

HASHIMOTO ENCEPHALOPATHY – NEUROLOGICAL AND PSYCHIATRIC PERSPECTIVE

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Abstract — Hashimoto encephalopathy (HE) is an autoimmune disease with neurological and neuropsychiatric manifestations and elevated titers of antithyroid antibodies in serum and cerebrospinal fluid. Patients are mostly women. Age varies from 8 to 86 years. Prevalence of HE is estimated to be 2.1/100,000. Neurological and/or psychiatric symptoms and signs constitute the clinical picture. The disease responds well to corticosteroid therapy, but sometimes other immunomodulatory therapies must be applied. Autoimmune mechanisms with antibodies against antigens in the brain cortex are suspected. The course of the disease can be acute, subacute, chronic, or relapsing/remitting. Some patients improve spontaneously, but a few died in spite of adequate therapy.

Key words: Hashimoto encephalopathy, antithyroid antibodies, corticosteroid therapy, neuropsychiatric manifestations

UDC 616.8:616.831

INTRODUCTION

Hashimoto encephalopathy (HE) is an autoimmune disease that accompanies some cases of Hashimoto subacute thyroiditis (Seipelt et al., 1999). It sometimes can occur independently. Besides HE, the most commonly used name, this entity is also called steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT) and nonvasculitic autoimmune meningoencephalitis. As HE is immediately recognizable, more than lengthy descriptive names, we will use the original name in this paper. Hashimoto thyroiditis (HT) has a prevalence of 8% of women, 3% of men, and 10% of women above 55 years (Vanderpump and Tunbridge, 2002). The incidence and prevalence of Hashimoto encephalopathy are not known but one study of unexplained encephalopathies found a prevalence of 2.1/100,000 in the general population (Ferracci et al., 2004). There are no reports of familial Hashimoto's encephalopathy.

Common in both HT and HE are the two main types of antibodies: thyroglobulin (TgAb) and/or thyroxin peroxidase (TPOAb) or anti microsomal antibodies. The pathogenetic significance of these antibodies is not clear as their prevalence is high in

normal populations (Chong and Rowland, 2006). The majority of patients are women (female to male ratio 4: 1) (Ferracci and Carnevale, 2006). This entity can be found in people of all ages from 8 to 86 years (mean 46 years) (Ferracci and Carnevale, 2006). In children there is no clear gender preponderance (Mocellin et al., 2007). About one third of these patients are hypothyroidic.

Hashimoto thyroiditis is an autoimmune thyroid disease characterized by the destruction of thyroid cells by various cell- and antibody-mediated immune processes with slow progression over a number of years. It is primarily a histological diagnosis first described by Hakaru Hashimoto, a Japanese surgeon working in Berlin, Germany (Hashimoto, 1912). He published a report, based on examination of the thyroid gland in four postoperative cases, in 1912.

The first description of HE dates back to 1966 (Brain et al.). The patient, who had Hashimoto thyroiditis and hypothyroidism, suffered 12 stroke-like episodes with confusion over a year. He did not respond to corticosteroid (prednisolone), but to thyroxin therapy alone. The next two patients were

described in 1974 (Thrush and Boddie). A woman who was euthyroid became depressed and developed recurrent seizures, myoclonus, and hallucinations. She was treated successfully with corticosteroids and cyclophosphamide. These patients inaugurated HE as a separate clinical entity, delineated the typical clinical pictures, and revealed efficacious therapy.

CLINICAL PICTURE

Clinical expression of HE is very diverse. The classical manifestations are: (1) occurrences of stroke-like episodes and (2) a clinical picture mimicking Creutzfeldt-Jakob disease (CJD). Patients can be euthyroid, hypothyroid, and even hyperthyroid with appropriate signs and symptoms. There are well-documented cases of monosymptomatic illness with psychiatric manifestations, progressive myelopathy, dementia, seizures, paraesthesiae, or cerebellar symptoms (Ferracci and Carnevale, 2006).

Hashimoto encephalopathy

Encephalopathy can be the first clinical manifestation accompanying subclinical thyroiditis. The most frequent signs are epileptic seizures, subacute confusion, myoclonus, cognitive impairment or dementia, and disturbances of consciousness, all present in more than 40% of patients each (Ferracci and Carnevale, 2006). Also there can be ataxia, tremor, personality disturbances, psychosis, hallucinations, sleep abnormalities, transient aphasia, pyramidal and/or extrapyramidal signs, dysarthria, headache, cerebellar symptoms, vertigo, myelopathy, and fatigue (Castillo et al., 2006; Ferracci and Carnevale, 2006). So far, only one patient with HE has been found to be febrile with exclusion of other possible causes, and this patient responded well to corticosteroid therapy (Papathanasopoulos et al., 2000). One possible explanation is that tumor necrosis factor alpha, found in sera of patients with HT, acts as an endogenous pirogen.

Stroke-like episodes occur with focal neurological signs, sometimes with seizures and impairment of consciousness. This type is sometimes called the "vasculitic type". The CJD-like presentation with progressive cognitive impairment leading to demen-

tia, with psychotic features and sometimes with seizures, is also called the "diffuse progressive" type. In contrast to CJD, in HE there are no major visual disturbances, startle reactions, or rapid progression, but there are fluctuations. There are no oligoclonal bands or protein 14-3-3. There is an increased prevalence of lipid disorders in association with untreated hypothyroidism (which can cause vascular damage), so thyroid function tests are obligatory. High serum levels of antithyroid antibodies and a CJD-compatible clinical picture can mean not only HE, but sometimes a comorbidity.

Seizures can be the first sign of HE or can develop later. The most common type of seizures is grand mal (78%), followed by simple partial or simple complex seizures with or without generalization (17%) and status epilepticus (13%) (Ferracci and Carnevale, 2006). A rare case of a patient with psychosis and generalized absence status has been reported (McKeon et al., 2004). Myoclonus can occur in both major types of HE. Myoclonus can be focal or multifocal, spontaneous or action-triggered, and also of the reflex type (a startle response).

In the progressive variety of HE, patients can suffer from dementia, depression, cerebellar, and extrapyramidal symptoms (Ferracci and Carnevale, 2006). Poor school performance is a frequent finding in children. Adults can have memory disturbances or progressive aphasia or apraxia corresponding to dementia. Some patients have fatigue.

Some patients become somnolent, and consciousness can deteriorate to coma. Focal neurological deficits can be motor or sensory. Tremor can be found in almost one third of the patients with characteristics of postural, action cerebellar, or rest tremors (Ferracci and Carnevale, 2006). There was a report of a patient with palatal tremor. Some patients have the presentation of Parkinsonism with rest tremor, hypokinesia, and rigidity. Chorea is a rare clinical presentation in HE. Some patients have cerebellar symptoms and signs suggestive of mul-

multiple system atrophy or progressive cerebellar ataxia (Nakagawa et al., 2007).

Neuropsychiatric symptoms and signs are frequent, with psychosis, persecutory delusions, disorganized speech, hallucinations (more of the visual type), and depression or elevated moods (Mocellin et al., 2007; Gómez-Bernal et al., 2007). Psychotic features can appear episodically and respond well to corticosteroid therapy (Arrojo et al., 2007). Personality disorders consist of anxiety, hyperemotionality, outbursts of anger, violent behavior, paranoia, and visual and auditory hallucinations. Some patients can have only psychiatric and not neurological symptomatology (Kinrys and Bostwick, 2001). Such disease expression may mimic various psychiatric entities.

Contrary to hypothyroidism – where negative symptoms prevail with psychomotor retardation, apathy, poor attention, somnolence, and lethargy (Doherty, 2005) – HE is characterized by a preponderance of prominent positive symptomatology, such as mania, psychosis, seizures, extrapyramidal rigidity, myoclonus, and stroke-like episodes (Chong et al., 2003).

Hashimoto myelopathy

Another clinical expression is spinal cord involvement or Hashimoto myelopathy (Azuma et al., 2000). A case was reported with primary involvement of the spinal cord and brain two months later in the context of HT with a thoracic level of sensitivity. The immunological process was active no matter how well she was substituted with thyroxin, and relapses occurred even on steroid therapy. In this and two other described cases, MRI of the thoracic spine was inconspicuous.

Thyroid function

Thyroid function does not significantly influence the clinical picture of HE. Patients can have normal serum thyroxin and thyrotropin concentrations, and elevated or decreased hormone levels. They may have additional signs and symptoms of thyroid dysfunction and the majority are hypothyroid. In HE patients, subclinical hypothyroidism was found in

35% of patients, overt hypothyroidism in 28%, sub-clinical hyperthyroidism in 2%, and overt hyperthyroidism in 5%, and 22% of patients were euthyroid (Chong et al., 2003).

In patients with hypothyroidism, the usual signs and symptoms are: fatigue, constipation, dry skin, weight gain (mostly due to fluid accumulation in interstitial tissues), cold intolerance, voice hoarseness, slowed movement and loss of energy, decreased sweating, mild nerve deafness, menstrual irregularities, galactorrhea, depression, dementia, memory loss, sleep apnea and daytime somnolence, joint pains and muscle cramps, and hair loss from an autoimmune process directed against the hair follicles. An elevated blood cholesterol level is a typical finding.

Objective findings in hypothyroidism are: puffy face and periorbital edema; cold, dry skin, which may be rough and scaly (the skin may appear yellow, but without sclera involvement); peripheral edema of hands and feet (typically nonpitting); thickened and brittle nails (which may appear ridged); hair loss (involving the scalp, the lateral third of the eyebrows, and, possibly, skin, genital, and facial hair); bradycardia; and diastolic hypertension (but blood pressure can be normal or even low and macroglossia). The thyroid gland is mostly enlarged and firm, but can be of normal size or not palpable at all.

Neurological examination shows diminished deep tendon reflexes, with a prolonged relaxation phase, most notable at the Achilles tendons; voice hoarseness; slow speech; cerebellar ataxia; and impairment of memory function. Patients may complain of muscle aches, tenderness and stiffness (especially in the shoulders and hips), and muscle weakness (mostly in the lower extremities). There are paresthesias from peripheral neuropathy. The possibility of hyponatremia from renal failure and consequent clinical manifestations must be considered.

Thyroid dysfunction is common in the elderly. The prevalence of hypothyroidism is 10% of females and 2% of males, while that of hyperthyroidism is 2% in patients more than 60 years old (Rehman et al., 2005). Symptoms of thyroid disease in the eld-

erly are often overlooked because they are subtle or even absent and are easily confused with coexisting illnesses, so the diagnosis is easily missed. Doctors should also think about the euthyroid sick syndrome, which accompanies many diseases and does not respond to hormone replacement.

Clinicians should distinguish signs and symptoms of HE and possible thyroid disease.

Peripheral nervous system involvement

Some patients have HE and other immune diseases. A possible common autoimmune pathogenesis was supposed in a 50-year-old man with HE and motor neuron disease (Harzheim et al., 2006). He presented with chronic progressive lower motor neuron symptoms (paraparesis and fasciculations in all extremities) and encephalopathy characterized by memory and attention deficits, emotional instability, aggressiveness, and dysarthria. Nerve conduction studies and electromyography were initially normal, but later showed signs of lower motor neuron disease. Both central and peripheral nervous system changes improved in response to intravenous pulse doses of methylprednisolone followed by oral tapering. Serum TPOAb also decreased.

Three case studies of peripheral neuropathy in HE have been published (Ferracci and Carnevale, 2006). Clinical presentations were sensory ganglionopathy (Cao et al., 2005), neuralgic amyotrophy (Kastrup et al., 2005), and demyelinating neuropathy associated with symptoms of encephalopathy (Sheng et al., 2005). Demyelinating peripheral neuropathy is difficult to distinguish from chronic inflammatory demyelinating polyneuropathy (CIDP).

Hashimoto encephalopathy in children

A recent literature search revealed 25 published reports of children diagnosed with HE aged 9–18 years (Alink and de Vries, 2008). The most frequent symptoms were seizures (80%), confusion (52%), headache (40%), hallucinations (32%), and ataxia (36%). Deterioration of school performance can be one of the first signs of encephalopathy. In children, TPOAbs were demonstrated in all patients and TGAb in slightly over one half. Of these, 52% were

hypothyroid and 48% euthyroid. Treatment with steroids was effective, with 55% of patients showing complete recovery.

There are some reports of very severe clinical presentation of HE with psychotic manifestations. Progressive, pharmacoresistant epilepsy, psychosis, and coma were reported in a six-year-old girl (Hoffmann et al., 2007). Another patient, a 12-year-old boy, had episodes of psychosis with hallucinations and epilepsy (Ray et al., 2007). He had signs of hypothyroidism and responded well to thyroxin alone.

The course of HE

The onset of HE can be acute or gradual, and the further course can be with remissions and relapses or progressive, with possible overlaps of these two types (Tamagno et al., 2006). The menstrual cycle can be associated with exacerbations in some cases. Spontaneous remissions are possible even in patients of advanced age with cognitive deterioration and stroke-like episodes (Katoh et al., 2007). Responsiveness to corticosteroids is frequent (Mocellin et al., 2007). Most patients with HE require hospitalization during the acute phase because of the severity of their deficits (Castillo et al., 2006). There are cases of steroid unresponsiveness and a few patients died (Fatourechi, 2005; Striano et al., 2006). A 27-year-old woman died after a several-month course of HE with myoclonus, depression, psychosis, and convulsive status epilepticus not responding to therapy (Striano et al., 2006). The patient died of cardiac failure. Autopsy revealed no vasculitic changes. Interestingly, relapses and recurrence of symptoms seem not to be a sign of ineffectiveness of steroid treatment. Duration of the disease according to earlier studies ranges between 2 and 25 years.

PATHOGENESIS

The pathogenesis of HE is not known. The most plausible hypotheses are autoimmune vasculitis and reversible leukoencephalopathy with a common antigen in the thyroid and brain. Antibodies of the TGAb and/or TPOAb type are always found, but

their role in HE is still not proved. The presence of antithyroid autoantibodies in the CSF might be a result of blood brain barrier leakage or intrathecal synthesis. The TPO antibody is a common marker of autoimmunity not only in HT, but also in most autoimmune neurological disorders, including paraneoplastic and nonparaneoplastic limbic encephalitis (Castillo et al., 2006). Anti-TSH, a thyroid-stimulating and cytotoxic antibody, can also be found in HT. A small percentage of patients with HT (10-15%) may be antibody-negative. It is supposed that in HE antibodies attack neurons in the brain. Anti TPOAbs in high titers were detected in the cerebrospinal fluid (CSF) of HE patients, but not in controls (Blanchin et al., 2007). In that study, TPOAbs reacted with monkey cerebellar cells and normal human astrocytes from primary cultures, suggesting a role for these autoantibodies in the pathogenesis of HE.

Some other etiological factors have been suggested, such as hypothyroidism itself, humoral factors, antigen-antibody complexes, vasculitis, demyelinating processes with disseminated encephalomyelitis, intrathecal thyroid antibodies, and global cerebral hypoperfusion (Castillo et al., 2006; Tamagno et al., 2006). Hypothyroidism is less likely to be the dominant etiology because HE patients can be not only hypothyroid, but euthyroid and even hyperthyroid. Other antibodies have been found in sera of these patients, and some have a pathogenetic role, as already mentioned. Evidence for dominant vascular involvement (cerebral hypoperfusion and/or vasculitis) is scarce. Some cases that were HE-like and did not respond to corticosteroids were ultimately confirmed at autopsy as prion disease.

Elevated brain thyrotropin-releasing hormone (TRH) can be the cause of seizures and tremor (Ishii et al., 2000). Immune mechanisms are thought to be important rather than hormonal changes, as a similar clinical picture can be seen in euthyroid, hyperthyroid, or hypothyroid patients. Transient hyperthyroidism secondary to increased T4 and T3 levels resulting from thyrocyte destruction can easily be overlooked, and much more pronounced signs of hypothyroidism are obvious with rapid disease progression. In many patients, the presentation may

be subclinical and found during routine screening of thyroid function. The usual finding is an elevated TSH level reflecting the early compensatory increase to maintain a nearly normal thyroid function.

There is some vasogenic edema that can be demonstrated occasionally and may be the reason for favorable effects of corticosteroid therapy. Edema can be a result of cerebral vasculitis (Ferracci and Carnevale, 2006). There are some similarities to acute demyelinating encephalomyelitis (ADEM) with perivascular lymphocytic infiltration. Alpha-enolase has been found as an autoantigen in HE patients, but not in controls including patients having HT without neurological symptoms (Ochi et al., 2002; Yoneda et al., 2007). Alpha-enolase is an antigen of the thyroid and the brain, being concentrated in endothelial cells and so a possible brain target. Autoantibodies against the amino terminal of alpha-enolase are a useful diagnostic marker of Hashimoto's encephalopathy. Anti alpha-enolase antibodies have a high prevalence (68%) and high specificity in patients with HE. A humoral antineuronal antibody was found in a patient with HE, but not in HT without HE (Oide et al., 2004). This antibody reacts with the 36-kDa protein obtained from human cerebral cortex.

Autoimmune etiology is further suggested by the fact that some patients have another autoimmune disorder, for example myasthenia gravis, pernicious anemia, systemic lupus erythematosus, or diabetes mellitus (Schäuble et al., 2003). Triphasic and atypical triphasic waves are sometimes present in HE, which is a non-specific characteristic in different types of encephalopathies.

Another proof of immune-mediated process is good response to corticosteroids and other immunosuppressive therapy in the majority of patients. The disorder is more common in women. There is a possible genetic predisposition, since in most of the patients in one series there were HLA B8 DRw3 haplotypes, but this is a common finding in patients

with autoimmune diseases in general and not specific for HE.

The role of undetectable levels of hypocretin-1 in the CSF of patients with disturbance of consciousness is possible (Castillo et al., 2004). Hypocretin-1-secreting hypothalamic neurons modulate consciousness. Lowered hypocretin-1 levels can also be secondary to arousal changes, and no autoantibodies against this antigen have been documented.

It is possible that HE will be classified as non-vasculitic autoimmune inflammatory meningoencephalopathy (NAIM) with limbic encephalitis associated with voltage-gated potassium channel antibodies and Sjogren encephalopathy (Josephs et al., 2004; Mocellin, 2007).

DIAGNOSIS

Antithyroid antibodies

Diagnosis of HE is based on the presence of neurological and neuropsychiatric symptoms and elevated serum antithyroid antibodies: TGA_b and/or TPOAb and occasionally antibodies blocking the TSH receptor. Positive thyroid antibodies are a frequent finding in the general population, with prevalence of nearly 10% increasing with advanced age, so their exact pathogenetic role is unclear. Antithyroid antibodies are found in serum of all patients, TPOAb in 100%, and TGA_b in 70% (Mocellin et al., 2007).

Antibody titers do not always correlate with the stage of the disease and the therapeutical response (Ferracci and Carnevale, 2006). Patients can be eu-, hypo-, or hyperthyroid (Seipelt et al., 1999). The thyroid gland can be goitrous, atrophic, or normal in size. Recently, serum autoantibodies against the amino (NH_2) terminal region of alpha-enolase (NAE) have been suggested as a useful diagnostic marker of Hashimoto's encephalopathy (Fujii et al., 2005).

Cerebrospinal fluid

Antithyroid antibodies can also be demonstrated in the CSF in cases of HE, but not all of them. In control patients, there were no elevated TGA_b nor

TPOAb CSF titers (Ferracci et al., 2003; Blanchin et al., 2007). In some patients, elevated antibody titers can be partially due to blood/brain barrier leakage, but other studies confirmed synthesis within the central nervous system (CNS) (Ferracci et al., 2004). Thus, CSF antithyroid antibody titers might represent a useful diagnostic marker in HE patients, and this index usually correlates well with disease activity. Antithyroid antibodies are undetectable in patients with autoimmune thyroiditis or other neurological disorders (Katoh et al., 2007).

Cerebrospinal fluid findings more often involve elevated protein content (in the majority of patients) than lymphocytic pleocytosis (Castillo et al., 2006). Pleocytosis can be up to 170 cells/mm³ and mild hyperproteinorrachia up to 1.8 g/L (Seipelt et al., 1999). Other potential diagnostic autoantibodies are also mentioned, but more extensive series of patients are lacking. Neuron-specific enolase and 14-3-3 protein levels in the CSF are normal (Castillo et al., 2006). The rate of IgG synthesis is seldom elevated, the IgG index is normal, and in a few patients oligoclonal bands were found (Castillo et al., 2006). Clinicians should be aware of the fact that normal CSF protein levels, normal cell counts and IgG synthesis rates, and absence of oligoclonal bands do not exclude a diagnosis of HE.

Neuroimaging

Magnetic resonance imaging (MRI) reveals normal findings or mild brain atrophy and sometimes focal or diffuse hyperintensities in the cerebral white matter and meningeal enhancement (Castillo et al., 2006). Cerebellar atrophy is rare. In myelopathy cases, there were no pathological MRI findings on the spinal cord. Rare patients underwent MR angiography (MRA) or MRI spectroscopy. One patient with a diffuse clinical picture showed transient narrowing of both middle cerebral arteries on MRA consistent with cerebral hypoperfusion (Isik et al., 2001). In one patient, MRI spectroscopy demonstrated reduction of N-acetylaspartate (NAA) (a marker of the integrity of neurons) and an increase in choline-containing compounds (a marker of myelin sheath integrity) in the frontal lobes (Nieuwenhuis et al.,

2004). Pathological findings returned to normal after steroid treatment.

Single photon emission computed tomography (SPECT) yielded both normal and pathological findings, with areas of reduced perfusion in the cerebral cortex and basal ganglia (Fatourechi, 2005). Some patients have global hypoperfusion (Ferracci and Carnevale, 2006). In patients with HT and no clinical sign of cerebral involvement, SPECT showed impaired cerebral perfusion (Zettinig et al., 2003). Cerebral angiography is generally normal (Castillo et al., 2006).

Positron emission tomography (PET) with 18 F-fluorodeoxyglucose (FDG-PET) in a female patient with HE and hyperthyroidism revealed diffuse non-uniform cortical hypometabolism consistent with encephalopathy (Seo et al., 2003). Clinically, she presented subacute progressive dementia, multifocal myoclonus, and raised levels of antithyroid autoantibodies. In contrast to FDG-PET, MRI findings were normal. The patient improved in response to high doses of corticosteroids (dexamethasone and then methylprednisolone followed by prednisolone tapering), and eventually both cognitive status and PET findings became normal.

Electroencephalography

Electroencephalography (EEG) shows slowing of background activity and slow waves that reflect the degree of severity of the underlying encephalopathy in practically all patients (Schäuble et al., 2003). Slow waves are mostly in the delta range and can be continuous, intermittent, diffuse, or focal. A number of patients have only moderate slowing. The EEG can also be normal in HE, and pathological findings are not specific. Despite frequent occurrences of seizures, epileptiform discharges are rarely described. The EEG findings often show improvement that parallels improvement of the clinical condition (Castillo et al., 2006). Periodic triphasic waves suggestive of CJD were never recorded, but atypical triphasic waves on a slow background were observed in some patients (Schäuble et al., 2003; Ferracci and Carnevale, 2006). As myoclonic jerks do not appear to have an EEG correlate, it was sug-

gested that myoclonus in HE has a spinal and not a cortical origin.

Other findings

The erythrocyte sedimentation rate is mildly to moderately elevated in one fourth of patients, the C-reactive protein level is elevated in one third, and about a half have elevation of serum aminotransferase levels (Castillo et al., 2006). Antinuclear antibodies, rheumatoid factor, and anti-gliadin antibodies can be detected in some patients.

Histopathological examination of brain tissue obtained at autopsy or brain biopsy has identified lymphocytic infiltration around small arterioles and venules of the leptomeninges and parenchyma (Chong and Rowland, 2006). Lymphocytes were predominantly of the T-type. At least one patient had normal biopsy findings (Fatourechi, 2005). Brain biopsy is indicated in steroid non-responders with deteriorating and atypical clinical features, but is not specific and frequently not a safe procedure.

Diagnostic criteria

The first set of criteria for the diagnosis of HE was published by Peschen-Rosin et al. (1999). These criteria encompassed unexplained occurrence of relapsing myoclonus, generalized seizures, psychiatric disorders or focal neurological deficits, three conditions of abnormal EEG, elevated thyroid antibodies, elevated CSF protein, excellent response to steroids, and unrevealing cerebral MRI. Since this early proposal, the clinical range of symptoms and signs has been greatly widened, and the response to steroids has been shown to vary substantially. These criteria also underestimate the significance of raised levels of antithyroid antibodies, which are a hallmark of HE.

Ferracci and Carnevale (2006) summarize the diagnostic principle followed by the majority of authors: after other diagnoses have been ruled out, elevated serum antithyroid antibodies support a diagnosis of HE, but are not confirmatory. The presence of HT is not necessary for the diagnosis of HE,

as some patients have elevated autoantibodies and brain disease without autoimmune thyroiditis.

The usual cluster of findings associated with HE includes recurrent neurological illness mostly presented as generalized seizures, myoclonus, ataxia, cognitive defects, focal neurological defects, and other signs; high levels of antithyroid antibodies; non-specific EEG changes; non-specific MRI white matter changes; elevated CSF proteins; and possibly abnormal thyroid functional tests (Karadeniz et al., 2005).

Castillo et al. (2006) expanded the diagnostic criteria to a set of seven: (1) encephalopathy manifested as cognitive impairment and one or more of the following: neuropsychiatric features (e.g., hallucinations, delusions, or paranoia), myoclonus, generalized tonic-clonic or partial seizures, and focal neurological deficits; (2) the presence of serum thyroid antibody; (3) euthyroid status (serum sensitive thyroid-stimulating hormone [TSH], 0.3-5.0 mIU/L) or mild hypothyroidism (serum sensitive TSH, 5.1-20.0 mIU/L) that would not account for encephalopathy; (4) no evidence in blood, urine, or CSF analyses of an infectious, toxic, metabolic, or neoplastic process; (5) no serologic evidence of the neuronal voltage-gated calcium channel, voltage-gated potassium channel, or other currently recognized paraneoplastic autoantibodies to indicate another diagnosis; (6) no findings in neuroimaging studies indicating vascular, neoplastic, or other structural lesions to explain the encephalopathy; and (7) complete or near complete return to the patient's neurological baseline status following corticosteroid treatment. These criteria do not take into account rare cases of spinal cord involvement, HE with hyperthyroidism, or steroid non-responders. The new feature of these criteria is the exclusion of paraneoplastic auto-antibodies.

Another set of clinical criteria is proposed for the diagnosis of defined, probable, or possible HE (Tamagno et al., 2006). The required criteria are: (1) acute or subacute onset of neurological/psychiatric symptoms in the absence of other possible causes; (2) exclusion of other known causes of encephalopathy (i.e., bacterial, viral, or fungal infections, metabolic

encephalopathy, Creutzfeldt-Jacob disease, etc.); (3) association with clinical or subclinical autoimmune thyroid disease; (4) serum thyroid hormone levels unable to justify the symptoms and persistence (or presentation) of symptoms or concomitant normal thyroid hormones; and (5) clinical response to corticosteroids. Other criteria are: elevated antithyroid autoantibodies levels in serum and/or CSF, hyperproteinorachia without pleocytosis, and unspecific EEG abnormalities. Defined HE should have all of the above mentioned criteria. For the diagnosis of probable HE one should have the required criteria plus one of the other criteria, and for possible HE only the required criteria are needed. These criteria do not recognize cases without autoimmune thyroid disease and occasional pleocytosis, and the required criteria do not include the presence of the autoantibodies that actually define this disease.

DIFFERENTIAL DIAGNOSIS

All other conditions leading to encephalopathy should be excluded in order to diagnose HE (Karadeniz et al., 2005). Typical diseases that should be considered are Creutzfeldt-Jakob disease, stroke, dementia from various causes, Wilson's disease, Pick's disease, brain cancer, and primary progressive aphasia, but also (less frequently) metabolic disorders, paraneoplastic disorders, cerebral vasculitides, infectious encephalopathies (meningitis or encephalitis), demyelinating and primary degenerative CNS diseases, paraneoplastic or idiopathic limbic encephalitis, primary CNS angiitis, autoimmune lymphocytic hypophysitis, and peripheral neuropathies of unexplained origin (Fatourechi, 2005; Castillo et al., 2006; Ferracci and Carnevale, 2006; Pavlović, 2008).

In some instances, there are other autoimmune disorders present, such as diabetes mellitus type 1, systemic lupus erythematosus, Crohn disease, sicca syndrome, primary Sjogren syndrome, subacute combined degeneration, and pernicious anemia (Chong et al., 2003). These diseases can either mimic or accompany HE. There is one reported case of encephalopathy in myasthenia gravis that poses further questions about specificity of various auto-antibodies. A clinician should keep in mind possible

autoimmune etiology in unexplained encephalopathies.

An important issue is differentiating HE from "myxedematous madness", as hypothyroidism is frequently comorbidity (Garrard et al., 2000). "Myxedematous madness" responds well to thyroxin supplementation, while HE is usually steroid-responsive. Also, many other psychiatric diseases should be included in differential diagnosis of HE, psychosis, depression, bipolar affective disorder, and personality disorders among others (Kinrys and Bostwick, 2001; Müssig et al., 2005; Mocellin et al., 2007).

THERAPY

Corticosteroids (methylprednisolone, dexamethasone, or prednisone) and/or cytostatics (azathioprine, methotrexate, cyclophosphamide) in the usual doses are the main therapeutic agents. There is no preferred type of steroid, dose, or schedule. Most patients respond well to steroid therapy, so it is the preferred initial choice. Some authors recommend a high dose methylprednisolone initially: one gram intravenously for 3-5 days (Castillo et al., 2006). After initial high doses, progressive tapering is suggested until withdrawal of the drug after 6-12 months, depending on clinical evolution and responsiveness (Tamagno et al., 2006) [28], but in some of our cases prolonged combined treatment courses for several years were necessary.

There are some occurrences of spontaneous remission. According to a recent analysis of published cases and case series, 42 patients on steroid therapy recovered without relapses, 38 relapsed or had no effect, 11 patients improved with residual deficits, and 19 had spontaneous improvement, of which 14 relapsed and five remained stable (Ferracci and Carnevale, 2006). The course after treatment differs, ranging from improvement (normal or with residual impairments) to chronic disease with fluctuations.

A few patients were treated with intravenous immunoglobulins (IVIG) and a combination of corticosteroids and azathioprine or cyclophosphamide. Some steroid-resistant patients responded well to

IVIG (Jacob and Rajabally, 2005). A small number of patients were treated with plasmapheresis and showed improvement of cognitive status and reduction of circulating antithyroid antibodies, confirming the autoimmune mechanism of HE (Nagpal and Pande, 2004; Nieuwenhuis et al., 2004; Hussain et al., 2005). At least on theoretical grounds, good results of antibody removal should be expected if they are the main pathogenetic factor. There are some patients who do not relapse in spite of cessation of therapy and persistently elevated antibodies.

Any accompanying thyroid disease should be treated appropriately (Chong et al., 2003). There are some patients that improve on thyroxin supplementation, but they might have HT with hypothyroidism and not HE. Hypothyroidism is characterized by elevated CSF protein content and EEG changes that all improve with hormone therapy. It is unclear if patients with subclinical hypothyroidism have any benefit from levothyroxine. As many HE patients have normal thyroid status or are hyperthyroid, hypothyroidism cannot be the only etiology of encephalopathy.

Various symptomatic medications might be needed, depending on the clinical presentation. Patients with seizures should receive antiepileptic medication along with immunosuppressive therapy, bearing in mind the possible side effects. Neuropsychiatric symptoms should be treated with atypical antipsychotics and/or antidepressants. It is necessary, in our experience, to treat any infection appropriately, since patients with HE can relapse or develop delirium.

A currently proposed algorithm for HE includes methylprednisolone intravenously, one gram daily for 3-5 days initially (Marshall and Doyle, 2006). Patients who are hypothyroid should receive levothyroxine and those with seizures antiepileptic medication. In the event of recurrence, methylprednisolone is given intravenously (1 gram daily for 3-5 days with prednisone). When the prednisone dose needs to be reduced or in resistant cases, steroids are

combined with azathioprine, cyclophosphamide, or methotrexate.

CONCLUSION

Hashimoto encephalopathy is probably less rare than is supposed and is a treatable condition. Unfortunately, HE is highly underdiagnosed, mostly because of lack of awareness and false diagnostic evaluation. The clinical picture differs considerably, ranging from generalized to focal deficits encroaching on both neurological and psychiatric signs and symptoms. Antithyroid autoantibodies are elevated in serum and in some patients in the CSF as well. Findings of MRI, EEG, SPECT, PET, and CSF are non-specific. Every effort should be made to make the correct diagnosis as soon as possible and start specific therapy. There are some diagnostic criteria, but none of them encompass all cases. Untreated HE can lead to serious brain injury with irreversible dementia and even death. The cornerstones of therapy are corticosteroids and sometimes other immunosuppressants. The pathogenesis probably involves autoimmune attack on cerebral vasculature and/or neural antigens. The course is variable, ranging from acute to chronic and relapsing/remitting.

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ХАШИМОТО ЕНЦЕФАЛОПАТИЈА – НЕУРОЛОШКА И ПСИХИЈАТРИЈСКА ПЕРСПЕКТИВА

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Хашимото енцефалопатија (ХЕ) је аутоимуна болест са неуролошким и неуропсихијатријским испољавањима и повишеним титровима антитиреоидних антитела у серуму и цереброспиналној течности. Болесници су углавном жене. Узраст варира од 8 до 86 година. Преваленца ХЕ се процењује на 2,1/100000. Неуролошки и/или психијатријски симптоми и знаци сачињавају клиничку

слику. Болест реагује добро на кортикостероидну терапију, али некад се мора применити и друга имуномодулаторна терапија. Претпоставља се аутоимуни механизам са антителима на антигени мождане коре. Ток болести може бити акутан, субакутан, хроничан и ремитентан. Неки болесници се опораве спонтано, али има и леталних исхода упркос адекватној терапији.