Tirzepatide Associated Dysesthesia with Atypical Sensory Distribution: A Case Report

Drew A. Wells, PharmD, BCPS, Miguel Rodriguez, MD, Cheran Elangovan, MD, Kerri Jones, PharmD, BCPS

Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1RA) and combined glucagon-like peptide-1 receptor agonists/glucagon insulinotropic polypeptide agonists (GLP-1/GIP) are becoming more commonly used to treat obesity and diabetes. Recent reports describe neurological adverse effects including dysesthesia and allodynia. A 42-year-old woman developed progressive anterior dysesthesia after initiating tirzepatide, prompting evaluation for ischemic stroke. Neuroimaging revealed an incidental left cerebellar infarct that did not correlate with symptoms. Cerebrospinal fluid studies were unrevealing, and symptoms improved following drug discontinuation. This case highlights a potential adverse neurological effect of GLP-1/GIP receptor agonist therapy and the importance of considering medication-associated causes in the differential for unexplained sensory symptoms.

Keywords: GLP-1/GIP receptor agonist, dysesthesia, medication adverse effect, incidental infarct

Background

Tirzepatide, a first-in-class glucagon-like peptide-1 receptor agonist (GLP-1RA) and dual GLP-1 / glucose-dependent insulinotropic polypeptide (GIP) receptor agonist, has rapidly gained prominence for the management of obesity and type 2 diabetes mellitus due to its favorable cardiometabolic profile and efficacy in promoting weight loss. While commonly reported adverse effects are gastrointestinal, emerging literature and pharmacovigilance data suggest that sensory disturbances such as dysesthesia, allodynia, and other central nervous system (CNS) effects may occur infrequently.[2,3] These symptoms, particularly when progressive or atypically distributed, can present diagnostic challenges.

Medication-associated neurologic adverse effects are an increasingly recognized but underreported contributor to acute neurologic presentations as the use of novel pharmacologic agents expands. In patients

DOI: 10.59236/sc.v3i3.119
ISSN: 2995-7494

presenting with focal or evolving neurologic symptoms, clinical–radiologic correlation is essential in eliminating confounders, particularly when imaging findings are discordant with examination. Failure to recognize nonvascular etiologies can lead to misattribution of symptoms to incidental infarcts and unnecessary escalation of stroke-directed therapies.

We report a case of subacute, ascending dysesthesia with an atypical anterior sensory level following recent initiation of tirzepatide, with an incidental acute left cerebellar infarct identified on diffusion-weighted MRI. This case highlights an uncommon but clinically significant potential adverse neurologic effect of tirzepatide and underscores the importance of considering medication-related etiologies in the differential diagnosis of unexplained sensory syndromes, particularly in stroke evaluation settings.

Case Presentation

A 42-year-old female presented to the hospital for numbness and tingling of bilateral thighs persistent for the previous two weeks. She reported sudden onset of symptoms two weeks prior to presentation. The sensation began in the right anterior thigh, radiated distally down the ipsilateral leg and foot, and subsequently progressed to involve the left lower extremity in a similar pattern, with additional ascending spread to the umbilical region.

She reported bilateral leg heaviness resulting in a shuffling gait. Past medical history was significant for morbid obesity (BMI 42.24 kg/m^2) with initiation of tirzepatide self-injection seven weeks prior to presentation. Since initiation of tirzepatide, the patient noted 30 pounds of weight loss. Initial patient examination conducted via telehealth video revealed bilateral lower extremity weakness with left leg worse than the right, and diminished sensation over the bilateral lower extremities with left worse than right. Initial labs were unremarkable except for elevated erythrocyte sedimentation rate (ESR) of 88 mm/hr, C-reactive protein (CRP) of 6.5 mg/dL, and low levels of folate of 6 ng/mL. Vitamin B12 levels were greater than 2,000 pg/mL. Initial computed tomography (CT) head, CT cervical, thoracic, and lumbar spine were unremarkable. Lumbar puncture (LP) was performed and cerebrospinal fluid (CSF) revealed slightly elevated protein, normal white cell count, and very elevated red blood cells (>2,000). Brain MRI demonstrated diffusion restriction in the left cerebellum, but without corresponding T2/FLAIR changes (Figure 1). Sensory symptoms did not localize to the cerebellar lesion, making the infarct unlikely to explain the presentation.

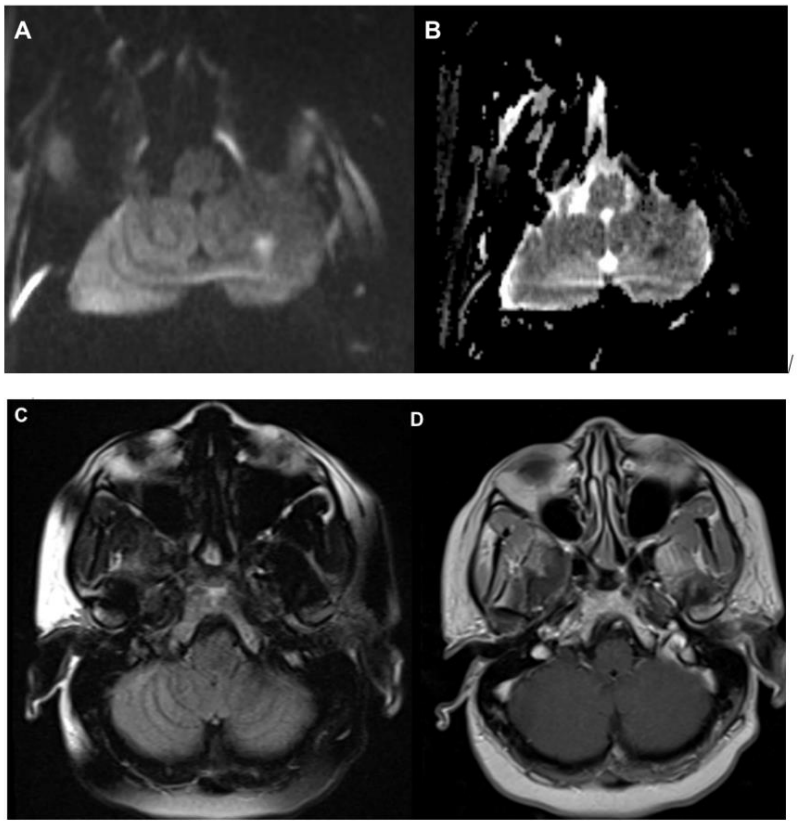
The patient was transferred to a tertiary center for a higher level of neurological care and further evaluation. Neurological exam by onsite neurologist was significant for numbness present with spinal sensory level at T10, but notably only anterior with sensation over the back spared (Figure 2). Patient was noted to have subjective lower extremity weakness, but no objective weakness on exam and all reflexes intact.

Repeat MRIs of the cervical, thoracic, and lumbar spine were unremarkable, except for mild degenerative changes. Repeat LP was

DOI: 10.59236/sc.v3i3.119
ISSN: 2995-7494

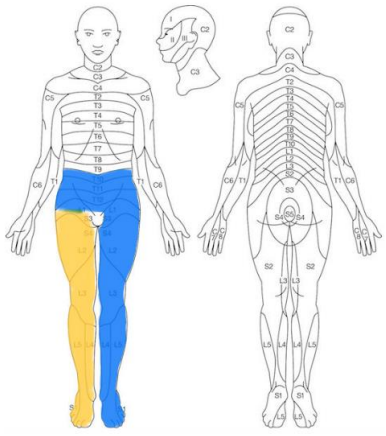
performed given the unremarkable repeat imaging with continued presence of

Figure 1: MRI Brain Axial Sequences with Diffusion Restriction



Note: A. DWI sequence with small hyperintensity in the left cerebellum. B. ADC sequence with small hypointensity correlating with DWI hyperintensity. C. T2 FLAIR with no changes in area of restricted diffusion. D. T1 post-contrast without enhancement.

Figure 2: Graphical Representation of Dysesthesia



DOI: 10.59236/sc.v3i3.119
ISSN: 2995-7494

Note: Yellow indicates location of initial sensory changes, namely right anterior thigh with progression inferiorly over right anterior leg and foot. Blue indicates location of the progression of the sensory changes, specifically, anterior thigh with progression inferiorly over left anterior leg and foot as well as superiorly to involve the anterior umbilical region. Note the sparing of the genital regions as well as the posterior regions.

symptoms. Repeat CSF revealed normal protein (35 mg/dL), mildly elevated white cell count (9/mm^3) with lymphocytic predominance (97%) and elevated red blood cells (246/mm^3). CSF infectious workup was negative, including West Nile virus and culture and gram stain. Extensive stroke workup and workup for other causes of atypical neuropathy were all negative, including autoimmune, heavy metal screen, HIV, and ganglioside antibodies. The non-specific inflammatory findings on the repeat LP combined with the negative imaging did not provide diagnostic clarity. The decision was made to empirically treat with methylprednisolone 1000 mg daily for three days. The patient reported subjective improvement in symptoms by day two. The patient was discharged in stable condition and instructed to hold the tirzepatide given concern for it being the precipitating cause.

Discussion

This case describes an atypical, sensory-predominant neurological syndrome presenting as progressive anterior dysesthesia with a discrete sensory level following recent initiation of tirzepatide. Comprehensive diagnostic workup, including cerebrospinal fluid analyses, and extensive infectious and autoimmune evaluations failed to identify a structural, vascular, or inflammatory etiology. In this context, tirzepatide-associated neurological adverse effects emerged as a leading diagnostic consideration.

Considerations for differential diagnosis initially raised concern for a stroke due to the history of sudden onset numbness, tingling, and bilateral lower extremity weakness. However, further history and examination revealed a more subacute, progressive course. MRI revealed an incidental, acute left cerebellar infarct that did not correlate with symptoms. Aside from obesity, the patient had no traditional vascular risk factors, no hypertension, diabetes, hyperlipidemia, smoking history, or prior thromboembolic disease. Additionally, the patient's presentation was notable for an anterior sensory level with sparing of posterior sensation, intact reflexes, and absence of objective motor weakness, features that are inconsistent with classic vascular territories or compressive myelopathies. Although inflammatory etiologies such as transverse myelitis, acute inflammatory demyelinating polyneuropathy, and infectious neuropathies were considered, the lack of supportive imaging findings, preserved reflexes, and largely nonspecific CSF abnormalities made these diagnoses less likely.

Unique to this patient was the use of tirzepatide, with recent initiation 7 weeks prior to presentation, with symptoms occurring 5 weeks after starting the medication. There have been reports of dysesthesias and allodynia following tirzepatide.[3] According to Ahern, the side effects seem to be dose-dependent and had a spontaneous remission; however, in the one

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case following tirzepatide use, the pain reoccurred and was severe, leading to drug discontinuation and resolution of the allodynia.[3] In addition to the case report highlighting allodynia and dysesthesia following tirzepatide and semaglutide, there is evidence that GLP-1 agonists are associated with the development of diabetic lumbosacral radiculoplexus neuropathy (DLRPN) and common fibular neuropathy (CFN).[4] Triplet and colleagues concluded that DLRPN was associated more with rapid reduction in hemoglobin A_1C, while CFN was associated more with rapid weight loss.[4] Proposed mechanisms remain speculative but may include altered central pain processing, effects on peripheral nerve signaling, or metabolic and nutritional changes related to rapid weight loss. In the present case, symptom onset followed an appropriate temporal relationship to tirzepatide initiation, alternative etiologies were largely excluded, and clinical improvement occurred following medication interruption and supportive therapy, suggesting a probable adverse drug reaction.

Rapid weight loss is an important confounding factor in this case. Significant reductions in body weight have been associated with various neuropathic syndromes, including length-dependent polyneuropathy and focal compressive neuropathies, particularly in the setting of nutritional deficiencies.[5,6] This patient experienced substantial weight loss over a relatively short period due to tirzepatide and lifestyle changes and was found to have low folate levels. Folate deficiency has been associated with peripheral neuropathy even in the presence of normal serum vitamin B12 concentrations.[7] However, unlike previously described weight-loss–associated and folate deficiency neuropathies, this patient's symptoms were not length-dependent and instead followed an ascending, truncal distribution with a sharp anterior sensory level, suggesting that nutritional deficiency alone is unlikely to fully explain the clinical presentation. Furthermore, the neurological exam also did not reveal any weakness, despite subjective reporting of weakness arguing against functional vitamin B12 deficiency or other nutritional deficiency.

Causality was assessed using the Naranjo Adverse Drug Reaction Probability Scale (Table 1). The patient's symptoms demonstrated a clear temporal relationship with tirzepatide initiation and progressed following continued exposure. Alternative etiologies, including vascular, infectious, autoimmune, inflammatory, and structural causes, were extensively evaluated and not identified. Partial clinical improvement occurred following discontinuation of tirzepatide and supportive therapy. While rechallenge was neither ethical nor clinically indicated, the overall profile fulfills criteria for a probable adverse drug reaction, with a total Naranjo score of 5.

From a stroke perspective, this case underscores the importance of maintaining a broad differential diagnosis in patients with atypical neurologic presentations, particularly when clinical findings are discordant with neuroimaging. This case adds to the growing recognition of atypical sensory- predominant neurologic adverse effects associated with GLP-1/GIP receptor

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ISSN: 2995-7494

agonist therapy and highlights the diagnostic challenges they may pose. As use of these agents continues to expand, stroke clinicians should remain vigilant for medication-associated neurologic syndromes when evaluating unexplained dysesthesia, particularly in the setting of clinical–radiologic mismatch. Early consideration of drug-related causality may help avoid misattribution to vascular pathology, reduce unnecessary invasive testing, and guide appropriate management, including medication discontinuation and close clinical follow-up. Further pharmacovigilance and mechanistic studies are needed to better define the incidence, risk factors, and pathophysiology of these uncommon but

Table 1. Naranjo Adverse Drug Reaction (ADR) Probability Scale

Naranjo Question	Response	Score
Are there previous conclusive reports on this reaction?	Yes (case reports of dysesthesia/allodynia with GLP-1 agonists)	+1
Did the adverse event appear after the suspected drug was administered?	Yes	+1
Did the adverse reaction improve when the drug was discontinued?	Yes	+1
Did the adverse reaction reappear upon re-administration of the drug?	Not performed	0
Are there alternative causes that could have caused the reaction?	No reasonable alternatives identified after evaluation	+2
Did the reaction reappear when a placebo was given?	Not applicable	0
Was the drug detected in any body fluid in toxic concentrations?	Not applicable	0
Was the reaction worsened upon dose increase or lessened upon dose decrease?	Unknown	0
Did the patient have a similar reaction to the same or similar drugs previously?	No	0
Was the adverse event confirmed by objective evidence?	No definitive objective biomarker	0

Naranjo Score: 5=Probable adverse drug reaction (5 to 8): The reaction followed a reasonable temporal sequence after a drug, followed a recognized response to the suspected drug, was confirmed by withdrawal but not by re-exposure to the drug, and could not be reasonably explained by the patient's known clinical characteristics.

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ISSN: 2995-7494

clinically significant adverse effects and their implications for stroke diagnostic workflows.

Conclusions

This case adds to emerging literature describing atypical sensory-predominant neurologic presentations associated with tirzepatide. As GLP-1–based therapies continue to expand, clinicians should consider medication-associated contributors when evaluating unexplained dysesthesia. Because such sensory syndromes may coexist with incidental cerebrovascular findings, clinicians in stroke settings should remain vigilant to GLP-1/GIP agonist adverse effects and rely on thorough history and examination to distinguish true stroke-related deficits from unrelated medication-induced neurologic symptoms.

Conflicts of Interest

The authors report no conflicts of interest.

Author Affiliations

Drew A. Wells, PharmD, BCPS
Clinical Pharmacy Specialist – Internal Medicine
Methodist University Hospital
Memphis, TN USA
drew.wells@mlh.org

Miguel Rodriguez, MD
University of Tennessee Health Science Center
College of Medicine, Department of Neurology
Memphis, TN USA
mrodri22@uthsc.edu

Cheran Elangovan, MD
University of Tennessee Health Science Center
College of Medicine, Department of Neurology
Memphis, TN USA
celangov@uthsc.edu

Kerri Jones, PharmD, BCPS
Clinical Pharmacy Specialist – Neurology
Methodist University Hospital,
Memphis, TN USA
kerri.jones@mlh.org

DOI: 10.59236/sc.v3i3.119
ISSN: 2995-7494

Stroke Clinician Volume 3, Issue 3, Summer 2026

Corresponding Author

Kerri Jones, PharmD, BCPS
Clinical Pharmacy Specialist – Neurology
Methodist University Hospital,
Memphis, TN USA
kerri.jones@mlh.org

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DOI: 10.59236/sc.v3i3.119
ISSN: 2995-7494