Hashimoto's Encephalopathy: Benefit from Chronic Immunosuppressive Therapy in Steroid Non-Responder

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Abstract: Hashimoto's Encephalopathy (HE) is thought to be a steroid-responsive process. However, there have been several cases reported in the literature that did not respond to steroids and requiredintravenous immunoglobulin, plasmapheresis or oral immunosuppressants. This is a case of a 67-year-old lady with rapidly progressing altered mental status over four weeks. MRI brain showed extensive diffuse white matter changes without contrast enhancement. EEG showed diffuse slowing and triphasic waves. Meningitis-encephalitis, paraneoplastic and autoimmune encephalitides, and Creutzfeldt-Jacob disease were ruled out through cerebrospinal fluid analysis and serological studies. Work-up revealed an elevated thyroid-peroxidase (TPO) antibody titer. Patient was treated for HE initially with 6-day course of high-dose IV methylprednisolone with a failure to improve; followed by a 5-day course of IVIG (2 mg/kg) with minimal improvement;then maintenance methotrexate 2.5 mg weekly with a good response -neurological exam improved significantly, and brain MRI demonstrated improvement of supratentorial lesions, and resolution of cerebellar T2/FLAIR hyperintensities. At 2-month clinic follow-up, patient's mentation was back to baseline with ability to perform activities of daily living (ADLs) with minimal support. Hence, methotrexate taper was attemptedbut had subsequent worsening of confusion and functional status, which required resumption of the therapy. The chronic management of this debilitating illness is poorly understood, especially in the steroid non-responders. Further clinical studies should be directed towards better understanding of the natural course of this disease and to reach a consensus about the chronic management of the relapsing forms. [Shah V Natl J Integr Res Med, 2019; 10(1):54-57]

Key Words: Hashimoto's Encephalopathy, Non-vasculitic autoimmune meningoencephalitis (NAIM), Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT)

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Introduction: Hashimoto's Encephalopathy (HE), also known as steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT)[1], falls under a broader category of encephalitides known as non-vasculitic autoimmune meningoencephalitis (NAIM).[2] This is a rare clinical entity defined as a syndrome of rapidly progressive encephalopathy associated with elevated serum antithyroid antibodies which is usually responsive to glucocorticoid therapy. [3]

This nomenclature is misleading as glucocorticoid responsiveness is not a norm and there have been several cases reported in the literature with no clear benefit from glucocorticoid therapy. Interestingly, Lord Brain's patient described in the Lancet paper of 1966, which was the first description of encephalopathy in association with autoimmune thyroiditis, did not respond to prednisone treatment for more than a year. [4]

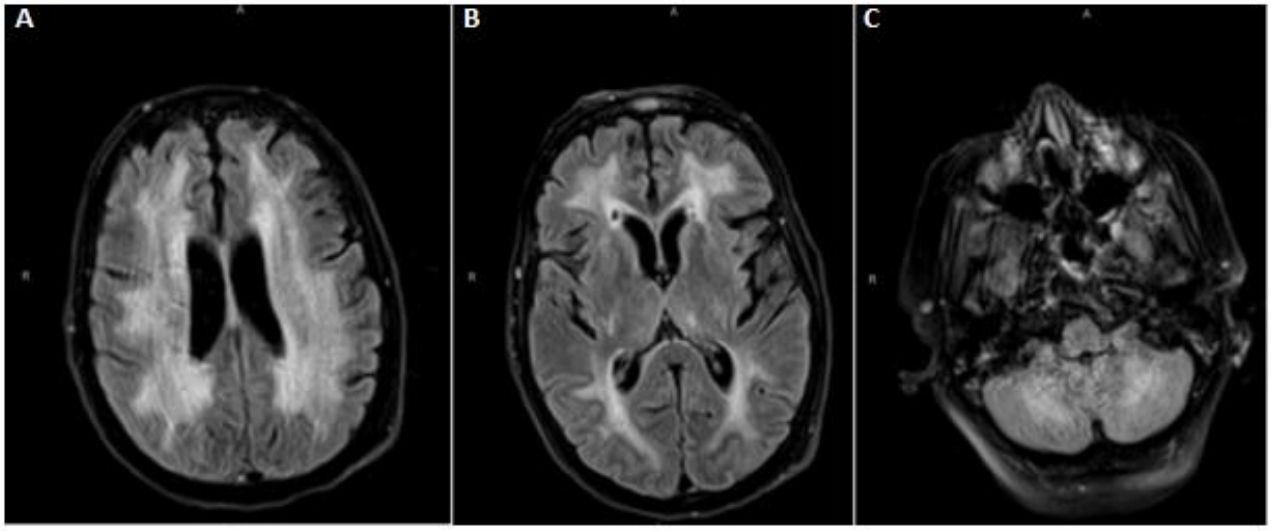
The exact pathophysiology and hence the best treatment approach for HE is still unclear. Female predilection, benefit from immunosuppression, and association with other autoimmune diseases point towards an immune-mediated process. However, a head-to-head comparison of steroid, plasma exchange, intravenous immunoglobulins, and immunosuppressants is lacking. Thus, there is no clear consensus as to how this disease should be treated. Further, whether this disease is a monophasic event or has a chronic relapsing course is poorly studied.

This is a case of encephalopathy associated with elevated TPO antibody titer– requiring chronic immunosuppressant therapy – highlighting the variability of clinical course and treatment response in this patient population..

Case Report: A 67-year-old right-handed Caucasian lady with a history of colon cancer and recent prolonged hospitalization for urosepsis and acute respiratory failure was transferred to our institute with rapidly progressing altered mental status over four-week duration. Clinical course was significant for a fluctuating mental status associated with agitation, behavioral changes, visual hallucinations and myoclonus without interval return to her pre-morbid baseline. Neurologic exam was remarkable for delirium, diffuse rigidity, generalized weakness from deconditioning and extensor plantar response in right foot. Initially, differential

diagnosis included paraneoplastic, infective or autoimmune process. MRI brain showed extensive diffuse white matter changes in periventricular white matter, deep white matter and cerebellum without contrast enhancement (Image 1).

Fig. 1: (A,B,C): MRI Brain T2/FLAIR Images prior to treatment show diffuse white matter disease in corona radiate (A), periventricular white matter (B), and cerebellum (C).

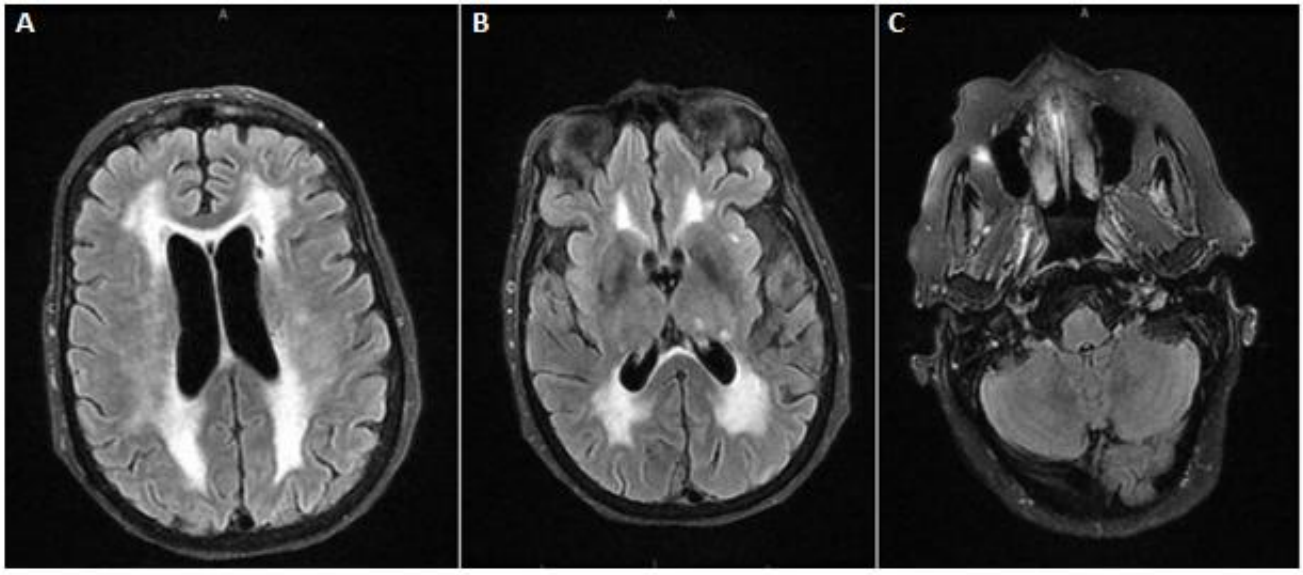


EEG showed diffuse slowing and triphasic waves. CSF studies for cell count, chemistry, cultures, cytology, meningitis-encephalitis panel, paraneoplastic panel, autoimmune-encephalitis panel, Anti-GAD Abs, electrophoresis, and JC virus were negative. Thyroid-peroxidase (TPO) antibodies titer was found to be 787.9 Units (Ref: 0-100 WHO Units), TSH was 1.69mIU/L and free T4 was 0.84 ng/dL. She was clinically euthyroid despite elevated TPO titer. Encephalopathy was attributed directly to the auto-immune process as there was no biochemicalor clinical evidence of thyroid dysfunction. Thus, the diagnosis of Hashimoto's Encephalopathy was made. She was started on 1 gm IV methylprednisolone, but after the first dose, her visual hallucinations and psychosis worsened. Steroid was held for two days following which it was resumed at 500 mg IV in two divided doses for a total of 5 more days. Her mentation continued to wax and wane and had persistent delusions and hallucinations. Intravenous immunoglobulin (IVIG) was started at a dose of 2 g/kg over 5 days. Mentation improved, and she became more conversational upon completion of IVIG therapy. Nonetheless, was not back to her premorbid functional status. Thus, a decision was reached to treat her with methotrexate for chronic immunosuppression. Plan was to start at 2.5 mg Methotrexate PO weekly with a slow up-titration towards a target dose of 15 mg weekly. In hospital, patient's neurological exam improved significantly, was more alert and interactive, and consistently followed 2-step commands. A repeat MRI brain at discharge demonstrated improvement of supratentorial white matter and brainstem lesions, and also resolution of cerebellar hyperintensities. (Image 2) At 2-month clinic follow-up, patient's mentation was back to baseline with ability to perform ADLs with minimal support and was still at a 2.5 mg weekly dose. TPO titer down-trended to 540.1 units. Methotrexate dose was reduced to 2.5 mg every two weeks, 2 months after initially starting it. She was noted to have worsening confusion, hallucination and delusions. Further follow up clinic visits, repeat MRI brain, and neuropsychological testing were not performed as family opted for hospice care.

Discussion: Hashimoto's Encephalopathy was originally described by Lord Brain in 1966. It was thought to be an autoimmune process unrelated to the systemic effects of thyroid dysfunction. It presents as a clinical syndrome of encephalopathy, seizures, myoclonus and neuropsychiatric symptoms along with elevated TPO antibodies.

HE is underreported in the literature [5, 6] and its prevalence is estimated to be 2.1 per 100,000. [7] Women are more prone to HE, with a mean age of onset of initial symptoms being 41 to 44 years. Etiopathogenesis is not clearly understood.

Fig. 2 (A,B,C): MRI Brain T2/FLAIR Images after treatment show marked improvement in the white matter changes in corona radiate (A), periventricular white matter (B), and cerebellum (C).



Direct antibody-mediated neuronal injury, immune complex mediated vascular injury, or primary demyelination like acute demyelinating encephalomyelitis has been suggested. [8, 9, 10]
The long-term clinical course could be self-limited, relapsing-remitting, or progressive. [11] Treatment options for these clinical variants differ and it should be bore in mind at the time of onset of therapy. While structured research studies lack in this field, Marshall et al. recommended a step wise treatment approach. Reversible causes like hypothyroidism, status epilepticus, and toxic-metabolic encephalopathy should be aggressively treated. [11]

Once no secondary explanation for altered mentation is found, 5-day high dose steroid trial must be attempted. If patient has a relapsing-remitting course with fluctuating symptoms, IVIG or plasma exchange may be tried in an acute setting. Ultimately; to help with long term remission, chronic immunosuppressant therapy with or without steroid should be tried. Literature review suggests use of azathioprine, methotrexate, cyclophosphamide, plaquenil, periodic IVIG or plasmapheresis in varied combination.[11] Choice of this agent should be carefully done depending on pre-existing comorbidities, social situation, adherence to treatment, ability to tolerate oral intake, and tolerance and response to therapy.

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