Case Reports in Women's Health 37 (2023) e00483

Contents lists available at ScienceDirect

Case Reports in Women's Health

journal homepage: www.elsevier.com/locate/crwh

# Short-term palinopsia after three doses of clomiphene: A case report

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ARTICLE INFO

*Keywords:*
Palinopsia
Clomiphene
Visual trailing
Visual phenomenon
Drug-induced
Reversible

ABSTRACT

Palinopsia is a phenomenon consisting of the persistence or recurrence of a visual image after the stimulus has been removed, and can be static or kinetic. Palinopsia can be caused by a variety of different factors. Drug-induced palinopsia usually takes the form of visual trailing, a subset of illusory palinopsia, where patients report that an object leaves after-images trailing behind the object. There have been few reported cases of clomiphene-induced palinopsia. All have led to permanent palinopsia. This report demonstrates a case of transient clomiphene-induced palinopsia. Palinopsia occurred after only three doses of clomiphene and resolved within 10 days of cessation of therapy.

## 1. Introduction

Clomiphene citrate has been used as the first-line treatment for infertility by millions of women since its approval in the United States in 1967. The most common side-effect is reversible ovarian enlargement but it is also associated with a variety of visual side-effects, including blurred vision, double vision and eye sensitivity to light [1]. Visual symptoms generally disappear a few days to weeks following discontinuation of therapy, with the exception of palinopsia. In all previously reported cases, palinopsia associated with clomiphene has persisted despite cessation of therapy [2].

The term palinopsia derives from the Greek *palin* (again) and *opsia* (seeing). It is a visual phenomenon consisting of the persistence or recurrence of a visual image after the stimulus has been removed. Images may be static or kinetic, with a variability in latency and durability reported [3]. Palinopsia can be separated into two groups: hallucinatory and illusory. Hallucinatory palinopsia is usually long-lasting, isochromatic and of high resolution. It is not usually affected by the environment. On the other hand, illusory palinopsia consists of unformed images of low resolution and is affected by ambient light and motion [4]. Palinoptic images are often further classified by subtype. The subtype of illusory palinopsia discussed in this case consists of visual trailing phenomena, where patients report that an object in motion leaves copies in its wake, like after-images. The "after-images" can last a few seconds and are identical in shape and colour to the original stimulus but are often less intense.

Palinopsia has a wide variety of etiologies, many of which relate to cerebral injury, which in turn may be caused by cerebrovascular accident (CVA), neoplasms, arteriovenous malformations(*AVM*)s, head trauma, seizures and cortical dysplasia affecting the post-geniculate. Metabolic or systemic diseases which may cause seizures such as hyperglycemia have been implicated, as well as infection that causes a cerebral abscess or diffuse cortical pathology. Other etiologies include migraines and psychiatric conditions. Palinopsia may be idiopathic or drug-induced, as in this report [4].

We present a case of short-term palinopsia occurring after only three doses of clomiphene, which resolved within 10 days of cessation of therapy. We also review the literature on the pathophysiology, epidemiology, and clinical aspects of palinopsia.

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[4] *Author's role:* was involved in patient care, was responsible for the conception of the case report, revised the article critically for important intellectual content, and approved final submitted manuscript.

https://doi.org/10.1016/j.crwh.2023.e00483
Received 12 January 2023; Received in revised form 27 January 2023; Accepted 30 January 2023
Available online 2 February 2023

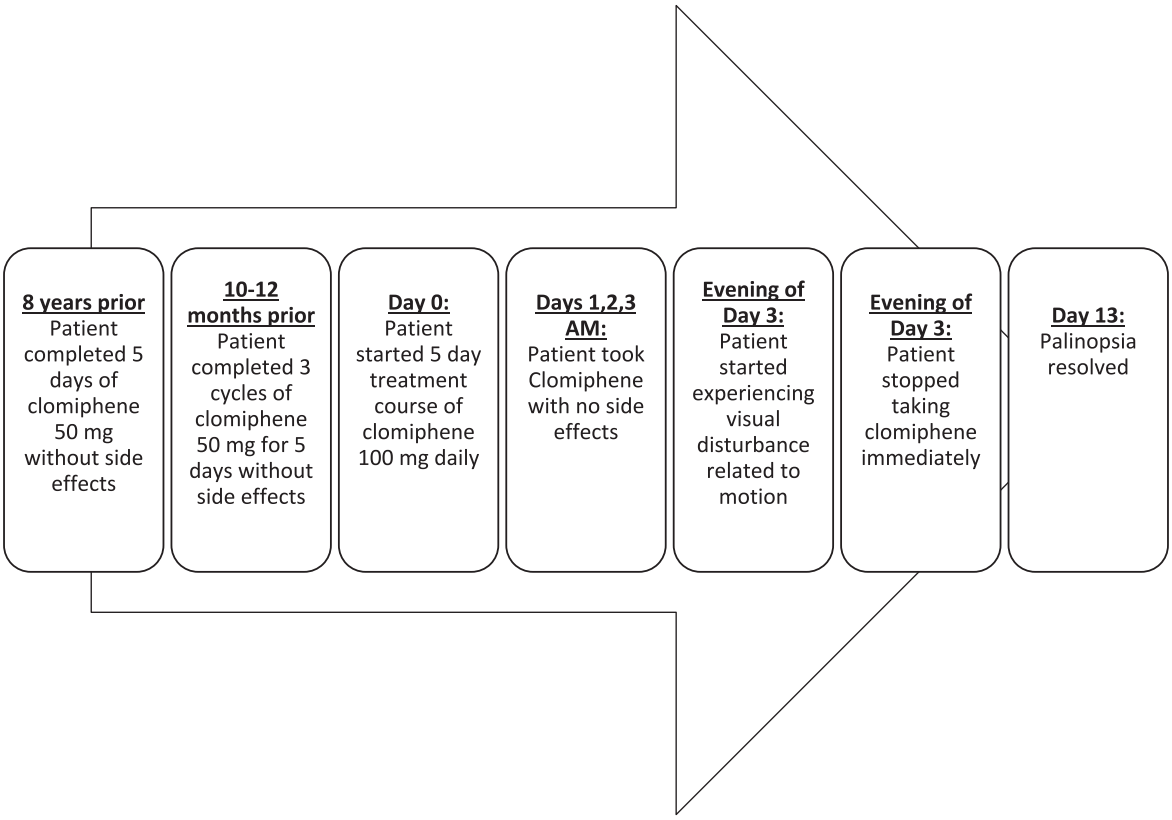


**Fig. 1.** Timeline of events following clomiphene use.

## 2. Case Presentation

A 39-year- old woman, G2P2, with a history of hypothyroidism treated with levothyroxine and infertility, presented to her general internal medicine doctor due to concerns about strange visual disturbances. The patient was on a 5-day course of clomiphene 100 mg daily. On the evening of day 3 of clomiphene, she noted a visual disturbance related to motion. She described it as a blurry trail of multiple fading after-images behind her hand as she moved it across her field of view. It was especially noticeable in low-light settings. She denied any tobacco, alcohol or recreational drug use. She did not take any "nutritional supplements" or herbal medications. She did not have a headache and did not have a history of migraines.

She had used 5 days of clomiphene 50 mg 8 years prior without side-effects. Prior to the current symptoms she had received 3 cycles of clomiphene 50 mg for 5 days, 10–12 months prior without side-effects (see Fig. 1 for timeline of events). Other medications received for infertility over the previous year included: leuprolide acetate 1.25 mg BID, menotropin 150 μg daily IM, progesterone 50 mg IM, follitropin beta 375 units SQ daily, somatropin 24 units SQ, letrozole 5 mg q d, medroxyprogesterone 10 mg q d, progesterone 200 mg q d and bupropion 150 mg BID.

Her vital signs were as follows: pulse rate, 88 beats per minute (bpm); blood pressure, 104/74 mmHg; respiratory rate, 14 breaths per minute; and temperature, 97.8 fahrenheit. On physical examination, she was well developed, well nourished, well hydrated, no distress. Conjunctiva were not injected, sclera anicteric, pupils were round and 6 mm in dim light and reactive to light bilaterally. Extraocular movements were intact. Fundoscopy showed normal discs, vessels and macula. Visual fields were normal to confrontation. Cardiac rhythm was regular, S1 and S2 were normal and there were no murmurs, no rubs, and no gallups. Lungs were clear to auscultation. Abdomen was nontender. She was alert and oriented X 3. Cranial nerves were intact to detailed examination. Motor – tone and bulk were normal and strength was 5/5 in all extremities. Sensation was intact to light touch and pin. Cerebellar function – no dysdiadochokinesia, dysmetria or ataxia on tandem gait. Rhomberg was negative. There was no pronator drift. Reflexes were 2+ symmetrically; plantar reflexes were downgoing.

The laboratory data showed a white blood cell count of 5.0 ×, hemoglobin level of 13.2 g/dL, platelet count of 229 × 10*9/L, estradiol 105 pg/mL, thyroid-stimulating hormone level 1.39 μIU/mL, thyroxine level of 1.10 ng/dL.

Given the concern clomiphene may have induced this visual disturbance, she discontinued clomiphene without taking any additional doses. Over the next two weeks the images faded and by day 10 had resolved completely.

## 3. Discussion

This case demonstrates short-term clomiphene-induced palinopsia. There have been a few previously documented cases of clomiphene-induced palinopsia but all lasted from greater than a year to more than 7 years despite stopping the drug. In 4 of the cases, patients had been taking clomiphene for multiple cycles and months before the start of symptoms [2,5,6]. In one case, palinopsia occurred after the 4th day of clomiphene. The symptom severity reduced after completion of the first cycle of clomiphene, enough for the second cycle to be completed. Symptoms worsened and persisted for at least the year of follow-up. Symptoms reduced after cessation of clomiphene. In this case, the patient had previously had 3 cycles of clomiphene 50 mg for 5 days around 12 months prior without any palinopsia. This suggests that there is an increased risk of palinopsia with an increased cumulative dose of clomiphene. However, cases of palinopsia have a wide range of onset for symptoms, from few days to multiple cycles; there must be an individual associated risk.

Palinopsia has been reported to be induced by many illicit drugs,

including lysergic acid diethylamide (LSD) most commonly, psilocybin (psychedelic mushrooms), 3,4 methylenedioxy-Nmethylamphetamine (MDMA or ecstasy), and cannabis (marijuana). It has also been reported with prescription drugs, including trazodone, nefazodone, mirtazapine, topiramate, risperidone and clomiphene. Drug-induced palinopsia is mainly of the illusory type. Symptoms usually occur after introducing a drug or increasing the dose and resolve after discontinuation. However, cases of clomiphene-induced palinopsia have been associated with permanent symptoms.

The theories for the pathophysiology of drug-induced palinopsia are based around alterations in neurotransmitters and their receptors. Examples for this include 5HT2a receptor excitotoxicity associated with LSD and trazodone, a 5HT2a receptor antagonist. Theories have been proposed that topiramate or clomiphene may be related to a disruption in GABAergic transmission, which is facilitated by the 5HT2a receptor in the posterior cortex. Pathophysiology may also be due to dysfunction in the feedback between the anterior and posterior visual pathways leading to dysfunction in light and motion perception [4].

Each case of clomiphene-induced palinopsia showed visual trailing. The pathophysiology is still not fully understood of how clomiphene induces the palinopsia in humans. There is an example of how clomiphene increases hypothalamic serotonin levels in a goldfish model [7]. This could link to the theory of 5HT2a receptor excitotoxicity causing palinopsia. Given this theory, a study attempted to treat the palinopsia with tianeptine, a serotonin uptake enhancer, and levetiracetam, an anticonvulsant, but no improvement was found.

As this is not the only medication that the patient in this case took, there may be an aspect of confounding. However, given previous examples of clomiphene-induced palinopsia with visual trailing, it is likely that clomiphene was the cause.

Normally workup should include visual fields and neuroimaging as well as routine labs such CBC and CMP to check for metabolic disturbances or hints of a neoplasm. However, with illusory palinopsia, the physical exam and work-up are almost always non-contributory and the diagnosis is largely based on information from the clinical history. As demonstrated with this case, the physical exam and labs were normal for the patient. It is important to note that the patient did not have a history of migraines. Given the high clinical suspicion that the palinopsia was clomiphene induced, clomiphene was stopped and symptoms resolved. No further work-up was done.

In conclusion, bringing light to clomiphene-induced palinopsia is an important consideration; the drug should be stopped as it can lead to long-lasting effects. Potentially this case of palinopsia resolved as clomiphene was quickly identified as the culprit and stopped immediately. Further investigation is still required to understand the mechanism of clomiphene-induced palinopsia, as well as potential risk factors and possible reversal methods.

*Contributors*

Naia McMillan-Castanares participated in the conception of the case report, acquired and interpreted the data, and drafted the manuscript.

Melissa Sue Melgar was involved in patient care, participated in the conception of the case report, acquired and interpreted the data, and revised the article critically for important intellectual content.

Thomas Austin Melgar was involved in patient care, was responsible for the conception of the case report, and revised the article critically for important intellectual content.

All authors approved final submitted manuscript.

*Funding*

This case report did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

*Patient consent*

The patient consented to publication of her case report.

*Provenance and peer review*

This article was not commissioned and was peer reviewed.

*Conflict of interest statement*

The authors declare that they have no conflict of interest regarding the publication of this case report.

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