FISEVIER

Contents lists available at ScienceDirect

# Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns



# Short communication

# Clinical manifestations, diagnostic criteria and therapy of Hashimoto's encephalopathy: Report of two cases

Milija Mijajlovic <sup>a,\*</sup>, Mihailo Mirkovic <sup>b</sup>, Jelena Dackovic <sup>a</sup>, Jasna Zidverc-Trajkovic <sup>a</sup>, Nadezda Sternic <sup>a</sup>

#### ARTICLE INFO

Article history:
Received 21 July 2009
Received in revised form 23 September 2009
Accepted 28 September 2009
Available online 28 October 2009

Keywords: Hashimoto's encephalopathy Clinical presentation Diagnostic criteria Therapy

## ABSTRACT

Hashimoto's encephalopathy (HE) is a rare, still not well understood, autoimmune disease with neurological and psychiatric manifestations. and elevated titers of antithyroid antibodies in serum and cerebrospinal fluid (CSF) as a hallmark of the disease. Patients are mostly women. Current diagnostic criteria include corticosteroide responsiveness, but it is the case in only 50% of patients with HE. In steroid non-responders other immunomodulatory therapies or plasmapheresis could be applied. Disease course can be acute, subacute, chronic or relapsing-remitting. Two distinct forms emerged from the reported cases: a vasculitic type characterized by multiple relapsing-remitting stroke-like episodes and mild cognitive impairment and a diffuse progressive type characterized by dementia and psychiatric symptoms. Both forms may be accompanied by depressed level of consciousness (stupor or coma), tremor, seizures, or myoclonus. We present two patients with two distinct forms of HE who had different clinical manifestations and response to therapy.

© 2009 Elsevier B.V. All rights reserved.

# 1. Introduction

Since the first description of this encephalopathy by Brain et al. [1] 40 years ago, just about 100 cases have been reported [2]. HE is characterized by various neuropsychological symptoms, including cognition and/or consciousness deterioration, personality changes, seizures and myoclonus [3–7]. Recently, this entity has attracted growing attention because it is included in the group of treatable dementias [5], and [8], it has also been recognized as one of the most important items for differential diagnosis of Creuzfeldt–Jakob disease [9–11]. Although autoimmune mechanisms are thought to play a pathogenetic role in HE, the etiology of the disease is still incompletely understood. It is closely associated with Hashimoto's thyroiditis (HT) and is thought to be caused by disorders of immune mechanisms. Most recent reports argue in favor of an inflammatory response to antineuronal antibodies [12,13].

Generally accepted diagnostic criteria are based on the presence of: cognitive impairment with or without neuropsychiatric symptoms; seizures; stroke-like events; focal neurological deficit or movement disorders; elevated antithyroid antibodies; and corticosteroid responsiveness [3]. Approximately 50% of HE cases have focal or diffuse nonenhancing brain magnetic resonance imaging (MRI) abnormalities and 50% respond to corticosteroid therapy.

On neurological examination, pyramidal tract signs without clear focal deficit are frequently found. Investigation of these patients characteristically shows diffuse electroencephalogram (EEG) abnormalities and high CSF protein levels without pleocytosis, although the most relevant issue is the high titre of antithyroid antibodies found in most cases [3]. Since there are no clinical, laboratory or neuroimaging findings that are specific for this entity, the exhaustive exclusion of infectious, metabolic, toxic, vascular, neoplastic and paraneoplastic causes of encephalopathy is mandatory.

We present two new cases with two distinct forms of HE: first with vasculitic or stroke-like type and second with diffuse progressive type.

## 2. Case 1

A 56-year-old woman with a history of relapsing stroke-like episodes of limbs weakness, especially legs, walking difficulties, tremor of arms and legs, cognitive and psychiatric changes, had 3 similar episodes during 2 years, and she was treated at the Institute of Neurology of the Clinical Center of Serbia in Belgrade. All episodes of limb weakness were of sudden onset. In the physical examination, the patient usually exhibited spontaneous and stimulus-induced myocloni in both arms and legs, she had severe paraparesis, inability to seat, stand or walk and she was extremely agitated, with visual hallucinations. Episodes of agitation lasted for several hours and were followed by somnolence lasting sometimes even up to 24h. The patient showed marked memory loss, and she reached 10 of 30 points in the Mini Mental State examination. The cranial MRI was normal and the EEG showed diffuse slowing without triphasic potentials. The CSF showed elevated total

<sup>&</sup>lt;sup>a</sup> Institute of Neurology, Clinical Center of Serbia, Dr Subotica 6, 11000 Belgrade, Serbia

<sup>&</sup>lt;sup>b</sup> Department of Neurology, General hospital Valjevo Sindjeliceva 62, 14000 Valjevo, Serbia

<sup>\*</sup> Corresponding author. Tel.: +381 11 2887348; fax: +381 11 2684 577. E-mail address: mmijajlovic@mail.neurologija.bg.ac.yu (M. Mijajlovic).

protein content (90 mg/dl), no pleocytosis and negative oligoclonal bands. There was no 14-3-3 protein in the CSF and we could not detect any antithyroid antibodies in the CSF.

In spite of intensive serological screening for infectious, toxic, paraneoplastic and metabolic etiologies, none could be determined. Routine blood tests, the levels of antinuclear and anti-DNA antibodies, angiotensin-converting enzyme, T3, T4, TSH and serum B12 and folic acid were normal. The serologic tests for borreliosis, syphilis and HIV were negative. The level of antithyroid peroxidase antibodies (TPO-Ab) in serum was raised (5250 IU/ml; normal < 50 IU/ml), while titer of antithyreoglobulin antibodies (TG-Ab) in serum was normal. She had HT which was histologically confirmed.

Following a high dose glucocorticoid therapy (methyl-prednisolone 1000 mg i.v.) over 5 days, the symptoms receded completely in all three relapses, with normalisation of EEG and serum level of antithyroid antibodies within 3–6 weeks. Subsequently, the methyl-prednisolone was tapered off within 6 weeks. At the same time, after last relapse, an immunsuppressive therapy with azathioprine was started, and she is taking it continuously until now. One year has passed after last relapse without new neuropsychiatric exacerbations and the patient returned to work and everyday activities.

#### 3. Case 2

A 75-year-old woman with slowly progressive memory loss during last 3 years, disorientation in space and time, lack of concentration, agitation and myocloni was admitted at the Neurology Department of General Regional Hospital in Valjevo. Past medical history revealed only a mild hyperthyroidism and HT which was proved by needle biopsy. In the Mini Mental Test she reached 20 of 30 points and detailed neuropsychological testing showed impairment of attention, declarative memory and executive functions. She was frequently confused with several episodes of moderate agitation lasting for several days. She had no focal motor, sensory, cranial nerve, or cerebellar abnormalities. Routine blood test, imunoserology, VDRL, TPHA, HIV, antibodies against Borelia burgdorferi, and serum vitamine B12 levels were normal.

Thyroid status showed euthyreosis with high titers of TG-Ab and TPO-Ab in serum (7884 IU/ml; normal <30 IU/ml and 8540 IU/ml, normal <50 IU/ml; respectively). In the CSF, by enzyme-immunoassay, we detected an elevated level of TPO-Ab:1133 IU/ml; (normal level:0); albumin CSF/serum quotient (Qalb) corrected by age was 7.7; (normal range: <9). The calculated intrathecal TPO-Ab index was 12.4, thus was suggestive of autochthone synthesis of thyroid autoantibodies in the CSF.

Angiotensin-converting enzyme in serum and CSF was in the normal range. Markers of autoimmune diseases were negative, including normal antinuclear antibody, rheumatoid factor level, anti-double stranded DNA antibody, anti-SS-A antibody, anti-SS-B antibody, anticardiolipin antibody and myeloperoxidase anti-neutrophil cytoplasmic antibody.

No clotting abnormalities were detected.

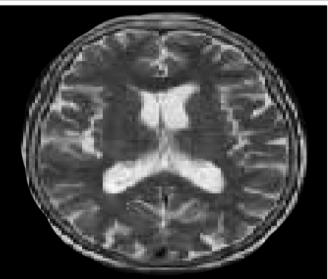
There was no CSF evidence of bacterial or viral infection, as determined by culture or molecular analysis, but total protein content was elevated (79 mg/dl) with parallel oligoclonal bands in CSF and serum. CSF showed normal pressure.

The EEG showed diffuse slowing without triphasic potentials and cranial MRI showed mild diffuse periventricular white matter hyperintensities on fluid-attenuated inversion recovery (FLAIR) and T2W images (Fig. 1).

She was treated with high dose glucocorticoid therapy (methyl-prednisolone 1000 mg i.v.) over 5 days, with tapering during 4 weeks but without clinical improvement.

Then an immunsuppressive therapy with azathioprine was introduced. Serum level of antithyroid antibodies was normalised, but in CSF it remained high and it correlated with no significant clinical improvement during 6 months of treatment and follow-up.





**Fig. 1.** Cranial MRI: FLAIR image and T2-weighted image reveals slight diffuse periventricular hyperintensities of the deep white matter.

#### 4. Discussion

The diagnosis of HE requires a relapsing-remitting or progressive encephalopathy associated with the existence of antithyroid antibodies [14,15]. Both cases fulfilled these general diagnostic criteria. In the first presented patient, symptoms and the clinical course belonged to the vasculitic or stroke-like type and in the second to the diffuse progressive type of HE.

The first set of criteria for the diagnosis of HE was published by Peschen-Rosin et al. in 1999 [7]. These criteria encompassed unexplained occurrence of relapsing myoclonus, generalized seizures, psychiatric disorders or focal neurological deficits and three conditions among which are: abnormal EEG, elevated thyroid antibodies, elevated CSF protein, excellent response to steroids and unrevealing cerebral MRI. After this early proposal the clinical range of symptoms and signs was much more widened and response to steroids has been shown to vary substantially. Recent publications suggest also that beside high serum titers, high cerebrospinal fluid titers of antithyroid antibodies could be more patognomonic [16] then corticosteroid responsiveness which occurs in only 50% of patients [7]. According to a recent analysis of published cases and case series, 42 patients on a 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 5 remained stable. Course after treatment differs from improvement (normal or with residual impairments) to chronic disease with fluctuations [17]. Our cases support this analysis of corticosteroid responsiveness in HE. Namely, the first patient with vasculitic type of HE had good response to corticosteroid therapy and remained stabile for 1 year, while the second, with diffuse progressive form of HE did not improve and the course of the disease after treatment was chronic with fluctuations.

Diagnostic criteria proposed by Peschen-Rosin et al. also underestimate the significance of raised antithyroid antibodies. Ferracci and Carnevale in 2006 [17] summarized the diagnostic principle followed by the majority of authors: after ruling out of other diagnoses, the elevated serum antithyroid antibodies support the diagnosis of HE but is 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 is recurrent neurological illness mostly presented as generalized seizures, myoclonus, ataxia, cognitive defects, focal neurological deficits and other signs, high antithyroid antibodies in serum and CSF, non-specific EEG changes, non-specific MRI white matter changes, elevated CSF proteins and possibly abnormal thyroid functional tests [18].

Elevated titers of antithyroid antibodies (especially TPO-Ab) are the most relevant paraclinical finding, which could be considered to be a hallmark of HE. We found elevated serum levels of TPO-Ab in the patient with vasculitic type HE and TPO-Ab and TG-Ab in the second patient with diffuse progressive type of HE. Both types of antibodies were predominantly detected in HE [19]. In the CSF, cell count is found to be normal in most cases [6,7], like it was in our patients.

Analysis of neurochemical CSF parameters reveals usually pathological results like oligoclonal bands [14] or an increased total protein concentration [17,20]. Both findings were shown in our patients. In our patient with diffuse progressive type of HE, there was evidence for an intrathecal synthesis of antithyroid antibodies. In the study of Ferracci and Carnevale, 16 HE patients were tested and all of them had elevated titers of TG-Ab and TPO-Ab in CSF. Serum and CSF specimens were evaluated also for albumin CSF/serum quotient (Qalb), specific TG-Ab and TPO-Ab index according to the formula AbCSF/AbSerum: IgGCSF/IgGSerum [17,21].

In 70 control patients there were neither elevated TG-Ab nor TPO-Ab CSF titers [17]. Antithyroid antibodies in CSF are undetectable even in patients with autoimmune thyroiditis or other neurological disorders [22]. The normal autoantibody concentration was zero or had an absorbance value that could not be reliably distinguished from zero (range 0–8 Ul/ml), even in the presence of blood–brain barrier dysfunction [16,17,21]. However, in our patient, the raised TPO-Ab-specific indexes and the normal Qalb are consistent with the integrity of the blood–brain barrier and the intrathecal synthesis of autoantibodies.

The second case we presented, points out the need for reevaluation of current diagnostic criteria for HE. Namely, this patient had not responded to glucocorticoid therapy, but had high CSF titers of antithyroid antibodies which remained elevated after high dose glucocorticoid therapy.

Further measurements of the antithyroid antibodies in CSF and serum in a larger number of subjects are needed to clarify the significance of the elevated CSF titer of antithyroid antibodies in the etiology and prognosis of HE.

The EEG is a good apparative marker for the effect of pharmacological treatment and correlates well with the clinical course of HE [7,10], as shown in our first case in which clinical improvement correlated with EEG normalisation.

The most common MRI findings are small bilateral subcortical highsignal lesions [6] like it was shown in our second case with diffuse progressive type of HE. Presented cases show, that all patients with recurrent stroke-like episodes, progressive cognitive impairment or with a dementia of unclear origin should be tested for an HE.

The diagnosis of HE should be considered even if Hashimoto's thyroiditis is not known in patients with even normal thyroid function but with high serum and/or CSF titers of antithyroid antibodies. It is important for the clinicians to be aware that only about 50% of cases respond completely to corticosteroid therapy, thus non-responsiveness should not be exclusion criteria for HE. In patients with steroid resistance, other therapeutical strategies should be tried: immunosuppresive therapy (azathioprine or cyclophosphamide) and recently proposed in some cases plasmapheresis or intravenous immunoglobulins [23] [24].

#### Acknowledgments

This work was funded by the Ministry of Science, Republic of Serbia (Project No. 145025D).

#### References

- [1] Brain L, Jellinek EH, Ball K. Hashimoto's disease and encephalopathy. Lancet 1966:2:512-4.
- [2] Chong JY, Rowland LP, Utiger RD. Hashimoto encephalopathy: syndrome or myth? Arch Neurol 2003;60:164–71.
- [3] Shaw PJ, Walls TJ, Newman PK, Cleland PG. Hashimoto's encephalopathy a steroid responsive disorder associated with high anti-thyroid antibody titers. Report of 5 cases. Neurology 1991;41:228–33.
- [4] Henchey R, Cibula J, Helveston W, Malone J, Gilmore RL. Electroencephalographic findings in Hashimoto's encephalopathy. Neurology 1995;45:977–81.
- [5] Ghika-Schmid F, Ghika J, Regli F, Dworak N, Bogousslavsky J, Städler C, et al. Hashimoto's myoclonic encephalopathy: an underdiagnosed treatable condition? Mov Disord 1996;11:555–62.
- [6] Kothbauer-Margreiter I, Sturzenegger M, Komor J, Baumgartner R, Hess CW. Encephalopathy associated with Hashimoto thyroiditis: diagnosis and treatment. J Neurol 1996;243:585–93.
- [7] Peschen-Rosin R, Schabet M, Dichgans J. Manifestation of Hashimoto's encephalopathy years before onset of thyroid disease. Eur Neurol 1999;41:79–84.
- [8] Galluzzi S, Geroldi C, Zanetti O, Frisoni GB. Hashimoto's encephalopathy in the elderly: relationship to cognitive impairment. J Geriatr Psychiatry Neurol 2002;15:175–9.
- [9] Forchetti CM, Katsamakis G, Garron DC. Autoimmune thyroiditis and a rapidly progressive dementia: global hypoperfusion on SPECT scanning suggests a possible mechanism. Neurology 1997;49:623–6.
- [10] Seipelt M, Zerr I, Nau R, Mollenhauer B, Kropp S, Steinhoff BJ, et al. Hashimoto's encephalitis as a differential diagnosis of Creutzfeldt-Jakob disease. J Neurol Neurosurg Psychiatry 1999;66:172-6.
- [11] Doherty CP, Schlossmacher M, Torres N, Bromfield E, Samuels MA. Hashimoto's encephalopathy mimicking Creutzfeldt–Jakob disease: brain biopsy findings. J Neurol Neurosurg Psychiatry 2002;73:601–2.
- [12] Oide T, Tokuda T, Yazaki M, Watarai M, Mitsuhashi S, Kaneko K, et al. Anti-neuronal autoantibody in Hashimoto's encephalopathy: neuropathological, immunohistochemical, and biochemical analysis of two patients. J Neurol Sci 2004;217:7–12.
- [13] Takahashi S, Mitamura R, Itoh Y, Suzuki N, Okuno A. Hashimoto encephalopathy: etiologic considerations. Pediatr Neurol 1994;11:328–31.
- [14] Hartmann M, Schaner B, Scheglmann K, Bucking A, Pfiste R. Hashimoto enzephalopathie. Nervenarzt 2000;71:489–94.
- [15] Nolte KW, Unbehaun A, Sieker H, Kloss TM, Paulus W. Hashimoto encephalopathy: a brainstem vasculitis? Neurology 2000;54:769–70.
- [16] Ferracci F, Moretto G, Candeago RM, Cimini N, Conte F, Gentile M, et al. Antithyroid antibodies in the CSF: their role in the pathogenesis of Hashimoto's encephalopathy. Neurology 2003;60:712–4.
- [17] Ferracci F, Carnevale A. The neurological disorder associated with thyroid autoimmunity. J Neurol 2006;253:975–84.
- [18] Karadeniz M, Erdogan M, Özgen AG. Hashimoto's encephalopathy. Turkish J Endocrinol Metab 2005;2:33–43.
- [19] Magy L, Vallat JS. Hashimoto's encephalitis. Rev Neurol (Paris) 2002;158:966-70.
- [20] Archambeaud F, Galinat S, Regouby Y, Magy L, Rebeyrotte I, Vallat JM, et al. Hashimoto encephalopathy. Analysis of four case reports. La Revue de Médicine Interne 2001;22:653–9.
- [21] Ferracci F, Bertiato G, Moretto G. Hashimoto's encephalopathy: epidemiologic data and pathogenetic considerations. J Neurol Sci 2004;217:165–8.
- [22] Katoh N, Yoshida T, Shimojima Y, Gono T, Matsuda M, Yoneda M, et al. An 85-year-old case with Hashimoto's encephalopathy, showing spontaneous complete remission. Intern Med 2007;46:1613–6.
- [23] Boers PM, Colebatch JG. Hashimoto's encephalopathy responding to plasmapheresis. J Neurol Neurosurg Psychiatry 2002;73:601.
- [24] Jacob S. Y A Rajabally, Hashimoto's encephalopathy: steroid resistance and response to intravenous immunoglobulins. J Neurol Neurosurg Psychiatry 2005;76:455–6.