Academic Journal of Neurology & Neurosurgery

Case Report

DOI: 10.51271/AJNN-0039

A case of Wernicke's encephalopathy in a patient receiving teprotumumab infusions for thyroid eye disease

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Received: 21/10/2025 ◆ Accepted: 27/12/2025 ◆ Published: 31/12/2025

Cite this article: Diaz Curbelo C, Babij R, Chung S. A case of Wernicke's encephalopathy in a patient receiving teprotumumab infusions for thyroid eye disease . *Acad J Neurol Neurosurg.* 2025;2(4):86-88.

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ABSTRACT

A 64-year-old male with clinically active thyroid eye disease was started on teprotumumab infusion for ongoing visual symptoms in the setting of managed systemic disease. After six weeks of treatment, and 3 infusions of teprotumumab, the patient developed unexplained symptoms of anxiety, confusion, and abnormal behavior over the course of several days, for which he was hospitalized. An extensive workup was unrevealing of a cause for the onset of these symptoms, and the patient did not improve until treated with supplemental thiamine, supporting a clinical diagnosis of Wernicke's encephalopathy. The authors will describe the circumstances of this episode and briefly summarize the available literature on encephalopathies as a serious complication in patients receiving a relatively novel treatment for thyroid eye disease.

Keywords: Graves ophthalmopathy, Wernicke's encephalopathy, monoclonal antibodies

INTRODUCTION

Teprotumumab is a monoclonal antibody against insulin-like growth factor receptor (IGFR-1) that was approved for treating thyroid eye disease (TED) in January 2020. It works by blocking the activation of orbital fibroblasts, integral to TED's pathogenesis.[1] In clinical trials, patients treated with teprotumumab had a significant and sustained reduction in proptosis and subjective diplopia, as well as increased quality of life, and vision.[1] Common side effects, such as blood glucose abnormalities, auditory issues, musculoskeletal issues, hair loss, fatigue, and reproductive issues, are well documented.[2-4] Nonetheless, teprotumumab's status as a relatively newly approved treatment suggests the potential for uncovering rare adverse effects. We describe a teprotumumab-treated patient who developed Wernicke's encephalopathy (WE), a neurological condition commonly characterized by nystagmus, ataxia, and confusion, and often due to a thiamine deficiency secondary to alcohol use disorder (AUD). Outside of AUD, other causes include malignancy, GI surgery and diseases, excessive vomiting, malnutrition, renal disease, transplantation, infection, intoxication, and uncontrolled thyroid diseases. Its variable presentations make WE often clinically underreported, but data from autopsies suggest the prevalence is between 0.4 and 2.8% in western countries.[5] Collection and evaluation of protected health information was compliant with the Health Insurance Portability and Accountability Act, and this manuscript adheres to the tenets of the Declaration of Helsinki, an informed consent form was obtained from the patient for gathering of data for research purposes.

CASE

A 64-year-old male recently diagnosed with hyperthyroidism presented with a year-long history of fluctuating diplopia and left eye exophthalmos. He denied vision loss, eye pain, tearing, or headaches. His ophthalmic history included left eye tear duct surgery six years prior. Visual acuity was 20/20 bilaterally, and examination revealed left eye esotropia and hypotropia, bilateral proptosis, eyelid edema and erythema, corneal superficial punctate keratitis, conjunctival injection, and chemosis. Measurements on Hertel exophthalmometry were 14 millimeters in the right eye, 20 on the left, and a base of 110. MRI of the orbits showed diffuse thickening and enhancement of the extraocular muscles consistent with TED. When compared to imaging from a year prior, there was an increase in left eye proptosis, crowding of the orbital apex, and size of the superior rectus; the right eye only showed mild enlargement of the inferior rectus. He had been treated with methimazole for the prior 8 months and had no history of thyroidectomy, or radioactive iodine. Direct T3 and T4 had normalized to 3.4 and 1.1 respectively, while thyroid-stimulating hormone levels remained low. The diplopia had

subjectively improved gradually since the onset of symptoms but still interfered with the patient's work. After discussing the risk and benefits of various treatment options, including symptomatic management, corticosteroids, orbital radiation, and surgical decompression, he chose to start teprotumumab for his significant diplopia and proptosis.

One week after his third infusion, the patient developed anxiety for several days, accompanied by behavioral changes like reduced speech frequency and incorrect naming of objects. His status fluctuated as he was taken to the emergency department, but he left before being worked up, reportedly feeling better. The following morning, his partner found him hard to rouse. He was admitted to the hospital for confusion. The patient's history was negative for any recent illness, fever, cough, shortness of breath, chest pain, palpitations, weakness, changes in vision, or GI/GU symptoms, as well as alcohol, tobacco, and recreational drug use. He had a history of major depressive disorder and no history of psychotic symptoms. The patient was well-appearing and in no acute distress. His cardiovascular, pulmonary, and abdominal exams were normal. His neurological exam was notable for a bilateral upper extremity intention tremor, which had begun 2 days prior. No cranial nerve deficits or weakness were noted, though the exam was limited by patient effort. There was an attempt to screen for mild cognitive impairment using the Montreal Cognitive Assessment (MoCA), however, a score could not be obtained because of a lack of patient cooperation.

Complete blood count and metabolic panels were unrevealing. The possibility of a thyroid storm was considered, but despite TSI and TrAb being elevated, TSH, free T3 and T4, and TPO antibodies were within normal limits. Toxicology reports were negative for barbiturates, opiates, benzodiazepines, amphetamines, cocaine, phencyclidine, THC, and alcohol. His urinalysis was only notable for over 80 mg/dl of ketones. Testing for HIV, syphilis, ANA, anti-dsDNA, C3/C4 hypocomplementemia, ANCA, hepatitis B and C, and COVID-19 were all negative. An ECG, head CT, and a brain MRI without contrast failed to reveal any abnormalities and ruled out a stroke.

It has been theorized that increased metabolic states associated with hyperthyroidism can lead to overutilization and depletion of thiamine reserves, predisposing patients to WE.[6] The patient's outpatient endocrinologist urged his care team to treat presumptive WE given the patient's thyroid history. The patient was treated for 3 days with 500 mg of IV thiamine every 8 hours, during which his mental status improved. The patient was discharged home with intramuscular thiamine, followed by oral thiamine and B complex vitamins. Vitamin B1 levels drawn before initiation of this therapy were 102.2 nmol/L, in the lower half of the reference range.

The patient had an otherwise excellent response to teprotumumab. Diplopia, periorbital edema, and lid retraction improved after just three infusions. His TED remained stable, with no episodes of compressive optic neuropathy and only residual diplopia. The patient suffered no permanent deficits from the episode, but because of his stable state and concerns about teprotumumab as a possible cause of his encephalopathy, infusions were discontinued. At a 7-week follow-up, his mental status was intact, and the neurological exam was only notable for impaired abduction and elevation of the left eye, consistent with the know pathology of his extraocular muscles. The patient was also seen by oculoplastic at 2 weeks, 5 weeks, 7 months, and 1 year after his hospitalization. His exam showed sustained improvement in his proptosis (Hertels of 15/110/117) and periorbital edema. His diplopia had subjectively improved but still occurred intermittently and did not respond to prisms. A second trial of teprotumumab was considered, but due to limited data on efficacy of the medication in inactive TED, and the serious complication he had experienced, this was not done. To date, no other interventions have been taken for his TED.

DISCUSSION

This case represents a unique instance of WE arising in a context lacking common etiologies such as alcohol use, making its temporal association with teprotumumab noteworthy. The best known diagnostic criteria for WE is the Caine Criteria, which was developed specifically for patients with a history of alcohol abuse issues, and requires any two dietary deficiencies, oculomotor abnormalities, cerebellar dysfunction, and either altered mental status or mild memory impairment.[7] Our patient demonstrated both altered mental status and memory impairment. He also presented with a new bilateral intention tremor, indicating cerebellar dysfunction. His wife confirmed there were no dietary deficiencies, and there were no new oculomotor deficits documented. It's worth noting that the patient was uncooperative during the neurological exam, hindering assessment of cranial nerves III, IV, and VI, as well as coordination, meaning that other pertinent findings may have been missed. Though his blood levels of thiamine were within the normal range, thiamine levels are not formally part of the diagnosis of WE. Measuring thiamine levels prior to treatment is recommended in the guidelines of the European Federation of Neurological Societies, but normal levels do not exclude the diagnosis, and there are other reports of normal-thiamine WE.[5,8] The patient denied alcohol use, had a varied diet, and had stable thyroid function before developing WE, eliminating many common causes of the condition. The only major change around the onset of symptoms was the initiation of teprotumumab infusions.

Although teprotumumab use has not previously been linked with WE, there was a reported case of Hashimoto's encephalopathy and two presumed autoimmune encephalopathies associated with teprotumumab that resolved with plasmapheresis.[2,9,10] Not much information is available in the case of Hashimoto's encephalopathy, but it was believed to be possibly related to teprotumumab, and lead to participant discontinuation from a randomized trial of the medication.[2] The first case of autoimmune encephalitis was a 76 year old male presenting with 6 weeks of executive dysfunction after 4 infusions of teprotumumab, later found to have high CSF protein. There was no response to steroids or IV immunoglobins, but the patient returned to baseline after 5 sessions of plasmapheresis. It is theorized that this treatment cleared teprotumumab induced autoantibodies impacting the CNS.[9] The second case was a 62-year-old woman who presented with 1 week of fluctuating mental

status, tremors, and psychiatric symptoms after 3 infusions of teprotumumab. Her treatment team was familiar with the previous case report and used plasmapheresis early on, leading to progressively shorter episodes of altered mental status until her symptoms completely resolved.[10]

CONCLUSION

Though documented instances of teprotumumab-associated encephalopathy are rare, the potential for serious neurological symptoms exists, as exemplified by this case, and the other published cases of encephalopathy. This possibility necessitates vigilance and prompt recognition by healthcare providers overseeing such treatments.

ETHICAL DECLARATIONS

Informed Consent

Written informed consent was obtained from the patient included in this report. Signed consent forms are retained by the authors and are available upon request.

Peer Review Process

This report underwent external peer review.

Conflict of Interest

The authors declare no conflicts of interest.

Financial Disclosure

This case report did not receive any financial support.

Author Contributions

All authors made substantial contributions to the clinical documentation, interpretation, and manuscript preparation. All authors approved the final version of the manuscript.

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