ENCEPHALOPATHY ASSOCIATED WITH AUTOIMMUNE THYROID DISEASE

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ABSTRACT

Autoimmune thyroid diseases (ATDs) are immune-endocrine disorders affecting the thyroid gland and, eventually, also a number of other systemic targets, including the brain and the nervous system. Encephalopathy associated with autoimmune thyroid disease (EAATD) is a rare, heterogeneous condition arising from the background of an ATD. It is characterised by neurological and/or psychiatric symptoms with acute or sub-acute onset, and virtually any neurological or psychiatric symptom can appear. However, EAATD often presents with confusion, altered consciousness, seizures, or myoclonus. The majority of cases are associated with Hashimoto's thyroiditis, but a number of patients with Graves' disease have also been described. EAATD is likely an immune-mediated disorder. Its exact prevalence has not been precisely elucidated, with an increasing number of cases reported in the last few years. Most EAATD patients respond in a dramatic manner to corticosteroids. However, the immunosuppressive treatment may require a long course (up to 12 months). The increasing number of EAATD cases reported in the literature demonstrates a growing interest of the scientific community about this condition, which still requires a better definition of its pathophysiology, the diagnostic criteria, and the most appropriate management, including the long-term follow-up of patients. The current clinical evidence about EAATD is mostly based on the report of single cases or small cohort studies. In this review, we present the current knowledge about EAATD, with a dedicated focus to the clinical management of the patients from a diagnostic and therapeutic perspective.

Keywords: Encephalopathy, Hashimoto's thyroiditis, Graves' disease, thyroid.

INTRODUCTION

Autoimmune thyroid diseases (ATDs), namely Hashimoto's thyroiditis (HT) and Graves' disease (GD), are complex and multifaceted immune-endocrine disorders. Suboptimal or delayed diagnosis and management of ATDs can lead to a number of systemic complications, including global decline in brain function as well as organic brain damage. Encephalopathy associated with autoimmune thyroid disease (EAATD) was first described by Brain and colleagues[1] back in 1966. It is an uncommon condition which is characterised by neurological and/or psychiatric symptoms with acute or sub-acute onset. Though any neurological or psychiatric symptoms can appear, EAATD often presents with confusion, altered consciousness, seizures, or myoclonus.[1,2] The majority of EAATD cases are associated with HT; however, it has also been reported to occur in patients with GD.[3] EAATD is likely an immune-mediated disorder and its exact prevalence has not been precisely elucidated yet, with an increasing number of cases reported in the last few years. The mean age of onset of the neurological or psychiatric symptoms is during the patient's fourth decade of life, with women being more commonly affected than men.[4-9]

EAATD

Pathophysiology

The mechanism of EAATD is still not fully understood. An overactive autoimmune process

seems to be the underlying cause.[10,11] Several mechanisms such as cerebral vasculitis with endothelial inflammation or immune complex deposition, global cerebral hypoperfusion, cerebral tissue-specific autoimmunity, and thyrotropin-releasing hormone-related neuronal deficit have also been proposed as causal factors.[11-18] In addition, some antigens such as alpha-enolase and a 36-kDa protein detected in soluble fractions from the cerebral cortex are thought to play a role in the pathogenesis of EAATD.[19,20] Pathogenesis based on the presence of cerebral vasculitis is supported by a number of pathological and neurophysiological findings. Pathology examination at autopsy and brain biopsy have identified lymphocytic infiltration around small arterioles and venules in some cases.[6,14,21] A picture of cerebral hypoperfusion compatible with that observed in diffuse brain vasculitis has been reported in some EAATD patients using single photon emission computed tomography (SPECT).[13,16] Moreover, both focal and diffuse patterns of cerebral vasculitis may be present in EAATD and could variously influence the clinical presentation.[5,6,22] Focal involvement of the brain could determine stroke-like clinical manifestations. Very peculiar clinical pictures like cerebellar sub-acute syndrome,[23] sensory ganglionopathy,[24] or a selective involvement of the nucleus accumbens[25] have been described in EAATD patients. A condition of diffuse cerebral hypoperfusion could lead to progressively worsening manifestations, often characterised by sub-acute onset and psychiatric symptoms. Despite the findings supporting the labelling of EAATD as a vasculitis-like process, the inclusion of EAATD within non-vasculitic autoimmune inflammatory meningoencephalitis (NAIM) cannot be ruled out yet.[26]

Clinical Features

From single case reports and a few cohort studies, two patterns of presentation of EAATD have been described. A stroke-like pattern of multiple and recurrent episodes of focal neurologic deficits with a variable degree of cognitive dysfunction and alteration of the level of consciousness occurs in approximately 25% of patients.[6] However, also a diffuse progressive pattern characterised by gradual cognitive impairment with dementia, confusion, hallucinations, or somnolence has been described.[5,27] Some cases develop suddenly or have a more fulminant presentation, i.e. where rapid deterioration to coma occurs.[5,28] In addition to the above mentioned changes, other neurologic signs are common in EAATD patients regardless of the dynamic of the clinical presentation. More than half of EAATD patients experience focal or generalised tonic-clonic seizures.[6,8,29,30] Status epilepticus has also been described.[29,31] Myoclonus, either focal or multifocal, or tremor are seen in up to 38% of patients.[6,8] Hyper-reflexia and other pyramidal tract signs can often be seen.[5] Psychosis, predominantly visual hallucinations, have been reported in up to 36% of patients.[6,8] The clinical manifestation of EAATD seems not to be affected by the nature of the underlying ATD, and no differences between patients with HT and patients with GD have been described. Regardless of the type of ATD, the neurological or psychiatric symptoms appear to be very heterogeneous. Altered consciousness, involuntary movements such as tremor and myoclonus, seizures, and cognitive impairment are the most frequently reported symptoms.[6,11,32] In both groups of patients, sensory alterations, headache, focal symptoms, ataxia, language impairment, signs of encephalitis, and psychiatric symptoms have also been described.[32-34]

Laboratory Features

Patients suspected of having EAATD often undergo numerous biochemical and haematological analyses. The presence of elevated serum levels of anti-thyroid antibodies remains an essential characteristic for diagnosis, and suggests the presence of thyroid autoimmunity. Elevated serum levels of anti-thyroid peroxidase antibody (anti-TPOAb) and/or anti-thyroglobulin antibody (anti-TgAb) are a common laboratory feature in EAATD patients. However, there is no clear relationship between the severity and onset of the neurological symptoms and the type or serum concentration of anti-thyroid antibodies. In addition, antibody levels may or may not decrease following treatment. Therefore, this cannot be considered to be a specific finding for EAATD.[3,4,6,8,28] In addition to serology analysis, anti-thyroid antibodies can also be measured in the cerebrospinal fluid (CSF). The specificity and sensitivity of anti-thyroid antibodies in the CSF is unclear and they have been reported to be either elevated or not detected.[4,10,32] Measurements of thyroid hormone levels appear to be variable among EAATD patients. However, thyroid hormones should not be so abnormal to determine the occurrence of neurological or psychiatric symptoms. In EAATD patients with HT, thyroid hormone levels can range from a

picture of hypothyroidism to a certain degree of hyperthyroidism, with a number of cases reported to be in euthyroid status.[6,8,35] The majority of GD patients with EAATD present with mild hyperthyroidism at the time of EAATD onset or shortly before it.[32] In some patients with EAATD, inflammatory markers like C-reactive protein and erythrocyte sedimentation rate are elevated. In addition, mild elevation of liver enzymes was also reported.[36] Other CSF laboratory findings include elevated protein concentration,[5,32] lymphocytic pleocytosis,[5,8,32] and the possible presence of oligoclonal bands.[5] Elevated levels of 14-3-3 protein have also been occasionally reported but this is not a general finding.[8,37,38]

Electroencephalography and Neuroimaging

Electroencephalography (EEG) abnormalities are seen in patients with EAATD both at the time of presentation and then again after resolution of the symptoms and in the recovery phase. EEG studies often show non-specific slowing of the background electric activity.[5,28,35,39,40] Focal spikes or sharp waves and transient epileptic activity are less frequently observed.[5,39] Triphasic waves and frontal intermittent rhythmic delta activity have also been described. In some cases, EEG abnormalities recover rapidly with steroid treatment,[39] whereas others note that EEG improvement lags behind clinical improvement.[28,41] Again, no significant differences in the EEG pattern have been reported between HT and GD patients with EAATD, with the majority of the patients with abnormal EEG recordings often characterised by diffuse and non-specific slowing of the background EEG activity regardless of the type of ATD.[32,35] It appears that the EEG electric alterations are mainly localised in the temporal and/or frontotemporal region, and alternatively prevail on the two sides.[33]

The most appropriate set of radiological investigations and the advisable long-term follow-up studies in patients with EAATD have not yet been defined. Magnetic resonance imaging (MRI) and computed tomography (CT) of the brain could show a normal radiological pattern or intracranial changes that are either focal or diffuse. MRI is frequently normal; however, cerebral atrophy or non-specific tesla-2 (T2) signal abnormalities in the subcortical white matter area may be observed.[6,42,43] The latter findings have been described in approximately half of patients and are not shown to be associated with gadolinium enhancement.[5,6,28] This may be an incidental finding, although a number of reports have described regression or resolution of these findings after immunosuppressive treatment.[6] In some cases, diffuse or focal white matter changes at MRI suggest a process of primary demyelination.[6,36,42,44,45] Other findings noted in individual case reports include meningeal enhancement[36] and T2 signal abnormalities in the hippocampus region.[45] Follow-up imaging may help and inform on the radiological regression or resolution with treatment.[6]

Other radiological modalities, including CT, also reveal non-specific findings.[32,33,35] For example, cerebral angiography, when performed, appeared to be normal,[5] and SPECT may show focal, multifocal, or global hypoperfusion.[6,13,28,32] It is uncertain whether the perfusion defect on SPECT is attributable to vasculitis or is a secondary feature related to the autoantibody-mediated cerebral inflammation and oedema. Metabolic imaging such as 18-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) has been occasionally performed, suggesting the presence of a diffuse and multifocal cerebral hypometabolism.[32,43] The hypometabolic state appears to be transient and reversible following corticosteroid therapy, improvement of central nervous system symptoms, and the decrease of the anti-thyroid antibody titres. The underlying pathogenesis of the PET abnormalities is still unclear, but an autoimmune-mediated inflammation in multifocal brain structures could be the probable cause.[45]

Diagnosis

Considering the complexity of the clinical, laboratory, and radiological features of EAATD, the diagnostic criteria have not yet been clearly defined.[6,35] The diagnosis of EAATD often depends on a number of factors, including the neurological and psychiatric manifestations as well as the results of the laboratory and radiological investigations.[33] The finding of elevated anti-TPOAb or anti-TgAb in patients with a compatible clinical presentation is anyway essential for the diagnosis of EAATD. Thyroid hormones should also be measured, and clinically relevant abnormalities with an impact on the neurological or psychiatric functions should be ruled out with certainty. Essential hospital-based investigations to confirm EAATD and, conversely, to exclude other possible diagnoses should also include lumbar puncture and CSF analysis with routine biochemistry, cultures for microorganisms, cytology, and possibly target antibody screening. Brain CT and/or MRI with gadolinium administration

and EEG are also required for EAATD diagnosis and follow-up. Other laboratory and radiology testing for the most common causes of delirium, confusion, altered levels of consciousness, and stroke-like symptoms may be appropriate to exclude other diseases or abnormalities causing the symptoms.

The most common differential diagnoses to consider when EAATD is suspected include degenerative dementia (Alzheimer's disease, Lewy body dementia, or frontotemporal dementia), migraine (basilar or hemiplegic), cerebrovascular accidents (stroke or transient ischaemic attack), Creutzfeldt-Jakob's disease, and infective or neoplastic meningitis. In addition, acute disseminated encephalomyelitis, meningoencephalitis, paraneoplastic encephalitis, toxic metabolic encephalopathies, and, finally, psychiatric diseases such as depression, anxiety, or psychosis should also be considered. In acute and early medical management, most patients with a clinical presentation indicative of EAATD - or otherwise suggestive of a similar neurological disorder - should be investigated with various neuroradiology imaging, EEG, lumbar puncture, and targeted testing for appropriate biomarkers. The exclusion of paraneoplastic or non-paraneoplastic processes is critical for the differential diagnosis of an encephalopathy of unknown origin. Specific immunological testing, including the study of a number of antibodies to neuronal proteins, may be warranted to aid and avoid misdiagnosis.[46-48]

Treatment and Prognosis

The cornerstone of the treatment of EAATD is represented by the administration of corticosteroids or, as second line approach, other immunosuppressants. Once the medical treatment has been appropriately started, EAATD prognosis is usually satisfactory. Nonetheless, the persistence of neurological alterations and death cannot be excluded.[46,49] On the other hand, a spontaneous remission might also occur.[4,33,40] Given the rarity of the disorder and the lack of dedicated guidelines or an international expert consensus, an optimal corticosteroid dose and the subsequent treatment plan have not been defined. Oral prednisone doses ranging from 50-150 mg daily have been used.[5] High dosages of intravenous methylprednisolone have been administered in some patients, but its benefit compared with oral corticosteroids is unknown. From the literature, the majority of EAATD patients respond well to corticosteroids. Symptoms typically improve in a few days and resolve over a time ranging from days to a few weeks or, more rarely, months. The duration of the treatment and the rate of taper are generally titrated based on patient response and tolerance, though a 6-12-month treatment can be required. Other immunosuppressive medications for the treatment of EAATD include azathioprine and cyclophosphamide. These drugs are generally reserved for patients who do not respond to or cannot tolerate the corticosteroids. They are also given to patients with EAATD relapse after or during tapering of corticosteroid therapy.[10,28,50] Clinical improvement with intravenous immunoglobulin[51,52] or plasmapheresis[53-55] has been reported in individual cases. In addition, optimisation of the medical treatment for the underlying thyroid disease, and eventually the treatment of seizures with anticonvulsants, may be necessary.

The overall prognosis of EAATD is mostly good. Delay to diagnosis, and therefore treatment, might be associated with a less rapid or, potentially, incomplete recovery. Case series and reports suggest that patients can improve with treatment even after a few years from the onset of the EAATD symptoms. However, residual cognitive impairment occurs in about 25% of patients with long-standing untreated disease.[28,36,40] Rarely, spontaneous recovery can occur;[4,33,40] however, most reports of long-term follow-up are in treated patients.[5,6,32] Many of these patients remain disease-free after discontinuation of corticosteroids over several years of follow-up. Of course, reinitiating the corticosteroid treatment due to EAATD relapse or continuation of the same or other immunomodulatory/immunosuppressive treatment are possible options to take into account for maintaining remission.[36]

Alternative Denominations in Use for Defining EAATD

To date, there is still no consensus among researchers and clinicians with regards to adopting a univocal denomination of this condition.[56] EAATD was historically denominated by Hashimoto's encephalopathy, due to the fact that most patients have HT as background thyroid disease. However, such denomination may be misleading as it does not fit precisely to patients with GD and encephalopathy related to the same, and has never been universally used. Steroid responsiveness, for example, has been proposed as one of the possible criteria for making the diagnosis of EAATD. Hence, the term steroid-responsive encephalopathy associated with autoimmune

thyroiditis (SREAT) has been proposed as a possible definition alternative to EAATD.[36,44] This terminology, however, may not be conclusive again as some patients do not respond or are poorly responsive to corticosteroid treatment. Finally, it has also been suggested that such encephalopathy could be a variant of a non-vasculitic autoimmune inflammatory process, broadly termed NAIM.[26]

In our opinion, EAATD is the most precise denomination of this condition, as it takes into account the relationship of the encephalopathy with the ATD, regardless of the nature of the same (either HT or GD, which is not a thyroiditis), and it does not limit the definition to the patients who respond to corticosteroids.

SUMMARY AND AUTHORS' PERSPECTIVES

EAATD is a heterogeneous and complex condition arising from the background of an ATD. Such a condition may occur either in HT or GD patients. It may present either as a medical emergency or with a more gradual onset. Its course may be either progressive or relapsing with variable response to corticosteroids and other immunosuppressive therapies. Prompt investigations and treatment are warranted in patients with EAATD in order to achieve remission and minimise the risk of complications. The increasing number of EAATD cases in the literature demonstrates the growing interest of the scientific and medical community about this rare condition, which still requires a more thorough understanding of its pathophysiology, the definition of the criteria for the diagnosis, and the optimisation of the most advisable therapeutic approach.

The current clinical evidence about EAATD is based mainly on the report of single or small cohort studies. A universal and optimal diagnostic and therapeutic protocol has not yet been established. We wish to highlight the need for the development of an internationally acceptable and multidisciplinary characterisation of EAATD, with a particular regard to the definition, diagnosis, and management of such a condition.

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