

# The Role of Cerebrospinal Fluid Thyroid Autoantibodies in the Diagnosis of Hashimoto's Encephalopathy: Case Report and Review of the Literature

## Hashimoto Ensefalopatisinde Beyin Omurilik Sıvısında Tiroid Antikorlarının Rolü: Olgu Sunumu ve Literatür Derlemesi

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**ABSTRACT** Hashimoto's encephalopathy (HE) is a rare disorder characterized by cognitive and behavioral changes, seizures, myoclonus, tremor and stroke like episodes. Although spontaneous remission is possible, fatal cases have been reported. Diagnosis is based on neurological symptoms and signs together with the exclusion of central nervous system infections and high serum thyroid autoantibodies. Although it is common in hypothyroidism, euthyroid and hyperthyroid patients have also been reported. We reported a case of relapsing encephalopathy with no serum thyroid autoantibodies but with high titers of cerebrospinal fluid (CSF) thyroid autoantibodies; the patient responded well to steroid treatment. This is the first reported case with negative serum and high CSF thyroid autoantibodies. We reported this case to discuss the value of CSF thyroid autoantibodies in HE.

**Key Words:** Hashimoto disease; anti-thyroglobulin

**ÖZET** Hashimoto ensefalopatisi (HA), bilişsel ve davranışsal değişiklikler, epileptik nöbetler, miyoklonus, tremor, inme benzeri ataklarla karakterize nadir görülen bir hastalıktır. Spontan remisyon olabildiği gibi, ölümcül vakalar da bildirilmiştir. Tanı, nörolojik belirti ve bulgular ile birlikte santral sinir sistemi enfeksiyonu olmadığının gösterilmesi ve serumda antitiroid antikorlarının yüksek olması ile konur. Sıklıkla hipotirodi ile birlikte görülmesine rağmen, ötiroid ve hipertiroid hastalar da bildirilmektedir. Tekrarlayıcı, steroide yanıtı ensefalopatisi bulunan, serumda tiroid antikorları bulunmamasına rağmen, beyin omurilik sıvısı (BOS)'nda tiroid antikorları titresi yüksek olan ve steroid tedavisine iyi yanıt veren bir olgu sunulmuştur. Bu, serum tiroid antikorları negatif, ancak BOS'ta tiroid antikorları titresi yüksek olduğu bildirilen ilk olgudur. Bu olguyu sunmamızın sebebi, HA'da BOS'taki tiroid antikorlarının değerini tartışmaktır.

**Anahtar Kelimeler:** Hashimoto hastalığı; anti-tiroglobülin

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**T**oxic and metabolic encephalopathies are due to heart and circulatory, respiratory, renal and hepatic and endocrine system disorders that affect brain functions.<sup>1</sup> HE is characterized by cognitive and behavioral changes, seizures, myoclonus, tremor and stroke-like episodes. In addition to these non-specific neurological symptoms, exclusion of a central nervous system infection and high serum antithyroid antibodies are required to establish the diagnosis. This is the first report of HE, in which thyroid antibodies were negative in the serum, but high in the CSF examination. Therefore, we believe that CSF should be studied in addition to serum thyroid antibodies in cases where HE is strongly suspected.

## CASE REPORT

A 68-year-old male patient was admitted to the hospital with a 1-week history of confusion, memory loss, twitching in the arms and legs, and unsteady gait. He was diagnosed with hyperthyroidism 1 week ago and treatment was initiated with propylthiouracil 100 mg once daily. On neurological examination, he was apathetic and had time and space disorientation; he had dysarthric speech, myoclonus in all limbs in addition to pyramidal and cerebellar findings. In the course of the differential diagnosis of encephalopathy, his routine biochemical screening was normal. The free thyroxine (FT4) was 1.86 ng/dL (normal range 0.9-1.7 ng/dL), and the thyroid stimulating hormone (TSH) level was low at 0.070  $\mu$ U/l (normal range 0.27-4.2  $\mu$ U/l). The electroencephalogram (EEG) displayed diffuse slowing with rare triphasic potentials (Figure 1a). Cranial magnetic resonance imaging (MRI) displayed cerebral atrophy. On the CSF examination the total protein was elevated (158 mg/dL) with normal biochemistry and cytology. With a preliminary diagnosis of HE, the thyroid antibodies (antithyroid peroxidase; TPOAB and antithyroglobulin antibodies; TGAB) in the serum were studied and all were negative. Therefore, he was diagnosed with possible Creutzfeldt-Jacob's Disease and risperidone was added to the treatment regimen. On the follow-up visit at 6 months, there was an unexpected cognitive improvement, but his gait ataxia persisted and he was only able to walk with assistance.

One year after his first symptoms, the patient was admitted again with confusion and increased gait ataxia. Neurological examination displayed apathy, pyramidal symptoms and diffuse myoclonus. He was bound to a wheelchair. His minimal status exam (MMSE) was 21/30. The serum routine biochemical screening and free triiodothyronine (2.55 pg/mL, normal range 0.93-1.7 pg/mL) free thyroxine (1.58 ng/dL) and TSH (0.400  $\mu$ U/l) levels were normal. The thyroid antibodies were also normal with the TGAB level less than 10 IU/mL (normal <115 IU/mL) and the TPOAB level 12.18 IU/mL (normal <115 IU/mL). The cranial MRI was repeated revealing only mild cerebral atrophy (Fi-

gure 2a). Cranial MR angiography (MRA) was normal (Figure 2b). Because of the relapsing-remitting nature of the encephalopathy and a strong suspicion of HE, this time the CSF examination included thyroid antibody studies, which displayed a high anti-TG level of 13.02 IU/mL and increased level of protein (115.8 mg/dL). Laboratory tests for human immunodeficiency virus, Venereal Disease Research Laboratory, and herpes simplex virus were repeated, all revealing negative results. Serum angiotensin-converting enzyme and protein electrophoresis were normal. The patient was started on pulse steroid therapy (1g IV methylprednisolone for 3 days) followed by oral treatment. There was a rapid response and the myoclonus, ataxia and confusion disappeared within the first few days. He has been symptom-free for the last 9 months and the last MMSE was 28/30 and his EEG was normal (Figure 1b). The CSF study was not repeated given



FIGURE 1a: The EEG displayed diffuse slowing with rare triphasic potentials.



FIGURE 1b: Normal EEG of the patient after treatment.

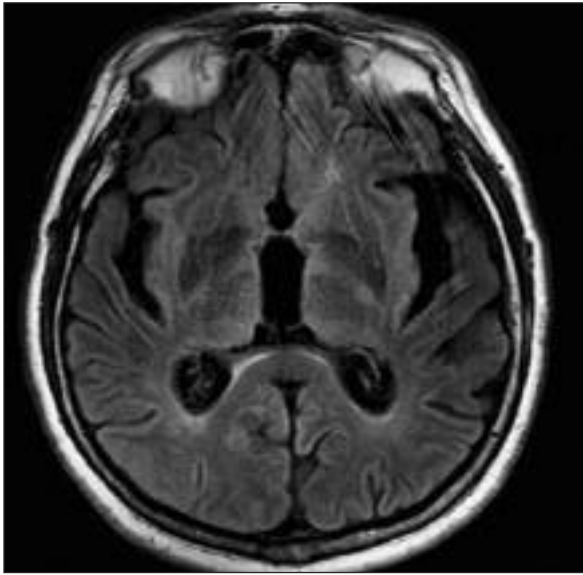


FIGURE 2a: Cranial MRI displayed cerebral atrophy.



FIGURE 2b: Normal Cranial MRA.

the fact that he was symptom-free for 9 months. The patient gave informed consent for the publication of this report.

## DISCUSSION

HE was first described by Brain et al in 1966.<sup>2</sup> It is an acute or subacute encephalopathy with cognitive and behavioral changes, confusion, tremor, seizures, ataxia, psychosis and stroke-like episodes related to autoimmune thyroiditis. The disease may show a progressive or a relapsing-remitting course.<sup>3</sup> In patients with myoclonus, seizures, focal neurological deficits or psychiatric symptoms of unidentified origin, diagnosis requires the presence of an abnormal EEG, high CSF protein levels, high serum antithyroid antibodies, steroid responsiveness, and non-specific MRI findings.<sup>4,5</sup> There is usually no relation to thyroid function tests.<sup>6</sup>

Because of the role of antithyroid antibodies in the etiopathogenesis and the fact that this entity can develop in the setting of hypo, hyper or euthyroidism, the disorder was suggested to be designated encephalopathy associated with autoimmune thyroid disease (EAATD) or corticosteroid-responsive encephalopathy associated with autoimmune thyroiditis instead of HE.<sup>7,8</sup> Tamagno et al proposed some criteria for the diagnosis of defined, probable, and possible EAATD (Table 1).<sup>9</sup>

All patients previously described had high serum antithyroid antibodies and cases with CSF analysis of antibodies are rare. A few cases with both high serum and CSF antibodies were reported.<sup>10-15</sup> Seipelt described 7 HE patients who had no CSF thyroid antibodies.<sup>16</sup> On the other hand, Ferraci et al found high CSF anti-thyroid antibodies in six patients with HE, but negative results in 21 controls. The patients had high serum levels of antibodies, but the TGAB-TPOA index was suggestive of intrathecal synthesis of these autoantibodies.<sup>10</sup> In their following paper, they suggested that CSF anti-thyroid antibodies were a reliable marker to distinguish HE from other encephalopathies of unknown origin.<sup>17</sup>

Spiegel studied CSF thyroid autoantibodies in two patients with HE and high serum thyroid autoantibodies, in four patients with multiple sclerosis, and in four patients with idiopathic facial nerve palsy. One HE patient and two controls (with idiopathic facial nerve palsy) showed high CSF antibody levels.<sup>14</sup>

High serum antithyroid antibodies were found in 70-95% of patients with Hashimoto's thyroiditis, regardless of neurological symptomatology.<sup>18</sup> The role of autoantibodies in HE is not clear.<sup>6-19</sup> Some reports describe a decrease in antibodies following

**TABLE 1:** Clinical criteria proposed for the diagnosis of defined, probable or possible encephalopathy associated with autoimmune thyroid disease. Tamagno G et al.<sup>9</sup>

Necessary criteria	Other criteria
1. Acute or subacute onset of neurologic/psychiatric symptoms in absence of other possible causes	1. Elevated antithyroid autoantibody levels in serum and/or cerebrospinal fluid
2. Exclusion of other known causes of encephalopathy (i.e., bacterial, viral or fungal infections, metabolic encephalopathy, Creutzfeldt-Jacob's disease, etc.)	2. Increased protein concentration in cerebrospinal fluid without pleocytosis
3. Association with clinical or subclinical autoimmune thyroid disease	3. Unspecific electroencephalographic abnormalities
4. Serum thyroid hormone levels unable to justify the symptoms and persistence (or presentation) of symptoms or concomitant normal thyroid hormones	Defined diagnosis: Necessary criteria plus all the above listed criteria
5. Clinical response to corticosteroids	Probable diagnosis: Necessary criteria plus one of the above listed criteria
	Possible diagnosis: Necessary criteria but none of the above listed criteria

steroid treatment, but most studies include only a small number of patients.<sup>20</sup>

Several mechanisms, such as autoimmune cerebral vasculitis, global cerebral hypoperfusion, cerebral tissue-specific autoimmunity, and thyrotropin-releasing hormone related neuronal deficit, have been suggested for HE.<sup>9,11,17,21-23</sup>

Nolte et al reported autopsy findings of HE with brain stem dominated vasculitic findings.<sup>24</sup> Utku et al reported (with MRA) that the cerebral vasculitic changes improved after corticosteroid and plasmapheresis in autoimmune Grave's disease.<sup>25</sup>

This is the first report of HE with undetected thyroid autoantibodies in the serum, and high levels in CSF. In our patient, the history of thyroiditis and the relapsing-remitting course of the encephalopathy were clues to the diagnosis. The normal level of serum antibodies delayed our diagnosis and treatment for 1 year. Following the CSF examination and steroid treatment, the patient was symptom-free. This is only one case, and we believe that further studies are needed to clarify the actual role of CSF antibodies in the pathogenesis of HE. The finding of normal serum antibodies and elevated CSF antibodies either means that there is a more

significant role of intrathecal synthesis than previously believed or that there are still undetected antibodies. Similar to our case, previous reports described that 53% of patients diagnosed with prion diseases were later diagnosed with HE.<sup>20</sup>

A "steroid responsive nonvasculitic autoimmune inflammatory meningoencephalitic syndrome" with progressive cognitive decline, psychosis, unsteady gait and elevated immunoglobulin IgG index was described by Caselli et al in 5 patients.<sup>26</sup>

This syndrome may be related to collagen vascular disorders or Hashimoto's disease and post-mortem findings display chronic inflammatory panencephalitis.<sup>27</sup> Although we do not have any pathological result for our patient, the clinical findings of myoclonus, tremor, ataxia and encephalopathy together with the electrophysiological and laboratory findings are all suitable with HE or EA-ATD.

In conclusion, since HE is a treatable encephalopathy, CSF levels should be studied regardless of negative serum antibodies in patients with a high suspicion of HE.

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