Hashimoto's Encephalopathy: A Case series and its Impact on Psychiatric Illness

Elizabeth Nicole Shaffer, M.D.[1], Sree Latha Krishna Jadapalle, M.D.[1] , Kenneth Fleishman, M.D.[1]
[1]Psychiatry, Cape Fear Valley Health System; Campbell University Psychiatry Residency Program, Fayetteville, North Carolina,
Eshaffer@capefearvalley.com, http://www.capefearvalley.com/residency/programs/psychiatry-home.html

Abstract

Background: Hashimoto's Encephalopathy (HE) was first described in 1966, and over 200 cases have been since described. HE is a rare condition, but if left untreated, it can have severe and long-lasting consequences. Schizophrenic-like presentations occur in less than 10% of patients with HE [5]. Steroids are considered a first-line treatment as HE is a steroid-responsive encephalopathy. Yet, steroids are seldomly used by most physicians if brain MRI is normal or psychosis is the primary symptom [4]. It is worth noting; a normal brain MRI is part of the diagnostic criteria for HE [Table 1.]

Cases/Discussion: We present three HE patients at different stages of lifespan; pediatric, adult, and geriatric. These cases illustrate challenges regarding treatment and outcomes, especially when symptoms are schizophrenic-like. Our pediatric patient (P1) presented with first-onset psychosis; her TSH was significantly elevated. When followed through with T3, T4, and TPO antibodies, psychiatry confirmed HE diagnosis. Her psychosis improved after Synthroid and antipsychotics. On outpatient follow-up, she had discontinued all treatments and decompensated, requiring another admission. Both adult (P2) and geriatric (P3) cases had previous diagnoses of schizophrenia. P2 was intellectually disabled and had never received treatment for HE despite a long history of thyroid issues per collateral. P3 had been non-compliant with her medications, and multiple trials of antipsychotics did not improve her psychosis. It was not until her Synthroid dose became therapeutic that her psychosis showed significant improvement. She had also developed early-onset dementia, which we believe is from chronic HE. Untreated HE can cause cognitive impairment (Savarimuthu, 2019). P1 & P3 both had received Synthroid and had significant improvement in psychotic symptoms after several weeks. P2 never started Synthroid and had minimal to no progress on antipsychotics alone. Still, treatment with steroids never commenced due to concerns for steroids' potential to worsen psychosis, and Internal medicine/neurology stated there was no indication. We believe this delay resulted in their prolonged disease process and subsequent relapse/re-admission.

Conclusion/Implications: These cases highlight the need for regular TSH screening and, if appropriate, screening for T3, T4, and TPO antibodies in psychotic patients, even in previously diagnosed schizophrenia. These cases also pose the question: 'should psychiatrists consider using steroids in acute HE cases?' Most physicians steer away from steroids, especially when psychosis is involved. The use of antipsychotics in cases of HE with psychosis does lead to some improvement. However, while antipsychotics treat the psychosis, its does not treat the actual cause [1,4,6]. In our cases, P1 & P3, both treated with Synthroid, showed significant improvement in psychosis. Whereas P2 did not receive treatment and her symptoms improved minimally on Abilify. We suspect ignoring the recommended therapy of steroids will lead to developmental delays/cognitive impairment and early onset of dementia. P1 developed new-onset developmental delays with the start of her symptoms, indicating HE's potential impact on cognitive functioning. P2 had an established diagnosis of intellectual disability with long-standing untreated thyroid disease. It is important to note that similar to SSRIs, Synthroid can take 3-6 weeks before TSH starts to decrease and symptoms resolve. Considering a brief course of steroids may be warranted for an accelerated symptom resolution, especially when symptomatology makes discharge difficult due to lack of functioning.

Learning Objectives:

- To learn and understand why steroids are the first-line treatment for HE.
- To learn and understand essential diagnostic criteria for HE in both pediatric and adult patient populations.
- To learn and understand the importance of regular TSH screening in patients with psychosis, even if it is not new-onset.

Introduction

HE is a rare and controversial neuropsychiatric illness with a recently estimated prevalence of 2.1/100,000. A literature review reported a mean age at onset of 44 years, about a fifth of cases under 18 years of age, and a 4:1 female/male ratio [4]. There is a strong suspicion for underdiagnosis of the pediatric population and those already labeled as schizophrenic [1].

The Neuropathophysiology of HE is suspected to derive from the deposition of immune complexes. Antithyroid antibodies and antigens cluster together within intracranial vessel walls—essentially causing a form of vasculitis, which ultimately causes infarction within cerebral tissues. As in other conditions of autoimmune encephalopathies, antibodies against NH2 terminal alpha-enolase (NAE) cause a breakdown of the blood-brain barrier and cause significant damage to brain parenchyma. Anti-NAE autoantibodies in CSF serum have a specificity of 90%.

However, CSF samples are not part of the diagnostic criteria in the pediatric population. Like vascular strokes, infarcts from HE appears to be easily reversible if caught early [1,5,6, Fig. 2]. In theory, this would further stress the need to diagnose and treat HE early.

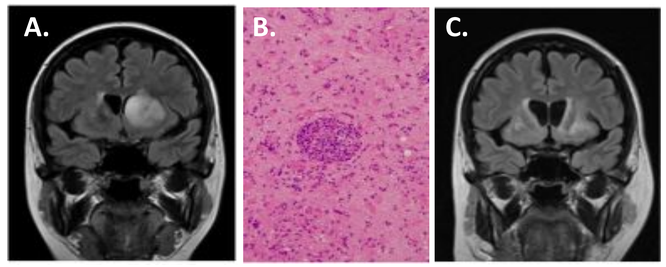

Fig. 2. Images taken from a recent case report illustrate pathology and the level of improvement that can be seen after using steroids or azathioprine. A) Coronal FLAIR-MRI showing HE before treatment. B) H&E stain of brain biopsy specimen show gliosis with perivascular lymphocytic infiltration. C) Axial and coronal FLAIR-MRI showing regression of signal intensity after administration of steroids or azathioprine. The particular patient was hospitalized for five months and received a brain biopsy for a suspected tumor. A simple CSF serum revealed anti-NAE autoantibodies at the end of a 5-month hospitalization. Diagnosis of HE was then considered confirmed. [6]

Diagnostic Criteria for Hashimoto's Encephalopathy

1. **Encephalopathy** with seizures, myoclonus, cognitive impairment, **hallucinations**, or stroke-like episodes
2. Presence of **high serum thyroid (TPO, TGB)** antibodies (no disease-specific cut-off)
3. Reasonable exclusion of alternative cause
4. **Neurological status** returns to **baseline after steroid therapy**.

Table 1. [4] Other literature reviews suggest additional criteria for diagnosis, such as the Absence of well-characterized neuronal antibodies in the serum or CSF, normal brain MRI or nonspecific abnormalities, and Subclinical or mild overt thyroid disease (usually hypothyroidism), in addition to the criteria mentioned above [8]. Using the more simplified criteria above may be more helpful, especially in cases like ours with severe paranoia or agitation. These types of patients may have delayed treatment due to unwillingness to participate in MRI or Lumbar Punctures.

Modified criteria for Pediatric HE

A. **Abrupt-onset cognitive regression** with deficits in one or more other neuropsychiatric domain(s).
B. The presence of **high titer antithyroid antibodies** with or without clinical thyroid disease following exclusion of other alternative diagnoses.

Table 2. [8] Modified diagnostic criteria for HE in pediatric patients

Cases/Discussion

We present three female HE patients at different stages of lifespan; pediatric (age 12: P1), adult (age 41: P2), and geriatric (age 64: P3).

P1 presented with new-onset psychosis and a recent decline in academic performance. She was also depressed with severe fatigue. The patient was found to have significantly elevated TSH (21.2), TPO (>400), and marginally low T4 & Free T3. She was admitted medically for further treatment, and although she met the diagnostic criteria for HE, she never received steroids and was only given Synthroid. She did show some improvement on Synthroid and was able to discharge shortly. However, on outpatient follow-up, the patient was non-compliant with her Synthroid, and her psychosis returned along with acute decompensation, which required rapid re-admission. Again, she was only treated with Synthroid, and symptoms did eventually improve, but recovery took much longer upon the second admission.

P2 presented with neuro-vegetative symptoms and psychosis and had an established diagnosis of schizophrenia despite only ever having three-lifetime episodes of "hearing voices." Four months before her psychiatric admission, she was treated for delirium on the medical floor, and at that time, her TSH was 14.9, and Free T4 was 0.92; she was never treated with Synthroid and was told to follow up outpatient. Upon admission to our inpatient psychiatry unit, she had a TSH of 3.86, low total T3/T4, and TPO of 463. Medicine was consulted, and she was recommended for outpatient follow-up. We suspect she developed chronic HE that had never been treated and was misdiagnosed as schizophrenic.

P3 presented with a history of schizophrenia which was not responsive to high dose Haldol or other antipsychotics. Her psychosis was severe, and she was admitted to our psychiatric inpatient unit for further treatment. She was placed under involuntary commitment (IVC) and required enforced medications for stabilization. She was found to have a TSH of 102 with a TPO of 245. Total T3 was 48. She was not improving with enforced antipsychotics, and we made a clinical decision to enforce Synthroid via Intramuscular injection. She did show significant improvement once Synthroid became therapeutic and TSH levels started to decrease. Once at baseline, she received a 14/30 on MoCA (Montreal Cognitive Assessment), which we suspect is partially due to chronic untreated HE.

None of our patients received steroids despite being a first-line treatment [1-7]. Systematic reviews show Synthroid can be administered as monotherapy or in combination with steroids. Synthroid monotherapy has only been found to have a success rate of 67%. In comparison, steroids as monotherapy have been shown to have a success rate of 98%. When both Synthroid and Steroids are administered in combination, the success rate is still high at 92% but not as effective as steroids alone [2]. According to most laboratories, a TSH between 4.5 to 5.0 mU/L is considered the upper limit of normal (ULN). Some argue the ULN should be decreased to 2.5mU/L as 95% of euthyroid young individuals have serum levels between 0.4 and 2.5 mU/L [7]. Our patient's for example, might have had further workup if this cut-off was lowered.

Normal Values/Lab	12 yo Patient (P1)	41 yo Patient (P2)	64 yo Patient (P3
Total T4 (10.4 -12 ng/dL)	7.3	9.3	Not Performed
Total T3 (71-180 ng/dL)	Not Performed	Not Performed	48
Free T4 (0.76 - 1.46 ng/dL)	0.85	0.89	0.43
Free, T3 (3.51 - 7.30 pg/mL)	2.7	1.85	Not performed
TSH (0.358-3.210 µIU/dL)	14.4 & 21.2 on repeat	14.9 & 3.860 on repeat	83.5 & 102 on repeat
TPO Antibody (0-30 IU/mL)	430	463	245
Vitamin B12 (200-900pg/mL)	457	487	521
RPR	(-)	Not performed	Not performed
HIV	(-)	Not Performed	Not performed
Brain MR W/WO contrast	Subtle signal intensity in left substantia nigra	Not Performed	Not performed
EEG	Normal	Not Performed	Not performed
CMP	Unremarkable	Unremarkable	Unremarkable
CBC	Unremarkable	At baseline Hb 6.3 Pt also has SCD	Unremarkable
UDS	(-)	(-)	(-)

Table 3. Laboratory/imaging finding Findings: Note: Some labs and imaging were unable to be performed due to severe agitation, paranoia or needle phobias.

Typical Findings in HE

- CSF - Elevated proteins, lymphocytes
- EEG- Diffuse slowing (most common)
- MRI- Nonspecific
- MRA- Narrowing of cerebral blood vessels

Recommended Treatment

- **Steroids** are **first-line** treatment.
- Oral prednisone 50 mg to 150 mg daily have been used.
- Symptoms typically resolve over weeks to months.
- **Steroids** have been shown to have a **success rate of 98%** when compared to Synthroid alone at 67% and 92% when combined.
- Immunosuppressive medications like azathioprine and cyclophosphamide have been used if steroids fail.
- Recent literature shows Rituximab being effective in HE

Table 4/5. [2,4,6,8] Typical laboratory/imaging findings & Treatments.

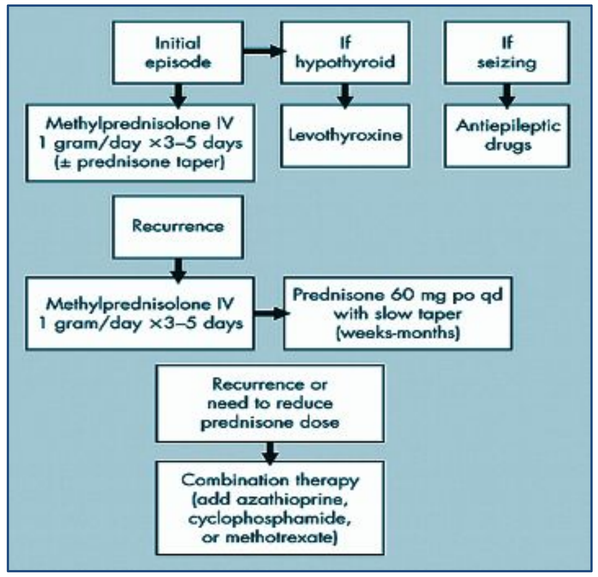

Table 6. [6,8] Inpatient algorithm for treatment

Conclusion/Implications

These cases highlight the need for regular TSH screening and, if appropriate, screening for T3, T4, and TPO antibodies in psychotic patients, even in those previously diagnosed with schizophrenia. These cases also pose the question: 'should psychiatrists consider using a brief course of steroids in acute HE cases?' According to most case reports and literature reviews on HE, most patients have rapid improvement with steroids alone. Along with other immunosuppressants, they are the only treatment that appears to target the cause of HE. Most physicians steer away from steroids, especially when psychosis is involved. The use of antipsychotics & Synthroid alone in cases of HE with psychosis appears to lead to minimal improvement; this is likely due to antipsychotics only treating the psychosis; they do not treat the actual cause. In our cases, P1 & P3 were treated with Synthroid and showed significant improvement in psychosis, but it was a slow process and did not completely resolve, resulting in rapid re-admission. Whereas P2 did not receive Synthroid and her symptoms only improved minimally on Abilify.

Ignoring the recommended treatment can eventually lead to developmental delays/cognitive impairment and the early onset of dementia [4]. It is important to note that, similar to SSRIs, Synthroid can take 3-6 weeks before TSH starts to decrease and symptoms resolve [4,5]. Considering a brief course of steroids may be warranted for an accelerated resolution, especially when symptoms make discharge difficult due to lack of functioning. The rarity of HE and lack of clear and available diagnostic criteria leads to a lack of treatment with steroids [1,4]. It is worth considering if psychiatrists should have steroids readily available in their tool belt rather than depend on Internal Medicine or Neurology, as rare cases such as these require an in-depth psychiatric evaluation and diagnostic criteria are not clear cut.

References

1. Garg, Sharma. "Hashimoto Encephalopathy in Children." Annals of the Indian Academy of Neurology, vol. 22, no. 3, Wolters Kluwer India Pvt. Ltd, July 2019, pp. 357–59, doi:10.4103/aian.AIAN_18_19.
2. Kutluk, Haznedar. "Hashimoto's Encephalopathy in Children: Different Manifestations of Five Cases." Acta Neurologica Belgica, vol. 119, no. 4, Springer International Publishing, Dec. 2019, pp. 595–99, doi:10.1007/s13760-019-01191-7.
3. Ransing, Mishra. "Neuropsychiatric Manifestation of Hashimoto's Encephalopathy in an Adolescent and Treatment." Indian Journal of Psychological Medicine, vol. 38, no. 4, Wolters Kluwer - Medknow Publications, Oct. 2016, pp. 357–60, doi:10.4103/0253-7176.185950.
4. Zhou, Xu. "Hashimoto Encephalopathy: Literature Review." Acta Neurologica Scandinavica, vol. 135, no. 3, Wiley Subscription Services, Inc, Mar. 2017, pp. 285–90, doi:10.1111/ane.12618
5. Savarimuthu, M., Tseringla, S., & Mammen, P. (2019, January 01). Psychotic symptoms of Hashimoto's encephalopathy: A diagnostic challenge. Retrieved February 21, 2021, from https://www.jkacap.org/journal/view.html?doi=10.5765%2Fjkacap.180022
6. Uwatoko, H., Yabe, I., & Sato, S. (2018, September 08). Hashimoto's encephalopathy mimicking a brain tumor and its pathological findings: A case report. Retrieved February 21, 2021, from https://www-clinicalkey-com.proxy.campbell.edu/#!/content/journal/1-s2.0-S0022510X18303708
7. Ross, D. S. (2021, May 20). Treatment of primary hypothyroidism in adults. UpToDate. Retrieved September 29, 2021, from https://www.uptodate.com/contents/treatment-of-primary-hypothyroidism-in-adults?search=hashimotos&source=search_result&selectedTitle=3~118&usage_type=default&display_rank=3#H2890829890
8. Adams, Ashley V., et al. "Evaluation of Diagnostic Criteria for Hashimoto Encephalopathy Among Children and Adolescents." *Pediatric Neurology*, vol. 107, Elsevier Inc, 2020, pp. 41–47, doi:10.1016/j.pediatrneurol.2019.12.011.

Abbreviation Key: CSF: cerebrospinal fluid, ; EEG: electroencephalography, NAE: NH2 terminal alpha enolase, MRA: MR angiography, MRI: MR imaging), TPO: Thyroperoxidase Antibodies, TSH: Thyroid Stimulating Hormone; Synthroid: Levothyroxine,

Acknowledgements

We would like to thank the psychiatry department at CFVH for all of their support and encouragement.