ODU TIP DERGİSİ/ODU MEDICAL JOURNAL (ODU MED J) **April 2025;12(1):14-18**

OLGU SUNUMU / CASE REPORT **DOI:** 10.56941/odutip.1663213

Sleep-Related Headache Following Metformin Use: Hypnic or Toxic?

Sukran Kaygisiz[1], Tuba Gul[1]

[1] Ordu University, Faculty of Medicine, Department of Neurology, Ordu, Turkiye

Received: 22 March 2025, Accepted: 25 March 2025, Published online: 30 April 2025

Abstract

Headache is among the most frequently encountered symptoms in clinical practice. Occipital neuralgia is characterized by sudden, sharp, electric shock-like pains in the distribution area of the occipital nerve. In this report, we present a 54-year-old female patient who developed occipital neuralgia-like symptoms shortly after the initiation of metformin treatment for type 2 diabetes mellitus. The symptoms resolved following the discontinuation of the drug. This case is discussed in light of the literature to highlight a potentially rare headache pattern triggered by metformin.

This case describes an unusual form of headache possibly associated with metformin therapy. It underscores the importance of considering uncommon side effects of commonly prescribed medications such as metformin in differential diagnoses.

Key Words: Occipital neuralgia, Metformin, Headache, Trigeminal neuralgia, Neuropathic pain

Metformin Sonrası Gelişen Uykuya Özgü Baş Ağrısı: Hipnik mi, Toksik mi?

Özet

Baş ağrısı, klinik pratikte en sık karşılaşılan semptomlardan biridir. Oksipital nevralji, özellikle oksipital sinirin innervasyon alanında ani, keskin, elektrik çarpması tarzında ağrılarla karakterizedir. Bu çalışmada, tip 2 diabetes mellitus tanısıyla başlanan metformin tedavisinden kısa süre sonra gelişen ve ilacın kesilmesiyle gerileyen, oksipital nevralji benzeri semptomlar gösteren 54 yaşındaki kadın hasta sunulmuştur. Bu olgu, metformin ile tetiklenmiş olabilecek nadir bir baş ağrısı paternini vurgulamak amacıyla literatür ışığında tartışılmıştır.

Bu olgu, metformin tedavisi ile ilişkili nadir bir baş ağrısı formunu tanımlamaktadır. Metformin gibi sık kullanılan ilaçların, alışılmadık yan etkilerle ilişkili olabileceği akılda tutulmalı ve ayırıcı tanıda bu tür ilişkiler göz önünde bulundurulmalıdır.

Anahtar kelimeler: Occipital neuralgia, Metformin, Headache, Trigeminal neuralgia, Neuropathic pain

Suggested Citation: Kaygisiz S and Gul T. Sleep-Related Headache Following Metformin Use: Hypnic or Toxic?. ODU Med J, 2025;12(1): 14-18.

Address for correspondence/reprints:

Sukran Kaygisiz

Telephone number: +90 (505) 925 39 04

E-mail: krnkygsz52@gmail.com

INTRODUCTION

Occipital neuralgia arises from irritation of the greater or lesser occipital nerves and is characterized by sudden, stabbing, electric shock-like pains, usually unilateral and radiating from the neck to the posterior head. Secondary

causes include trauma, cervical disc pathologies, and vascular compressions (1). In some cases, no specific etiology can be identified.

Metformin is a biguanide widely used in the treatment of type 2 diabetes mellitus. Although generally well tolerated, it may occasionally lead to neurological side effects such as vitamin B12 deficiency and peripheral neuropathy (2).

CASE REPORT

A 54-year-old female patient presented with a two-month history of posterior head pain described as a sensation of pressure or brief electric shock-like episodes, particularly triggered by minor stimuli. There was no history of trauma or febrile illness. Notably, 3–4 years ago, she experienced a transient loss of consciousness following a playful slap to the nape.

The patient had been taking sertraline 100 mg/day for 23 years due to panic disorder. She reported experiencing chest tightness, a pressing pain in the heart, and emotional tension when she missed a dose. Despite regular use of the medication, episodes of intense stabbing chest pain, psychological distress, and even insomnia for several days could still occur in the context of emotional upset. Otherwise, her sleep was reported as regular.

A neurosurgeon had previously evaluated the patient and found no abnormalities on brain MRI. Cervical MRI revealed signs suggestive of cervical disc herniation, for which a regimen including Geralgine-K and Dexfort was initiated, to be taken as needed. The patient reported partial symptom relief with these medications.

She experienced a baseline persistent headache accompanied by paroxysmal, electric shock-like episodes predominantly occurring at night, often waking her up. These attacks tended to recur at similar times during the night.

Two months earlier, the patient was evaluated by her primary care physician, and laboratory tests revealed an HbA1c level of 7.0%. She was diagnosed with diabetes mellitus by an internal medicine specialist and started on metformin 850 mg twice daily. Approximately one week after starting metformin, she developed severe headaches. Ambulatory blood pressure monitoring revealed elevated readings, and the patient was diagnosed with hypertension. Candesartan 16 mg/day was initiated, resulting in blood pressure normalization from 190/100 mmHg to 110/70 mmHg. She continued to experience nocturnal headaches despite normotensive readings during these episodes.

Past medical history: No prior history of trauma, febrile illness, or smoking. The patient did not have asthma. She was undergoing regular follow-up for bilateral fibrocystic breast adenomas.

Family history: Positive for neuralgic disorders. Her father had required long-term pharmacological treatment for neuralgia, and her sister had undergone surgical intervention for trigeminal neuralgia after inadequate response to medical therapy.

Neurological examination: Revealed a left peripheral facial palsy, noted as a long-standing sequela, and a minimal essential tremor in the right hand. Other neurological findings were unremarkable.

Neuroimaging findings: Brain MRI was within normal limits. Cervical MRI demonstrated mild anterior bulging at the C4–C5 level and right-sided bulging at C5–C6 with borderline nerve root contact.

Initial treatment with propranolol 2x1 and triptans for acute episodes was ineffective. One month later, due to persistent symptoms, topiramate was initiated but did not result in improvement. Occipital nerve block (GON block) was then administered, and partial benefit was achieved after the second session.

At this stage, a possible association between the clinical picture and metformin therapy was considered. The patient was referred back to internal medicine, and metformin was discontinued. A three-month period of dietary and exercise-based glucose control was advised, without initiating an alternative pharmacological agent.

Within one week of discontinuing metformin, the patient reported a rapid reduction in headache intensity. Complete resolution of symptoms was observed by the third week post-discontinuation. As symptoms resolved, there was no further need for occipital nerve block therapy.

At the three-month follow-up, the patient's HbA1c had increased to 7.2%, prompting the initiation of a sulfonylurea by the internal medicine specialist. At both the 6- and 12-month follow-up visits in the neurology outpatient clinic, the patient remained asymptomatic with regard to headaches. Neurological follow-up was therefore concluded.

DISCUSSION

Metformin, a biguanide derivative, is widely recommended as a first-line agent in the treatment of type 2 diabetes. Although generally safe, rare but significant adverse effects may occur. The most common side effects are gastrointestinal; however, serious complications such as B12 deficiency, lactic acidosis, and peripheral neuropathy are also documented (1,2).

This case highlights the development of occipital neuralgia-like headaches shortly after metformin initiation, which resolved completely following drug withdrawal. Reports linking metformin and headache are scarce. A study by Wile and Toth

suggested an increased risk of peripheral neuropathy in patients using metformin, possibly related to B12 deficiency (2).

However, B12 levels were normal in this case. One possible mechanism for the headache is the increase in nitric oxide (NO) production induced by metformin. NO's effect on vascular structures is known to trigger headaches (3). Moreover, metformin may reduce asymmetric dimethylarginine (ADMA) levels, thus increasing endothelial NO synthesis, which may lead to cerebral vasodilation and headache (4).

Occipital neuralgia is typically paroxysmal, electric shock-like pain resulting from irritation of the occipital nerves (5).

Secondary causes include cervical disc disorders, trauma, tumors, or vascular anomalies. Although cervical MRI in this case revealed only minimal pathology, the temporal relationship between symptom onset and metformin use, along with complete resolution upon discontinuation, points to a pharmacological rather than structural cause.

There are few documented cases of metformin-induced headaches in the literature. One report described a patient developing cluster-like headache following metformin initiation, with resolution upon discontinuation (3). In our case, the partial response to occipital nerve block and rapid, sustained improvement after stopping metformin further supports a causal relationship. Additionally, the family history of neuralgic disorders suggests a possible genetic predisposition that may enhance susceptibility to drug-related neurological effects (6,7).

Interestingly, the nocturnal pattern of headaches in this patient raises the differential diagnosis of hypnic headache. Hypnic headache typically affects individuals over 50, awakens them from sleep, and presents with pulsating or dull pain in brief episodes (8,9). According to ICHD-3 criteria, hypnic headache is often treated successfully with caffeine or indomethacin. However, in this case, the clear temporal correlation with metformin use and the complete resolution upon its cessation suggest a drug-induced neurological side effect rather than primary hypnic headache. Nonetheless, typical features, accompanying symptoms, and medication history should be carefully reviewed when considering this diagnosis.

CONCLUSION

While metformin is generally regarded as a safe antidiabetic agent, clinicians should remain vigilant for rare neurological side effects. A thorough drug history should be obtained in patients presenting with headache or neuralgia-like symptoms, and the potential neurotoxicity of widely used medications like metformin should be considered. This case underscores the importance of including metformin-induced

occipital neuralgia-like symptoms in the differential diagnosis.

REFERENCES

1. Viollet B, Guigas B, Garcia NS, Leclerc J, Foretz M, Andreelli F. Cellular and molecular mechanisms of metformin: an overview. Clin Sci (Lond). (2012);122(6):253–270.
2. Wile DJ, Toth C. Association of metformin, elevated homocysteine, and methylmalonic acid levels and clinically worsened diabetic peripheral neuropathy. Diabetes Care. (2010);33(1):156–161.
3. Akpınar ÇK, Erdoğan S, Yazıcı T, Özbenli T. "Cluster-like headache due to metformin therapy." Agri: Agri (Algoloji) Dernegi'nin Yayin Organidir= The Journal of the Turkish Society of Algology (2016): 118-118.
4. Aydın M, Armutçu F, Yiğitoğlu M. Asimetrik Dimetil Arjinin (ADMA) Metabolizması. International Journal of Basic and Clinical Medicine. (2015);1(1):61-6.
5. Austin M, Hinson MR. Occipital Nerve Block. [Updated 2023 Apr 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK580523/
6. Fan Z, Su D, Li ZC, Sun S, Ge Z "Metformin attenuates central sensitization by regulating neuroinflammation through the TREM2-SYK signaling pathway in a mouse model of chronic migraine." Journal of Neuroinflammation 21.1 (2024): 1-17.
7. Bennett DL, Woods CG. Painful and painless channelopathies. Lancet Neurol. 2014;13(6):587-599. doi:10.1016/S1474-4422(14)70024-9
8. Lindner D, Scheffler A, Nsaka M, Holle-Lee D. Hypnic Headache - What do we know in 2022?. Cephalalgia. 2023;43(3):3331024221148659. doi:10.1177/03331024221148659
9. Liang, Jen-Feng, and Shuu-Jiun Wang. "Hypnic headache: a review of clinical features, therapeutic options and outcomes." Cephalalgia 34.10 (2014): 795-805.