

A Case of Steroid-Responsive Encephalopathy Associated with Autoimmune Thyroiditis (Hashimoto's Encephalopathy)

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ABSTRACT

A case of steroid-responsive encephalopathy associated with autoimmune thyroiditis (Hashimoto's encephalopathy)

Hashimoto's encephalopathy (HE) is a syndrome which represents itself with diverse neuropsychiatric symptoms and high titers of antithyroid antibodies, the syndrome has no specific radiological or EEG findings, and it can be dramatically resolved with corticosteroid treatment. HE can show different clinical findings such as, confusion, stupor, coma, stroke like episodes, epileptic seizures, myoclonus, behavioral changes, hallucinations and delusions. The cause of HE has been proposed to be autoimmune because of its association with other immunologic disorders, female predominance, inflammatory findings in cerebrospinal fluid and response to treatment with steroids. Because the disease has a wide range of symptom scala and has no specific radiological findings and also has no proven pathogenetic mechanism that can explain the occurrence of the disease it is thought that the diagnosis of the syndrome can be delayed or the disease can be misdiagnosed. This knowledge is thought to be crucial as we know that corticosteroid treatment can lead to quick and dramatic response when the syndrome is diagnosed early. In this case report, a patient who applied to our clinic with findings of cognitive and psychotic disturbances and was followed up with the HE diagnosis is presented.

Keywords: Hashimoto's encephalitis, psychosis, thyroiditis



ÖZET

Steroide yanıt veren otoimmün tiroiditle ilgili ensefalopati olgusu (Hashimoto ensefalopatisi)

Hashimoto enfesalopatisi (HE); nöropsikiyatrik semptomlar ve yüksek antitiroid antikor seviyeleri ile karakterize olan, kendine özgü radyolojik ya da EEG bulguları olmayan ve steroid tedavisiyle hızlı bir klinik düzelmeye gözlenen bir bozukluktur. HE; konfüzyon, stupor, koma, inme benzeri tablolar, titreme, epileptik nöbetler, miyoklonus, davranış değişiklikleri, varsanı ve hezeyan gibi pek çok farklı klinik görünümle ortaya çıkabilmektedir. Hastalığın kadınlarda daha sık görülmesi, beyin omurilik sıvısında enflamasyon bulgularına rastlanabilmesi, steroid tedavisine iyi yanıt vermesi ve diğer otoimmüne hastalıklarla birlikte görülebilmesi otoimmünitenin bu bozukluğun gelişiminde üzerinde önemle durulması gereken bir olgu olduğunu düşündürmektedir. HE'nin geniş bir yelpazeyi içeren klinik görünümle kendini gösterebilmesi, spesifik görüntüleme bulgularının olmaması, patogenezinin henüz tam olarak anlaşılmasından dolayı bu sendroma ilişkin tanı koymada gecikilebileceği hatta bazı olgularda bu tanının atlanabileceği, erken tanı konulması halinde ise steroid tedavisiyle hızlı ve dramatik bir iyileşme gözlenebileceği düşünülmektedir. Bu vaka sunumunda kliniğimize kognitif bozukluk ve psikotik bulgularla başvuran ve HE tanısıyla takip edilen bir olgu bildirilmektedir.

Anahtar kelimeler: Hashimoto ensefaliti, psikoz, tiroidit

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INTRODUCTION

Hashimoto encephalopathy (HE), defined first in 1966 by Brain et al. (1), is a syndrome with clinical signs resembling encephalopathy, which is supposed to be developed by high serum antithyroid antibody levels related to autoimmune etiology. The prevalence of HE, which is a rare syndrome, was determined approximately as 2.1/100.000 in a hospital based epidemiological study (2). Although the syndrome is commonly encountered in middle aged people, 20% of patients were diagnosed younger than 18 years of age, and it is also 4-folds more common in women than men (3).

HE may present itself in various neuropsychiatric clinical pictures such as confusion, coma, stupor, stroke-like pictures, epileptic seizures, myoclonus, behavior changes, hallucination and delusion (4). According to previous clinical studies these clinical presentations were classified into two; the first one is vasculitic type which shows acute images such as stroke-like findings, epileptic seizures or cognitive disorders; and the second is diffuse progressive type, which presents with more insidious psychotic and demential findings, and makes up of approximately 75% of cases (5).

There are some suggestions for pathogenesis of the syndrome. Various mechanisms have been proposed in the development of syndrome such as autoimmune vasculitis, autoantibodies developed against brain-thyroid antigens, encephalomyelitis-related demyelination, and cerebral hypoperfusion (6).

Although syndrome presents itself in different clinical pictures, and ideas for its pathogenesis are still at hypothesis level, we can define some common criteria to diagnose HE in the literature. First criteria is the presence of neuropsychiatric findings mentioned above, which cannot be explained by another disease; second one is detection of high serum thyroid autoantibody levels while symptoms are continuing; and third one is quick respond of symptoms to steroid treatment (3). Steroid-related clinical recovery is so dramatic that the name of syndrome is also defined as “autoimmune thyroiditis related, steroid responsive encephalopathy” (7).

No specific electroencephalogram (EEG) or imaging examination has been determined in studies performed until today. EEG or cranial imagining methods are used to perform differential diagnosis with other diseases (8). However, it has been reported that protein increase and thyroid antibodies are detected in cerebrospinal fluid (CSF) examinations in patients with HE (9).

As HE may be observed in many different clinical pictures, there are no specific imaging findings for diagnosis, and its pathogenesis has not been completely understood, diagnosis of this syndrome may be delayed, or even it may be missed. If the correct diagnosis is made, there will be a rapid and dramatic recovery with steroid treatment. Despite its definition in 1966, there are limited number of case reports until today (1,7,8,9). Therefore, we presented a case who applied with cognitive disorder and psychotic findings, and followed up with the diagnosis of HE.

CASE

She was a 28 years old patient, and applied to our psychiatry outpatient clinic with complaints of unhappiness, fatigue, wiling to cry, reluctance, skepticism, and nervousness. The patient had irregular previous psychiatric applications, and her last application was 2 years ago. She told that she had anxiety, and received a drug of which name she did not remember. She reported that she stopped taking this medicine because her appetite was increased. Her depressive symptoms were started 1 week ago without and trigerring stressor event. In her psychiatric examination, her affect was apathic, mood was depressed, psychomotor activity was decreased, reaction time was prolonged and she had persecution and reference delusions with visual hallucinations. Her parents told that her cognitive abilities and psychotic signs was fluctuating during the day. The patient was hospitalized for differential diagnosis and treatment, and venlafaxine 37.5mg/day (dose increase was planned by titration), and risperidone 1mg/day were started. Her routine laboratory tests revealed low levels of thyroid stimulating hormone (TSH), and high

levels of free triiodothyronine (T3) and thyroxine (T4), so consultation was requested from the internal medicine clinic. Thyroid ultrasonography (USG), serum thyroid autoantibody tests were performed. Pseudo-nodular image consistent with thyroiditis was determined in thyroid USG, and thyroid peroxidase antibody (anti-TPO), TSG receptor antibody (TRAB), and anti-thyroglobulin antibody (TG) levels were determined high in autoantibody tests. Patient was reevaluated with the test results by the internal medicine clinic, and she was diagnosed with Hashimoto thyroiditis. As her thyroid function tests were consistent with hyperthyroidism, propylthiouracil was started at 300mg/day dose. It was observed at the service that cognitive abilities and psychotic signs of the patient were changing, and the clinical picture seemed to be developed acutely, and there was no stressing life event which could explain depressive signs; cranial computerized tomography, cranial magnetic resonance imaging, and EEG were performed to differentiate an intracranial pathology, but no pathology was detected. Cerebrospinal fluid (CSF) analysis was suggested for differential diagnosis, but when she was informed about lumbar puncture (LP) procedure, she developed a persecution delusion, and her relatives did not allow LP procedure, so CSF analysis could not be performed.

Because her orientation to person and insight to visual hallucinations and presecution delusions were fluctuated during the day and laboratory tests and thyroid USG results were consistent with Hashimoto thyroiditis, the patient was diagnosed with HE, and oral methylprednisolone 8mg/day was added to her treatment. Four days after addition of methylprednisolone, fluctuations in orientation to person, and psychotic signs were markedly improved during day. The patient was discharged on the 10th day with complete clinical recovery.

During her outpatient clinic follow-up, she continued her treatment with venlafaxine 75mg/day, risperidone 1mg/day, methylprednisolone 16mg/day, propylthiouracil 300mg/day, and complete recovery in her clinical depressive and psychotic signs were sustained.

DISCUSSION

HE is a disorder which is characterized by neuropsychiatric symptoms, and high anti-thyroid autoantibody levels, but does not have radiological or electroencephalography (EEG) findings related to the disorder, and which can show rapid clinical recovery by using steroid treatment. It is believed that autoimmunity plays an important role in development of this disorder, because it is more commonly diagnosed in women, inflammation signs can be determined in CSF, it responds to steroid treatment, and it can be accompanied by other autoimmune diseases such as myasthenia gravis, glomerulonephritis, primary biliary cirrhosis, and pernicious anemia. Archambeaud et al. (10) reported that elevations in sedimentation rate, CRP and antinuclear antibody (ANA) were determined in 16% of HE cases, and HE could be accompanied by autoimmune diseases such as sarcoidosis, psoriatic arthritis, and sicca syndrome. In our case, levels of anti-TPO, TRAB, and TG were elevated. While anti-TPO and TG had higher disease specificity for Hashimoto disease, TRAB was more related with Graves' disease, but it was also known that 14% of patients with Hashimoto thyroiditis had also TRAB positivity (11). The role of thyroid antibodies in pathogenesis is not known clearly. Yet, it has not been proven scientifically that there was any sign of antibodies affecting brain tissue or neuron functions, or there was a direct correlation between neuropsychiatric signs of the disorder and antibody levels. However, it was reported in previous studies that HE might develop an autoimmune cerebral vasculitis picture due to endothelial inflammation damage or immune complex accumulation (3,12). In studies about autoimmunity, it was reported that an antibody which was directed to amino terminal of alpha enolase enzyme, which took place in glycolysis reactions, might be a bio-marker for this disorder (12,13). In a study conducted on Hashimoto thyroiditis patients with HE, without HE, and health control groups, and it was reported that antibody against alpha enolase was markedly higher in the patients with HE (13). Presence of alpha enolase antigen on endothelial cells in addition to brain and thyroid tissues supports the idea that autoimmune vasculitis is related to HE pathogenesis.

There are studies indicating that there have been cortical hypoperfusion in Single photon emission computed tomography (SPECT) and positron emission tomography (PET) imaging studies performed in HE patients, and authors have commented this condition as micro-circulation disorder which has been developed due to immune complex or antibody accumulations (14,15).

Acute onset persecution delusions, visual hallucinations and fluctuated insight to these psychotic symptoms, impairments and fluctuations in orientation to person were present in this case. This clinical picture covers some of the symptoms that can be seen in clinical presentation of HE. During the clinical progression of HE, 51% of patients might have cognitive disorders, 48% have high cortical function disorders, 32% have myoclonus, 26% have psychotic symptoms (delusion or hallucinations), 21 have stroke-like symptoms, 12% have tremor and involuntary movements, 8% have speech disorder, and 6% have ataxia signs (16).

Thyroid function test of our case revealed signs consistent with hyperthyroidism characterized by low TSH, and high T3 and T4 levels. It is known that euthyroidism, hypothyroidism, and hyperthyroidism periods may be observed during clinical progression of Hashimoto thyroiditis. Additionally, it was reported that there was subclinical hypothyroidism in 23-35%, hypothyroidism with clinical signs in 17-20%, hyperthyroidism in 7%, and euthyroidism in 18-45% of HE patients (3,12). Hyperthyroidism and TRAB positivity in our case were signs to be evaluated for Graves' disease, but there was no subcutaneous tissue changes resulting from long-term hyperthyroidism in Graves' disease, such as exophthalmos, and pretibial myxedema in our patient, so it suggested that Hashimoto disease in which clinically short-term hyperthyroidism was more possible. Thyroid biopsy required for definite diagnosis could not be performed, because our patient did not give her consent. However, there are also HE cases accompanying Graves' disease reported in the literature (17,18).

After clinical and laboratory evaluation of our case, HE diagnosis was made, and propylthiouracil and methylprednisolone were added on antipsychotic and SSRI treatment after consulting with the internal medicine clinic, and then neuropsychiatric signs of the

patient were rapidly improved. It was observed during outpatient clinic controls that her signs did not recur under regular drug use. There are studies reporting that successful treatment results in HE were achieved by using agents affecting thyroid (propylthiouracil, levothyroxine), antiepileptics for symptomatic relief, antipsychotics for psychotic findings, and azathioprine, cyclophosphamide, intravenous immunoglobulin, and plasmapheresis which are related to autoimmunity (3). However, corticosteroids are the most commonly indicated, rapidly effective, and the most important treatment agents in this disorder. Therefore, the disease was named as steroid responsive autoimmune thyroiditis related encephalopathy. In previous studies, it was reported that rapid and sustained recovery was observed in neuropsychiatric signs by using steroid treatment (3).

In the psychiatry literature, there are many cases reported with psychotic clinical picture due to steroid use, but on the contrary to the literature knowledge, psychotic signs in HE recovers with steroid treatment rapidly, and even if steroid treatment is discontinued during clinical follow-up, psychotic signs have been flared up (17). Besides limbic encephalitis (LE), which shows similar features with HE in symptomatology and improvements of psychotic sign under steroid treatment, is a very important entity in the differential diagnosis. LE is a paraneoplastic syndrome which evolves due to autoimmune reactions, and is characterized by psychotic symptoms developed acutely within days or weeks, memory problems or epileptic seizures, and LE is observed in patients with a known or occult malignancy (19). In the majority of LE cases, bioelectrical abnormalities are observed in temporal area of the involved site, and there were elevation of protein, and lymphocytic pleocytosis in CSF examination. Moreover, serum antineural antibodies have been detected positive in 60% of LE patients (19). As there was no known or clinically suspected malignancy, absence of signs consistent with temporal involvement of EEG, and known thyroid disease history of our patient helped us to exclude LE diagnosis.

In conclusion, although HE has been first defined in 1966, there is not enough information about this disorder in the literature despite 50-years' time. As it

has a wide range of signs in clinical picture, and there is no specific laboratory or imaging studies for the disorder, it is considered that HE is an easily missed disorder in differential diagnosis in the daily clinical practice. Early diagnosis is very important in this disorder, because if diagnosed early before complete establishment of neuropsychiatric signs, then rapid and non-recurrent treatment response is possible. Future studies should increase awareness of this disorder by reporting many cases, and aim to determine specific markers of this disorder.

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