Cureus
Part of SPRINGER NATURE

Open Access Case Report

Wernicke's Encephalopathy Following Glucagon-like Peptide-1 (GLP-1) Receptor Agonist Use: A Case Report

Anne Milligan [1], Joseph G. Timmons [1, 2]

1. Endocrinology and Diabetes, University Hospital Wishaw, Wishaw, GBR 2. School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, GBR

Corresponding author: Anne Milligan, anne.milligan3@nhs.scot

Review began 09/24/2026
Review ended 10/29/2026
Published 11/05/2026

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DOI: 10.7759/cureus.119151

Abstract

Wernicke's encephalopathy (WE) is a neurological emergency resulting from vitamin B1 (thiamine) deficiency. It has a classic triad of symptoms: oculomotor dysfunction, ataxia, and altered mental status. WE is mostly associated with alcohol use disorder, malnourishment, and hypercatabolism. An emerging group at risk of developing WE are those taking glucagon-like peptide 1 (GLP-1) receptor agonists (RAs). GLP-1 RAs have been revolutionary in the treatment of obesity, and worldwide use has risen exponentially. An emerging risk from these agents is nutritional deficiency. We describe a case of a 48-year-old teetotal man using tirzepatide for weight loss who developed WE.

Categories: Pharmacology, Nutrition, Endocrinology/Diabetes/Metabolism
Keywords: glp-1 receptor agonist, obesity management, semaglutide, thiamine deficiency, weight loss, wernicke's encephalopathy

Introduction

Glucagon-like peptide 1 (GLP-1) receptor agonists (RAs) have had an increasing role in the management of type 2 diabetes over recent years. This role has been enhanced further by increasing evidence of the cardioprotective effects of this class of drugs in people with and without diabetes. GLP-1 RAs have shown impressive results in obesity management, reducing total body weight by 15% or more, and therefore revolutionising the field of non-surgical obesity management. Nevertheless, complications and consequences of these agents continue to emerge. While current guidance focuses primarily on gastrointestinal side effect management, the value of good nutritional counselling is arguably underappreciated [1].

Studies have demonstrated that only 43% of GLP-1 RA users take dietary supplements, and only 12% received guidance from their healthcare provider around dietary supplementation [1]. Muscle loss represents a significant consequence of poor nutritional support whilst using GLP-1 RAs. In the absence of regular strength training, the SURMOUNT1 trial demonstrated that female and male GLP-1 RA users can expect loss of muscle mass to represent 10-15% and 20-25% of their total body weight loss, respectively. Moreover, a return to pre-treatment baseline weight approximately one year after GLP-1 RA cessation is common, so the value of robust nutritional guidance is multi-factorial; both in preventing deficiency and in helping mitigate weight gain on stopping these drugs [2]. Currently, there is no specific nutritional or dietary advice offered by the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom [3] or the FDA in the United States [4].

Thiamine stores are depleted only four weeks after thiamine intake becomes insufficient, meaning GLP-1 RA users are particularly at risk of this soon after starting this treatment [5]. There are two primary mechanisms by which GLP-1 RAs can result in the development of WE: inadequate thiamine intake due to early satiety and delayed gastric emptying; or side effects of vomiting and diarrhoea reducing thiamine absorption [1].

Presenting symptoms of WE are often nonspecific, particularly in those with non-alcoholic WE, making prompt diagnosis and treatment challenging [5,6]. While WE is reversible, Korsakoff's psychosis (KP) is a catastrophic consequence of inadequate treatment of WE. It is an irreversible condition characterised by anterograde and retrograde amnesia, confabulation, and disorientation. This often leads to the loss of independent living and the negative social and economic consequences that this brings. Inadequate thiamine replacement is associated with a 20% mortality rate and, among survivors, 85% develop KP [7]. There is no single diagnostic test for WE, but treatment (IV thiamine 200mg three times daily) is simple, safe, and should not be delayed when there is any suspicion [8].

There is emerging evidence of WE secondary to GLP-1 RA use, and the incidence is likely to increase as these agents are increasingly prescribed. Indeed, a global pharmacovigilance study and literature review, published by Clinical Nutrition in early 2026, reported 15 confirmed cases of GLP-1 RA-associated

WE [9]. The study involved analysis of the FDA adverse event reporting system (FAERS) database to identify cases of WE associated with GLP-1RA use between 2014 and 2024. Of note, 14 of these confirmed cases were reported in 2023-2024, perhaps owing to widened accessibility to GLP-1 RA for obesity management worldwide in recent years. This data compounds the idea that nutritional optimisation in the context of GLP-1 RA is underappreciated.

This case report was previously presented as a poster at the European Congress of Endocrinology in Prague, May 2026.

Case Presentation

A 48-year-old male, ex-smoker, with a past medical history of obesity, hypertension, migraine, silicosis, and previous opiate addiction (managed with buprenorphine), first presented to the Emergency Department (ED) with confusion, delusional ideation, and gait disturbance. There was no history of alcohol intake or illicit substance use. He had been taking tirzepatide for the preceding two months and had lost 12 kg in weight. His dose had recently been increased from 2.5 mg to 5 mg, with his most recent administration being three days prior to presentation. A CT brain was performed, and subsequently a non-contrast MRI, which did not demonstrate any acute pathology. The patient was discharged after three days as symptoms were improving.

The patient re-presented eight days later. On this occasion, he had worsening confusion and gait disturbance, with new dysarthria. He described periods of amnesia and vivid visual hallucinations, for example, believing he could see fires and a man making a cabinet. He gave a history of early satiety and loss of appetite, and was eating only one meal daily on tirzepatide 5 mg weekly. Examination revealed normal speech, but diplopia on left lateral gaze, bidirectional horizontal nystagmus, and globally impaired coordination. He was ataxic, without any focal neurological findings affecting the limbs. Reflexes, sensation, tone, and power were retained globally. He had continued tirzepatide.

This time, his presentation was discussed with the on-call neurology team, who advised empirical treatment with IV high-dose thiamine replacement to treat a possible diagnosis of WE. Within two days, his symptoms had improved dramatically. The only ongoing sign was nystagmus. A repeat MRI was performed with contrast. The case was discussed at a regional neuroradiology multidisciplinary team (MDT). Contrast MRI appearances were felt to be unusual, with mammillary body asymmetry and a “bulky” hypothalamus, raising the possibility of a hypothalamic glioma (Figure *1*), which was later excluded with CSF sampling.

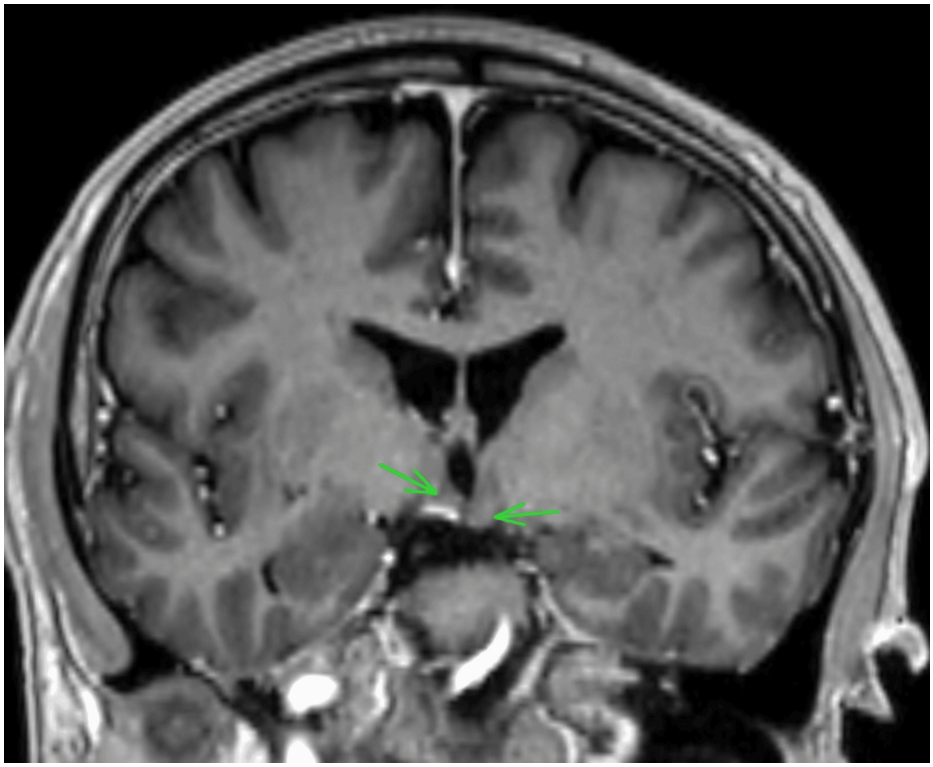


FIGURE 1: Annotated contrast MRI demonstrates hypothalamic asymmetry with a slightly "bulky" and low-lying left mammillary body when compared with the right.

Green arrows highlight the position of the hypothalamus, with the low-lying left mammillary body appreciable on the right side of the image.

EEG was undertaken and showed only minor nonspecific changes. With Addenbrooke's Cognitive Assessment version B [10], the patient scored 92/100. The patient received 500 mg of IV thiamine three times daily for eight doses, then 250 mg IV three times daily for six doses. Thereafter, oral thiamine supplementation was commenced at 50 mg four times daily. He was discharged after 11 days in hospital. Tirzepatide was stopped.

Five days later, the patient presented again with a recurrence of his symptoms. Clinical examination findings mimicked the previous presentation, with nystagmus, ataxia, and confusion. He had been taking oral thiamine supplements and had begun to eat more, regaining a small amount of weight since his last GLP-1 RA injection. Within 24 hours of intravenous thiamine replacement, his symptoms improved once more. Several additional investigations were conducted to exclude alternate diagnoses (Table *1*). RBC vitamin B1 was checked. This was normal following IV thiamine replacement. During this admission, the patient received prolonged high-dose IV thiamine supplementation, 500 mg thrice daily for 15 days. He was discharged on oral thiamine and remains off tirzepatide. On follow-up at one year, the patient remains stable, without further readmission to the hospital. The clinical timeline is shown in Figure *2*.

Test	Patient result	Reference range
Serum		
Calcium (adjusted)	2.33	2.2-2.6mmol/L
Phosphate	1.3	0.8-1.5mmol/L
Magnesium	0.85	0.7-1mmol/L
Vitamin B12	271	197-771pg/ml
Folate	6.89	3.9-26.8ng/ml
Vitamin B1	483	275-675ng TDP/g Hb

Copper	13.8	10-22umol/L
Caeruloplasmin	0.25	0.16-0.47g/L
Ethanol	<10	<10mg/100ml
Prolactin	333	0-349mU/L
Cortisol	237	133-537nmol/L
Free T4	12.4	12-22pmol/L
TSH	1.99	0.27-4.2mU/L
ESR	9	1-25mm/hr
ANA	Negative	-
ANCA	Negative	-
Myeloperoxidase antibodies	<0.2	0-3.5AI
PR 3	<0.6	0-2IU/ml
HIV	Negative	-
Hepatitis B + C	Negative	-
Syphilis screen	Negative	-
Lyme serology	Negative	-
Glycine receptor antibodies	Negative	-
GABA-B receptor antibodies	Negative	-
AMPA ½ receptor antibodies	Negative	-
CASPR2 antibodies	Negative	-
LGI1 antibodies	Negative	-
NMDA receptor antibodies	Negative	-
Cerebrospinal Fluid		
Glucose	3.1	2.5-4.4mmol/L
Protein	0.58	0.15-0.45
Xanthochromia	Negative	g/L
ACE	0.5	0-1.2umol/min/L
Oligoclonal bands	Negative	-
Viral PCR	Negative	-
Germ Cell Markers	Negative	-
Urine Drug Screen		
Amphetamines	Negative	-
Benzodiazepines	Negative	-
Opiates	Negative	-
Cocaine	Negative	-

TABLE 1: Extensive investigations undertaken with cerebrospinal fluid, serum and urine.

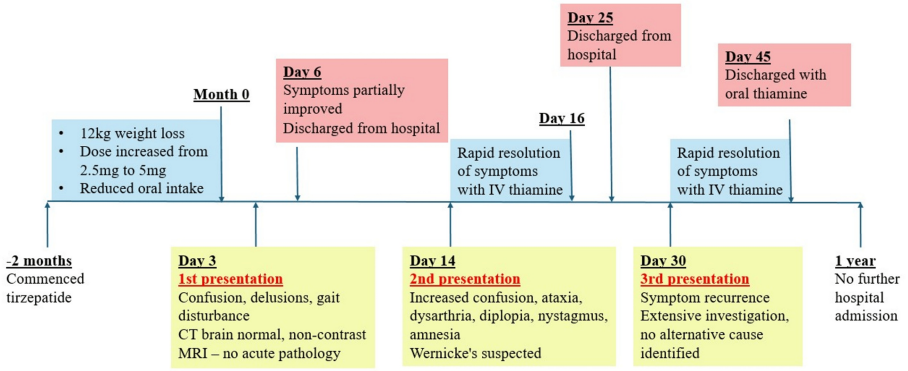


FIGURE 2: Timeline demonstrating patient journey.

Month 0 represents the time of symptom onset

Discussion

WE is a neurologic emergency characterised by ophthalmoplegia, ataxia, and altered mental state [11]. In the developed world, malnutrition in the context of alcohol dependence is its most common precipitant, with a 24-50% prevalence of mild/moderate malnutrition in substance abuse disorder patients [12]. Non-alcohol-related WE is a rarer diagnosis, with an estimated prevalence of 0.04-2.8% [13]. Among this group, patients receiving GLP-1 RAs for obesity management represent an emerging cohort at risk, particularly those who may have other risk factors for malnutrition such as previous alcohol dependence or a poor diet [8].

Clinical pathological studies support the idea that a diagnosis of WE can be made in alcohol dependent patients when two of the four characteristic symptoms are present. These are nutritional deficiency, oculomotor disturbance, cerebellar syndrome, and altered mental status. The diagnostic sensitivity of this criterion is 85%. The European Federation of Neurological Societies (EFNS) supports the application of these same diagnostic criteria to cases not associated with alcohol [8]. In this instance, there was a strong history supportive of nutritional deficiency: poor oral intake and rapid weight loss due to GLP-1 RA use. Therefore, all four diagnostic criteria were met in this case.

Contributing to diagnostic uncertainty in WE is the lack of a definitive diagnostic test. It remains a clinical diagnosis. As in this case, a therapeutic trial of high-dose parenteral thiamine replacement when history and examination findings raise suspicion of WE often adds most diagnostic value. Indeed, our patient experienced a rapid resolution of almost all signs and symptoms within 24 hours of intravenous thiamine. At the time of specialist neurology review, this served as further diagnostic evidence that his acute neurological disturbance was, in fact, a result of vitamin B1 deficiency and resultant WE.

Whilst it's possible to measure serum thiamine level, it lacks specificity, and there remains debate surrounding its value in obtaining a rapid WE diagnosis [14]. Results are thought to be partly influenced by genetic susceptibility, which could render serum thiamine levels normal at the time of presentation despite clinical findings in keeping with WE [11]. This is among the reasons why the test is not widely used or relied upon for diagnosis. Nevertheless, using high-performance liquid chromatography (HPLC) for thiamine detection has greater diagnostic reliability when compared with its predecessor, which measured blood transketolase activity as a marker of thiamine's active form, thiamine pyrophosphate (TPP) [14]. Ultimately, their role is limited by the fact that this laboratory test isn't widely available, and results may take days. For this reason, treatment should not be delayed, but a pre-treatment thiamine assay (with HPLC) may be used to confirm a diagnosis, if this is available. In the current case, it was only at the time of the third presentation of worsening neurology, despite thiamine supplementation, that the serum thiamine level was checked. Unsurprisingly, in this instance, levels came within the normal range following high-dose IV replacement.

MRI imaging, particularly using T2-weighted, diffusion-weighted (DWI), and fluid-attenuated inversion recovery (FLAIR), has a role in diagnosing WE. Studies demonstrate a specificity and positive predictive value of 93% and 89%, respectively [15]. However, with a sensitivity of only 53%, a normal MRI brain cannot exclude WE as a diagnosis. To optimise its diagnostic value, MRI imaging should be obtained prior to parenteral thiamine administration. This limits its application in making an early definitive

diagnosis in practice, since access to emergency MRI is often limited.

Nevertheless, the current patient did undergo MRI. On review by the neuroradiology team, mammillary body asymmetry was observed, with unilateral atrophy, which is not among typical WE MRI findings. In general terms, typical MRI features are symmetrical lesions surrounding the third ventricle, associated with high signal intensity on T2-weighted imaging. Based on pathological studies, typical symmetrical mammillary body hypointensity is felt to be the result of hemosiderin deposition secondary to necrosis, vascular proliferation, and astroglial/microglial proliferation due to petechial haemorrhage. However, supportive of this case, there are reports of many atypical findings, which seem to correspond, more commonly, with non-alcohol-related WE diagnoses [15].

In this instance, the presumed diagnosis of WE was initially undertreated, leading to rapid relapse of neurological symptoms following first hospital discharge. High-dose IV thiamine is recommended. Guidance from EFNS [8] and NICE [16] is conflicting, with the former recommending high-dose parenteral thiamine until there is no further improvement in symptoms, while the latter suggests a minimum of five days, unless a WE diagnosis can be confidently excluded. The current patient's first course of parenteral thiamine was one dose short of a complete five days. The dose he received was halved after eight doses. These are factors which may have contributed to his under-treatment. On re-presentation, he received a high dose (500 mg thrice daily) intravenously for 15 days, corresponding with a full resolution of symptoms. Typically, we expect ophthalmoplegia to resolve within hours of thiamine repletion, though there is residual horizontal nystagmus in 60% of individuals [17]. Certainly, this mirrors our case as, within 24 hours of administration, nystagmus was the only remaining clinical sign. Though the current patient's risk of future WE may have been mitigated with cessation of GLP-1 RA, his oral thiamine supplements were continued on discharge. With this, he has had no further relapse of acute neurological symptoms.

Conclusions

This case illustrates the importance of adequate nutritional supplementation whilst using GLP-1 RAs and, in particular, the consequence of thiamine depletion secondary to reduced oral intake and weight loss. Healthcare professionals prescribing these drugs should offer nutritional advice and counsel patients on the risk of nutritional deficiencies. As ever more people are prescribed these drugs, WE diagnoses among this cohort should be considered, particularly if there were pre-existing risk factors prior to starting GLP-1 RA.

A therapeutic trial of IV thiamine should not be delayed when there is suspicion of nutritional deficiency in association with acute neurological symptoms. It has an invaluable role in diagnosis and in avoiding irreversible Korsakoff's psychosis. Despite these conclusions, we acknowledge the limitation of this single case report in establishing a definitive causal relationship between GLP-1 RAs and WE. Further studies to establish this relationship would be of great value.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Anne Milligan, Joseph G. Timmons

Acquisition, analysis, or interpretation of data: Anne Milligan, Joseph G. Timmons

Drafting of the manuscript: Anne Milligan

Critical review of the manuscript for important intellectual content: Joseph G. Timmons

Supervision: Joseph G. Timmons

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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