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Movement disorders in non-encephalopathic Hashimoto´s thyroiditis

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Abstract

Background: Encephalitis as a neurologic manifestation of Hashimoto`s thyroiditis (HT) is a well recognized entity, but less has been discussed about movement disorders as a clinical presentation of this autoimmune condition.

Objective: To discuss the clinical features, laboratory findings and response to treatment of movement disorders associated to HT.

Methods: We report two cases presenting as movement disorders associated to thyroiditis, which show improvement with treatment of the underlying disorder.

Results: The presence of thyroid antibodies in the cerebrospinal fluid is a key finding for the diagnosis, as thyroid function measures are not necessarily altered.

Conclusion: Increased awareness of movements disorders as a neurologic manifestation of thyroiditis is relevant for identifying potentially treatable cases.

Background

Since the seminal report of Lord Brain et al. in 1966[1], neurologic manifestations of Hashimoto´s thyroiditis (HT) have been increasingly recognized and it is now evident that clinical features are diverse and response to steroids is variable[2-6]. The term "steroid-responsive encephalopathy associated with autoimmune thyroiditis" (SREAT) has been proposed for this condition[7] , however, as illustrated here, encephalopathy may be absent, as may clinical response to steroids, thus we choose to use the original term. Movement disorders occur most often in the setting of encephalopathy; myoclonus is the commonest manifestation but also dystonia, ataxia, tremor, and rarely chorea, have been described[4-6]. We present two patients with movement disorders as the initial and dominant neurologic manifestation, and discuss their variable responses to treatment.

Case reports

Case 1

A 61-year-old patient without a family history of neurologic disease presented to our clinic with a 6-year history of myoclonic jerks in limbs and trunk.

Cognition was normal. He had mild dysarthria and severe myoclonus affecting both upper limbs, more prominent on the right, present at rest, and increased with action. He also had dystonia of the right hand (video segment 1). Gait was mildly ataxic and appeared rigid due to leg dystonia.

MRI of the brain, DAT scan and EEG were normal, as were routine laboratory evaluations. CSF was normal apart from the presence of oligoclonal bands. Anti-DNA, ENA, anti-phospholipid, and anti-cardiolipin antibodies were all negative. CSF and serum samples were negative for antibodies to cell surface and intracellular neuronal

antigens (including the glycine receptor). No expansion of the *FMR1* gene was found, and genetic testing for spinocerebellar ataxias (SCA) 1, 2, 3, 6, and 17 was unremarkable.

Anti-transglutaminase and anti-endomisium antibodies had been abnormal prior to the appearance of his neurologic symptoms. At the time of neurological presentation, he was on a strict gluten-free diet, and celiac antibodies and duodenal biopsy were normal.

Anti-thyroxine peroxidase (TPO) antibodies were high at 174 IU/ml (normal <34) in serum and in CSF (18 IU/ml). Anti-thyroglobulin antibodies and thyroid hormones were normal. Thyroid gland ultrasound showed signs of thyroiditis.

He was treated with intravenous (i.v.) immunoglobulin with no improvement. One month later he was given methylprednisolone 1g daily for 5 days, then oral prednisone 1 mg/kg for 4-6 weeks followed by a slow taper, without benefit. Plasma exchange also resulted in no benefit. Rituximab therapy was then started with only mild improvement in spite of reduction of thyroid antibodies to normal range.

Case 2

This 38-year-old female with a negative family history of neurologic disease was well until age 34 when she had a sudden onset (overnight) and rapid progression of slurred speech, choreoathetosis of the left upper limb, dystonia of the both arms, and gait instability (video segment 2). Routine laboratory evaluations and brain imaging were normal. Repeat expansion testing of huntingtin (*HTT*) gene and *C9orf72*, and targeted mutation screening of ferritin light chain (*FTL*), SCAs 1, 2, 3, 17, and DRPLA genes were negative.

After 2 years of follow-up, chorea became generalized and dysarthria was severe, significantly affecting her activities of daily living. Haloperidol, risperidone,

trihexyphenidyl and clonazepam were administered sequentially, with short-lived partial relief of the symptoms.

On follow-up at four years she had worsened chorea and dystonia, dysphagia, and dysarthria although cognition remained normal. She was found to have high serum titers of anti-TPO (770 IU/ml; normal < 34), anti-thyroglobulin (TG) antibodies (106 IU/ml) (normal < 100), and thyroid ultrasound was consistent with thyroiditis. Thyroid hormones were normal. CSF was normal apart from the presence of oligoclonal bands. CSF anti-TPO antibodies were elevated (61.1 IU/ml) as were thyroglobulin antibodies (21 IU/ml).

The patient was treated with methylprednisolone 1g daily for 5 days and i.v. immunoglobulin with clear improvement (video segment 3), which was maintained at 2 months of follow-up.

Discussion

Our experience provides further evidence[2,4] that patients with HT can present with a movement disorder without encephalopathy, and emphasizes that the analysis of thyroid antibodies in serum and CSF must be included in the screening of a patient with a movement disorder with uncertain diagnosis even if thyroid functioning is normal and the clinical evolution is chronic.

The term Hashimoto´s encephalopathy classically denotes a condition with a relapsing and remitting course which includes seizures, stroke-like episodes, cognitive decline, neuropsychiatric symptoms, and myoclonus. Thyroid function is usually clinically and biochemically normal[1,6,8].

A direct causal relationship between thyroid antibodies and neurological manifestations is unlikely because at least one of our patients showed reduction of thyroid antibodies with the immunosuppressive therapy without marked clinical improvement. Case 2 with

disease duration of 4 years had a marked improvement with immunotherapy, whereas case 1 with a 6 year history did not, thus it is possible that the longer the symptomatic period before a correct diagnosis is made and treatment initiated, the lower the chance of improvement after immunodulatory therapy.

There is a high prevalence of thyroid antibodies in healthy subjects[6], thus the association with a particular neurological manifestation may be questionable[4,6]. However, evidence of intrathecal synthesis of antibodies may be more definitive evidence of an etiologic relationship[2,3,6,8]. Ferraci and colleagues reported the presence of TPO and TG antibodies in CSF in their 6 neurologic patients but not in 21 control subjects (one of whom had positive serum antibody titers)[2]. Serum antibody levels did not correspond with the severity of the clinical deficits[3,6], suggesting that they are more useful for the initial screening of the condition; the clinically relevant issue for diagnosis seems to be the presence of thyroid antibodies in CSF that are normally absent [2,6,8]. More recently, investigators have detected anti α-enolase antibodies in patients diagnosed with Hashimoto's encephalopathy, but not controls[9].Although this auto-antigen is detected in brain and thyroid tissue, its significance in Hashimoto's encephalopathy and utility in diagnosis remains to be demonstrated.

The underlying pathogenesis of the disorder remains unclear. The putative role of thyroid autoimmunity in the pathogenesis of the neurologic manifestations is complicated by the fact that serum anti-TPO antibody levels are elevated in approximately 10% of healthy adults[6]. Thyroid autoantibodies are also commonly found in patients with other autoimmune neurologic disorders, including paraneoplastic and non-paraneoplastic limbic encephalitis[6]. It therefore seems unlikely that the thyroid antibodies are the direct cause of the neurological manifestations; it is possible that they are only a marker of the condition, and that other unidentified autoantibodies are more directly involved in the pathogenesis of neurological syndromes caused by HT.

This diagnosis should be considered in any patient with a chronic, undiagnosed movement disorder regardless of whether they are euthyroid or mildly hypothyroid. We hypothesize that a favorable treatment response is more likely in patients with a shorter disease duration, thus early diagnosis is critical. Further investigations assessing the reliability of the detection CSF thyroid autoantibodies or other antibodies no yet identified are needed to improve the diagnosis and understanding of the pathophysiology of this condition.

Author contributions

M. Miranda - Study conception, organization, and execution; writing of the first draft and review of the manuscript.

M.L. Bustamante - Study conception and review; manuscript review.

M. Campero – Study execution and review; manuscript review.

E. Wainstein - Study execution and review; manuscript review and critique.

P. Toche – Study execution; manuscript review.

A.J. Espay - Critical revision of the manuscript for important intellectual content.

R.H. Walker - Critical revision of the manuscript for important intellectual content.

A.E. Lang -critical revision of the manuscript for important intellectual content.

Dr. Ruth H. Walker and Dr. Anthony Lang contribute equally as co-last authors.

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Legend to the video:

Case 1 with right hand and bilateral lower limb dystonia (on standing), bilateral rest, postural and action myoclonus, more severe in the right limbs.

Case 2 with bilateral arm dystonia, choreoathetosis of left arm, risus sardonicus, before and after immunotherapy, with a significant improvement in her symptoms.

References

1. Lord Brain, Jellinek EH, Ball K. Hashimoto's disease and encephalopathy. Lancet 1966;ii:512–514.
2. Ferracci F, Moretto G, Candeago RM, et al. Antithyroid antibodies in the CSF: their role in the pathogenesis of Hashimoto's encephalopathy. Neurology 2003;60:712-714
3. Ferracci, F, Bertiato G, Moretto G. Hashimoto's encephalopathy: epidemiologic data and pathogenetic considerations. J Neurol Sciences 2004;217,165-168
4. Selim M, Drachman DA. Ataxia associated with Hashimoto's disease: progressive non-familial adult onset cerebellar degeneration with autoimmune thyroiditis. J Neurol Neurosurg Psychiatry 2001;71:81–87
5. 5. Rožanković PB, Rožanković M, Šušak I,Vlahović I, Sporis D. Steroid-responsive autoimmune encephalopathy associated with autoimmune thyroiditis (SREAT) presenting with myoclonus-dystonia syndrome. J Neurol Sci 2015;354(1-2):110-111
6. Mocellin R, Walterfang M, Velakoulis D. Hashimoto's encephalopathy : epidemiology, pathogenesis and management. CNS Drugs 2007;21(10):799-811
7. Castillo P, Woodruff B, Caselli R, Vernino S, Lucchinetti C, Swanson J, et al. Steroid responsive encephalopathy associated with autoimmune thyroiditis. Arch Neurol Feb 2006;63(2):197–202.
8. Shaw PJ, Walls TJ, Newman PK, et al. Hashimoto's encephalopathy: a steroid responsive disorder associated with high antithyroid antibody titres—report of 5 cases. Neurology 1991;41:228–233.

9. Fujii A, Yoneda M, Ito T, et al. Autoantibodies against the amino terminal of alpha-enolase are a useful diagnostic marker of Hashimoto's encephalopathy. J Neuroimmunol 2005; 162: 130-136