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Case Report / Olgu Sunumu

Manifestation of Hashimoto's Encephalopathy with Psychotic Signs: a Case Presentation

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ABSTRACT

Manifestation of Hashimoto's encephalopathy with psychotic signs: a case presentation

Hashimoto's encephalopathy (HE) is a rare autoimmune disease with unclear pathophysiology, developing on the basis of Hashimoto's thyroiditis (HT), associated with antithyroid antibodies, that presents with autoimmune, neuroendocrine, and neuropsychiatric findings. The disease is characterized by generalized or focal slowing in the EEG, elevated antithyroid antibody titration in the serum, elevated cerebrospinal fluid protein level, and the presence of antithyroid antibodies. HE is known as an autoimmune disorder of the central nervous system. With this feature, it is differentiated from cognitive alterations observed in hypothyroidism or hyperthyroidism. The response to treatment with corticosteroids in line with the autoimmune nature of HE supports this diagnosis. This report shows a case presenting with neuropsychiatric symptoms, elevated antithyroid antibody titration in the serum, and complete response to steroid therapy. A clear indicator for the diagnosis of HE has not yet been found. Therefore, other potential causes need to be considered in the differential diagnosis of this clinical picture until they can be excluded after investigations. With this case report, we want to emphasize that in differential diagnosis of patients presenting with a variety of neuropsychiatric symptoms, Hashimoto's encephalopathy – though being seen quite rarely – should not be disregarded, given the dramatic improvement of patients receiving a correct diagnosis and appropriate treatment.

Keywords: Hashimoto's encephalopathy, neuropsychiatric symptoms, thyroid antibodies

ÖZET

Psikotik bulgularla seyreden Hashimoto ensefalopatisi: Olgu sunumu

Hashimoto ensefalopatisi (HE); hashimoto tiroiditi (HT) zemininde gelişen, patofizyolojisi henüz net olmayan, antitiroid antikor ile ilişkili olan, nadir görülen, otoimmün, nöroendokrin ve nöropsikiyatrik bulgularla seyreden bir hastalıktır. EEG'de yaygın veya fokal yavaşlama, serumda antitiroid antikor yüksekliği ve beyin omurilik sıvısında protein yüksekliği, antitiroid antikor varlığı ile karakterizedir. HE merkezi sinir sisteminin otoimmün bozukluğu olarak bilinir. Bu yönüyle hipotiroidizm veya hipertiroidizmde görülen bilişsel değişikliklerden ayrılır. Otoimmün doğası nedeniyle kortikosteroidlere yanıt alınması tanıyı desteklemektedir. Bu yazıda nöropsikiyatrik belirtilerle başvuran ve serumda tiroid antikor titrasyon yüksekliği saptanan ve steroid tedavisine tam olarak yanıt veren bir olgu sunulmuştur. HE tanısı için henüz net bir belirteç bulunmamaktadır. Bu nedenle ayırıcı tanıda bu klinik tabloyu yapabilecek diğer nedenler düşünülmeli ve tetkikler sonrası dışlanmalıdır. Bu olgu; farklı nöropsikiyatrik belirtilerle başvuran hastaların ayırıcı tanısında, oldukça nadir görülen HE tanısının da unutulmaması gerektiğinin ve doğru tanı konulan ve uygun tedavi gören hastalarda tedaviyle gerçekleşen dramatik düzelmenin vurgulanması amacıyla bildirilmiştir.

Anahtar kelimeler: Hashimoto ensefalopatisi, nöropsikiyatrik belirtiler, tiroid antikoru

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INTRODUCTION

Hashimoto's encephalopathy (HE) is a rare (2.1/100,000) clinical picture related with high antithyroid antibody titer and an autoimmune etiology, showing dramatic improvement with steroid therapy (1). Clinical signs can be acute, such as stroke-like episodes, seizure, and impaired consciousness, or more insidious, like dementia or psychosis. Though generally presenting with anomalies in electroencephalography (EEG) and brain scans, these findings are not disease-specific. While the pathogenesis is not entirely

understood, mechanisms such as autoimmune cerebral vasculitis, antineuronal antibody-mediated reaction, or autoimmune reactions against antigens shared between the thyroid and the central nervous system have been suggested. Single photon emission computed tomography (SPECT) studies have shown a diffuse homogeneous hypoperfusion in the brain and suggested a microcirculation disorder with immune complex or antibody deposition (2). This impairment can lead to global hypoperfusion and cause encephalopathic changes. First defined in 1966, this rare presentation was called HE (3). There are also views suggesting that some autoimmune encephalopathy cases related with Graves' disease can be assessed as "encephalopathy associated to autoimmune thyroid disease" (4). Even though the new definition is still debated, in our case presentation we are using the diagnosis "HE" supported by Brain et al. (5).

Our report describes the case of an 84-year-old HE patient presenting with psychiatric signs and symptoms.

CASE

A female patient aged 84 years, housewife, presented with complaints of hallucinating, forgetting things she learned, and not recognizing her relatives. The patient was hospitalized for medication and written informed consent was obtained during this time.

She had first presented 8 years earlier because of difficulties to remember new information. At the time, after first evaluation, she had been diagnosed with a vitamin B12 deficiency-related neuro-anemic syndrome and hypothyroidism and started on a treatment with levothyroxine sodium and cyanocobalamin. After these treatments, the forgetfulness complaints resolved. Seven months earlier, the patient started to dream frequently and to develop behavioral disorders, being unable to distinguish these dreams from reality. Despite a treatment with quetiapine being initiated, the complaints continued in a fluctuating manner. The week before presenting to our clinic, she had suffered an increase in agitation, insomnia, and auditory and visual hallucinations.

In the neurological examination, she was conscious, her cooperation limited, temporal orientation impaired, place-person orientation moderately preserved, while no signs of lateralization were found.

Regarding her mental state, she showed agitation, early, middle, and late insomnia, and auditory and visual hallucinations; insight and capacity of assessing reality were insufficient.

Cognitive function examination found deficit in attention and executive function, loss of insight, and impairment of social relationships. In the Mini Mental State Exam (MMSE) for educated people, she scored 13/30, at the clock drawing test 6/10.

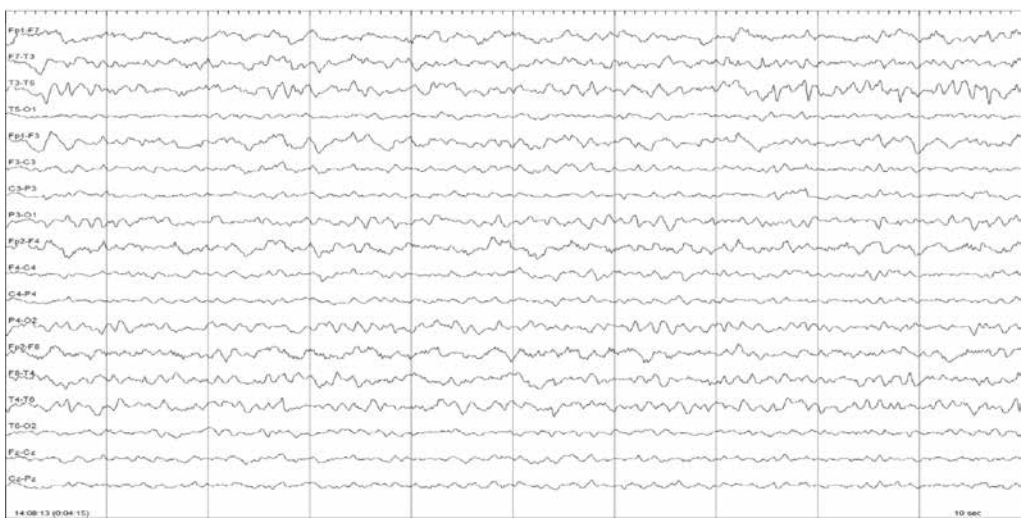

Figure 1: Patient's EEG before therapy

In the medical examination, hemogram, sedimentation, B12 and CRP levels were in the normal range. Vasculitis markers were negative. In the search for malignancy, chest radiography and whole abdomen ultrasonography were normal, tumor markers negative.

In the thyroid function tests, results were for free T3:2.46pg/mL (2.5-3.9), free T4:0.91ng/dL (0.54-1.24), and TSH:5.96µIU/mL (0.34-5.6). A diagnosis of hypothyroidism was made. Thyroid autoantibodies were found to be positive: anti-TPO (antithyroid peroxidase):703.5IU/mL (0.25-9), anti-TG (antithyroglobulin antibody):5.9IU/mL (2.2-4.9).

Thyroid ultrasonography determined signs of thyroiditis. Endocrinologists only recommended to continue the patient's treatment with levothyroxine sodium 50mg 1x1.

In the patient's EEG, the base rhythm was characterized by 5-7Hz theta bands, and the base activity was slowed down, more markedly in the frontal region (Figure 1).

In the brain magnetic resonance imaging (MRI), apart from a moderate atrophy, there were no findings. Evaluation of the magnetic resonance angiography (cranial-cervical MRA) was normal.

All these results suggested a case of Hashimoto's encephalopathy, and the patient was given 1gr/day intravenous methylprednisolone treatment for three days. Following pulse treatment, she was started on 1mg/kg oral prednisolone treatment. After four weeks, the oral prednisolone treatment was gradually reduced and discontinued. As the symptoms partly resolved on the 8th day of treatment, the patient was discharged with thyroid hormone replacement therapy. At control one month later, psychiatric findings and cognition had distinctly improved, the MSSE scored 23/30, the clock drawing test 9/10.

DISCUSSION

HE is a rare syndrome that may accompany the more commonly observed Hashimoto's thyroiditis (HT). HE was first described by Brain et al. (5) in 1966. It is clinically defined as a subacute encephalopathy presenting with tremor, myoclonus, convulsion, and changes in consciousness level (6). Data regarding HE are shown in Table 1.

In hypothyroidism, various psychiatric presentations are seen (7-9), most commonly cognitive

Table 1: Data regarding Hashimoto's encephalopathy

Demographic characteristics		**Clinical findings**	
Prevalence	2.1 / 100,000	Tremor	84%
Age at onset	44 (9-78)	Temporary aphasia	73%
Pediatric onset	22%	Epileptic seizure	66%
Female sex	81%	Status epilepticus	12%
Relapsing-remitting type	60%	Myoclonus	38%
		Hypersomnolence	63%
		Gait ataxia	63%
		Psychosis	36%
		Stroke-like episodes	27%
Thyroid state		**Antithyroid antibodies**	
Goiter	62%	Anti TPO	100%
Subclinical hyperthyroidism	35%	Anti M	95%
Euthyroid	30%	Anti TG	73%
Distinct hypothyroidism	20%		
Hyperthyroidism	7%		
CSF		**Nonspecific increases**	
Increased protein	78%	ANA, ESR, CRP, LFT	16%
> 100 cells	4%		
OCB	27%		

Anti TPO: antithyroid peroxidase, Anti M: antimicrosomal antibody, Anti TG: antithyroglobulin, CSF: cerebrospinal fluid, OCB: oligoclonal band, ANA:antinuclear antibody, ESR: erythrocyte sedimentation rate, CRP: c-reaktive protein, LFT: liver function tests

disorders characterized by mental retardation, attention and short-term memory disorders, and impairment of abstract thinking. Jensovsky et al. (10) reported that thyroid hormone affects the electrophysiological functioning of the brain and can cause impairment in cognitive symptoms. In rare cases, hypothyroidism is accompanied by psychotic symptoms (11). Bokhari et al. (12) reported a case hospitalized with psychotic symptoms in the third month post partum where HT occurred in the form of thyrotoxicosis; when returning to a euthyroid state, the psychotic presentation resolved. The authors indicated that there might be an autoimmune link between the two presentations.

In our case, cognitive function loss was distinctive at presentation. Her attention, executive functions, and social functionality were impaired and she suffered a loss of insight. In the Mini Mental State Exam (MMSE) for educated people, she scored 13/30, at the clock drawing test 6/10. The sudden onset of cognitive function impairment and the short duration of around one week did not suggest dementia. The dramatic improvement of her cognitive functions after therapy also supports the diagnosis of HE.

The prevalence of HE is estimated to be 2.1/100,000 (13). Mean age at onset is 41-44 years. In 20% of the cases, onset is seen below the age of 18 (14). In our case, age at disease onset was 81 years. Though the onset age does not fit the pattern, age is not a determining factor for a diagnosis of HE. We also should not forget that in late-onset psychosis presentations, as in our case, organic factors are seen more frequently.

In HE biochemistry, the levels of TSH and thyroid hormone can be normal, or the condition may come with hypo- or hyperthyroidism (15). Elevated or positive results for thyroid peroxidase antibody (anti-TPO Ab) or antithyroglobulin antibody (TG Ab) serum or CSF levels support the diagnosis and indicate thyroid autoimmunity. However, the role of thyroid autoantibodies in the pathogenesis of HE is not entirely known. There is no evidence that these autoantibodies affect neuronal functions (13). Sensitivity and specificity of CSF antithyroid antibodies are not fully known. A study by Ferraci et al. (16) found that in 13% of the patients, CSF antithyroid antibodies were high, but they could not establish a correlation between CSF antithyroid antibody titers and the clinical stage of the disease. In addition to elevated CSF proteins, OCB (oligoclonal band) and lymphocytic pleocytosis can be seen, while the glucose level is normal. No source of infection is to be found in the CSF that could explain the clinical picture (14,15). While elevated protein in the CSF and diffuse anomalies in the EEG are described as typical (17,18), it is reported that these are not specific (6,15,17,19). A definitive specific biochemical marker for the diagnosis of this disease has not yet been found.

In our case, the positive detection of thyroid autoantibodies in the serum supports the HE diagnosis biochemically. Lumbar puncture had been planned but could not be carried out because the patient did not accept the procedure.

EEG signs in HE may be a nonspecific slowing of the background rhythm, focal sharp and steep waves, triphasic rhythmic activity, frontal intermittent rhythmic activity, and temporary epileptic activities (14). While the EEG findings in our case support HE, they are not specific to this disease.

The MRI is usually normal in HE. With cerebral atrophy and T2-weighted sequences, nonspecific signal anomalies can be seen in the subcortical white matter, and SPECT shows focal, multifocal, or global hypoperfusion especially in the cortical region or in the basal ganglia (20). In our case, the MRI was normal apart from an age-appropriate moderate atrophy.

In the differential diagnosis of HE, conditions to be taken into consideration include autoimmune limbic encephalopathy, seizures, delirium, stroke or temporary ischemic attack, cerebral vasculitis, carcinomatous meningitis, toxic or metabolic encephalopathy, paraneoplastic syndromes, Creutzfeldt-Jakob disease, degenerative dementia, or psychiatric diseases. Given that the autoimmune limbic encephalitis antibodies and vasculitis markers were negative, malignancy examinations were normal, the anamnesis did not indicate exposure to toxic agents or eating disorders, the EEG did not show periodic discharges and movement disorders such as myoclonus were not found, differential diagnosis could exclude

other diseases. At the same time, the HE diagnosis was supported by the fact that our patient had presented with neuropsychiatric findings, serum analysis had found thyroid antibodies, neuroimaging showed nonspecific changes, and corticosteroid therapy resulted in a dramatic response.

Immunosuppressive agents are used in the therapy. Corticosteroids, high-dose intravenous methylprednisolone (1gr/day for 3-5 days) or oral prednisolone (50-150mg/day) are recommended. Early steroid therapy can reduce symptoms without causing aftereffects (17). Clinical improvement begins from the first day, and within one to six weeks, complete recovery is seen. In 90-98% of the cases, a dramatic response to steroid is observed. Treatment response, continuation, and how to discontinue or reduce the dose, are arranged according to the clinical response. A retrospective study showed that 96% of the patients responded to glucocorticoid treatment (21). Boers and Colebatch (22) suggested that in cases not entirely resolved with corticosteroid treatment, additional clinical and serological improvement could be achieved with plasmapheresis. In the therapy, azathioprine, cyclophosphamide, and IV immunoglobulins can also be used (23-25). Once the diagnosis has been confirmed by autoimmune source and good response to corticosteroids, the treatment needs to begin immediately. Prognosis is generally good. However, some cases live with permanent neurological deficits or lose their lives (6). In our case, steroid therapy was started as soon as the diagnosis was assumed. Response began after 8 days, but distinctive improvement was realized after 4 weeks. At the end of one month, treatment was gradually discontinued. The patient's psychiatric signs receded, cognitive function losses distinctively recovered and an MMSE score of 23/30 was reached. Social functionality increased, and she was again able to complete her daily tasks on her own.

HE manifests itself in very different clinical pictures, which makes diagnosing the condition rather difficult, requiring the exclusion of other diseases. Patients are often followed with diagnoses such as stroke, dementia, or psychotic disorder, and not being given the right treatment for a long time, their clinical presentation does not improve. Behavioral changes and psychiatric complaints occurring before the age of 12 or after the age of 40, absence of a previous history of psychiatric disease, acute-onset paranoid psychosis (within the last 3 months), distinctive visual hallucinations, contemporary physical symptoms and abnormal vital signs, psychosis manifesting with a reduction in cognitive function (orientation disorder, memory problems, clouding of consciousness) or with movement disorders (orofacial dyskinesia, catatonia), focal neurological signs, new medications or states of immunosuppression, unexpected side effect of antipsychotics (collapse, dropping blood pressure), and lack of response to treatment have to be on our mind as warning symptoms in these patients. It is our task, especially when patients present with psychiatric complaints, to consider organic foundations and notice these signs, being able to look at the patients from this perspective. When we manage to diagnose the disease from this perspective, we spare patients years of wrong treatment and save them from the side effects of the drugs they are using. In addition, there are good chances for improvement with the right treatment, and their quality of life will improve.

Contribution Categories	**Name of Author**
Follow up of the case	A.K., K.B., S.S., D.S.
Literature review	A.K., K.B., S.S., D.S.
Manuscript writing	A.K., K.B., S.S., D.S.
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