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Case Report

Sudden Blurring of Vision and Micropsia Following Acute Hot Pepper Consumption: A Case Report and Hypothesis

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Abstract: Background: Retinal hemorrhages are an important ophthalmic diagnostic sign of underlying systemic vascular disorder. Capsaicin is a bioactive component of chili peppers used in most countries. Capsaicin crosses the blood–brain barrier in an efficient manner. Human exposure to capsaicinoids through diet is frequent and often substantial. Presumed lack of capsaicin toxicity in diet does not preclude rare adverse effects related to actions on the central neural system. Particularly on the retina, due to the reasons outlined in this case report. **Methods:** A case of a 34-year-old man, who reported sudden blurring of vision and micropsia in his left eye following ingestion of a considerable amount of red pepper. **Results:** The case study suggests that acute or chronic consumption of substantial amounts of hot red pepper in individuals with high reactivity towards TRPV1 agonists and/or higher expression of TRPV1 receptors in retinal ganglion cells causes retinal neovascularization. **Conclusion:** Acute consumption of red pepper may harm vision. This hypothesis can be easily evaluated retrospectively in larger sets of data.

Keywords: Capsaicin; Red Chili; Retinal hemorrhage; Optometry; Micropsia

Introduction

Retinal hemorrhages are an important ophthalmic diagnostic sign for underlying systemic vascular disorder. They range from small dot and blot to large sub-hyaloid hemorrhages. The size, distribution and location of hemorrhages indicate etiology and underlying systemic conditions such as hematologic disorders, vascular disease, and infections, dyscrasias, hypoxia or trauma. In rare cases, hemorrhages also express in idiopathic form. Most entail detailed systemic work-up to discover underlying cause. Management entails precise observation, treating the primary cause, and also intraocular management to diminish ischemic and neovascularization sequelae following hemorrhages [1].

Capsaicin is a bioactive component of chili peppers. Capsaicin is a capsaicinoid. Capsaicinoids are the bioactive compounds that make chili peppers “hot.” Dietary intake of capsaicin by humans can reach as high as 0.5–4 mg/kg/day. Natural sources of capsaicinoid family are classified as GRAS (Generally Regarded As Safe) substances [2], even though there is often no scientific basis for that belief. Capsaicin can function as double-edged sword. From the perspective of retinal vascular disease, it may ameliorate diabetic retinopathy by activating vanilloid receptor type 1 (TRPV1) and suppressing the PPAR γ -poldip2-Nox4 pathway in rat model [3]. Also, capsaicin, through the release of endogenous somatostatin, has anti-inflammatory and retinal protective effects on ischemia-

induced injuries [4]. On the other hand, findings from in culture studies have shown that cannabinoids can induce cell death and promote P2X7 receptor signaling in chick embryo retinal progenitor cells [5].

As shown in experimental animal studies, capsaicin crosses the blood–brain barrier in an efficient manner [6,7]. Most pepper constituents metabolize in the liver, with the lung the second organ metabolizing the capsaicin. Capsaicin is also metabolized in the skin and intestine [7]. It is commonly believed that capsaicin is completely metabolized within 20 minutes in rat and human microsomes [8]. Human exposure to capsaicinoids through their diet is frequent and often considerable [2]. Here, we present a case of a 34-year-old man who reported sudden blurring of vision and micropsia on his left eye following ingestion of a large amount of red pepper. The presumed lack of toxicity of capsaicin in usual diet does not preclude rare adverse effects related to its actions on the central neural system particularly on the retina, thus we will present a specific case in this short paper.

Case Report

After a stressful period, a 34-year-old, slightly myopic male university teacher reported sudden blurring of vision and micropsia on his left eye. He also reported consumption of 10 grams of red pepper powder and two fresh hot red peppers shortly before occurrence of subjective symptoms. At the first visit the best corrected visual acuity was RE: 6/12, LE: 6/9. Recorded intraocular pressure (IOP; Goldman applanation tonometer) RE: 40 mm Hg, LE: 39 mm Hg. There was no history of trauma, steroid use, or any other cause for secondary micropsia. There was no family history of secondary micropsia or myopia. Patient mentioned he had refractive surgery to correct myopia.

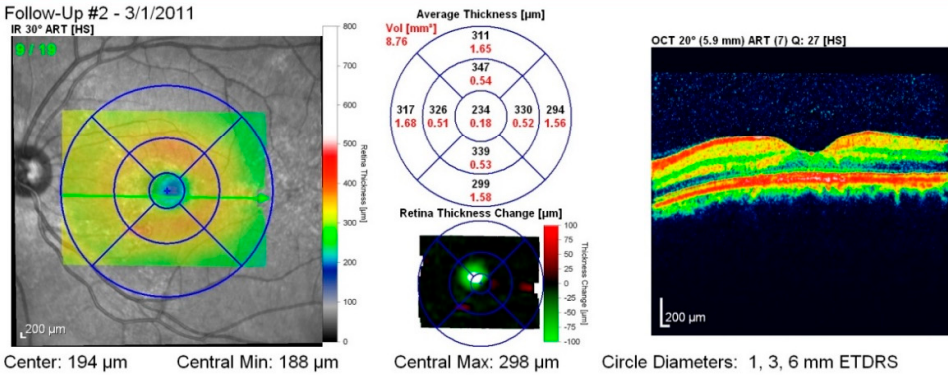
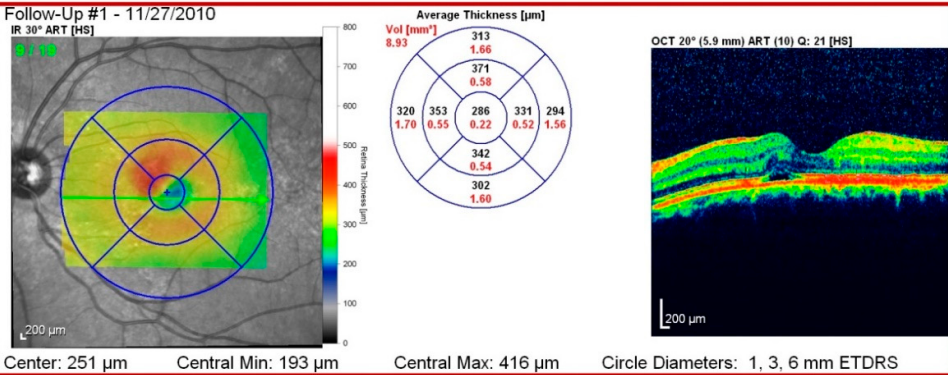
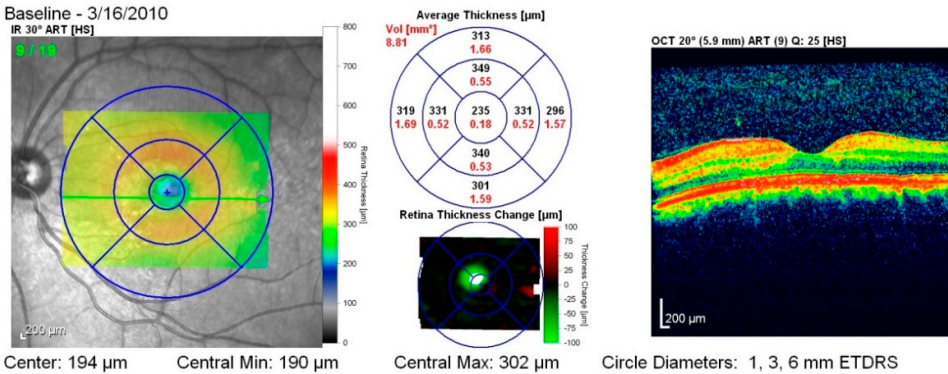
Ophthalmoscopic examination and OCT revealed normal appearance of the right fundus and sharp bordered, half disc-sized, sub-pigment epithelial edema involving the fovea on the left eye. Fluorescein angiography revealed one leakage. Diagnoses revealed hemorrhage in the left retina and recurrent episodes of subretinal fluid accumulation.

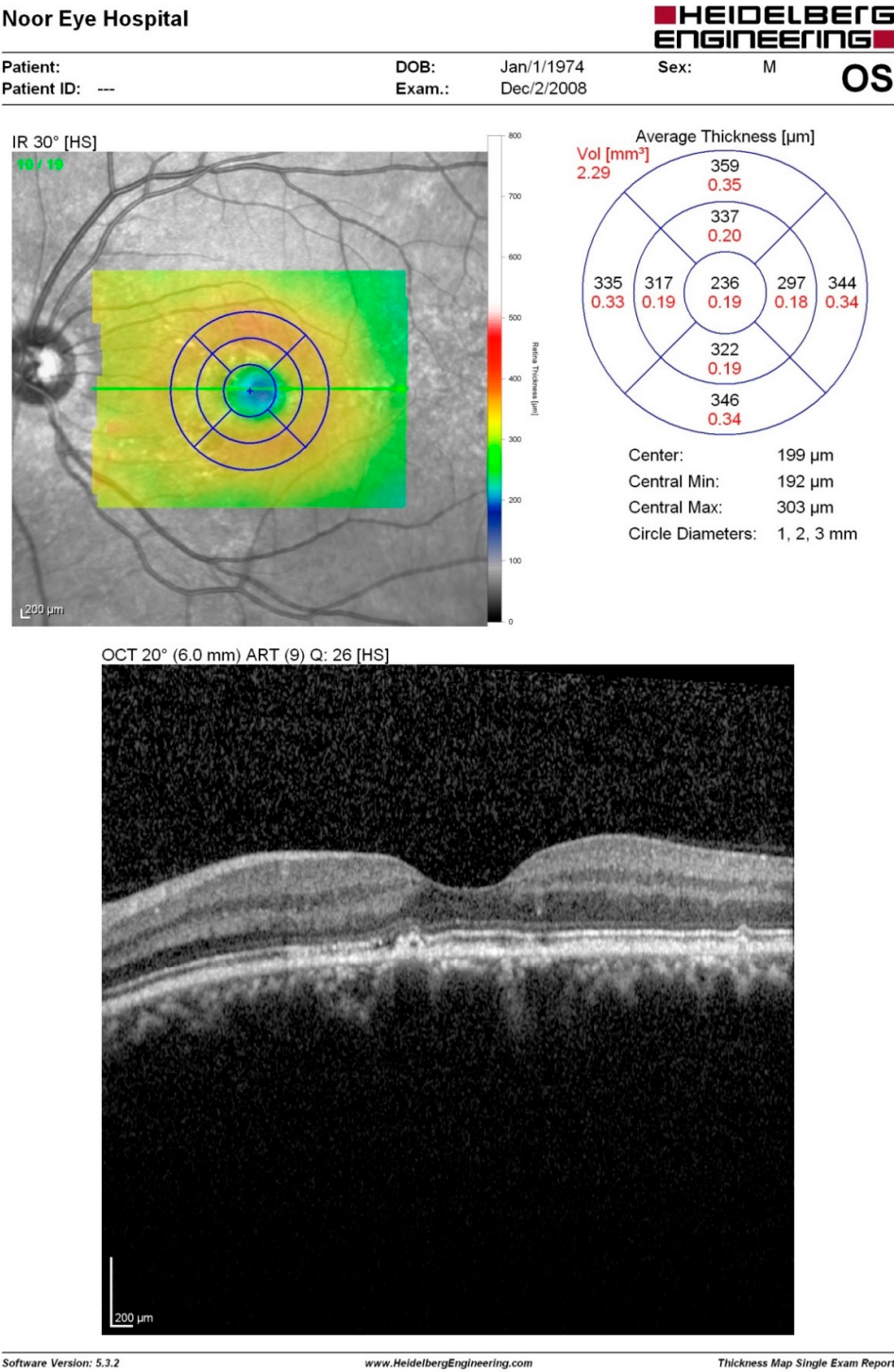
Intravitreal Avastin injection was performed three times. After Avastin treatment, his vision acuity and fundus condition got better within about 10 days and about six months later the diagnosis was “inactive central serous retinopathy” by the local ophthalmologist. However, during the next 3 years, observation identified small relapses following red pepper consumption. Approximately 3 years after the beginning of the disease the patient received further intravitreal Avastin injection. Although advised to stop eating red pepper the patient failed to follow this recommendation. The patient provided written consent for this report.

Noor Eye Hospital



Patient: DOB: Jan/1/1974 Sex: M OS
Patient ID: ---

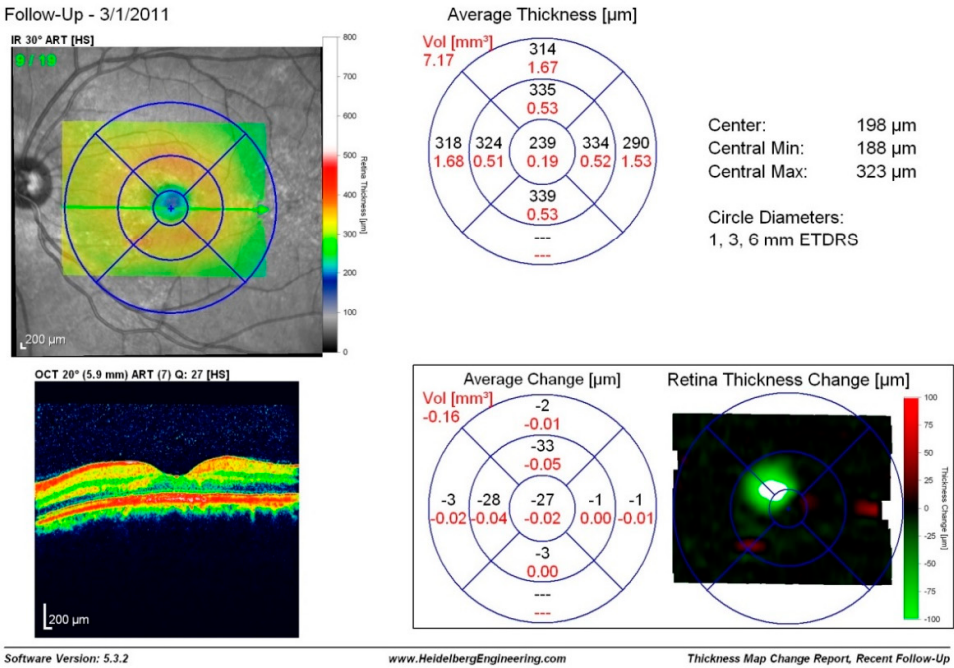
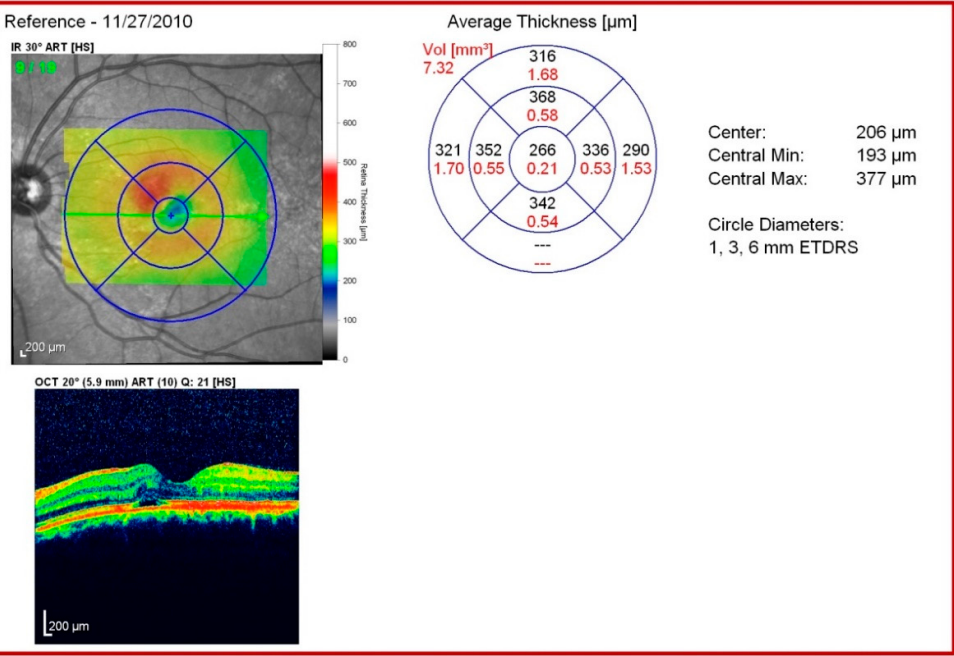




Noor Eye Hospital



Patient: Patient ID: --- DOB: Jan/1/1974 Sex: M OS



Software Version: 5.3.2

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Thickness Map Change Report, Recent Follow-Up

C

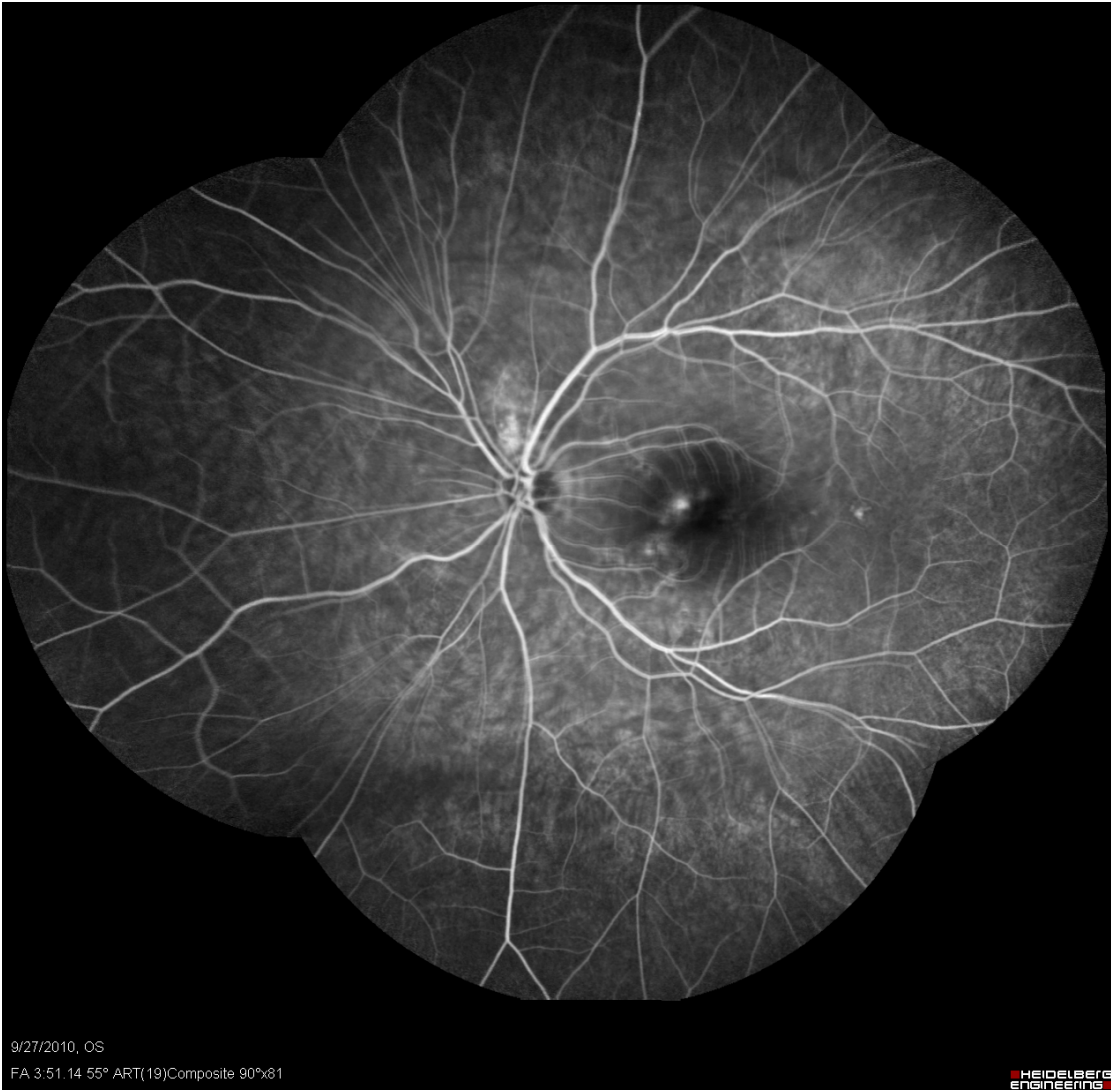
Figure 1. A–C demonstrate the optical coherence tomography (OCT) of the left eye on 2nd December 2008 (3 days after the occurrence of the problem, i.e., the day patient come to the eye hospital), 10th March 2010, and 27th November 2010.



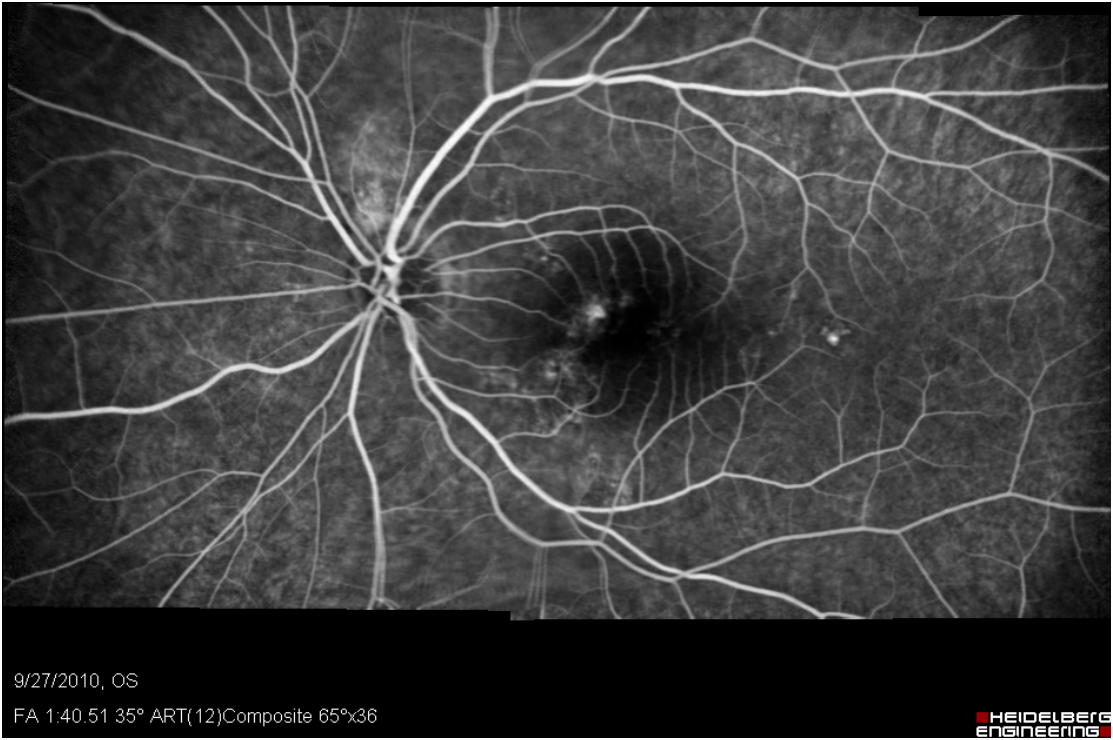
A



B



C



D

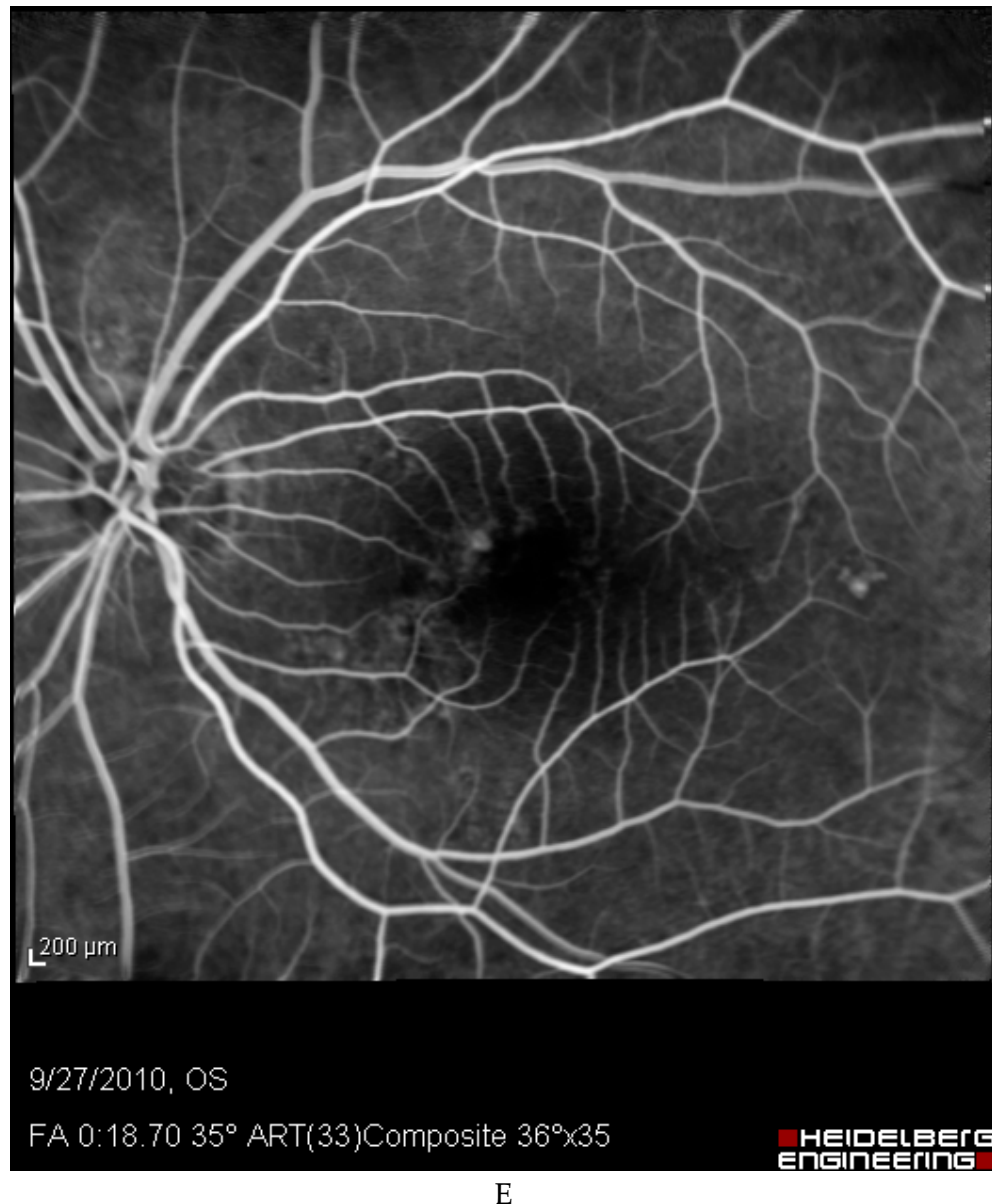


Figure 2. A-2E demonstrate the angiography of the left eye on 27th September 2010.

Discussion

For choroidal neovascularization, 34 years old represents a young age of onset. At such age, a common cause of recurrent subretinal fluid induced by stress is central serous chorioretinopathy (CSC), but that is not associated with retinal hemorrhage, which would rather be more suggestive of wet macular degeneration with choroidal neovascularization [9]. Choroidal neovascularization is indeed most common among the elderly, often with macular drusen present in the macula. It can also arise in highly myopic individuals, or those with preexisting macular scars, such as those caused by histoplasmosis or other forms of inflammation, such as multifocal choroiditis. Choroidal neovascularization can also develop from areas of scarring caused by repeated episodes of CSC [10]. In that situation, stress could have caused episodes of CSC, and macular scars from CSC could later evolve into wet macular degeneration [10–13]. Avastin could minimize fluid for both CSC and wet macular degeneration [14,15]. Therefore, it is important to utilize individualized therapy with Avastin in wet age-related macular degeneration. To the best of the authors' knowledge, although

people consume pepper in substantial amounts, there have been no reports on the deterioration of CSC or wet macular degeneration after eating peppers.

Researchers have not addressed whether red pepper consumption in stressed individual causes deterioration of CSC or wet macular degeneration because of (i) the lack of any hypothesis connecting these situations to each other, and (ii) the extremely low prevalence of these conditions which might occur concomitantly.

It is questionable whether or not pepper intake alone induces retinal neovascularization and retinal ganglion cell death in humans. Pathogenesis of retinal neovascularization is multifactorial; high pepper intake may promote the disease progression, but hot pepper intake may only function as a trigger of the disease. Most pepper constituents degrade in the liver and currently there is no direct evidence to show that capsaicin reaches the retina in sufficient amounts in humans. There are at least 3 potential possibilities to explain our observation:

- (i) The most straightforward explanation for this observation is that retinal issues following capsaicin consumption are not consistent. However, the fact that our patient experienced the same retinal problems three times following considerable amounts of red pepper, merits investigations.
- (ii) The second possibility-albeit with low likelihood- is that capsaicin may have been capable of crossing the blood-brain-barrier (BBB). Indeed, there is evidence to support this possibility [6,7,16,17]. After being transported into the portal vein and then into the whole body in both human and rodents, about 5% of unmodified capsaicin crosses the BBB and goes into the brain tissue [16,17]. This suggests that acute consumption of capsaicin could be another rationale explanation. This, in turn, may create a further possibility, i.e., there might be individuals who are extremely sensitive or hyper-reactive to high and acute intake of capsaicin. There is also evidence showing that capsaicin increases the permeability of the blood-spinal cord barrier and this effect is mediated by the activation of TRPV1-expressing primary sensory neurons [18]. If it is conceivable that capsaicin can cross in sufficient amounts in hyper-reactive individuals, then the common belief that red pepper is safe requires reconsideration. This also may affect the design of future studies investigating related ocular conditions, because there is a robust possibility that high intake of red pepper may create an uncertainty or a bias, particularly in non-randomized clinical trials. This case report may also have implications for the design of capsaicin-related food supplements and drugs, particularly considering high inter-individual differences in capsaicin bioavailability [19] and metabolism, detoxification, and bioactivation of capsaicin as well as alkyl dehydrogenation and oxygenation of capsaicinoids by P450 enzymes [20]. In this regard, it of interest to mention the hypertensive crisis in a 19-year-old man with a prior abundant ingestion of peppers likely associated to a decrease in protecting calcitonin gene-related peptide [21] as well of myocardial infarction due to cayenne pepper pills in a young man [22].
- (iii) Another hypothetical explanation for this case report is the involvement of aquaporins (AQPs). Experimental animals have a set of homeostatic mechanisms that continuously work together to maintain body-fluid osmolality within a narrow range around a set point (~300 mOsm/kg) [23]. AQPs have been implicated in retinal neovascularization both in animal models and humans [24–26]. Namely, AQP1 is required for hypoxia-inducible angiogenesis in human retinal vascular endothelial cells [24]. Relatedly, activating stimuli such as AQPs, protons and temperature synergistically enhance osmosensitivity of TRPV1.

It is established that TRPV1 and TRPV4 channels are involved in retinal angiogenesis [2,27]. Cairnion O'Leary et al. [28] for the first time investigated TRPV1 molecular and functional expression in detail in retinal ECs in vivo. They examined the localization of TRPV1 channels in the bovine retinal vasculature and cultured retinal microvascular endothelial cells (RMECs). They found that TRPV1 and TRPV4 channels act by specifically modulating tubulogenesis. They subsequently showed that pharmacologic inhibition of TRPV1 or TRPV4 channels suppressed in vitro retinal angiogenesis through a mechanism involving the modulation of tubulogenesis, proving the causal relationship. Further in vitro studies indicated that blockade of TRPV1 and TRPV4 channels had no effect on VEGF-stimulated angiogenesis or Ca²⁺ signals. Patch-clamp and PLA and studies showed that TRPV1 and TRPV4 form functional heteromeric channel complexes in RMECs. Inhibition of these

two channels reduced retinal neovascularization and promoted physiologic revascularization of the ischemic retina in the oxygen-induced retinopathy mouse model [28]. It may also help to note that TRPV1 is mainly expressed in the horizontal system of the retina (horizontal and amacrine cells) in adult vervet monkeys with high similarity to humans in genome and structure [31]. [32].

In support of this hypothesis, it was recently shown that TRPV4 channels promote vascular permeability in the retinal vein occlusion murine model [29]. These findings are pertinent to the present case report, because there is evidence showing that TRPV1 channels are expressed in human retinal microvascular endothelial cells [3,32]

Although, pesticides have been reported in red pepper crops [33], and these chemicals have a known noxious effect on redox system and overall body [34], the isolated case suggests ruling out this hypothesis.

Capsaicin, like other natural plant-, fermented food- and marine-derived compounds maintains an interesting profile for potential neuroprotective diseases [35]-[40] as well as in longevity research [41]-[42]. Nonetheless, the present case report may represent a learning opportunity for the physician and nutritionist to pay some care and understanding.

Given the information above, acute or chronic consumption of substantial amounts of hot red pepper could be involved in retinal neovascularization in individuals with high reactivity towards TRPV1 agonists and/or higher expression of TRPV1 receptors in retinal ganglion cells. This hypothesis **seems to be the one needing great** consideration.

Authors' contributions: RR wrote the initial draft, critically appraised the case report and wrote the case report. GSC helped in discussion section, FM critically appraised the paper, CA wrote the discussion, and FH interpreted the data. All authors approved the final manuscript.

Availability of data and materials: The data supporting this case report are available upon request.

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References

1. Venkata M. Kanukollu and Syed Shoeb Ahmad, "Retinal Hemorrhage," in StatPearls [Internet], StatPearls Publishing, 2022).
2. Christopher A. Reilly, "Cytochrome P450-Dependent Modification of Capsaicinoids: Pharmacological Inactivation and Bioactivation Mechanisms," *Role of Capsaicin in Oxidative Stress and Cancer*, 2013, 107-129.
3. Kou Liu, Xiang Gao, Chengyang Hu, Yanchao Gui, Siyu Gui, Qinyu Ni, Liming Tao, and Zhengxuan Jiang, "Capsaicin ameliorates diabetic retinopathy by inhibiting poldip2-induced oxidative stress," *Redox biology*, 2022, 56: 102460.
4. Jun Wang, Wenke Tian, Shuaiwei Wang, Wenqiang Wei, Dongdong Wu, Honggang Wang, Li Wang, Ruisheng Yang, Ailing Ji, and Yanzhang Li, "AntiGÇEinflammatory and retinal protective effects of capsaicin on ischaemiaGÇEinduced injuries through the release of endogenous somatostatin," *Clinical and Experimental Pharmacology and Physiology*, 2017, 44: 803-814.
5. Hércules Rezende Freitas, Alinny Rosendo Isaac, Thayane Martins Silva, Geyzara Oliveira Ferreira Diniz, Yara dos Santos Dabdab, Eduardo Cosendey Bockmann, Mar+ lia Zaluvar Passos Guimar+úes, Karin da Costa Calaza, Fernando Garcia de Mello, and Ana Lucia Marques Ventura, "Cannabinoids induce cell death and promote P2X7 receptor signaling in retinal glial progenitors in culture," *Molecular neurobiology*, 2019, 56: 6472-6486.
6. Jessica O'Neill, Christina Brock, Anne Estrup Olesen, Trine Andresen, Matias Nilsson, and Anthony H. Dickenson, "Unravelling the mystery of capsaicin: a tool to understand and treat pain," *Pharmacological reviews*, 2012, 64: 939-971.
7. A. Saria, G. Skofitsch, and F. Lembeck, "Distribution of capsaicin in rat tissues after systemic administration," *Journal of Pharmacy and Pharmacology*, 1982, 34: 273-275.
8. Sanjay Chanda, Mohammad Bashir, Sunita Babbar, Aruna Koganti, and Keith Bley, "In vitro hepatic and skin metabolism of capsaicin," *Drug Metabolism and Disposition*, 2008, 36: 670-675.
9. Maria Wang, Inger Christine Munch, Pascal W. Hasler, Christian Pr+nte, and Michael Larsen, "Central serous chorioretinopathy," *Acta ophthalmologica*, 2008, 86: 126-145.
10. Mark S. Blumenkranz, Stephen R. Russell, Marcia G. Robey, Recia Kott-Blumenkranz, and Neal Penneys, "Risk factors in age-related maculopathy complicated by choroidal neovascularization," *Ophthalmology*, 1986, 93: 552-558.

11. Junwon Lee, Seonghee Choi, Christopher Seungkyu Lee, Min Kim, Sung Soo Kim, Hyoung Jun Koh, Sung Chul Lee, and Suk Ho Byeon, "Neovascularization in fellow eye of unilateral neovascular age-related macular degeneration according to different drusen types," *American Journal of Ophthalmology*, 2019, 208: 103-110.
12. Junwon Lee, Min Kim, Christopher Seungkyu Lee, Sung Soo Kim, Hyoung Jun Koh, Sung Chul Lee, and Suk Ho Byeon, "Drusen subtypes and choroidal characteristics in Asian eyes with typical neovascular age-related macular degeneration," *Retina*, 2020, 40: 490-498.
13. Richard F. Spaide, Donald Armstrong, and Richard Browne, "Choroidal neovascularization in age-related macular degeneration: What is the cause?," *Retina*, 2003, 23: 595-614.
14. W. C. Huang, W. L. Chen, Y. Y. Tsai, C. C. Chiang, and J. M. Lin, "Intravitreal bevacizumab for treatment of chronic central serous chorioretinopathy," *Eye*, 2009, 23: 488-489.
15. Karen B. Schaal, Alexandra E. Hoeh, Alexander Scheuerle, Florian Schuett, and Stefan Dithmar, "Intravitreal bevacizumab for treatment of chronic central serous chorioretinopathy," *European journal of ophthalmology*, 2009, 19: 613-617.
16. V. S. Govindarajan and M. N. Sathyanarayana, "Capsicum: production, technology, chemistry, and quality. Part V. Impact on physiology, pharmacology, nutrition, and metabolism; structure, pungency, pain, and desensitization sequences," *Critical Reviews in Food Science & Nutrition*, 1991, 29: 435-474.
17. Peijian Wang, Zhencheng Yan, Jian Zhong, Jing Chen, Yinxing Ni, Li Li, Liqun Ma, Zhigang Zhao, Daoyan Liu, and Zhiming Zhu, "Transient receptor potential vanilloid 1 activation enhances gut glucagon-like peptide-1 secretion and improves glucose homeostasis," *Diabetes*, 2012, 61: 2155-2165.
18. Simon Beggs, Xue Jun Liu, Chun Kwan, and Michael W. Salter, "Peripheral nerve injury and TRPV1-expressing primary afferent C-fibers cause opening of the blood-brain barrier," *Molecular pain*, 2010, 6: 1744-8069.
19. William D. Rollyson, Cody A. Stover, Kathleen C. Brown, Haley E. Perry, Cathryn D. Stevenson, Christopher A. McNees, John G. Ball, Monica A. Valentovic, and Piyali Dasgupta, "Bioavailability of capsaicin and its implications for drug delivery," *Journal of Controlled Release*, 2014, 196: 96-105.
20. Christopher A. Reilly and Garold S. Yost, "Metabolism of capsaicinoids by P450 enzymes: a review of recent findings on reaction mechanisms, bio-activation, and detoxification processes," *Drug metabolism reviews*, 2006, 38: 685-706.
21. Patanè S, Marte F, La Rosa FC, La Rocca R. Capsaicin and arterial hypertensive crisis. *Int J Cardiol*. 2010 Oct 8;144(2):e26-7. doi: 10.1016/j.ijcard.2008.12.080.
22. Akçay M, Gedikli Ö, Yüksel S. An unusual side effect of weight loss pills in a young man; acute myocardial infarction due to cayenne pepper pills. *Anatol J Cardiol*. 2017 Oct;18(4):310-311. doi: 10.14744/AnatolJCardiol.2017.8031
23. B. Anderson, "Regulation of body fluids," *Annual review of physiology*, 1977, 39: 185-200.
24. Kentaro Kaneko, Kazuo Yagui, Asami Tanaka, Kei Yoshihara, Kou Ishikawa, Kazuo Takahashi, Hideaki Bujo, Kenichi Sakurai, and Yasushi Saito, "Aquaporin 1 is required for hypoxia-inducible angiogenesis in human retinal vascular endothelial cells," *Microvascular research*, 2008, 75: 297-301.
25. Javier Ruiz-Ederra and A. S. Verkman, "Aquaporin-1 Independent Microvessel Proliferation in a Neonatal Mouse Model of Oxygen-Induced Retinopathy," *Investigative ophthalmology & visual science*, 2007, 48: 4802-4810.
26. Wang Xun, Yanbo Liu, Gu Qing, Xu Xun, Zhu Dongqing, and Wu Haixiang, "Aquaporin 1 expression in retinal neovascularization in a mouse model of retinopathy of prematurity," *Preparative Biochemistry & Biotechnology*, 2009, 39: 208-217.
27. Holly C. Cappelli, Brianna D. Guarino, Anantha K. Kanugula, Ravi K. Adapala, Vidushani Perera, Matthew A. Smith, Sailaja Paruchuri, and Charles K. Thodeti, "Transient receptor potential vanilloid 4 channel deletion regulates pathological but not developmental retinal angiogenesis," *Journal of cellular physiology*, 2021, 236: 3770-3779.
28. Caitriona O'Leary, Mary K. McGahon, Sadaf Ashraf, Jennifer McNaughten, Thomas Friedel, Patrizia Cincola, Peter Barabas, Jose A. Fernandez, Alan W. Stitt, and J. Graham McGeown, "Involvement of TRPV1 and TRPV4 channels in retinal angiogenesis," *Investigative ophthalmology & visual science*, 2019, 60: 3297-3309.
29. Catarina Micaelo-Fernandes, Joseph Bouskila, Roberta M. Palmour, Jean François Bouchard, and Maurice Ptito, "Age and Sex-Related Changes in Retinal Function in the Vervet Monkey," *Cells*, 2022, 11: 2751.
30. Eric J. Vallender, Charlotte E. Hotchkiss, Anne D. Lewis, Jeffrey Rogers, Joshua A. Stern, Samuel M. Peterson, Betsy Ferguson, and Ken Sayers, "Nonhuman primate genetic models for the study of rare diseases," *Orphanet journal of rare diseases*, 2023, 18: 20.
31. Anri Nishinaka, Miruto Tanaka, Kentaro Ohara, Eiji Sugaru, Yuji Shishido, Akemi Sugiura, Yukiko Moriguchi, Amame Toui, Shinsuke Nakamura, and Kaoru Shimada, "TRPV4 channels promote vascular permeability in retinal vascular disease," *Experimental Eye Research*, 2023, 228: 109405.

32. Lei Wen, Yue Chun Wen, Gen Jie Ke, Si Qin Sun, Kai Dong, Lin Wang, and Rong Feng Liao, "TRPV4 regulates migration and tube formation of human retinal capillary endothelial cells," *BMC ophthalmology*, 2018, 18: 1-6.
33. Lee D, Ahn H, Lee KG. Analysis of 207 residual pesticides in hot pepper powder using LC-MS/MS. *Food Sci Biotechnol*. 2023 Oct 25;33(6):1337-1350. doi: 10.1007/s10068-023-01443-6.
34. Yaduvanshi SK, Srivastava N, Marotta F, Jain S, Yadav H. Evaluation of micronuclei induction capacity and mutagenicity of organochlorine and organophosphate pesticides. *Drug Metab Lett*. 2012 Sep 1;6(3):187-97. doi: 10.2174/1872312811206030006
35. Tyagi S, Shekhar N, Thakur AK. Protective Role of Capsaicin in Neurological Disorders: An Overview. *Neurochem Res*. 2022 Jun;47(6):1513-1531. doi: 10.1007/s11064-022-03549-5.
36. Marotta F, Mao GS, Liu T, Chui DH, Lorenzetti A, Xiao Y, Marandola P. Anti-inflammatory and neuroprotective effect of a phytoestrogen compound on rat microglia. *Ann N Y Acad Sci*. 2006 Nov;1089:276-81. doi: 10.1196/annals.1386.033.
37. Barbagallo M, Marotta F, Dominguez LJ. Oxidative stress in patients with Alzheimer's disease: effect of extracts of fermented papaya powder. *Mediators Inflamm*. 2015;2015:624801. doi: 10.1155/2015/624801
38. Sedriep S, Xia X, Marotta F, Zhou L, Yadav H, Yang H, Soresi V, Catanzaro R, Zhong K, Polimeni A, Chui DH. Beneficial nutraceutical modulation of cerebral erythropoietin expression and oxidative stress: an experimental study. *J Biol Regul Homeost Agents*. 2011 Apr-Jun;25(2):187-94.
39. Marotta F, Chui DH, Yadav H, Lorenzetti A, Celep G, Jain S, Bomba A, Polimeni A, Zhong K, Allegri F. Effective properties of a sturgeon-based bioactive compound on stress-induced hippocampal degeneration and on in vitro neurogenesis. *J Biol Regul Homeost Agents*. 2012 Jul-Sep;26(3):327-35
40. Cervi J, Rastmanesh R, Moghadam Ahmad A, Ayala A, Aperio C, et al. Effect of a fermented functional food versus vitamin e on nrf2 and are-signalling in untrained middle-age/elderly after exercise: a rct, double-blind clinical study. *Functional Food Science* (2024, in press).
41. Elkhedir A, Iqbal A, Albahi A, Tao M, Rong L, Xu X. Capsaicinoid-Glucosides of Fresh Hot Pepper Promotes Stress Resistance and Longevity in *Caenorhabditis elegans*. *Plant Foods Hum Nutr*. 2022 Mar;77(1):30-36. doi: 10.1007/s11130-021-00939-y.
42. Kumar P, Chand S, Chandra P, Maurya PK. Influence of Dietary Capsaicin on Redox Status in Red Blood Cells During Human Aging. *Adv Pharm Bull*. 2015 Nov;5(4):583-6. doi: 10.15171/apb.2015.078. 2;

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