Title page:

Authors:
Julio González Martín-Moro[1,2] (M.D.; Ph.D.) ORCID: 0000-0002-8056-2630
Elena Gutierrez Almagro[1] (M.D.)
Nestor Ventura Abreu[3] (M.D.; Ph.D.)
Fernando Neria Serrano[2](Ph.D.)

(1) Department of Ophthalmology. Hospital Universitario del Henares. Coslada. Madrid. Spain.
(2) Grado de Medicina. Universidad Francisco de Vitoria. Madrid. Spain.
(3) Department of Ophthalmology. Hospital Clinic. Barcelona. Spain

Corresponding author:
Julio González Martín-Moro
Hospital Universitario del Henares
Av. Marie Curie sn
28820 Coslada, Madrid, España
juliogmm@yahoo.es
juliogazpeitia@gmail.com

ABSTRACT:

Aim: To review the available literature on poppers maculopathy (PM).

Material and methods: 64 patients (60 with bilateral and 4 with unilateral involvement), for a total of 124 eyes reported in Pubmed, Google Scholar and Embase. Patterns were analyzed according to country, age, gender, sexual orientation, HIV status, consumption habits, visual acuity at presentation (VAP), final visual acuity (VAF) and optical coherence tomography (OCT).

Results: Most cases (110 eyes) of PM were reported in European countries and affected middle-aged men (only 8 eyes from female users). The median age was 38.7 years (SD=10.5 years). Final visual acuity (Median=0.8; Interquartile range: 0.67-1) was higher than visual acuity at presentation (Median=0.67; Interquartile range: 0.4-0.8). Many articles lack data on sexual orientation and HIV status as this is considered very personal information. VAF was higher than VAP. One third of the eyes (40 eyes) developed PM after a single exposure. No significant differences were found between eyes that developed PM after a single exposure and those which developed the condition after several exposures. The most commonly reported pattern was an interruption of the ellipsoid line (68 eyes).

Conclusion: PM is more prevalent in Europe or European ophthalmologists are more likely to diagnose PM. PM usually affects middle-aged men given that this condition generally appears with chronic exposure to poppers. VAF was higher than VAP, suggesting that this toxicity is in part reversible. Information about HIV status was not provided in most recent articles, thus it is not possible to make inferences about the possible implication of HIV drugs as cofactors for the development of this retinal toxicity.

Keywords

Maculopathy, poppers, nitrites, *retinal toxicity, inhalatory drugs.*

INTRODUCTION

Poppers is the generic name given to a group of volatile substances belonging to the alkyl nitrite family of compounds that are often used recreationally, normally through inhalation. These substances do not produce dependence and are not generally perceived as dangerous by users and there is a legal vacuum regarding their consumption(1). For decades, these substances have been commonly used within the homosexual community and, more recently, at electronic music festivals(2). Despite the perception of low-risk among users, these substances may have retinal toxicity.

MATERIAL AND METHODS

A search was made of Pubmed, Embase and Google Scholar using the following tags: *(poppers maculopathy) OR (poppers retinopathy) OR (poppers and fovea) OR ((inhalatory drugs) and retinopathy) OR ((inhalatory drugs) AND maculopathy) OR ((inhalatory drugs) AND fovea) OR (chemsex AND maculopathy) OR (chemsex AND retinopathy) OR (chemsex AND fovea).*

Case reports and series that reported individual data were included in the analysis while series reporting only aggregated data were excluded(3-5). Only articles published in English, French, German and Spanish were included. Poster abstracts also were excluded from the analysis. When double publication was suspected the smaller series was eliminated. The Davies et al. report of 2012 was included in the later series from that year (6-9). The information reported in the published articles was transferred into a Excel document for further analysis.

Although some unilateral cases have been reported, PM is usually a bilateral condition. Due to the strong correlation between patient´s eyes, a lineal mixed model (LMM) was used to evaluate differences between groups.(10) Age, gender, sexual orientation and HIV status (when reported), initial and final visual acuity (VAP and VAF) and OCT characteristics were collected in an Excel table. OCT descriptions were classified into the seven different patterns: interruption of the photoreceptors layer, vitelliform deposits, vitelliform deposits and interruption of the photoreceptor layer, foveal detachment, irregularity of the ellipsoid line, foveal detachment and macular holes.

Patterns of drug consumption were recodified as a dichotomic variable. If visual loss took place after the first exposure, this was codified as “one-exposure toxicity” (acute). In the case of a prior history of drug consumption (regardless of the duration of exposure), this was codified as “several exposure toxicity” (chronic).

Data were analyzed with R v4.1. Significant differences were considered when $p \leq 0.05$.

RESULTS

Our search located 26 articles which provided detailed information on the reported cases. Most of these were published in ophthalmology journals. Only one article was published in a neurology journal (11), one in an emergency medicine journal (12) and two alert letters were published in two high-impact general medical journals (13, 14). No articles were found on this topic in journals on mental health or addiction.

Of the 124 eyes of the study, over 90% of cases were published by doctors working at European centers (Table 1). Only three articles (7 patients, 14 eyes) came from non-European countries. Eight from Australia(2), four from Canada (15, 16), and one from USA(17).

Patients reported as part of series that described only aggregated data were excluded from the analysis (6 patients from Schulze et al series, 10 patients from Bral et al series, and 39 patients from Van Bol et al series).(3-5) Nevertheless some of these authors have published other articles on this topic in which some of the excluded patients may have been reported.

The demographic characteristics of the sample are summarized in Table 1. More than 90% (59/64) of cases correspond to male subjects. The mean age of reported cases was 38.7±10.5 years (Table 1). Final visual acuity (median=0.8) was higher than visual acuity at presentation (median=0.67). There was statistically significant correlation between VAF and VAP (Spearman r: 0.622 $p<0.001$), and between right and left eyes VA values, indicating, as expected, a strong inter-eye correlation (Figure 1). As a classical mean or intervals comparation (ie. T test or Wilcoxon test) won't reflect this correlation, a linear mixed model approach was employed to fully consider this effect. In all the following analysis, the "fixed" variable was either the HIV status or the presentation (acute vs chronic consumption) and the patient was considered as the "random" effect in the LMM.

Information about sexual orientation is provided in the earlier articles but is lacking in most recent publications. Similarly, HIV information is lacking in nearly two thirds of the cases. Taking in account the lack of completed data for these variables, we evaluated the influence of HIV status in the VA values, both at presentation and at follow-up. There were no significant differences between HIV-positive and HIV-negative patients in both VAP and VAF (Table 2) when evaluated by the LMM. However, as a complementary approach, if both non referred and HIV-negative patients were grouped (as HIV positive

is a rare status) and analyzed against HIV-positive, we found a significant difference (p= 0.047) for VAF and almost significant for VAP (p=0.082).

To determine the influence of chronic consumption, the visual acuity of patients suffering PM from their first exposure was compared with those having more than one previous exposure. VAP and VAF were higher among those who reported only one exposure to poppers than in those who reported more than one previous exposure. However, no significant differences were found when analyzed with the LMM (Table 3).

DISCUSSION

History

Poppers were generally considered safe unless misused, for example, ingested (18, 19). The first case of visual loss following nitrite inhalation was report by Fledelis(20). Notably, despite decades of use of nitrites for several cardiac conditions, this was the first report of visual loss following nitrite exposure; this was considered atypical given that the patient was a 15 year-old boy who probably suffered bilateral non-arteritic ischemic optic neuropathy (the author's diagnosis for this case report was bilateral ischemic papilledema).

Although the first case of PM was reported by Pece et al in 2004, most cases of PM have been diagnosed since 2010. Some years earlier, regulatory changes required isobutyl nitrite be replaced with isopropyl after the former was classified as a type-2 carcinogen. It has been speculated that this change of substance is the cause of PM(6). Prior to this change, few cases of PM associated with the use of poppers were reported. Research has questioned whether the increased frequency of diagnosis is due to the change in

substance or whether this higher prevalence is due to the increased consumption of poppers, while also coinciding with improved image quality in optical coherence tomography (OCT). The most common pattern of PM is subtle interruptions of the ellipsoid layer. In most cases, these changes are beyond the resolution of time-domain OCT. Therefore, until the development of spectral domain OCT these minute changes were undetectable. In fact, in the first report of PM, the authors described the OCT scan (time domain OCT) as normal despite the presence of typical fundus manifestations (21). Spectral-domain OCT was developed in 2006 and did not become widespread until some years later, coinciding with the first reported cases of PM(18, 22).

Epidemiology

PM is very rare. Most published reports refer to isolated case reports, while many series include patients from several university hospitals(7, 18). The occurrence of symptoms after nitrite consumption is also rare. In a recent international survey that received 21,575 valid responses, only 2.2% of participants responded that the use of poppers affected eyesight, while 10% responded that it may affect eyesight(23). By contrast, a recent cohort found OCT changes compatible with PM in 20 out of 36 eyes of asymptomatic users(5), however the scans were not analyzed by blind examiners and the study did not include controls.

Most published cases of PM are European or were published by doctors working in European centers. Our search located only seven non-European cases (14 eyes). This geographical distribution may be explained by different patterns of drug consumption but this seems highly unlikely in today's globalized world. Indeed, in a recent survey, the percentage of subjects reporting having used poppers in the last year was higher in the

United States than in England (33% vs 26%). This paradox has not been addressed in previous literature (23). Having limited the search to four languages may introduce some king of bias that may justify the absence of cases from some countries. Nevertheless, in the last decades English has become Medicine Lingua franca and now publications written in English constitute nearly 90% of all the publications include in the Index medicus. We believe that due to this anglicization of medicine this language bias is not very important in our review.(24) In any case, this language limitation would never justify the very low number of cases published by North American, Indian, South American and Australian authors.

This fusion cohort had a similar age and gender composition compared to the largest series published by Van Bol et al (39 patients; 78 eyes). In the series from Van Bol et al., the mean age was also 39 years and only 2/39 patients (5%) were women. Improvement in OCT technology, the increasing popularity of the drug, and more exhaustive questioning of patients by physicians have resulted in more frequent diagnoses. Nonetheless, visual loss is not severe in most cases (median VAP was 0.67 in decimal scale in the global cohort), and thereby, probably not all users who suffer visual loss present for ophthalmologic care and many of the patients may not remember or admit poppers exposure. A significant underdiagnosis may explain why this condition has been so seldom reported in many countries (18).

Risk factors

PM is more frequently diagnosed in males with very few reports of females suffering from PM (7, 25, 26). Although hormonal factors may influence this distribution, it probably mirrors male predisposition to use drugs (44) including poppers (23).

In one of the initial series, six out of six patients were HIV positive and this may have influenced subsequent authors to seek this diagnosis in HIV patients (18). However, many publications lack information on sexual orientation and HIV status (27) (Table 2). Thirty of the patients included in this review (nearly one quarter of the selected cases) corresponded to HIV positive patients. HIV positivity was not linked to lower VA (table 3). However as it has been previously stated, HIV status was not specified in nearly half of the reported eyes, and a secondary analysis considering those patients in which HIV status was not referred as HIV negative demonstrated an association between HIV status and initial visual acuity and almost found an association between HIV status and final VA.

Taking into consideration that HIV status and sexual orientation may be confounding factors associated to the exposure to this drug and that ophthalmologists are more prone to seek this diagnosis in HIV patients, we believe it premature to assert that HIV infection or retroviral drugs lower the threshold for popper toxicity. This association may be spurious and probably arises from notions of risk-taking behavior among this group of patients (45,46) as well as ophthalmologist bias in seeking this diagnosis in this subgroup of patients.

Another source of bias is that HIV status and sexual orientation were referenced in early studies while most recent studies omit this information. This reflects changes in social norms and makes it difficult to draw conclusions about the influence of both factors.

Although drug consumption generally begins in the teenage years, most reported cases are of men in their forties. It is possible that younger retinas are more resilient and therefore are able to endure the metabolic overload induced by nitric oxide (NO).

Nonetheless, this discordance may point to a cumulative effect. Although some cases have been reported after one isolated exposure (9, 27), in most cases patients have consumed poppers for several years. Indeed, Davies et al. found a dose-related effect. In their series, patients who reported long-term regular use had the most severe changes, lower VA and showed no signs of improvement after reducing usage or complete abstinence (7). In one aggregated series published in 2012 the number of years of exposure was higher among those with maculopathy (20.2 years) compared to those who did not suffer macular toxicity (15.7 years) (5). Nevertheless, the difference in the number of years of exposure was not large and patients with a longer history of exposure are most likely older (in this series the age of the patients was not reported) (5).

We were unable in the present study to determine the influence of the length of the exposure, although we differentiated between patients who developed PM after a single exposure. VAP and VAF were higher among those who had only one previous exposure, but the difference was non statistically significant.

Pathophysiology

Several different brands are most commonly involved. A recent article by Rewbury et al. offers a list of eight products (27), all with flamboyant names such as “Jungle juice”, “Hard on”, “Berlin XXX” or "Liquid gold”. Most of them contain a fifty-fifty mix of Isopropyl nitrite and isopropyl alcohol, although other alcohols and nitrites are also present. Differences in the formulation must play a key role. In the Rewbury et al. series, in three out of twelve cases of those using poppers for 20 years visual loss took place when the subject switched to a new brand (27). Sega et al published a case in which,

despite continuous use, visual symptoms disappeared after the subject was able to identify which brands induced the visual symptoms (28). A synergetic effect with other drugs has also been suggested. Bral et al. reported the case of a patient who had used poppers for years without visual symptoms and suffered visual loss the first time when these were combined with sildenafil (4). Given that sildenafil inhibits the phosphodiesterase, thus inducing a rise in cGMP, a synergetic mechanism between both substances is plausible (29).

In one recent case report, the authors found voids in the choriocapillaris using OCT-Angiography (OCT-A) in one patient with PM. The authors hypothesized that retinal damage could be secondary to microvascular toxicity in the choriocapillaris (30). Notably, similar findings have been described in patients with photic retinopathy (31), although these could be genuine or merely artifacts. If not artifacts, these changes could be primary or secondary to retinal atrophy or may be a consequence of diminished retinal metabolism (32). It is well known that vascular endothelial growth factor (VEGF) derived from the retinal pigment epithelium (RPE) plays an essential role in the maintenance of the choroidal vasculature (33, 34).

The precise mechanism of poppers has yet to be fully identified. Alkyl nitrites induce an upregulation of nitric oxide synthase, increasing the production of nitric oxide (NO). Photoreceptors are among the most sensitive retinal neurons to the toxicity of nitrites. Experimental studies have provided evidence of induced photoreceptor apoptosis due to high concentrations of NO(18). NO activates guanylate cyclase in photoreceptors, increasing the calcium current and thereby causing the inhibition of calcium. As photopsias are one of the most frequent symptoms, it is believed that this toxicity may

be related to an excess activation of photoreceptors (13, 18). There may also be an interference with the protective macular pigment (27).

Nevertheless, there is no explanation why these changes are limited to the foveal region. The morphological similarities between PM and solar maculopathy have led Fajgenbaum (35) to open a debate on whether PM could be a form of solar retinopathy (32, 35, 36). This hypothesis is based on the morphological similarities between both conditions and in some reported cases of photic maculopathy among patients who stared at the sun after consuming other drugs, such as LSD (lysergic acid diethylamide).

However, there are significant differences in the psychoactive effects of both drugs. LSD induces behavioral changes, has a mydriatic effect and deactivates other protective mechanisms such as blinking due to its depressive action (32, 37-39).

Popper inhalation can also alter consumer's behavior, making them more vulnerable to these dangers. Audo et al. postulate that NO interacts with the macular pigment zeaxanthin which protects the macula against light damage which thus explains phototoxicity (18). However, to the best of our knowledge, none of these patients reported having looked at the sun and nitric oxide does not have a mydriatic effect (40). Nevertheless, this does not rule out the possibility that NO consumption may have a photosensitizing effect. Notably, in the only series that takes into consideration amblyopia and strabismus, two eyes had unilateral involvement, one having amblyopia and the other requiring strabismus surgery. In these two cases, due to its eccentric fixation, the non-dominant eye could have been spared from the toxic effect of light. Therefore , it cannot be ruled out that NO may have a photosensitizing effect, with exposure to light being a necessary cofactor (27). Nevertheless, it is difficult to explain the presence of photopsias during intoxication. This symptom suggests chronic

activation of central cones rather than their inhibition, which would be expected only if guanylate cyclase activation was involved (18).

Clinical expression

Poppers maculopathy is a well-established condition and studies describe similar symptoms: visual acuity loss, central scotoma, glare and phospenes, blurred vision, metamorphopsia, and fluctuating vision.

Both short- and long-term consumption of poppers appears to be a risk factor in the development of maculopathy, although a degree of dose-response is generally accepted. The condition has a wide spectrum of expression. As the global survey by Davies et al. suggests, mild cases could occur with isolated photopsias without histological changes (23) while more severe cases occur with macular syndrome (decreased VA, and metamorphopsia). Dyschromatopsia, macropsia or micropsia have not been reported as common manifestations.

The degree of visual impairment described is usually moderate (23). Median visual acuity at presentation in the selected cases was 0.67 (0.4-0.8). Mean visual acuity in the Van Bol case series was very similar (0.8). Nevertheless, severe cases in which ON exposure leads to the development of full thickness macular holes have also been described (26).

PM usually involves both eyes. In a recent survey, 82% reported bilateral involvement (23). The disease usually has a highly symmetric expression; in fact, in some series VA was expressed with a single figure because it was identical in both eyes (7). In a recent series, only two of twelve cases had unilateral involvement (27).

In young patients, optic nerve toxicity could be more common than retinal toxicity. The two described cases of optic disc edema following nitrite inhalation occurred in 15- and 13-year-old patients (20, 26).

Diagnosis

An accurate medical history is essential in the diagnosis of this condition. Diagnosis can often be complicated by initial patient denial (2). Funduscopy often reveals the presence of altered foveal reflex and yellow foveal spots, although in many cases changes are tiny and fundus examination can be normal. Retinal involvement is usually limited to the macular area.

Given the only slight changes to funduscopy, spectral-domain OCT remains the most effective tool for the diagnosis of PM. The most commonly reported pattern is the interruption of the external retina (68 cases, 54.8%). OCT scans show bilateral disruption of the junction between the inner and outer photoreceptor segments (IS/OS junction or ellipsoid zone) in the foveal area. This pattern was referred to in the first series (6, 7, 13, 18).

A recent publication by Van Bol et al. described three different patterns: disturbance on the ellipsoid layer, vitelliform lesions, and microholes (3). However, less severe changes, such as slight foveal detachment (18), subfoveal hypodensities or mere irregularity or fuzziness of the ellipsoid line (2), as well as more severe conditions (full thickness macular holes) have been also described. In the series from Van Bol et al, vitelliform-like lesions were found to be more common among chronic users (3).

Only one recent article refers to an OCT-A performed on a patient with PM. The authors found voids in the choriocapillaris which persisted even after the complete structural

restoration of the outer retinal layers on SD-OCT. They hypothesized that retinal damage could be secondary to microvascular toxicity at the choriocapillaris (30). Nevertheless, as mentioned above, these changes are not specific and may be secondary to reduced retinal metabolism. Only two articles have reported on the utility of adaptive optics scanning laser ophthalmoscopy (AOSLO) technology to demonstrate central cone loss(17, 18).

Few publications have studied electrophysiology for patients with PM. As could be expected, visually evoked potentials (VEP) were usually normal. Electrooculography (EOG) is considered a useful tool in demonstrating drug toxicity, however, to the best of our knowledge, EOG has only been studied in two patients and showed no abnormalities (41).

One article found altered electro-retinogram (ERG) in two patients affected by PM (41). The authors of this article suggest that retinal toxicity is not limited to the foveal area and therefore believe the condition should be renamed. Nevertheless, other authors, Brunnix et al. and Audo et al., found normal ERG responses in several patients with PM (18, 42). Even in cases of involvement of the entire retina, this involvement is subclinical and thus the term “popper maculopathy” should be preferred over “popper retinopathy” (41).

Some series include cases in which multifocal electro-retinogram was performed on isolated patients. In one of the cases the results were normal (9), while in another the central responses were mildly diminished (11). A later study included six patients with PM and concluded that slightly reduced N1 and P1 responses were present, but these changes were slight and the authors concluded that this technology was not useful in

diagnosing PM (43). In summary, it appears there is not enough evidence of the utility of electrophysiology for these patients.

Some authors have reported central scotomas in 30-2 visual fields (9). The utility of 10-2 visual fields has not been studied. In most cases, the scotomas associated with PM are likely beyond the sensitivity of conventional perimetry but some authors have found decreased foveal sensitivity using microperimetry (2).

Differential diagnosis

Solar maculopathy is the most important differential diagnosis and clinical expression, fundus and OCT patterns may be identical. This differential diagnosis has been addressed in a number of earlier studies (32, 36, 44). As with solar maculopathy, poppers maculopathy can “phenocopy” retinal dystrophies involving a foveal gap, such as rod monochromatism or Stargardt disease. Cases of PM with vitelliform lesions can be confused with stage 2 vitelliform macular dystrophy and if there is any doubt after a complete clinical history an EOG should be ordered.

In cases of slight foveal detachment, central serous chorioretinopathy, age-related macular degeneration, and vitreofoveal traction should be ruled out. Other potential diagnoses are: tamoxifen toxicity (usually with crystalline deposits in the inner retina), and juxtafoveolar telangiectasiae which can be evidenced with fluorescein angiography. Accordingly, a complete clinical history of light and poppers exposure should be performed before initiating genetic study of possible retinal dystrophy.

Prognosis

There is an association between the time between the improvement of visual symptoms and the findings of OCT imaging showing decreased disruption in the ellipsoid zone

following cessation of use**.** Ophthalmologic symptoms may precede involvement evidenced on OCT.

A prognosis is not easy to establish. Long term follow-up is difficult in these patients as many fail to attend follow-up visits(27). Subjective visual improvement has been reported and some authors have suggested that cessation of exposure is linked to improvement in visual acuity (30, 45). A study by Audo et al. reported improvement in the four patients who stopped popper intake (18) while an article by Pahlitzsch et al. reported similar findings (9). In a later series, Van Bol similarly reported complete resolution in 8 patients after cessation (3). Even those patients with exposures of up to 30 years can have complete restitution after stopping their drug use (27) although anatomical normalization with complete restitution of the integrity of ellipsoid zone has seldom been reported (30). In some cases a complete resolution of OCT changes can occur after ceasing the exposure (2). Nevertheless, reports of patients showing no changes or even a marked worsening in VA even after complete cessation of poppers intake have also been described.

Although our analysis is not able to prove an association between exposure and final visual acuity, prognosis is most likely associated to the magnitude of the exposure. Several authors have found more severe foveal changes and worse VA in chronic consumers (2).

In a recent article, Fortunati et al. reported a patient whose VA improved from 6/10 to 10/10 after 10 months of abstinence despite an increase in the area of disruption of the ellipsoid line. The authors suggest this discordance was likely due to the development of eccentric fixation (46).

The global analysis of the reported cases supports this hypothesis, VAF was higher in single exposure eyes (1 vs 0.8) (Table 2).

Treatment

In one case of a macular hole resulting from popper consumption, good recovery was achieved by standard macular hole surgery (vitrectomy, peeling of the internal limiting membrane and SF6 exchange) (26).

Although there is no proven therapy at present, initial reports on the effectiveness of oral lutein therapy show that this supplementation may be beneficial (8, 9). Considering the history of the condition, this presumed beneficial effect should be closely examined since, in many cases, stopping consumption has led to improvement in visual acuity. Thus, abstinence should be considered as the most appropriate treatment.

Conflict of Interest: The authors have no financial or proprietary interest in a product, method, or material described herein.

Bibliography

Reference List

1. Asensio-Sanchez VM. Intraoperative floppy iris syndrome and warfarin: coincidence or side effect? Arch Soc Esp Oftalmol. 2013;88(4):160.
2. Hui M, Galvin J, Chilov M, Gabrielle PH, Fung AT. POPPER MACULOPATHY: LONG-TERM FOLLOW-UP AND CASE SERIES. Retin Cases Brief Rep. 2017.
3. Van Bol LB, Kurt RA, Keane PA, Pal B, Sivaprasad S. Clinical Phenotypes of Poppers Maculopathy and Their Links to Visual and Anatomic Recovery. Ophthalmology. 2017;124(9):1425-7.
4. Bral NOG, Marinkovic M, Leroy BP, Hoornaert K, van Lint M, ten Tusscher MPM. Do not turn a blind eye to alkyl nitrite (poppers)! Acta ophthalmologica. 2016;94(1):e82-e3.
5. Schulze-Dobold C, Ben Denoun M, Dupas B, Paques M, Massin P. Retinal toxicity in users of "poppers". Ann Intern Med. 2012;156(9):670-2.
6. Davies AJ, Kelly SP, Bhatt PR. 'Poppers maculopathy'--an emerging ophthalmic reaction to recreational substance abuse. Eye (London, England). 2012;26(6):888-.
7. Davies AJ, Kelly SP, Naylor SG, Bhatt PR, Mathews JP, Sahni J, et al. Adverse ophthalmic reaction in poppers users: case series of 'poppers maculopathy'. Eye (London, England). 2012;26(11):1479-86.
8. Pahlitzsch M, Draghici S, Mehrinfar BM. Poppers-associated maculopathy. Klinische Monatsblatter fur Augenheilkunde. 2013;230(7):727-32.
9. Pahlitzsch M, Mai C, Joussen AM, Bergholz R. Poppers Maculopathy: Complete Restitution of Macular Changes in OCT after Drug Abstinence. Seminars in ophthalmology. 2016;31(5):479-84.
10. Huang J, Huang J, Chen Y, Ying GS. Evaluation of Approaches to Analyzing Continuous Correlated Eye Data When Sample Size Is Small. Ophthalmic Epidemiol. 2018;25(1):45-54.
11. Savary P, Biotti D, Abouaf L, Bernard M, Chaise F, Guerrier O, et al. Poppers toxic maculopathy misdiagnosed as atypical optic neuritis. Eur J Neurol. 2013;20(7):e90-e1.
12. Caré W, Lepori J-C, Villa A, editors. Maculopathie toxique induite par les poppers2018.
13. Vignal-Clermont C, Audo I, Sahel J-A, Paques M. Poppers-associated retinal toxicity. The New England journal of medicine. 2010;363(16):1583-5.
14. Gruener AM, Jeffries MAR, El Housseini Z, Whitefield L. Poppers maculopathy. Lancet (London, England). 2014;384(9954):1606-.
15. Law G, Ching G, Docherty G, Navajas E. Acquired Bilateral Central Vision Loss in a Young Adult Due to “Poppers Maculopathy”. Jpn J Ophthalmol Res 2019;1(1004).
16. Docherty G, Eslami M, O'Donnell H. "Poppers Maculopathy": a case report and literature review. Canadian journal of ophthalmology Journal canadien d'ophtalmologie. 2018;53(4):e154-e6.
17. Rojas CN, Fawzi AA, Gill MK. AOSLO imaging in poppers maculopathy shows high resolution loss of central macular cones. American journal of ophthalmology case reports. 2021;23:101166.

18. Audo I, El Sanharawi M, Vignal-Clermont C, Villa A, Morin A, Conrath J, et al. Foveal damage in habitual poppers users. Archives of ophthalmology (Chicago, Ill : 1960). 2011;129(6):703-8.
19. Wunder AF, Oelckers M, Lock G. Partynight outcome. Dtsch Med Wochenschr. 2015;140(21):1611-3.
20. Fledelius HC. Irreversible blindness after amyl nitrite inhalation. Acta ophthalmologica Scandinavica. 1999;77(6):719-21.
21. Pece A, Patelli F, Milani P, Pierro L. Transient visual loss after amyl Isobutyl nitrite abuse. Semin Ophthalmol. 2004;19(3-4):105-6.
22. Fujimoto J, Swanson E. The Development, Commercialization, and Impact of Optical Coherence Tomography. Invest Ophthalmol Vis Sci. 2016;57(9):OCT1-OCT13.
23. Davies AJ, Borschmann R, Kelly SP, Ramsey J, Ferris J, Winstock AR. The prevalence of visual symptoms in poppers users: a global survey. BMJ Open Ophthalmol. 2017;1(1):e000015-e.
24. Baethge C. The languages of medicine. Deutsches Arzteblatt international. 2008;105(3):37-40.
25. Rabot A, Pinon F, Baillif S. SD-OCT appearance in acute poppers-associated macular toxicity. Journal francais d'ophtalmologie. 2013;36(4):388-9.
26. Dyrda A, Català-Mora J, Rey A, Díaz-Cascajosa J, Vidal-Santacana M. Macular Hole After Poppers (Alkyl Nitrate) Inhalation in a Child. Ophthalmic surgery, lasers & imaging retina. 2018;49(11):897-900.
27. Rewbury R, Hughes E, Purbrick R, Prior S, Baron M. Poppers: legal highs with questionable contents? A case series of poppers maculopathy. Br J Ophthalmol. 2017;101(11):1530-4.
28. Sega R, Urbancic M. Waxing and waning poppers maculopathy. Can J Ophthalmol. 2021.
29. Ahmadi J, Keane JR, McCormick GS, Fallis RJ, Miller CA. Ischemic chiasmal syndrome and hypopituitarism associated with progressive cerebrovascular occlusive disease. AJNR Am J Neuroradiol. 1984;5(4):367-72.
30. Romano F, Arrigo A, Sperti A, Bandello F, Battaglia Parodi M. Multimodal imaging of poppers maculopathy. European journal of ophthalmology. 2019:1120672119887918-.
31. Tomasso L, Benatti L, La Spina C, Lattanzio R, Baldin G, Carnevali A, et al. Optical coherence tomography angiography findings in laser maculopathy. Eur J Ophthalmol. 2017;27(1):e13-e5.
32. Gonzalez Martin-Moro J, Hernandez Verdejo JL, Zarallo Gallardo J. Photic maculopathy: A review of the literature (ii). Arch Soc Esp Oftalmol. 2018;93(11):542-50.
33. Marneros AG, Fan J, Yokoyama Y, Gerber HP, Ferrara N, Crouch RK, et al. Vascular endothelial growth factor expression in the retinal pigment epithelium is essential for choriocapillaris development and visual function. Am J Pathol. 2005;167(5):1451-9.
34. Saint-Geniez M, Kurihara T, Sekiyama E, Maldonado AE, D'Amore PA. An essential role for RPE-derived soluble VEGF in the maintenance of the choriocapillaris. Proc Natl Acad Sci U S A. 2009;106(44):18751-6.
35. Fajgenbaum MA. Is the mechanism of 'poppers maculopathy' photic injury? Eye (Lond). 2013;27(12):1420-1.

519 36. Gonzalez Martin-Moro J, Hernandez Verdejo JL, Zarallo Gallardo J. Photic
520 maculopathy: A review of the literature (I). Arch Soc Esp Oftalmol. 2018;93(11):530-41.
521 37. Fuller DG. Severe solar maculopathy associated with the use of lysergic acid
522 diethylamide (LSD). Am J Ophthalmol. 1976;81(4):413-6.
523 38. Schatz H, Mendelblatt F. Solar retinopathy from sun-gazing under the influence
524 of LSD. Br J Ophthalmol. 1973;57(4):270-3.
525 39. Ewald RA. Sun gazing associated with the use of LSD. Ann Ophthalmol.
526 1971;3(1):15-7.
527 40. Masjedi M, Ghanbari A, Bakhodaei HH, Jowkar T, Hosseni V, Rakhshan M.
528 Pupillary response to nitrous oxide administration in cataract surgery under general
529 anesthesia. J Chin Med Assoc. 2017;80(11):733-6.
530 41. Clemens CR, Alten F, Loos D, Uhlig CE, Heiduschka P, Eter N. Poppers
531 maculopathy or retinopathy? Eye (Lond). 2015;29(1):148-9.
532 42. Bruninx R, Lepiece G. Didactic image poppers maculopathy. Bulletin de la
533 Societe belge d'ophtalmologie. 2013(322):133-5.
534 43. Pahlitzsch M, Salchow D, Rossel M, Bergholz R. Multifocal Electroretinography
535 in Patients with Poppers Maculopathy. Klinische Monatsblatter fur Augenheilkunde.
536 2019;236(8):1004-11.
537 44. Raoof N, Bradley P, Theodorou M, Moore AT, Michaelides M. The New
538 Pretender: A Large UK Case Series of Retinal Injuries in Children Secondary to
539 Handheld Lasers. Am J Ophthalmol. 2016;171:88-94.
540 45. Luis J, Virdi M, Nabili S. Poppers retinopathy. BMJ case reports.
541 2016;2016:bcr2016214442.
542 46. Fortunati M. Poppers maculopathy: OCT appearance after 10 months of drug
543 abstinence. Journal francais d'ophtalmologie. 2017;40(2):e49-e50.
544

		Patients (n=64)	Eyes (n=124)
Age (years)		38.7 ± 10.5	38.7 (SD:9.9) years
Sex (Male)		59 (92.2 %)	116 (93.5%)
Sexual orientation	HomosexuaL	5 (7.8%)	10 (8.1%)
	Non-defined	59 (92.2%)	114 (91.9%)
HIV status	Negative	10 (15.6%)	20 (16.1%)
	Positive	16 (25%)	30 (24.2%)
	Non-defined	38 (59.4%)	74 (59.7%)
Presentation	Acute, after one consumption	20 (31.3%)	38 (30.6%)
	Chronic, after several consumptions	37 (57.8%)	72 (58.1%)
	Non-defined	7 (10.9%)	14 (11.3%)
Country	UK	21 (32.8%)	40 (32.3%)
	France	14 (21.9%)	28 (22.6%)
	Germany	9 (14.1%)	18 (14.5%)
	Spain	6 (9.4%)	10 (8.1%)
	Australia	4 (6,3%)	8 (6.5%)

	Italy	3 (4,7%)	6 (4.8%)
	Belgium	2 (3.1%)	4 (3.2%)
	Canada	2 (3.1%)	4 (3.2%)
	Slovenia	1 (1.6%)	2 (1.6%)
	Turkey	1 (1.6%)	2 (1.6%)
	USA	1 (1.6%)	2(1.6%)
VA (decimal)	**Visual acuity at presentation (VAP)**		Median=0.67 (IQR:0.4-0.8)(n=124)
	Visual acuity at follow-up (VAF)		Median=0.8 (IQR: 0.67-1)(n=79)
OCT findings	Interruption of the photoreceptors layer		68 (54.8%)
	Vitelliform deposits		13 (10.5%)
	Irregularity of the ellipsoid line		13 (10.5%)
	Vitelliform deposit and Interrupción		4 (3.2%)
	Macular hole		2 (1.6%)
	Foveal detachment		2 (1.6%)
	Hiporeactividad subfoveal		2 (1.6%)
	Non defined		20 (16.1%)

Table 1. Demographic and clinical data of the included patients.
IQR=interquartile range

	Eyes HIV status		
	Positive, N = 32[1]	Negative, N = 20[1]	p-value[2]
Visual acuity at presentation (VAP)	0.57 (0.48-0.67)	0.54 (0.40-0.67)	0.682
Visual acuity at follow-up (VAF)	0.71 (0.52-0.90)	0.77 (0.54-1.00)	0.679

[1]Linear-mixed model estimates (95% CI)

[2]LMM ANOVA analysis

557 Table 2. Impact of HIV infection on visual acuity.
558
559

	Eyes Presentation		
	One exposure, N = 40[1]	More than one exposure, N = 74[1]	p-value[2]
Visual acuity at presentation (VAP)	0.73 (0.63-0.84)	0.63 (0.55-0.70)	0.103
Visual acuity at follow-up (VAF)	0.86 (0.69-1.02)	0.85 (0.73-0.96)	0.926

[1]Linear-mixed model estimates (95% CI)

	Eyes Presentation		
	One exposure, N = 40[1]	More than one exposure, N = 74[1]	p-value[2]

[2]LMM ANOVA analysis

Table 3. Impact of exposure on visual acuity.

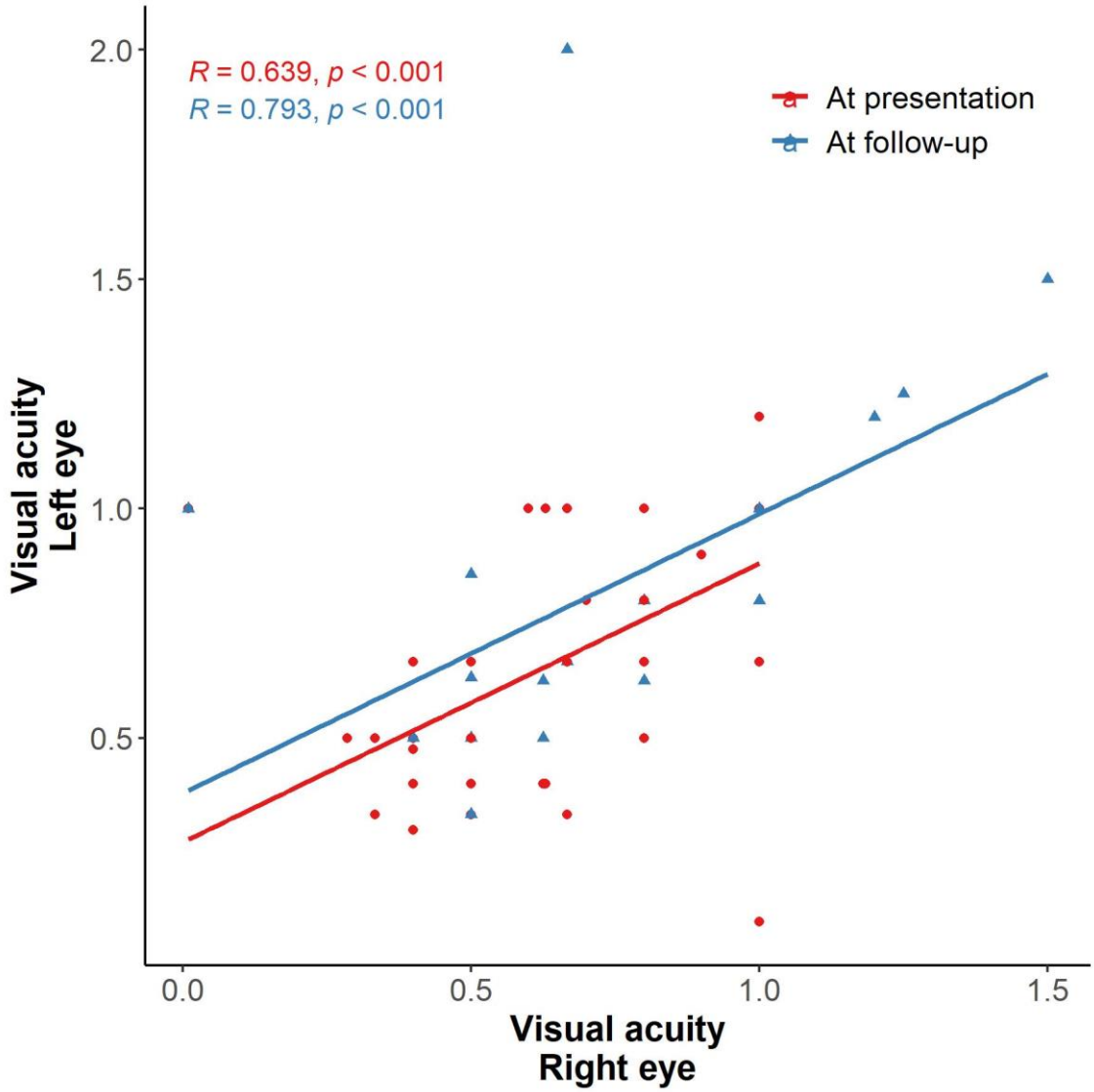

Figure 1.