SKIN

BRIEF ARTICLE

Potential Neurologic Side Effects of Oral Isotretinoin: A Case of Peripheral Neuropathy

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ABSTRACT

Oral isotretinoin is a well-known, effective medication used in the treatment of severe cystic acne. While efficacious, the potential side effects of isotretinoin are often discussed and may cause concern for patients. Although most side effects of this medication are mild, other more concerning adverse effects have been reported. Of note, isotretinoin has the potential to affect the central nervous system (CNS), causing headaches, pseudotumor cerebri, and fetal CNS malformations. In contrast, the effects on the peripheral nervous system are not well documented. The objective of this case report is to present an instance of oral isotretinoin leading to foot drop in an adolescent patient.

INTRODUCTION

Isotretinoin is recognized as one of the most effective treatments available for nodulocystic acne. Aside from its effectiveness in treating the acne itself, isotretinoin has also been noted to improve the psychosocial aspects of severe acne including depression, anxiety, and quality of life.[1] Despite its effectiveness, the drug is publicly known for its association with adverse effects such as xerosis, epistaxis, cheilitis, and myalgias as well as less common side effects like depression, anxiety, insomnia, suicidal ideation, sun sensitivity, vision changes, and hair loss.[2] While a variety of side effects have been reported, the potential effect of isotretinoin on the peripheral nervous system remains an area of further investigation. Here we present a case of a patient who developed foot drop while being treated with oral isotretinoin.

CASE REPORT

A 14-year-old female with a past medical history of acne, seborrheic dermatitis, atopic dermatitis, and hypertrichosis presented to our dermatology clinic seeking treatment for treatment-resistant acne. Over the past three years, the patient had failed sufficient trials of adapalene, clindamycin 1% gel, dapsone 7.5% gel, doxycycline 100mg PO QD, spironolactone 25mg PO BID, and adapalene/benzoyl peroxide. She was subsequently started on oral isotretinoin. Based on her weight of 50.8kg, she was started on 40mg daily and continued this treatment successfully for six months for a total cumulative dosage of 141.7mg/kg. She experienced common side effects such as cheilitis, xerosis, and intermittent headaches without signs of increased intracranial pressure. At a follow-up visit two months following the completion of her treatment course, her father, a physician, mentioned

that her cheilitis and xerosis had resolved. However, he stated that during the end of her treatment course, she developed weakness in her left lower extremity. She was evaluated by a neurologist and was diagnosed with foot drop based on clinical presentation and diagnostic assessment by nerve conduction study. The patient experienced no other neurological symptoms and improved within three months of diagnosis following nerve transposition surgery and six weeks of physical therapy.

DISCUSSION

Isotretinoin is a medication well known for both its effectiveness as well as its diverse adverse effect profile. While the most common of these adverse effects impact the skin and mucosal surfaces, others such as insomnia, vision changes, hair loss, and GI upset have also been reported[1]. The effects of isotretinoin on the central nervous system are well documented and include severe headache and pseudotumor cerebri.[3] The potential effects on the peripheral nervous system have not been extensively discussed in detail previously. In contrast to isotretinoin, other vitamin A derivatives such as etretinate and all-trans retinoic acid (ATRA) have demonstrated multiple documented cases of resulting peripheral neuropathy.[4] In the case of etretinate, nerve biopsy has shown a decreased number of myelinated fibers as well as axonal degeneration and abnormal Schwann cell complexes.[5] Yamaji et al. describe a case of multiple mononeuropathies associated with ATRA use for acute promyelocytic leukemia. After three weeks of ATRA therapy, the patient complained of diplopia as well as dysesthesia of the dorsum of the left hand and right foot. The patient also showed weakness in these extremities and a decrease in right peroneal nerve conduction velocity and amplitude during electrophysiologic study[9]. The mechanism by which isotretinoin may cause peripheral neuropathy is still unknown, but Aydogan and Karli hypothesize that nerve conduction is negatively affected by changes in lipid composition of peripheral nerve membranes secondary to isotretinoin therapy.[4]

Additionally, in a study assessing isotretinoin's effects on action potentials of nerve fibers, it was found that 72% of the 28 patients had significant decreases observed in the mean sensory conduction velocities of median, ulnar, sural, medial plantar, medial dorsal cutaneous, and dorsal sural nerves 6 months after the onset of treatment.[6] In contrast to this study, another small study of 18 patients done by Chroni et al. found that the standard dose of 1mg/kg of isotretinoin over a short-term course of 1-3 months did not cause a clinical or subclinical peripheral neuropathy.[7] While the sample sizes and dosing regimens of the studies are equal, the duration of the studies differ, suggesting that there is still potential for peripheral neuropathy at longer treatment durations and/or higher cumulative dosages.

Pritchard et al. describe two cases of Guillain-Barré syndrome developing in patients taking isotretinoin.[8] One case showed undetectable sensory nerve potentials and F waves, while the other showed increased F wave latency. Both patients had severe illness and were eventually dependent on ventilatory support. While the authors acknowledged that two cases are not sufficient to make a direct association, they serve as another example of the potential negative effect of isotretinoin on the peripheral nervous system.

CONCLUSION

Our case represents an example of isotretinoin's potential impact on peripheral nerve pathology. While the studies evaluating peripheral neuropathy as a side effect of isotretinoin are limited, there is evidence that peripheral neuropathy is a potential adverse effect of taking isotretinoin. We believe clinicians should be aware of this possible adverse effect when prescribing this drug. Further investigation is needed to determine whether or not a direct causation exists and at what treatment duration/cumulative dosage patients may be at risk for developing peripheral neuropathy.

Conflict of Interest Disclosures: None

Funding: None

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References:

1. Marron S, Tomas-Aragones L, & Boira S. Anxiety, Depression, Quality of Life and Patient Satisfaction in Acne Patients Treated with Oral Isotretinoin. *Acta Dermato Venereologica,* 2013;93(6), 701–706.
2. Brzezinski P, Borowska K, Chiriac A, et al. Adverse effects of isotretinoin: A large, retrospective review. *Dermatologic Therapy,* 2017;30(4), e12483.
3. Bigby M, & Stern RS. Adverse reactions to isotretinoin. *Journal of the American Academy of Dermatology, 1988;*18(3), 543–552.
4. Aydogan K, Karli N. Effects of oral isotretinoin therapy on peripheral nerve functions: a preliminary study. *Clin Exp Dermatol*. 2007;32(1):81-84.
5. Danon MJ, Carpenter S, Weiss V, et al. Sensory neuropathy associated long-term etretinate (ET) therapy. *Neurology* 1986; 36 (Suppl. 1): 321.
6. Altun Y, Inan E. Mid-term oral isotretinoin therapy causes a predominantly sensory demyelinating neuropathy. *Ideggyogy Sz.* 2019;72(5-6):159-164.
7. Chroni E, et al. Short-term oral isotretinoin therapy does not cause clinical or subclinical peripheral neuropathy. *Jounral of Dermatological Treatment.* 2006; 17(1):6-8.
8. Pritchard J, Appleton R, Howard R, et al. Guillain-Barré syndrome seen in users of isotretinoin. *BMJ.* 2004;328(7455), 1537.
9. Yamaji S, Kanamori H, Mishima A, et al. All-trans retinoic acid-induced multiple mononeuropathies. Am J Hematol. 1999 Apr;60(4):311. doi: 10.1002/(sici)1096-8652(199904)60:4<311::aid-ajh11>3.0.co;2-r. PMID: 10203107.