

Current knowledge on Hashimoto's encephalopathy: a literature review

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Abstract

Hashimoto's encephalopathy is a rare disease, with a reported prevalence of 2.1 per 100 000. Clinical manifestations include confusion, decreased state of consciousness, cognitive deficit, seizures, myoclonus, ataxia, and focal neurological deficits. Due to the wide variety of signs and symptoms, clinical diagnostic suspicion is essential. Diagnosis is based on three pillars: the presence of neurological clinical manifestations after ruling out other causes of encephalopathy. 2) Presence of increased antithyroid antibodies. 3) Significant clinical improvement after the administration of immunomodulation. The treatment of Hashimoto's encephalopathy pursues two objectives: to control the autoimmune process and to control the complications of the disease. Although in most cases recovery is complete with treatment, the risk of relapse can range from 12.5 to 40% in follow-ups to 2 years.

Key ideas

- Hashimoto's encephalopathy is a rare disease, described only in case reports.
- After a systematic search in different databases, we summarize the published cases in this article.
- We suggest a classification scheme based on the time of presentation of the main clinical manifestations of this disease.

Introduction

Hashimoto's encephalopathy is a disease that was originally reported by Brain *et al.* in 1966¹, who reported a possible autoimmune mechanism of action². It is a rare disease characterized by the presentation of encephalopathy with diverse neuropsychiatric manifestations, and positive antithyroid titers³. It should be considered as a differential

diagnosis in patients without history of neurological disease⁴ and after ruling out other causes such as infection⁵. In most cases, thyroid function tests are normal, and corticosteroids elicit a rapid remission of the clinical manifestations⁶.

Due to its unusual presentation, it is important to be aware of the clinical characteristics associated with this pathology for a timely and

precise diagnosis and treatment, because if left untreated, this condition may be potentially fatal.

The objective of this review is to provide a glimpse of the current knowledge on the pathophysiology, diagnosis, and management for the specialist.

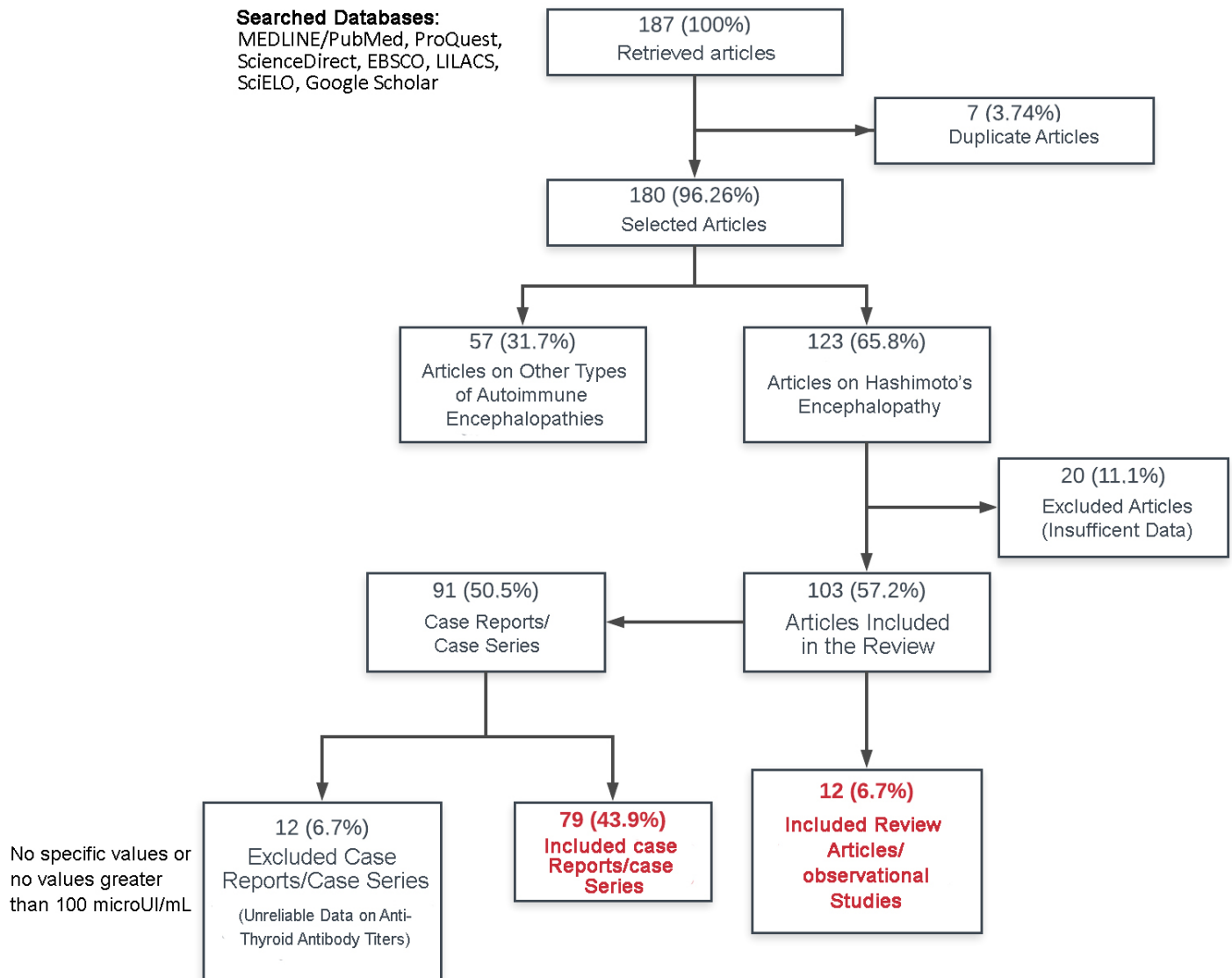
Methods

This article is based on the systematic review of various databases and a critical analysis of the literature. Due to the rarity of this condition, the available evidence is mainly based on observational studies; therefore, the articles included in our review are mostly case series and case reports, as well as narrative reviews.

Inclusion criteria

In a first instance, all the retrieved publications in Spanish and English in the last five years were included, and any relevant references published before the search timeframe that were important for the discussion were also included. Cases described only as abstracts at meetings and/or letters to the editor were excluded because of conciseness. In a second instance, each case report or case series was evaluated individually and those where specific values of antithyroid antibodies were not considered (phrases such as "high antibodies" or "antibodies outside the normal range") or where the reported value of the antibody titers was not high enough to be considered diagnostic (that is, at least one antithyroid antibody titer that exceeded the minimum cutoff point of 100 $\mu\text{UI/mL}$) were excluded (see Figure 1).

Figure 1. Literature search flowchart.



Search strategy

Publications available in main databases such as MEDLINE/PUBMED, ScienceDirect, ProQuest, EBSCO, LILACS, SciELO, and other search engines such as Google Scholar were evaluated. The key terms, “*Hashimoto’s encephalopathy*”, “*steroid-responsive encephalopathy associated with autoimmune thyroiditis*” and “*Hashimoto’s encephalitis*” were searched in English and Spanish within title and abstract domains, using Boolean operators “AND” and “OR”. This process was carried out independently by both investigators.

Results

Prevalence

Hashimoto’s encephalopathy is a rare disease. With a reported prevalence of 2.1 cases/100,000 population, it predominantly affects adults starting at 50 years old, and females (female-to-male ratio of 5:1)⁷ In children, there are reports of presentation starting from 14 months of age⁸, although it most frequently affects adolescents⁹ with a peak at 14 years old.

Causes

Hashimoto’s encephalopathy has a presumable autoimmune etiology. Its clinical presentation, as well as its predominance in females and its coexistence with other autoimmune diseases such as systemic lupus erythematosus, myasthenia gravis, and other collagen disorders in up to 30% of the cases¹⁰ place this pathology within the group of immunologic diseases.

Due to its autoimmune nature, recently some authors have renamed it “encephalopathy associated with autoimmune thyroiditis”¹¹. This name hints better at its etiology and gives us the option to associate it to the whole range of antibodies found in thyroid autoimmune conditions, not just those closely related to Hashimoto’s thyroiditis (antibodies against thyroid peroxidase, TPO). The decision to retain the traditional name of Hashimoto’s encephalopathy in this review is intended to facilitate the bibliographic search.

Regarding the pathophysiology, there are currently two possible explanations. The first, the most accepted, states that anti-thyroglobulin (anti-Tg), anti-thyroid peroxidase (anti-TPO), or anti-TSH receptor (anti-TSHR, also known as thyrotropin receptor antibodies, TRAb) antibodies would trigger the pathophysiological cascade in this disease. There is supporting evidence that anti-TPO antibodies bind to astrocytes and alter central nervous system function³.

The second explanation refers to other antibodies directed against autoantigens of the cerebral vascular endothelium causing damage to neuronal tissues¹². High titers of anti- α -enolase –a 34-kDa cytosolic protein of the erythrocyte glycolytic pathway¹³ common for thyroid and cerebral tissue⁵– were found in patients with Hashimoto’s encephalopathy who had excellent responses to corticoids¹⁴. These antibodies would attack only the terminal *N*-amino end of the α -enolase¹⁵ and could be used as a confirmatory diagnostic test¹⁶.

Other antibodies currently under investigation are IgG antibodies against dimethylargininase I (a 36-kDa protein present in neuronal

and endothelial cells) and aldehyde reductase I (present in vascular and neuronal cells)^{11,17}. Less clearly, antibodies against parietal cells or intrinsic factor have also been implicated¹⁸. The elucidation of the pathophysiology is far from complete.

The literature proposes two forms of presentation. The first is a recurrent vasculitic form with cerebral edema and a reduced cerebral blood flow due to microvascular damage in an insidious manner, presenting with cognitive decline and stroke-like features. A second progressive form is expressed as an encephalopathy (confusion, psychosis, coma), where antithyroid antibodies would cross the blood-brain barrier producing brain injury¹⁹.

Clinical manifestations

Although classic Hashimoto’s encephalopathy has been described as a neuropsychiatric syndrome that causes unresponsiveness in varying degrees of severity, causing even coma²⁰, its spectrum of neurological manifestations is quite broad and may predate established encephalopathy by days to months. Therefore, it is possible to distinguish 2 distinct stages:

Pre-encephalopathy: Neurological manifestations in this stage are diverse and can simulate almost any central nervous system pathology. In a case series of 13 patients, the most frequently observed manifestations were cognitive impairment and behavioral changes in 10 patients (predominantly with frontal and temporal involvement in neuropsychological evaluation), seizures in 6, sleep disorders in 9 (hypersomnia in 6 and hyposomnia in 3), and headache in 4 patients⁴. It has also been associated with sudden-onset narcolepsy with cataplexy²¹. There are much more complex reported cases where the predominant neurological alterations are psychiatric features such as catatonia²², auditory hallucinations, psychosis²³, persecutory delusions, and mood disorders, sometimes misdiagnosed as senile dementia²⁴ or masked by depression in elderly subjects²⁵. Not all patients present this stage.

Encephalopathy: Sudden or progressive unresponsiveness that can be isolated or preceded by a pre-encephalopathic stage. In both cases, the key for the diagnosis is the presence of elevated antithyroid antibody titers and a rapid clinical improvement after starting immunomodulating therapy²⁶.

Additionally, for didactic purposes, we can also classify Hashimoto’s encephalopathy according to the central nervous system manifestation that predominates in the patient, whether in the pre-encephalopathic or the encephalopathic stage (see Table 1).

Autonomic disturbances such as hypotension, bradycardia, and hypothermia are related to hypothalamic and neurovegetative ganglion involvement² and, in these cases, it is important to rule out involvement of the hypothalamic–pituitary–adrenal axis. Cerebellar involvement associated or not with encephalopathy may be manifested as hypotonia, opsoclonus, dysmetria, and dysdiadochokinesia¹. In both cases, the form of presentation is a manifestation of a generalized cerebral vasculitis.

The duration of the clinical manifestations is variable. Durations between two days up to 8 months have been reported¹⁸, depending on

the time of initiation of treatment, although the most frequent presentation is a sudden onset with a rapid clinical improvement after the onset of corticosteroid therapy.

The presence of thyroid function abnormalities can lead to confusion at the time of diagnosis. Uncompensated hypothyroidism may present neurological complications such as seizures, dementia, or psychosis, but it differs from Hashimoto's encephalopathy in that the neurological manifestations improve after thyroxine replacement. Less frequently, it is associated with hyperthyroidism²⁷, which requires ruling out thyrotoxic psychosis. In any case, clinical suspicion leads to the diagnosis.

Some metabolic disorders such as hyponatremia, hyperglycemia, or uremia may coexist with the presentation of encephalopathy²⁸, which makes a correct diagnosis more difficult to achieve. In any case, unsuccessful management of the specific metabolic disturbances may lead to the differential diagnosis.

Diagnosis

The diagnosis of Hashimoto's encephalopathy is an exclusion diagnosis; it is necessary to first rule out all possible pathologies afflicting the central nervous system (tumoral, infectious, autoimmune, etc.), as well as metabolic pathologies and paraneoplastic syndromes.

Although there are no globally accepted diagnostic criteria for Hashimoto's encephalopathy yet, its diagnosis is based on the presence of central nervous system clinical manifestations such as: confusion, decreased level of consciousness, cognitive decline, seizures, myoclonus, ataxia and/or focal neurological deficits²⁹, with exclusion of other possible causes of encephalopathy⁹.

In addition, it is essential to have evidence of significantly elevated titers for at least one antithyroid antibody. The literature indicates that anti-TPO titers would have to be greater than 200 μ UI/ml (more than 5 times the normal value) and some authors set a cut-off point of 500 μ UI/ml as threshold¹⁷. Despite this, there are many published cases that do not follow this standard and make a diagnosis with much lower values (see Table 1), which casts doubt on the diagnosis. Given that a positivity to anti-thyroid antibodies is very prevalent in the healthy population and that the symptoms are diverse, the diagnosis of Hashimoto's encephalopathy becomes difficult³⁰ and this is where questions arise: Is this disease a real condition? Are we just seeing the manifestations of a purely cerebral autoimmune pathology that we still don't know about?

We suggest using a cutoff value ≥ 100 μ UI/mL of any antithyroid antibody to substantiate the diagnostic suspicion, but a higher cutoff value (≥ 200 μ UI/ml) in at least one of the 3 types of antithyroid antibodies (anti thyroid peroxidase, anti-thyroglobulin and/or anti-TSH receptor) would make the diagnosis more evident. In any case, after ruling out other central nervous system pathologies, the diagnosis would be confirmed with a marked clinical improvement after corticotherapy.

Anti-thyroid antibodies are necessary but not sufficient for the diagnosis, and their titers are not directly correlated with the severity of the disease^{84,85}. Additionally, when the thyroid function is studied,

it is found that most patients are euthyroid at the time of presentation of encephalopathy.

Cerebrospinal fluid analysis may show an inflammatory pattern with elevation of the protein level, whose values usually improve after treatment⁸⁴, although up to 80% of patients have normal characteristics¹⁹. Antithyroid antibodies may occasionally be isolated and their titers may be persistently elevated even after the patient's recovery³³. It is important to notice that it is possible to find antithyroid antibodies in cerebrospinal fluid in patients with several thyroid diseases or other central nervous system pathologies such as neurosyphilis⁸⁶, without having evidence of Hashimoto's encephalopathy at the time of testing.

The electroencephalogram usually renders nonspecific findings that may vary according to the specific neurological manifestations seen in patients. The most frequently observed abnormality was the presence of slow wave activity associated to encephalopathy⁸² and in cases of seizures, epileptogenic foci could be observed.

Brain imaging study findings (computed tomography and/or magnetic resonance imaging) are in most of the cases normal or nonspecific, but these are crucial to rule out other etiologies. Between 49% and 50% of patients may present diffuse cerebral atrophy in cortical or subcortical locations¹⁹, infarcts, and/or cortical focal abnormalities⁸⁷. In 2 of the cases, abnormalities similar to lesions in the region of the sella turcica were reported.

Treatment

The treatment of Hashimoto's encephalopathy has two objectives: the first, to halt the autoimmune process with the use of immunomodulators or plasma exchange, and the second, to control the complications of the disease with therapies such as antiepileptic drugs in case of seizures or mannitol in case of cerebral edema³⁸.

The first line of immunomodulating therapy are corticosteroids. Initial administration of intravenous methylprednisolone should be given for 3 to 7 days (adults: 1 g/day, children: 20–30 mg/kg/day)³³, followed by high doses of oral prednisone (doses of 1–2 mg/kg/day), which should be tapered down slowly according to clinical improvement^{29,88}. Maintenance doses can be administered for months up to 1-2 years¹⁵.

Other immunomodulators include intravenous immunoglobulin, monoclonal antibodies, azathioprine, and methotrexate. Intravenous immunoglobulin is useful when patients have an incomplete response to corticosteroids⁹ or when relapses occur during tapering down. In the case of monoclonal antibodies, the suggested dose of rituximab is 1,000 mg intravenously on days 1 and 14, and then once every 6 to 9 months depending on the white blood cell count⁸⁹. Rituximab is well tolerated and induces a sustained remission without the need for additional corticosteroids⁹⁰.

Plasmapheresis was thought to work by removing circulating antithyroid antibodies, but as it has been shown that the severity of the disease is not related to the antibody titers, it is now thought that plasmapheresis may induce clinical improvement by removing other

antibodies, autoimmune complexes, cytokines, and/or other inflammatory mediators currently unknown⁶². The number of plasma exchange courses may vary from 3 to 10³⁶.

Prognosis

Most patients improve completely after the onset of corticotherapy, but the risk of relapse may be as high as 12.5%-40% in a two-year follow-up²⁹, and 12.5% of patients do not respond to corticosteroids and will require immunosuppressors⁸⁴. Frequency of presentation of neurological sequelae in adults has not been reported, but persistent neurological deficits were identified in more than 20% of children after a four-year follow-up⁹¹.

Conclusion

The reviewed cases suggest that this disease is probably underdiagnosed, so it is reasonable to recommend that every patient with an inexplicable encephalopathy, especially women, is ruled out for Hashimoto's encephalopathy. For this reason, it is necessary to request anti-thyroid antibodies.

Positivity for antithyroid antibodies, an electroencephalogram with slow waves and/or focal epileptiform activity that suggests the presence of epileptogenic foci, a brain cerebral magnetic resonance with normal findings or findings of vasculitis or diffuse ischemic lesions, and a clinical improvement after immunotherapy (corticosteroids, IVIG, or plasmapheresis) are helpful hints to make the diagnosis.

Notes

Author Contributions

IP: Concept and design, research, methodology, project management, monitoring, visualization, drafting of the manuscript, reviewing, and editing.

JP: Concept and design, research, methodology, monitoring, visualization, drafting of the manuscript, reviewing, and editing.

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Conflict of Interest

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Table 1. Clinical features, laboratory values, images, and treatment of published cases and case series classified according to predominant form of presentation

Form of presentation	n	Gender n(%)	Age (years) Mean (min–max)	Antibody titers		Thyroid function at diagnosis n(%)	CSF Characteristics	EEG ⁺	Imaging studies [#] (CT, MRI)	Treatment
				Serum (μUI/mL) Mean (min–max)	CSF* Anti-TPO (+)					
Focal neurological manifestations 2,7,10,12,15,20,27,31-59 (partial or generalized seizures, stroke)	46	Females: 32 (69%) Males: 14 (31%)	33.39 (8-89)	Anti-TPO 1148.13 (14.5-10640) Anti-Tg: 780,13 (8-2821)	3 cases	Euthyroid: 21 (46%) Hypothyroidism: 14 (31.1%) Hyperthyroidism: 5 (11.1%) Subclinical presentation: 5 (11.1%)	Normal: 21 (51.2%) Elevated cell count: 4 (9.8%) Elevated protein: 15 (36.6%) Elevated glucose: 1 (2.4%)	Abnormal: 35 (85.4%)	Abnormal: 23 (50%)	Corticosteroids only: 33 (77.3%) Plasmapheresis and/or intravenous immunoglobulins (IVIg): 11 (24.4%) Leviracetam: 1 (2.2%) Complete recovery: 41 (91.1%) Partial recovery: 1 (2.2%) Death: 3 (6.7%)
Cognitive decline 16,24,29,46,60-63 (executive function, planning, learning, speech)	9	Females: 8 (88.9%) Males: 1 (11.1%)	50.67 (13–82)	Anti-TPO 2269.6 (21-10000) Anti-Tg: 539.12 (21.5–1205)	1 case	Euthyroid: 6 (66.7%) Hypothyroidism: 1 (11.1%) Hyperthyroidism: 1 (11.1%) Subclinical presentation: 1 (11.1%)	Normal: 4 (44.4%) Elevated cell count: 2 (22.2%) Elevated protein: 3 (33.3%)	Abnormal: 4 (44.4%)	Abnormal: 2 (22.2%)	Corticosteroids only: 7 (77.8%) Plasmapheresis and/or IVIg: 2 (22.4%) Complete recovery: 8 (88.9%) Partial recovery: 1 (11.1%) Death: 0
Memory impairment 64,65 (retrograde, anterograde)	2	Females: 2 (100%)	55 (52–58)	Anti-TPO 1279 (1258-1300) Anti-Tg: 1101.85 (154–2049.7)	NR	Euthyroid: 1 (50%) Subclinical presentation: 1 (50%)	NR	Abnormal: 2 (100%)	Abnormal: 2 (100%)	Corticosteroids only: 2 (100%) Complete recovery: 2 (100%)
Basal ganglia dysfunction 12,66-69 (involuntary movements)	5	Females: 3 (60%) Males: 2 (40%)	37 (8-78)	Anti-TPO 1227.5 (1087 – 1300) Anti-Tg :	NR	Euthyroid: 1 Subclinical presentation: 1 NR: 3	Normal: 4 (80%) Elevated protein: 1 (20%)	Abnormal: 4 (80%)	Abnormal: 5 (100%)	Corticosteroids only: 5 (100%) Complete recovery: 4 (80%) Partial recovery: 1 (20%) Death: 0

				22.24 (0–37.73)						
Psychiatric disorders <small>3,38,63,70-79</small> (visual and/or auditory hallucinations, psychosis, repetitive thoughts, etc.)	16	Females: 15 (93.8%) Males: 1 (6.3%)	38.87 (10-84)	Anti-TPO 1042.1 (132-3000) Anti-Tg : 696.12 (5.9-2500)	3 cases	Euthyroid: 5 (33.3%) Hypothyroidism: 8 (53.3%) Hyperthyroidism: 1 (6.7%) Subclinical presentation: 1 (6.7%)	Normal: 7 (53.9%) Elevated cell count: 2 (15.4%) Elevated protein: 4 (30.8%)	Abnormal: 6(42.9%)	Abnormal: 8 (50%)	Corticosteroids only: 14 (87.5%) Plasmapheresis and/or IVIG: 2 (12.5%)
										Complete recovery: 14 (87.5%) Partial recovery: 2 (12.5%) Death: 0
Peripheral nervous disease ^{80,81}	2	Females: 1 (50%) Males: 1 (50%)	31.5 (13–50)	Anti-TPO 1131 (886-1376) Anti-Tg : 1176.5 (232-2121)	NR	Euthyroid: 2 (100%)	Elevated protein: 2 (100%)	Alterado: 1(50%)	Abnormal: 1 (50%)	Corticosteroids only: 2 (100%) Complete recovery: 2 (100%)
Cerebellar dysfunction <small>1,82,83</small> (ataxia, unstable gait, nystagmus, etc.)	3	Females: 3 (100%)	55 (47–72)	Anti-TPO 1317 (1300-7651) Anti-Tg: 119 (1 case)	NR	Euthyroid: 3 (100%)	Elevated protein: 2 (100%) NR: 1	Alterado: 2(100%) NR:1	Abnormal: 2 (100%) NR: 1	Corticosteroids only: 3 (100%)
										Complete recovery: 2 (66.3%) Partial recovery: 1 (33.7%) Death: 0

Source: prepared by the authors based on the literature review.

Cases are classified according to the predominant form of presentation.

* Other cases do not specify whether the CSF test was taken or not.

+ Slow waves, epileptogenic foci.

The most common alterations were areas of hyperintensity, and findings similar to vasculitis or stroke; in only 2 cases, a slight increase in hypophyseal volume was reported.

EEG: electroencephalography.

NR: Not reported.

MRI: Magnetic resonance imaging.

CT: multi-slice computed tomography.

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