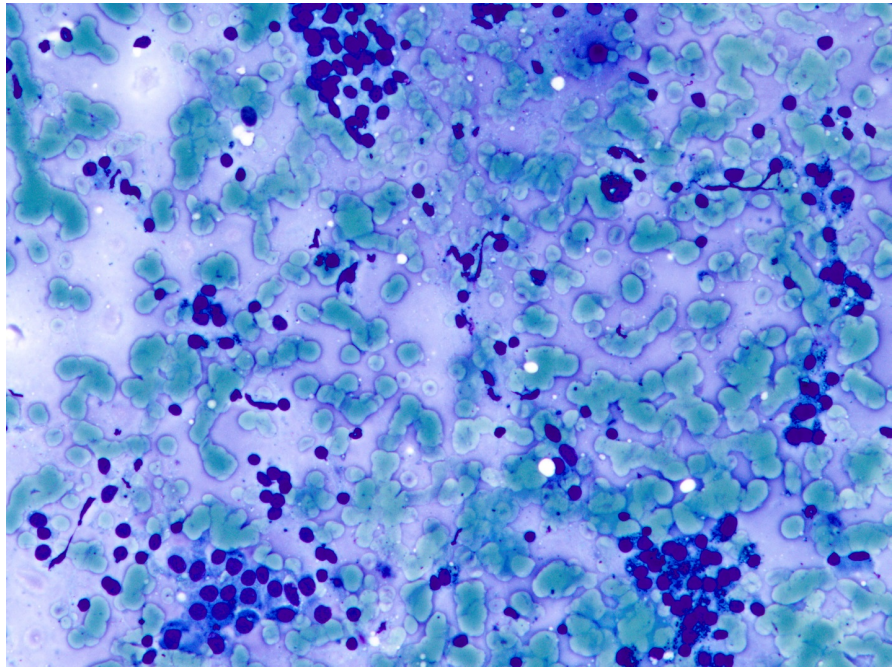


Figure 1. Hashimoto's thyroiditis. Fine needle aspiration in a Diff-Quik® staining of a goiter in a background of lymphocytic thyroiditis. There is a thin background of purple colloid in between grey staining red blood cells amid follicular cells and dark blue staining nucleated lymphocytes recognized by crush or stringing effects (Magnification 200×).

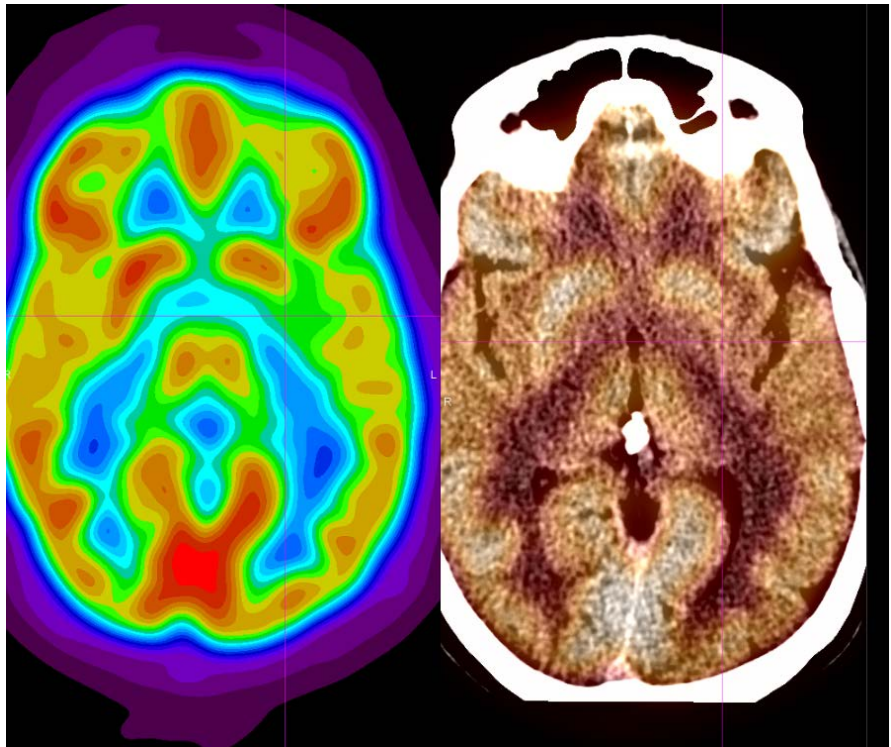


Figure 2. Hashimoto's encephalopathy. Positron emission tomographic (PET) imaging from the vertex to foramen magnum following injection of 10 mCi ^{18}F -Fluoro-D-glucose (left image) shows severely reduced metabolic activity in the posterior half of the left putamen on standard PET imaging, and with fusion to gadolinium-enhanced magnetic resonance imaging (MRI) (right image).

3.4. Literature Cases

Rowland and coworkers [61] characterized the clinicpathologic findings of literature cases of Hashimoto's encephalopathy, beginning with the patient described by Brain and colleagues [59] through 2002, and adding their own patient. The authors [61] searched Medline database using the terms "Hashimoto", "autoimmune thyroid disease" and "encephalopathy". They identified 105 literature reports of Hashimoto's encephalopathy. Eighty-five met inclusion criteria of encephalopathy (clouding of consciousness with reduced wakefulness, attention, or cognitive function); with absence of cerebrospinal fluid evidence of bacterial or viral infection, and measurably high titers of circulating TPO or Tg antibodies [62]-[102] to which the authors [61] added one additional case of their own. There were 20 literature reports excluded for lack of encephalopathy [103]-[109], and other single reports for lack of CSF [110] or absent measurement of serum anti-thyroid antibodies [111]. Patients with stroke-like or postictal focal signs, seizures, dementia, or psychiatric symptoms were included if consciousness was depressed.

Two patients studied histologically at postmortem examination disclosed congestion of cerebral vessels without focal infarction on macroscopic examination [59], or lymphocytic infiltration of brainstem veins [2] consistent with vasculitis. Two patients underwent brain biopsy showing lymphocytic infiltration of the walls of cerebral arterioles and veins [92], and small perivascular cuffs of lymphocytic cells [61].

3.5. Clinical Presentation

In the series of Rowland and coworkers [61] the mean age at onset of symptoms of Hashimoto's encephalopathy was 44 years (range, 9 - 78 years); 19 of whom were boys or girls, age 18 years or younger. Among the adults, there were 53 women and 13 men. In addition to encephalopathy as required, stroke-like signs presented in 23 (27%) case, seizure in 56 (66%), myoclonus in 32 (38%), and visual hallucination or paranoid delusion in 31 (36%). The course was relapsing and remitting in 51 (60%) of cases.

3.6. Laboratory Investigation

In the series of Rowland and coworkers [61], both Tg and microsomal or TPO antibodies were together in 60 (71%) cases with one antibody of the two normal in 20 (24%) cases. There was no relationship between the neurologic symptoms and signs and the type or serum concentration of anti-thyroid antibodies. Altogether, 30 (35%) cases were sub-clinically hypothyroid, 19 (22%) were euthyroid, and 17 (20%) were overtly hypothyroid. Fourteen (16%) cases had an elevated erythrocyte sedimentation rate or antinuclear antibody, and three had a concomitant connective tissue disease (psoriatic arthritis, Sjogren's syndrome, and sarcoidosis). An elevated CSF protein level was noted in 66 (78%) patients, with abnormal findings in neuroimaging in 40/82 (49%) or electroencephalography in 80/82 (98%) patients. A goiter was detected in 24/39 (62%) patients, with a

serum microsomal antibodies in 55/58 (95%), TPO antibodies in 26/26 (100%), and Tg antibodies in 45/62 (73%) patients.

3.7. Immunopathogenic Mechanisms

Unlike the close relation between anti-thyroid antibodies and thyroiditis in AITD, neither high titers of anti-thyroid antibodies nor presence of subclinical or overt hypothyroidism accounted for the observed encephalopathy in the series of Rowland and coworkers [61]. The neurological findings in patients that were euthyroid were similar to those with subclinical or overt hypothyroidism. High serum anti-thyroid antibody titers have been associated with neuropathy and myopathy [112], depression [113] bipolar disease [114], and dementia [115]. Their increased prevalence in healthy individuals and patients with subclinical hypothyroidism makes it difficult to consider a high titer a defining feature of any disorder other than AITD [61]. Given the lack of a well-defined pathophysiologic link between antithyroid antibodies or Hashimoto's thyroiditis and encephalopathy, Hashimoto's encephalopathy may be a misleading term, the disorder being one of a larger group of autoimmune encephalopathies [61].

Ochi and colleagues [116] provided a link between Hashimoto's thyroiditis autoimmunity and the central nervous system. They developed a human brain proteome map using two-dimensional electrophoresis and applied it to the immunoscreening of brain proteins that reacted with serum antithyroid antibodies in Hashimoto's encephalopathy patients, identifying the novel antigen α -enolase, encoded on 1p36.23, as a candidate biomarker for Hashimoto's encephalopathy-related pathology and corticosteroid sensitivity. Kishitani and coworkers [3] extended the findings of Ochi and colleagues [116] noting anti-NH₂-terminal of α -enolase antibodies in 24% of Hashimoto's encephalopathy patient sera, and limbic abnormalities on MRI demonstrating abnormal signal in unilateral or bilateral medial temporal lobes, and diffuse slow wave activity with epileptogenic discharges. These findings suggested that limbic encephalitis-associated with anti-NH₂-terminal of α -enolase antibodies could be a possible manifestation of Hashimoto's encephalopathy in some cases. Graus and colleagues [117] proposed Hashimoto's encephalopathy as an autoimmune encephalopathy or encephalitis after exclusion of other syndromes associated with well-defined autoantibodies. The authors [117] noted that α -enolase antibodies, like antithyroid antibodies, were present in up to 68% of patients with Hashimoto's encephalopathy and antithyroid antibodies [118], making them useful in the serological diagnosis of suspected cases. However, they were of limited reliability as a biomarker of the brain disease since they were detectable in healthy individuals and in patients with other autoimmune disorders.

In support of an antibody-mediated autoimmune mechanism in Hashimoto's encephalopathy, it is notable that patients with meningoencephalitis and corticosteroid-responsive encephalopathy [119] [120] may present with circulating antithyroid antibodies, rheumatoid factor, antinuclear antibody, Sjogren's serology, and cardiolipin antibodies like those with AITD and Hashimoto's encephalopathy.

phalopathy [44]. In five such patients [120], one had high serum anti-thyroid antibody levels compatible with Hashimoto's encephalopathy (anti-thyroid levels were not mentioned in the other four) and brain tissue biopsy revealed perivascular lymphocytic infiltrates without vessel wall invasion similar to the case described by Rowland and colleagues [61]. At present, it is unclear whether antithyroid antibodies represent an immune epiphenomenon in a subset of patients with encephalopathy or are truly associated with pathogenic mechanisms of the disorder [121] [122]. In turn, the significance of classifying encephalopathies under the term Hashimoto's encephalopathy will be determined in the future once the relevance of the role of antithyroid antibodies is demonstrated or dismissed by more detailed experimental and immunopathological studies.

According to Rowland and colleagues [61], one subgroup of patients with Hashimoto's encephalopathy present with stroke-like episodes. Inoue and colleagues [123] described a patient with progressive Parkinsonism and normal cognitive and intellectual performance. Slow background activity on electroencephalography was the only sign of encephalopathy, which normalized after treatment with corticosteroids. Our patient differed in many respects from the case described by Inoue and colleagues [123] making it unique to the literature. First, our patient had hemiparkinsonism and hemiparesis consistent with a stroke-like onset. Second, neuroimaging with brain MRI and FDG-PET metabolic imaging showed focal hypometabolism in the putamen contralateral to the hemiparesis and hemiparkinsonism. Third, neuroimaging also showed a lateralized area of metabolically abnormal association cortex correlating with encephalopathy and neurocognitive impairment.

A vasculitic pathogenesis appears to be equally likely in some cases of Hashimoto's encephalopathy based upon the tendency for increased autoimmunity in Hashimoto's thyroiditis [51] [52] [53] [54]. The available histopathology in Hashimoto's encephalopathy also supports an inflammatory vasculopathy, so noted in one postmortem case that showed lymphocytic infiltration of brainstem veins [2], and in brain biopsy tissue from another case categorized as isolated angiitis due to lymphocytic infiltration of the walls of arterioles and veins [92]. It is noteworthy that patients with Hashimoto's encephalopathy and circulating α -enolase antibodies are at risk for heightened autoimmune activity [124], and a tendency for systemic and invasive autoimmune disorders including systemic vasculitis [125]. Further insight in this area may be found on-line (<http://www.davidsyounger.com>).

3.8. Treatment

The significance of corticosteroid sensitivity in Hashimoto's encephalopathy is widely accepted as a criterion for the diagnosis. However, as Rowland and colleagues suggested [61], it would be unwise to define any condition by response to any particular therapy especially if not replacing a specific deficit or directing it at a particular target. Patients with Hashimoto's encephalopathy improve in association with, but not necessarily due to corticosteroid therapy. Moreover,

those that respond to corticosteroids have no distinguishing clinical characteristics nor receive treatment in other fashions for a meaningful comparison.

4. Conclusion

The terms Hashimoto's thyroiditis and encephalopathy are deeply entrenched in the scientific literature. While the former is now well understood and a cornerstone for understanding AITD, the latter remains a challenge to clinicians not so much for its lethal nature, but because of the potential for unraveling an important feature of autoimmune encephalopathy in some cases, and the continued complexity of possible central nervous system vasculitis in others.

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References

- [1] Shaw, P.J., Walls, T.J., Newman, P.K., *et al.* (1991) Hashimoto's Encephalopathy: A Steroid-Responsive Disorder Associated with High Anti-Thyroid Antibody Titers-Report of 5 Cases. *Neurology*, **41**, 228-233. https://doi.org/10.1212/WNL.41.2_Part_1.228
- [2] Nolte, K.W., Unbehaun, A., Sieker, H., *et al.* (2000) Hashimoto Encephalopathy: A Brainstem Encephalitis? *Neurology*, **54**, 769-770. <https://doi.org/10.1212/WNL.54.3.769>
- [3] Kishitani, T., Matsunaga, A., Masamichi, I., *et al.* (2017) Limbic Encephalitis Associated with Anti-NH2-Terminal of A-Enolase Antibodies. A Clinical Subtype of Hashimoto Encephalopathy. *Medicine*, **96**, e6181.
- [4] Sawin, C.T. (2002) The Heritage of Dr. Hakaru Hashimoto (1881-1934). *Endocrine Journal*, **49**, 399-403. <https://doi.org/10.1507/endocrj.49.399>
- [5] Hashimoto, H. (1912) Zur Kenntniss der lymphoatosen Veränderung der Schilddrüse (Struma lymphomatoa). *Langenbecks archiv fur klinische chirurgie*, **97**, 219-248.
- [6] Graves, R.J. (1835) Newly Observed Affection of the Thyroid Gland in Females. Clinical Lectures. *London Medical and Surgical Journal*, **7**, 516-517.
- [7] Riedel, M.C.L. (1896) Die chronische, zur Bildung eisenharter Tumoren führende Entzündung der Schilddrüse. Verhandlungen der deutschen Gesellschaft für Chirurgie.
- [8] Harach, H.R. and Williams, E.D. (1983) Fibrous Thyroiditis—An Immunopathological Study. *Histopathology*, **7**, 739-751. <https://doi.org/10.1111/j.1365-2559.1983.tb02286.x>
- [9] Hertzler, A.E. (1935) Surgical Pathology of the Thyroid Gland. JB Lippincott, Philadelphia.

- [10] Means, J.H. (1937) *The Thyroid and Its Diseases*. JB Lippincott, Philadelphia.
- [11] McClintock, J.C. and Wright, A.W. (1937) Reidel's Struma and Stuma Lymphomatosa (Hashimoto): A Comparative Study. *Annals of Surgery*, **106**, 11-32. <https://doi.org/10.1097/0000658-193707000-00003>
- [12] Witebsky, E. and Rose, N.R. (1956) Studies on Organ Specificity. IV. Production of Rabbit Thyroid Antibodies in the Rabbit. *The Journal of Immunology*, **76**, 408-416.
- [13] Witebsky, E., Rose, N.R., Terplan, K., *et al.* (1957) Chronic Thyroiditis and Autoimmunization. *JAMA*, **164**, 1439-1447. <https://doi.org/10.1001/jama.1957.02980130015004>
- [14] Roitt, I.M., Doniach, D., Campbell, P.H., *et al.* (1956) Autoantibodies in Hashimoto's Disease (Lymphadenoid Goiter). *The Lancet*, **271**, 820-821.
- [15] Beare, R.L.B. (1958) Lymphadenoid Goiter (Hashimoto Disease): Clinic-Pathologic Study. *British Medical Journal*, **1**, 480-486. <https://doi.org/10.1136/bmj.1.5069.480>
- [16] Woolner, L.B., McConahey, W.M. and Beahrs, O.H. (1959) Struma Lymphomatosa (Hashimoto's Thyroiditis) and Related Thyroidal Disorders. *The Journal of Clinical Endocrinology & Metabolism*, **19**, 53-83. <https://doi.org/10.1210/jcem-19-1-53>
- [17] McConahey, W.M., Keating, F.R., Beahrs, O.H., *et al.* (1962) On Increasing Occurrence of Hashimoto's Thyroiditis. *The Journal of Clinical Endocrinology & Metabolism*, **22**, 542-544. <https://doi.org/10.1210/jcem-22-5-542>
- [18] Dayan, C.M. and Daniels, G.H. (1996) Chronic Autoimmune Thyroiditis. *The New England Journal of Medicine*, **335**, 99-107. <https://doi.org/10.1056/NEJM199607113350206>
- [19] Roitt, I.M. and Doniach, D. (1958) Human Auto-Immune Thyroiditis: Serological Studies. *The Lancet*, **2**, 1027-1033.
- [20] Doniach, D. (1967) Thyroid Autoimmune Disease: Symposium on Thyroid Gland, 1966. *Journal of Clinical Pathology*, **20**, 385-390.
- [21] Wang, C. and Crapo, L.M. (1997) The Epidemiology of Thyroid Disease and Implications for Screening. *Endocrinology Metabolism Clinics of North America*, **26**, 189-218.
- [22] Hollowell, J.G., Staehling, N.W., Flanders, W.D., *et al.* (2002) Serum TSH, T4, and Thyroid Antibodies in the United States Population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *The Journal of Clinical Endocrinology & Metabolism*, **87**, 489-499. <https://doi.org/10.1210/jcem.87.2.8182>
- [23] Tunbridge, W.M., Evered, D.C., Hall, R., *et al.* (1977) The Spectrum of Thyroid Disease in a Community: The Wickham Survey. *Clinical Endocrinology*, **7**, 481-493. <https://doi.org/10.1111/j.1365-2265.1977.tb01340.x>
- [24] Vanderpump, M.P., Tunbridge, W.M., French, J.M., *et al.* (1995) The Incidence of Thyroid Disorders in the Community: A Twenty-Year Follow-Up of the Wickham Survey. *Clinical Endocrinology*, **43**, 55-68. <https://doi.org/10.1111/j.1365-2265.1995.tb01894.x>
- [25] Furszyfer, J., Kurland, L.T., Mc, C., *et al.* (1972) Epidemiologic Aspects of Hashimoto's Thyroiditis and Graves' Disease in Rochester, Minnesota 1935-1967 with Special Reference to Temporal Trends. *Metabolism: Clinical and Experimental*, **21**, 197-204.
- [26] Masi, A.T. (1965) Hashimoto's Disease: An Epidemiological Study Based on a Community-Wide Hospital Survey. *Journal of Chronic Diseases*, **18**, 35-57.
- [27] Jacobson, D.L., Gange, S.J., Rose, N.R., *et al.* (1997) Epidemiology and Estimated Population Burden of Selected Autoimmune Diseases in the United States. *Clinical Immunology and Immunopathology*, **84**, 223-243.

- <https://doi.org/10.1006/clin.1997.4412>
- [28] Pedersen, I.B., Knudsen, N., Jørgensen, T., *et al.* (2003) Thyroid Peroxidase and Thyroglobulin Autoantibodies in a Large Survey of Populations with Mild and Moderate Iodine Deficiency. *Clinical Endocrinology*, **58**, 36-42. <https://doi.org/10.1046/j.1365-2265.2003.01633.x>
- [29] Jenkins, R.C. and Weetman, A.P. (2002) Disease Associations with Autoimmune Thyroid Disease. *Thyroid*, **12**, 977-988. <https://doi.org/10.1089/105072502320908312>
- [30] Phillips, D., McLachlan, S., Stephenson, A., *et al.* (1990) Autosomal Dominant Transmission of Autoantibodies to Thyroglobulin and Thyroid Peroxidase. *The Journal of Clinical Endocrinology & Metabolism*, **70**, 742-746. <https://doi.org/10.1210/jcem-70-3-742>
- [31] Hall, R. and Stanbury, J.B. (1967) Familial Studies of Autoimmune Thyroiditis. *Clinical & Experimental Immunology*, **2**, 719-725.
- [32] Tomer, Y. and Davies, T.F. (2003) Searching for the Autoimmune Thyroid Disease Susceptibility Genes: From Gene Mapping to Gene Function. *Endocrine Reviews*, **24**, 694-717. <https://doi.org/10.1210/er.2002-0030>
- [33] Ueda, H., Howson, J.M.M., Esposito, L., *et al.* (2003) Association of the T-Cell Regulatory Gene CTLA4 with Susceptibility to Autoimmune Disease. *Nature*, **423**, 506-511. <https://doi.org/10.1038/nature01621>
- [34] Tomer, Y. (2002) Genetic Dissection of Familial Autoimmune Thyroid Disease Using Whole Genome Screening. *Autoimmunity Reviews*, **1**, 198-204.
- [35] Barbesino, G. and Chiovato, L. (2000) The Genetics of Hashimoto's Disease. *Endocrinology Metabolism Clinics of North America*, **29**, 357-374.
- [36] Lesage, S. and Goodnow, C.C. (2001) Organ-Specific Autoimmune Disease: A Deficiency of Tolerogenic Stimulation. *The Journal of Experimental Medicine*, **194**, F31-F36. <https://doi.org/10.1084/jem.194.5.F31>
- [37] Awata, T., Kurihara, S., Iitaka, M., *et al.* (1998) Association of CTLA-4 Gene A-G Polymorphism (IDDM12 Locus) with Acute-Onset and Insulin-Depleted IDDM as well as Autoimmune Thyroid Disease (Graves' Disease and Hashimoto's Thyroiditis) in the Japanese Population. *Diabetes*, **47**, 128-129. <https://doi.org/10.2337/diab.47.1.128>
- [38] Kotsa, K., Watson, P.F. and Weetman, A.P. (1997) A CTLA-4 Gene Polymorphism Is Associated with Both Graves' Disease and Autoimmune Hypothyroidism. *Clinical Endocrinology*, **46**, 551-554. <https://doi.org/10.1046/j.1365-2265.1997.1710996.x>
- [39] Donner, H., Braun, J., Seidl, C., *et al.* (1997) Codon 17 Polymorphism of the Cytotoxic T Lymphocyte Antigen 4 Gene in Hashimoto's Thyroiditis and Addison's Disease. *The Journal of Clinical Endocrinology & Metabolism*, **82**, 4130-4132.
- [40] Wang, B., Shao, X., Song, R., *et al.* (2017) The Emerging Role of Epigenetics in Autoimmune Thyroid Disease. *Frontiers in Immunology*, **8**, 396. <https://doi.org/10.3389/fimmu.2017.00396>
- [41] Cai, T.T., Muhali, F.S., Song, R.H., *et al.* (2015) Genome-Wide DNA Methylation Analysis in Graves' Disease. *Genomics*, **105**, 204-210.
- [42] Sarumaru, M., Watanabe, M., Inoue, N., *et al.* (2016) Association between Functional SIRT1 Polymorphisms and the Clinical Characteristics of Patients with Autoimmune Thyroid Disease. *Autoimmunity*, **49**, 329-337. <https://doi.org/10.3109/08916934.2015.1134506>
- [43] Chen, J., Tian, J., Tang, X., *et al.* (2015) MiR-346 Regulates CD4(+) CXCR5(+) T Cells in the Pathogenesis of Graves' Disease. *Endocrine*, **49**, 752-760.

- <https://doi.org/10.1007/s12020-015-0546-5>
- [44] Becker, K.L., Ferguson, R.H. and McConahey, W.M. (1963) The Connective-Tissue Diseases and Symptoms Associated with Hashimoto's Thyroiditis. *The New England Journal of Medicine*, **268**, 277-280.
<https://doi.org/10.1056/NEJM196302072680601>
- [45] Cabot, R., Scully, R.E., Mark, E., *et al.* (1982) Case 13-1982: A 54-Year-Old Man with an Enlarged Thyroid Gland and Hypothyroidism. *The New England Journal of Medicine*, **306**, 793-798. <https://doi.org/10.1056/NEJM198204013061308>
- [46] Katz, S.M. and Vickery, A.L. (1974) The Fibrous Variant of Hashimoto's Thyroiditis. *Human Pathology*, **5**, 161-170.
- [47] Mariotti, S., Caturegli, P., Piccolo, P., *et al.* (1990) Antithyroid Peroxidase Autoantibodies in Thyroid Diseases. *The Journal of Clinical Endocrinology & Metabolism*, **71**, 661-669. <https://doi.org/10.1210/jcem-71-3-661>
- [48] Devendra, D. and Eisenbarth, G.S. (2003) Immunological Endocrine Disorders. *Journal of Allergy and Clinical Immunology*, **111**, 624-636.
<https://doi.org/10.1067/mai.2003.81>
- [49] Chistiakov, D.A. (2005) Immunogenetics of Hashimoto's Thyroiditis. *Journal of Autoimmune Diseases*, **2**, 1. <https://doi.org/10.1186/1740-2557-2-1>
- [50] Giordano, C., Stassi, G., De Maria, R., *et al.* (1997) Potential Involvement of Fas and Its Ligand in the Pathogenesis of Hashimoto's Thyroiditis. *Science*, **275**, 960-963.
- [51] Jordan, S.C., Johnston, W.H. and Bergstein, J.M. (2009) Immune Complex Glomerulonephritis Mediated by Thyroid Antigens. *Pediatric Nephrology*, **24**, 605-608.
- [52] O'Regan, S., Fong, J.S.C., Kaplan, B.S., *et al.* (1976) Thyroid Antigen-Antibody Nephritis. *Clinical Immunology and Immunopathology*, **6**, 341-346.
- [53] Awaki, E., Onoda, K., Takahashi, K., *et al.* (1988) A Case of Chronic Thyroiditis Associated with Vasculitic Neuropathy. *Rinsho Shinkeigaku*, **28**, 501-506.
- [54] Nicholson, G.C., Gutteridge, D.H., Carroll, W.M., *et al.* (1984) Autoimmune Thyroid Disease and Giant Cell Arteritis: A Review, Case Report and Epidemiological Study. *Australian & New Zealand Journal of Medicine*, **14**, 487-490.
<https://doi.org/10.1111/j.1445-5994.1984.tb03622.x>
- [55] Pendergraft, W.F. and Nachman, P.H. (2015) Recent Pathogenic Advances in ANCA-Associated Vasculitis. *La Presse Médicale*, **44**, e223-e229.
- [56] Cooper, D.S., Halpern, R., Wood, L.C., *et al.* (1984) L-Thyroxine Therapy in Subclinical Hypothyroidism: A Double-Blind, Placebo-Controlled Trial. *Annals of Internal Medicine*, **101**, 18-24. <https://doi.org/10.7326/0003-4819-101-1-18>
- [57] Takasu, N., Yamada, T., Takasu, M., *et al.* (1992) Disappearance of Thyrotropin-Blocking Antibodies and Spontaneous Recovery from Hypothyroidism in Autoimmune Thyroiditis. *The New England Journal of Medicine*, **326**, 513-518.
<https://doi.org/10.1056/NEJM199202203260803>
- [58] Hegedus, L., Hansen, J.M., Feldt-Rasmussen, U., *et al.* (1991) Influence of Thyroxine Treatment on Thyroid Size and Anti-Thyroid Peroxidase Antibodies in Hashimoto's Thyroiditis. *Clinical Endocrinology*, **35**, 235-238.
<https://doi.org/10.1111/j.1365-2265.1991.tb03528.x>
- [59] Brain, L., Jellinek, E.H. and Ball, K. (1966) Hashimoto's Disease and Encephalopathy. *The Lancet*, **2**, 512-514.
- [60] Jellinek, E.H. and Ball, K. (1976) Hashimoto's Disease, Encephalopathy, and Splenic Atrophy. *The Lancet*, **1**, 1248.
- [61] Chong, J.Y., Rowland, L.P. and Utiger, R.D. (2003) Hashimoto Encephalopathy. Syndrome or Myth? *Archives of Neurology*, **60**, 164-171.

- <https://doi.org/10.1001/archneur.60.2.164>
- [62] Alegre, S., Rubio, S.A., Ruiberez de Torres, R., *et al.* (1998) Hashimoto Encephalopathy. *Medicina Clinica*, **10**, 437-438.
- [63] Arain, A., Abou-Khallil, B. and Moses, H. (2001) Hashimoto's Encephalopathy: Documentation of Mesial Temporal Seizure Origin by Ictal EEG. *Seizure*, **10**, 438-441. <https://doi.org/10.1053/seiz.2001.0531>
- [64] Archambeaud, F., Galinat, S., Regouby, Y., *et al.* (2001) Hashimoto's Encephalopathy: Report of Four Cases. *La Revue de Médecine Interne*, **22**, 653-659.
- [65] Azuma, T., Uemici, T., Funauchi, M., *et al.* (2000) Myelopathy Associated with Hashimoto's Disease. *Journal of Neurology, Neurosurgery, & Psychiatry*, **68**, 679-683. <https://doi.org/10.1136/jnnp.68.5.681>
- [66] Grosso, S., Garibaldi, G., *et al.* (1999) Alternating Hemiplegia of Childhood or Hashimoto's Encephalopathy? *Journal of Neurology, Neurosurgery, & Psychiatry*, **66**, 548-549. <https://doi.org/10.1136/jnnp.66.4.548>
- [67] Barker, R., Zajicek, J. and Wilkinson, I. (1996) Thyrotoxic Hashimoto's Encephalopathy. *Journal of Neurology, Neurosurgery, & Psychiatry*, **60**, 234. <https://doi.org/10.1136/jnnp.60.2.234>
- [68] Boers, P.M. and Colebatch, J.G. (2001) Hashimoto's Encephalopathy Responding to Plasmapheresis. *Journal of Neurology, Neurosurgery, & Psychiatry*, **70**, 132. <https://doi.org/10.1136/jnnp.70.1.132>
- [69] Bohnen, N.I., Parnell, K.J. and Harper, C.M. (1997) Reversible MRI Findings in a Patient with Hashimoto's Encephalopathy. *Neurology*, **49**, 246-247. <https://doi.org/10.1212/WNL.49.1.246>
- [70] Bostantjouboulos, S., Zafiriou, D., Katsarou, Z., *et al.* (1996) Hashimoto's Encephalopathy: Clinical and Laboratory Findings. *Functional Neurology*, **11**, 247-251.
- [71] Byrne, O.C., Zuberi, S.M., Madigan, C.A., *et al.* (2000) Hashimoto's Thyroiditis: A Rare but Treatable Cause of Encephalopathy in Children. *European Journal of Paediatric Neurology*, **4**, 279-282. <https://doi.org/10.1053/ejpn.2000.0380>
- [72] Canton, A., de Fabregas, O., Tintore, M., *et al.* (2000) Encephalopathy Associated to Autoimmune Thyroid Disease: A More Appropriate Term for an Underestimated Condition? *Journal of the Neurological Sciences*, **176**, 65-69.
- [73] Chen, H.C. and Marsharani, U. (2000) Hashimoto's Encephalopathy. *The Southern Medical Journal*, **93**, 504-506. <https://doi.org/10.1097/00007611-200093050-00014>
- [74] Claussmann, C., Offner, C., Chevalier, Y., *et al.* (1994) Encephalopathy and Hashimoto Thyroiditis. *Revista De Neurologia*, **150**, 166-168.
- [75] Cohen, L., Mouly, S., Tassan, P., *et al.* (1996) A Woman with a Relapsing Psychosis Who Got Better with Prednisone. *The Lancet*, **347**, 1228.
- [76] Desai, J. and Wadia, N. (1999) Hashimoto's Encephalopathy. *Journal of the Neurological Sciences*, **163**, 202-204.
- [77] Forchetti, C.M., Katsamakis, G. and Garron, D.C. (1997) Autoimmune Thyroiditis and a Rapidly Progressive Dementia: Global Hypoperfusion on SPECT Scanning Suggests a Possible Mechanism. *Neurology*, **49**, 623-626. <https://doi.org/10.1212/WNL.49.2.623>
- [78] Ghawche, F., Bordet, R. and Destee, A. (1992) Hashimoto's Encephalopathy: Toxic or Autoimmune Mechanism? *Revista De Neurologia*, **148**, 371-373.
- [79] Ghika-Schmid, F., Ghika, J., Regli, F., *et al.* (1996) Hashimoto's Myoclonic Encephalopathy: An Underdiagnosed Treatable Condition? *Movement Disorders*, **11**, 555-562. <https://doi.org/10.1002/mds.870110511>

- [80] Gucuyener, K., Serdaroglu, A., Bideci, A., *et al.* (2000) Tremor and Myoclonus Herald Hashimoto's Encephalopathy. *Journal of Pediatric Endocrinology and Metabolism*, **13**, 1137-1141. <https://doi.org/10.1515/JPEM.2000.13.8.1137>
- [81] Hartmann, M., Schaner, B., Scheglmann, K., *et al.* (2000) Hashimoto Encephalopathy: Steroid-Sensitive Encephalopathy in Hashimoto Thyroiditis. *Nervenarzt*, **71**, 489-494. <https://doi.org/10.1007/s001150050613>
- [82] Hernandez Echebarria, L.E., Saiz, A., Graus, F., *et al.* (2000) Detection of 14-3-3 Protein in the CSF of a Patient with Hashimoto's Encephalopathy. *Neurology*, **54**, 1539-1540. <https://doi.org/10.1212/WNL.54.7.1539>
- [83] Ishii, K., Hayashi, A., Tamoaka, A., *et al.* (1995) Case Report: Thyrotropin-Releasing Hormone-Induced Myoclonus and Tremor in a Patient with Hashimoto's Encephalopathy. *The American Journal of the Medical Sciences*, **310**, 202-205. <https://doi.org/10.1097/00000441-199511000-00005>
- [84] Latinville, D., Bernardi, O., Cougoule, J.P., *et al.* (1985) Hashimoto's Thyroiditis and Myoclonic Encephalopathy: Pathogenic Hypothesis. *Revista De Neurologia*, **141**, 55-58.
- [85] Manto, M., Goldman, S. and Bodur, H. (1996) Cerebellar Syndrome Associated with Hashimoto's Encephalopathy. *Revista De Neurologia*, **152**, 202-204.
- [86] McCabe, D.J., Burke, T., Connolly, S., *et al.* (2000) Amnesic Syndrome with Bilateral Mesial Temporal Lobe Involvement in Hashimoto's Encephalopathy. *Neurology*, **54**, 737-739. <https://doi.org/10.1212/WNL.54.3.737>
- [87] McGinley, J., McCabe, D.J., Fraser, A., *et al.* (2000) Hashimoto's Encephalopathy: An Unusual Cause of Status Epilepticus. *Irish Medical Journal*, **93**, 118.
- [88] Papathanasopoulos, P., Mallioris, K., Karanasios, P., *et al.* (2000) Febrile Hashimoto's Encephalopathy. *Journal of Neurology, Neurosurgery, & Psychiatry*, **68**, 795. <https://doi.org/10.1136/jnnp.68.6.795>
- [89] Querol Pascual, M.R., Aguirre Sanchez, J.J., *et al.* (2000) Hashimoto's Encephalitis: A New Case with Spontaneous Remission. *Neurologia*, **15**, 313-316.
- [90] Quilichini, R., Mateo, A., Robion, M., *et al.* (1996) Hashimoto's Encephalopathy: A New Case. *La Presse Médicale*, **25**, 687.
- [91] Shein, M., Apter, A., Dickerman, Z., *et al.* (1986) Encephalopathy in Compensated Hashimoto Thyroiditis: A Clinical Expression of Autoimmune Cerebral Vasculitis. *Brain & Development*, **8**, 60-64.
- [92] Shibata, N., Yamamoto, Y., Sunami, N., *et al.* (1992) Isolated Angiitis of the CNS Associated with Hashimoto's Disease. *Rinsho Shinkeigaku*, **32**, 191-198.
- [93] Skodda, S., Kraus, M., Durwen, H., *et al.* (1999) Hashimoto's Encephalopathy Associated with Isolated ACTH Deficiency and Hyponatremia: A Case Report. *Journal of Neurology*, **246**, 970-971. <https://doi.org/10.1007/s004150050493>
- [94] Sue, C.M. and Morris, J.G. (1997) Another Case of Hashimoto's Encephalopathy. *Movement Disorders*, **12**, 471-472.
- [95] Sybesma, C.A., Pinxteren-Nagler, E., Sinnige, L.G., *et al.* (1999) Hashimoto Encephalopathy in a 12-Year-Old Girl. *European Journal of Pediatrics*, **158**, 867-868. <https://doi.org/10.1007/s004310051226>
- [96] Takahashi, S., Mitamura, R., Itoh, Y., *et al.* (1994) A Hashimoto Encephalopathy: Etiologic Considerations. *Pediatric Neurology*, **11**, 328-331.
- [97] Thrush, D.C. and Boddie, H.G. (1974) Episodic Encephalopathy Associated with Thyroid Disorders. *Journal of Neurology, Neurosurgery, & Psychiatry*, **37**, 696-700. <https://doi.org/10.1136/jnnp.37.6.696>

- [98] Van Oostrom, J.C., Schaafsma, A. and Haaxma, R. (1999) Variable Manifestations of Hashimoto's Encephalopathy. *Nederlands Tijdschrift voor Geneeskunde*, **143**, 1319-1322.
- [99] Watemberg, N., Willis, D. and Pellock, J.M. (2000) Encephalopathy as the Presenting Symptom of Hashimoto's Thyroiditis. *Journal of Child Neurology*, **15**, 66-69. <https://doi.org/10.1177/088307380001500116>
- [100] Wilhelm-Gossling, C., Weckbecker, K., Brabant, E.G., et al. (1998) Autoimmune Encephalopathy in Hashimoto's Thyroiditis: A Differential Diagnosis in Progressive Dementia Syndrome. *Deutsche Medizinische Wochenschrift*, **123**, 279-284. <https://doi.org/10.1055/s-2007-1023949>
- [101] Maydell, B.V., Kopp, G., Komorowski, A., et al. (2002) Hashimoto Encephalopathy: Is It Underdiagnosed in Pediatric Patients? *Neuropediatrics*, **33**, 86-89. <https://doi.org/10.1055/s-2002-32364>
- [102] Crozier, S., Verstichel, P., Masson, C., Nys, P.M., et al. (1994) Cortico-Dependent Hashimoto Encephalitis. *La Presse Médicale*, **23**, 1400-1401.
- [103] Garrard, P., Hodges, J.R., De Vries, P.J., et al. (2000) Hashimoto's Encephalopathy Presenting as "Myxedematous Madness". *Journal of Neurology, Neurosurgery, & Psychiatry*, **68**, 102-103. <https://doi.org/10.1136/jnnp.68.1.102>
- [104] Henchey, R., Cibula, J., Helveston, W., et al. (1995) Electroencephalographic Findings in Hashimoto's Encephalopathy. *Neurology*, **45**, 977-981. <https://doi.org/10.1212/WNL.45.5.977>
- [105] Kothbauer-Margreiter, I., Sturzenegger, M., Komor, J., et al. (1996) Encephalopathy Associated with Hashimoto Thyroiditis: Diagnosis and Treatment. *Journal of Neurology*, **243**, 585-593. <https://doi.org/10.1007/BF00900946>
- [106] Peschen-Rosin, R., Schabet, M. and Dichgans, J. (1999) Manifestation of Hashimoto's Encephalopathy Years before Onset of Thyroid Disease. *European Neurology*, **41**, 79-84. <https://doi.org/10.1159/000088007>
- [107] Seipelt, M., Zerr, I., Nau, R., et al. (1999) Hashimoto's Encephalitis as a Differential Diagnosis of Creutzfeldt-Jakob Disease. *Journal of Neurology, Neurosurgery, & Psychiatry*, **66**, 172-176. <https://doi.org/10.1136/jnnp.66.2.172>
- [108] Vasconcellos, E., Pina-Garza, J.E., Fakhoury, T., et al. (1999) Pediatric Manifestations of Hashimoto's Encephalopathy. *Pediatric Neurology*, **20**, 394-398.
- [109] Selim, M. and Drachman, D.A. (2001) Ataxia Associated with Hashimoto's Disease: Progressive Non-Familial Adult Onset Cerebellar Degeneration with Autoimmune Thyroiditis. *Journal of Neurology, Neurosurgery, & Psychiatry*, **71**, 81-87. <https://doi.org/10.1136/jnnp.71.1.81>
- [110] Vrancken, A.F., Braun, K.P., de Valk, H.W., et al. (2000) Epilepsy, Disturbances of Behavior and Consciousness in the Presence of Normal Thyroxine Levels: Still, Consider the Thyroid Gland. *Nederlands Tijdschrift voor Geneeskunde*, **144**, 5-8.
- [111] Sawka, A., Fatourechi, V., Boeve, B., et al. (2002) Rarity of Encephalopathy Associated with Autoimmune Thyroiditis: A Case Series from Mayo Clinic from 1950 to 1996. *Thyroid*, **12**, 393-398. <https://doi.org/10.1089/105072502760043477>
- [112] Bai, Y. (1990) Neuropathy and Myopathy in Patients with Chronic Lymphocytic Thyroiditis. *Acta Academiae Medicinae Sinicae*, **12**, 296-299.
- [113] Nemeroff, C.B., Simon, J.S., Haggerty, J.J., et al. (1985) Antithyroid Antibodies in Depressed Patients. *The American Journal of Psychiatry*, **142**, 840-843. <https://doi.org/10.1176/ajp.142.7.840>
- [114] Haggerty, J.J., Silva, S.G., Marquardt, M., et al. (1997) Prevalence of Antithyroid Antibodies in Mood Disorders. *Depress Anxiety*, **5**, 91-96.

[https://doi.org/10.1002/\(SICI\)1520-6394\(1997\)5:2<91::AID-DA5>3.0.CO;2-8](https://doi.org/10.1002/(SICI)1520-6394(1997)5:2<91::AID-DA5>3.0.CO;2-8)

- [115] Lopez, O., Rabin, B., Huff, J., Rezek, D., *et al.* (1992) Serum Autoantibodies in Patients with Alzheimer's Disease and Vascular Dementia and in Nondemented Control Subjects. *Stroke*, **23**, 1078-1083. <https://doi.org/10.1161/01.STR.23.8.1078>
- [116] Ochi, H., Horiuchi, I., Araki, N., *et al.* (2002) Proteomic Analysis of Human Brain Identifies α -Enolase as a Novel Autoantigen in Hashimoto's Encephalopathy. *FEBS Letters*, **528**, 197-202.
- [117] Graus, F., Titulaer, M.J., Balu, R., *et al.* (2016) A Clinical Approach to Diagnosis of Autoimmune Encephalitis. *The Lancet Neurology*, **15**, 391-404.
- [118] Yoneda, M., Fujii, A., Ito, A., *et al.* (2007) High Prevalence of Serum Autoantibodies against the Amino Terminal of Alpha-Enolase in Hashimoto's Encephalopathy. *Journal of Neuroimmunology*, **185**, 195-200.
- [119] Caselli, R.J., Scheithauer, B.W., O'Duffy, J.D., *et al.* (1993) Chronic Inflammatory Meningoencephalitis Should Not Be Mistaken for Alzheimer's Disease. *Mayo Clinic Proceedings*, **68**, 846-853.
- [120] Caselli, R.J., Boeve, B.F., Scheithauer, B.W., *et al.* (1999) Nonvasculitic Autoimmune Inflammatory Meningoencephalitis (NAIM): A Reversible Form of Encephalopathy. *Neurology*, **53**, 1579-1581. <https://doi.org/10.1212/WNL.53.7.1579>
- [121] Schiess, N. and Pardo, C.A. (2008) Hashimoto's Encephalopathy. *Annals of the New York Academy of Sciences*, **1142**, 254-265. <https://doi.org/10.1196/annals.1444.018>
- [122] Servettaz, A., Guilpain, P., Tamas, N., *et al.* (2008) Natural Anti-Endothelial Cell Antibodies. *Autoimmunity Reviews*, **7**, 426-430.
- [123] Inoue, K., Kitamura, J., Yoneda, M., *et al.* (2012) Hashimoto's Encephalopathy Presenting with Micrographia as a Typical Feature of Parkinsonism. *Neurological Sciences*, **33**, 395-397. <https://doi.org/10.1007/s10072-011-0750-x>
- [124] Li, M., Li, J., Li, Y., *et al.* (2017) Serum Levels of Anti- α -Enolase Activity in Untreated Systemic Lupus Erythematosus Patients Correlates with 24-Hour Protein and D-Dimer. *Lupus*.
- [125] Pancholi, V. (2001) Multifunctional Alpha-Enolase: Its Role in Diseases. *Cellular and Molecular Life Sciences*, **58**, 902-920. <https://doi.org/10.1007/PL00000910>



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