

# Presumed isotretinoin-induced extraocular myopathy

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## ABSTRACT

Isotretinoin a synthetic analogue of vitamin A is primarily used for cystic acne not responding to conventional treatment. Several ocular side effects including blurring of vision, decreased dark adaptation, corneal opacities and meibomian gland atrophy have been reported with prolonged use of isotretinoin. There have been reports of muscular damage caused by isotretinoin. Extra ocular myopathy as an adverse effect of long term used of isotretinoin has never been mentioned in literature. We report a case of a young male who presented to us with complaints of diplopia after using isotretinoin for a prolonged period. He was diagnosed as a case of presumed isotretinoin extraocular myopathy after imaging and other blood investigations.

**Key words:** Extraocular muscles, isotretinoin, myopathy

## INTRODUCTION

Isotretinoin (13-cis-retinoic acid), a synthetic analog of Vitamin A, is used primarily for severe cystic acne and acne that has not responded to conventional treatments.<sup>[1]</sup> Ocular side effects of isotretinoin are usually dose related. They include abnormal meibomian gland secretion, blepharoconjunctivitis, corneal opacities, decreased dark adaptation, decreased tolerance to contact lens, decreased vision, increased tear osmolarity, keratitis, meibomian gland atrophy, myopia, ocular discomfort, ocular sicca, and photophobia.<sup>[2]</sup> Extraocular myopathy caused by isotretinoin has never been mentioned in literature. We herewith report a rare case of extraocular myopathy which was most likely caused by isotretinoin intake for a prolonged period.

## CASE REPORT

A 31-year-old male presented to our oculoplasty clinic with chief complaints of gradual outward deviation of left eye and double vision in right gaze for the past 2 years. There was no history of pain, trauma, diurnal variation, diminution of vision, vomiting, or headache. He was not a known case of diabetes mellitus, hypertension, thyroid disorder, or any other chronic disease.

Visual acuity of both eyes was 20/20. There was right face turn with left exotropia. Extraocular movements in left eye revealed complete limitation of adduction and mild limitation of depression [Figure 1]. There were no signs of thyroid ophthalmopathy. Rest of the anterior and posterior segment examination were within normal limits. A differential diagnosis of thyroid eye disease and ocular myasthenia gravis was considered and a thyroid function test (serum free T3, serum free T4, and serum thyroid stimulating hormone assay) and serum acetylcholine receptor antibody were ordered.

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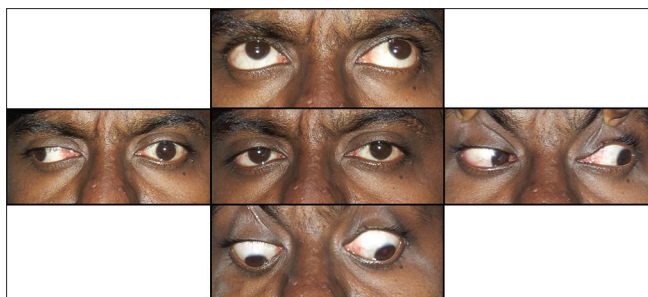
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**Figure 1:** External photograph of the patient showing left exotropia and complete limitation of adduction and mild limitation of depression in the left eye

Thyroid function test was within normal limits and serum acetylcholine receptor antibody was negative. Magnetic resonance imaging (MRI) of the brain and orbit showed hyperintensity in the belly of left medial and inferior rectus. There was no enlargement of the muscles and orbital fat content was normal [Figure 2a and b]. The features on MRI were neither suggestive of thyroid eye disease nor idiopathic orbital inflammation.

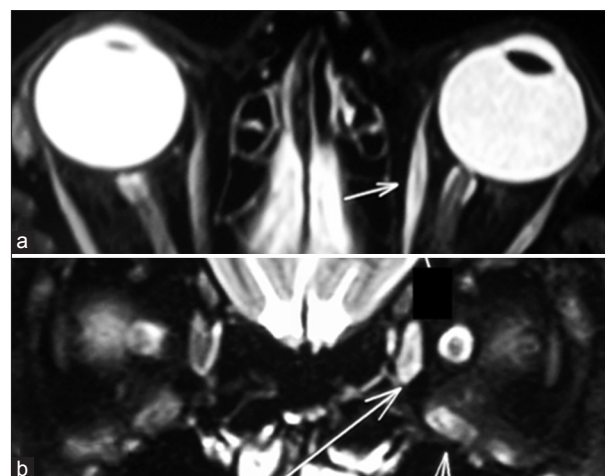
On further inquiry, the patient gave history of isotretinoin intake for 3 months (1 mg/kg/day) for cystic acne just before the symptoms started and continued the drug for next 5 months. A provisional diagnosis of isotretinoin-induced myopathy was made and the patient was asked to stop isotretinoin. The patient was also started on a course of oral steroid in tapering fashion to take care of any associated inflammatory pathology. There was no improvement in extraocular motility after 3 months of oral steroids, and a repeat MRI showed no improvement, suggesting fibrosis. The patient was prescribed prism glasses to take care of his diplopia.

## DISCUSSION

Exact mechanism of action of isotretinoin is not known. It has been shown to induce apoptosis in various cells of the body including sebaceous glands, and thereby helping in the treatment of acne vulgaris.<sup>[3]</sup>

One study suggests that the drug amplifies production of neutrophil gelatinase-associated lipocalin in the skin, which has been shown to reduce sebum production by inducing apoptosis in sebaceous gland cells while exhibiting an antimicrobial effect on *Propionibacterium acnes*.<sup>[3,4]</sup> The drug decreases the size and sebum output of the sebaceous glands.

About 15% of patients treated with isotretinoin have developed musculoskeletal symptoms and on rarer occasions increased creatine kinase (CK) activities.<sup>[5]</sup> There are reports of clinical and electromyographic evidence of muscle damage during treatment with isotretinoin. The acute muscle damage caused by isotretinoin was reversible on discontinuation of the drug.<sup>[6]</sup>



**Figure 2:** (a) Magnetic resonance image, axial cut, T2 sequence showing hyperintensity in left medial rectus belly. The muscle belly is smooth without any enlargement. (b) Magnetic resonance image, coronal cut, T2 sequence showing hyperintensity in left medial rectus and inferior rectus belly (arrow). The muscle belly is smooth without any enlargement

Myalgia and muscle stiffness have been reported in 16%–51% of patients treated with isotretinoin while elevated serum CK levels have been found in up to 41% of patients.<sup>[7]</sup> There have been several reports of severe and debilitating muscular symptoms due to isotretinoin where CK levels were normal.<sup>[8]</sup> In such patients, myopathy or a disorder of myoneural junction was suggested by muscle biopsy.

The exact mechanism of isotretinoin-induced myopathy has not yet been elucidated; however, it has been hypothesized that all therapeutic as well as adverse effects of isotretinoin are caused by its “proapoptotic mechanisms” mediated by forkhead box O and its isoforms (Melnik). The latter are proteins that are involved in regulating gene expression in a variety of conditions including inflammatory and immune-mediated processes.

Regarding the patient presented in this case report, there is a possible relationship between isotretinoin intake and his extraocular myopathy.

Drug-induced myositis is a condition which implies the exclusion of other entities responsible for myositis such as infectious or autoimmune diseases or idiopathic cause. The three strong differentials in the present case were thyroid-related ophthalmopathy, ocular myasthenia gravis, and idiopathic orbital inflammatory disease. The thyroid eye disease was ruled out in view of normal thyroid levels, absence of ocular signs of thyroid eye disease, and no evidence of increase in size of extraocular muscles or orbital fat on MRI. Ocular myasthenia gravis was ruled out by the absence of diurnal variation in the symptoms, symptoms being stable for the past 2 years without any variability, and a negative serum acetylcholine receptor antibody assay.

Idiopathic orbital inflammatory disease commonly presents with pain and the imaging shows diffuse irregular enlargement of extraocular muscles involving the whole length of the muscle. The present case did not have any pain and the MRI showed a smooth hyperintensity in the muscle belly without any enlargement. Thereby, considering the clinical and radiological findings, the most likely diagnosis in this case was an isotretinoin-induced myopathy. Isotretinoin has been reported to have some immunomodulating effects that may induce some autoimmune diseases such as Crohn's disease, immune-mediated diabetes, and Guillain-Barré syndrome.<sup>[9,10]</sup> There has been a case report regarding possible association between isotretinoin intake and concomitant autoimmune thyroiditis and ocular myasthenia gravis.<sup>[11]</sup>

There is considerable evidence in the literature that isotretinoin can induce an autoimmune reaction resulting in various autoimmune conditions;<sup>[9-11]</sup> we presume that a similar mechanism would have been responsible to produce an autoimmune thyroid eye disease-like condition in the present case. Stopping the drug will result in cessation of the inflammatory response but the fibrosis induced by the inflammation would result in residual limitation of extraocular movements as in the present case.

We conclude that though rare, isotretinoin-induced extraocular myopathy should be considered in the differential diagnosis of any patient presenting with diplopia and extraocular motility restriction, with concomitant isotretinoin intake.

#### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other

clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

#### Conflicts of interest

There are no conflicts of interest.

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