Trigeminal neuralgia associated with isotretinoin use: a very rare complication

Murat Guntel[1]

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ABSTRACT

Background: Trigeminal neuralgia (TN) is a term used in short-term acute pain in the trigeminal nerve distribution that feels like stabbing or electric shock. Isotretinoin (13-cis-retinoic acid) is a commonly used medication for the treatment of severe cystic acne that does not respond to other therapies. Isotretinoin treatment has been associated with rare but serious complications on multiple systems.

Case Presentation: This case report presents a patient who developed TN while using oral isotretinoin therapy for acne vulgaris. This rare adverse event has not been well documented in the medical literature.

Conclusion: The author want to emphasize with this case report that physicians should keep in mind that TN is one of the possible negative effects of isotretinoin.

Keywords: Isotretinoin, trigeminal neuralgia, rare complication, case report.

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Correspondence to: Murat Guntel
Assistant Professor, Mustafa Kemal University, Neurology Department, Antakya, Turkey.
Email: muratguntel@hotmail.com
Full list of author information is available at the end of the article.

Background

Isotretinoin is a synthetic retinoid that is a vitamin A derivative. Acne vulgaris is a chronic inflammatory disease that affects the pilosebaceous unit. Oral isotretinoin is used in the treatment of severe nodulocystic acne and acne resistant to systemic antibiotic treatments. Many side effects related to the use of isotretinoin have been reported in the literature. The systemic use of synthetic retinoids, which are effective in the growth and differentiation of cells, can cause mucocutaneous, gastrointestinal, neuromuscular, and ocular side effects. Trigeminal neuralgia (TN) is the most common type of cranial neuralgia. It is a clinical picture characterized by very severe and very short-term pain (between 2 seconds and 2 minutes) like an electric shock pain paroxysm occurring in the sensory distribution area (V1, V2, and V3) of the trigeminal nerve. The author wanted to present this report because the author did not encounter a case of TN that developed due to the use of isotretinoin in the literature.

Case Report

A 35-year-old woman was admitted to the neurology clinic due to sudden pain on the right side of her face. Her pain was started last night from the front of her right ear and spread to her chin. Especially, pain was more prominent in the upper jaw. She described the pain as very severe, intolerable, intermittent shock-like, and always unilateral. She revealed that eating, swallowing, brushing teeth, and even on touching could trigger her pain. Pain episodes last for 2–3 seconds, and she had painless periods lasting for 3–5 minutes. In the medical history, she was receiving metformin treatment (1000 mg 2 × 1) due to the diagnosis of diabetes for 5 years. In addition, it was learned that Hashimoto's thyroiditis was also diagnosed, but she was followed up without medication due to the euthyroid state. About 3 weeks ago, isotretinoin was prescribed by the dermatologist for the treatment of acne resistant to systemic antibiotics, and it was learned that she used it as 40 mg/day.

Her neurological examination was completely natural, and no abnormal value was detected in the laboratory tests. Panoramic chin radiography taken from the painful localization was normal, and no pathology was detected in cranial magnetic resonance imaging and magnetic resonance angiography.

The patient was diagnosed with TN associated with isotretinoin use. Then, isotretinoin treatment discontinued, and carbamazepine (KBZ) treatment was started as 100 mg/daily and gradually increased to 400 mg/daily due to intolerable pain. The patient's pain decreased by 50% at the end of the 2nd week, so a dose increased to 800 mg/day. At the end of the 1st month, the pain was completely under control.

Discussion

TN is the most common type of cranial neuralgia. It is a clinical picture characterized by very severe and very short-term pain (between 2 seconds and 2 minutes) like an electric shock pain paroxysms occurring in the sensory distribution area (V1, V2, and V3) of the trigeminal nerve [1]. The etiology in idiopathic TN is still controversial; Efaptic transition (the illusion of stimulation perception due to demyelinated fibers neighboring with unmyelinated fibers); Stimulation of trigeminal ganglion (neurogenic vasodilation); The presence of an epileptogenic focus on the brain stem (central origin); Demyelination/remyelination and degenerative hypermyelination after nerve compression can be listed among the etiological factors that may cause. The diagnosis of TN is made clinically. Starting an effective treatment in the early period prolongs the remission period and prevents exacerbations. The first option in treatment is KBZ. The dose should be started with 100 mg 2 × 1, and the dose titration should be increased with an interval of 4–7 days and the effective dose should be accepted as the treatment dose (200–1,200 mg/day). Monotherapy should be preferred, and if there was no response, gabapentin should be added to the treatment [3].

Isotretinoin (13-cis-retinoic acid) is a natural physiological compound formed by vitamin A metabolism. It is one of the most prescribed and most effective treatments for severe acne vulgaris and various other dermatological diseases. It can also be used in higher doses and other forms in the treatment of some carcinomas. The long duration of treatment, the high cost, and especially, the side effects seen during the treatment limit the use of isotretinoin today [4]. Side effects can be divided into two groups as mucocutaneous and systemic. The frequency and severity of most of the side effects other than teratogenicity are dose dependent. The most important side effect of isotretinoin is undoubtedly teratogenicity. The pregnancy category is X, and the use of this drug in pregnant women is contraindicated. The most common side effects during isotretinoin use are mucocutaneous side effects, and among them, cheilitis is the most common. Xeroderma, dryness in mucous membranes, eczematous dermatitis, epistaxis, atrophic scar, facial erythema, alopecia, acne exacerbation, herpes simplex infection, pruritus, and pyogenic granuloma are other mucocutaneous side effects that can be observed [5,6]

Many systemic side effects can also be observed during isotretinoin use. Systemic side effects are mainly on the visual system, musculoskeletal system, gastrointestinal tract, central nervous system (CNS), and psychological problems. Xerophthalmia, night blindness, conjunctivitis, keratitis, blepharitis, and optic neuritis are among the ophthalmological side effects. Corneal opacities, cataracts, and visual loss, which may be temporary or permanent, have also been reported during isotretinoin use [7]. Myalgia is the most common musculoskeletal finding in patients using isotretinoin. Hyperostosis, demineralization, severe bone pain, and early closure of epiphysis in children can be observed in patients taking isotretinoin for a long time. Furthermore, arthritis, arthralgia, back pain, and osteoporosis may develop during isotretinoin use. Unlike other side effects, the side effects on the bone can be permanent after the end of treatment and can be seen even on the radiographs a few years later [8,9].

It is anticipated that the high doses of isotretinoin can cause cardiac problems; however, cardiac findings are limited to case reports. Palpitations, chest pain, dyspnea, hypertriglyceridemia, hypercholesterolemia, and impaired liver function tests are other systemic side effects that can be observed [10].

The effects of isotretinoin on CNS are rare. The most common of these are headache, nausea, and vomiting. Furthermore, in the presence of persistent headache, nausea, vomiting, and blurred vision, accompanied by papillary edema, pseudotumor cerebri should be suspected, and treatment should be discontinued immediately. Since the risk of pseudotumor cerebri increases during concomitant tetracycline use, these two drugs should not be used together. Optic nerve edema develops as a result of pseudotumor cerebri, which is thought to be caused by retinoic acid. In addition, the fact that it causes neurological side effects such as headache, disulfiram-like reaction, hearing loss, and oculogyric crisis, showing that retinoids can cause neurotoxicity on CNS. Although diplopia and optic neuritis have been reported as "possible" ocular side effects related to isotretinoin, it is difficult to say that these diseases are caused by a direct cause–effect relationship with the use of isotretinoin. However, unlike the effects on the optic nerve and subclinical changes in auditory brainstem functions related to isotretinoin, it can be explained by the drug's ability to make a transmission or function defect in the synaptic cleft [6,11,12].

Although isotretinoin is known to cause headaches, there are no studies or case reports in the literature that it can trigger TN. The author could not find any data from the literature that what type of headache isotretinoin can trigger, so, in this respect, this case report is the first of its kind. In a study using data from the Food and Drug Administration (FDA) and conducted through a web address created by eHealthMe, "30,986 people have side effects when taking Accutane. Among them, 20 people (0.06%) have TN. TN found, especially for people who are female, 30–39 years old, have been taking the drug for 1–6 months, also take medication ibuprofen, and have impaired gastric emptying"[13].

Although the mechanism of action of isotretinoin is not fully known, a few studies have reported that isotretinoin induces apoptosis in various cells, such as meibomian glands, hypothalamus cells, hippocampus cells, and

sebaceous glands. Another study showed that isotretinoin significantly changed the expression of hundreds of genes in the skin after 8 weeks of treatment [14]. We do not know how isotretinoin can trigger TN, but the illusion of stimulation perception due to demyelinated fibers neighboring with unmyelinated fibers, stimulation of trigeminal ganglion (neurogenic vasodilation), or making a transmission or function defect in the synaptic cleft may be the causing factors. Or it may be an idiosyncratic reaction. Idiosyncratic reactions are reported to occur at a variable time during treatment, have no predictable pattern, and cannot be monitored [15]. The quality of evidence is not high because potentially contributing reasons may not always be fully explored. Therefore, it becomes difficult to establish causality.

Conclusion

This case shows the importance of a detailed drug list review when evaluating a patient with TN. If it is clearly demonstrated, the treatment of the underlying etiology is the cornerstone of management because this approach also prevents recurrent attacks. Severe pain during isotretinoin therapy requires further investigation, and the patients should be aware of this possible side effect. However, this diagnosis should be made carefully after the exclusion of common causes. Avoiding isotretinoin to prevent future attacks can be beneficial if a similar efficacy drug can be replaced.

What is new?

Severe pain during isotretinoin therapy requires further investigation, and physicians should keep in mind that TN is one of the possible negative effects of isotretinoin.

List of Abbreviations

CNS	Central Nervous System
FDA	Food and Drug Administration
KBZ	Carbamazepine
RA	Retinoic Acid
TN	Trigeminal Neuralgia

Consent for publication

Written informed consent was obtained from the patient.

Ethical approval

Ethical approval is not required at the institution to publish an anonymous case report.

Author details

Murat Guntel[1]

1. Department of Neurology, Hatay Mustafa Kemal University, Antakya, Turkey

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Summary of the case

1	**Patient (gender, age)**	Female, 35-year-old
2	**Final diagnosis**	Trigeminal neuralgia
3	**Symptoms**	Severe, intolerable, intermittent shock-like, unilateral, sudden pain
4	**Medications**	Carbamazepine
5	**Clinical procedure**	Carbamazepine treatment was started as 100 mg daily and gradually increased to 400 mg daily. The patient's pain decreased by 50%at the end of the second week, so dose increased to 800 mg a day.
6	**Specialty**	Neurology