CASE REPORTS

Photo-infrared pulsed biomodulation in age-related macular degeneration associated to neurological disease: one interventional case report and mini-review

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INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of blindness in industrialized countries. Other than a heart-healthy diet and lifestyle changes, no known treatments currently exist for early-AMD. Advanced-AMD may be of two kinds: the atrophic form, the most prevalent, for which there is no treatment, and the neovascular form, for which existing treatments are applicable only to a reduced number of patients and generally aim at delaying the devastating progression of the disease. Here, we report the first case of bilateral geographic atrophic AMD (gaAMD) and associated neurological disease treated with a novel infrared pulsed laser device (IPLD) through an action mechanism designated photo-infrared pulsed bio-modulation (PIPBM)[1].

METHOD

The Helsinki Declaration was followed and a legal authorization was obtained. Use of the IPLD in humans was approved by Venezuelan regulatory agencies: Ministry of Health, and Ministry of Science and Technology (CONICIT)[2].

Clinical diagnoses were based on physical examination confirmed by visual function testing, fluoresceinography (FRG), full field electroretinogram (ERG), magnetic resonance imaging (MRI) and the Mental Status Questionnaire. Other currently-used technologies were unavailable at the time of consultation (1990 ~ 1991). Main outcome measures were: Visual acuity (VA), ocular fundus (OF), intraocular pressure (IOP), FRG, ERG, and MRI. A total fractioned daily radiant exposure of 4.5×10^4 J/m^2/day (power-density 4.5×10^3 mW/cm^2) was administered by using the IPLD (904 nm pulsed at 3 MHz, peak power was 35 mW) (U. S. Patent No 5,231,984). Energy was transferred non-invasively and at a distance, preventing direct adverse ocular events. See Ref 2 for more details.

CASE REPORT

The patient (XY), an 86-year-old, right-handed, non-smoking, Caucasian man and former chemist narrated being previously ametropic and abruptly becoming more reading-and driving-impaired, seeing all things red in color, and developing in both upper visual fields a "black stain"-larger in his right eye-approximately 20 years prior to consultation following a by-pass surgery with immediate post-surgical complications. After his recovering, XY had an apparently stable visual condition which allowed him to maintain a fairly independent lifestyle until five years before consultation, when he began to notice gradual loss of vision in both eyes that hindered routine visual activities. Antecedents included a prolonged labor-related exposure to chemicals, chronic sinusitis, stroke, systemic arterial hypertension, arteriosclerosis, mixed vertiginous syndrome. Medication was pentoxyfilline, dipyridamole, niphedipine, enalapril, diphenidol, acetylsalicylic acid, isosorbide dinitrate. There was no history of medication with steroids and/or antioxidants. Family history was without known blinding ocular or systemic maladies.

The following findings were documented.

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Pre-IPLD treatment (Time 0)

XY exhibited an action tremor predominantly on his upper right extremity and mild ataxic gait. He was cooperative and cognitive function was preserved; Mental Status Questionnaire score was 8/10 (suggests no-dementia), Romberg's test was positive. XY had left-sensory inattention, hiporeflexia on his right side, pure alexia, prosopagnosia, full-field panachromatopsia (erythropsia), and motor impersistence. He could not identify hands in any of the four quadrants of both eyes during visual field (confrontation technique) examination. Testing with Amsler grid and central and peripheral field techniques with Goldmann perimeter were inconclusive. Best-corrected VA (BCVA) W/Specs (Snellen chart) was (OD) 20/100-1 PH: NI and (OS) 20/60 + 2 PH: NI. Contrast sensitivity was reduced. XY failed the Ishihara test; he did not identify desaturation of the target's red color. Both pupils were round, central and mildly dilated in room light. Pupillary anisocoria in dim and bright illumination was not noted. Light direct pupillar reflex was apparently not reactive in OU. It was not possible to detect a consensual reflect response in OU. There was no conjugated deviation of gaze. Ductions and versions were present in OU, but limited to the central field of vision. There was no response upon exploring convergence. Corneal reflex was reduced. XY could smile, frown, blink, and wrinkle forehead. Slit-lamp examination showed no ptosis, partial iris atrophy in OU (without rubiosis or segmentary paralysis of the pupillar sphincter), brunescent nuclear cataracts in OU and incipient anterior and posterior sub-capsular cataracts OD > OS. IOP (OU) was 22 mm Hg. Gonioscopy (OU) was Grade IV in all sectors without neovascularization. OF showed well-defined optic discs with a 0.3 excavation, pallor in the peripheral half of the neuroretinal rim and a pinkish color in its remaining inner area, constriction of the vasculature (OU), mild peripapillary atrophy (OD > OS), markedly reduced visibility of the retinal nerve fiber layer, peripapillary chorioretinal atrophy (OU), and extensive areas of geographic atrophy of the RPE and choriocapillaries (approximate diameter of 2 to 3 optic disc area), which made possible observing choroidal circulation and surpassed temporal vascular arcades (OU). In OS, the atrophic area had a lobular and well-defined contour with isolated circumferential areas, which were almost confluent at the superior portion. Atrophic areas comprised the fovea in OU, but there was a small, irregular, vertically elongated, central area preserved in OD, and a triangular inferotemporal area spared in OS. Three small drusen bordered the superotemporal vessels in OS and medium sized drusen were found in the peripheral retina. MRIs, FRG, and ERG results are given in Figures 1, 2 and Table 1, respectively.

Diagnoses

* Hypermetropic astigmatism, cataracts, and gaAMD, in OU.
* Ischemic optic neuropathy / Partial optic atrophy
* Cortical and sub-cortical visual loss caused for multi-infarct syndrome.
* Striate-peristriate (central achromatopsia / erythropsia) and ventral-occipitofugal (pure alexia, prosopagnosia) syndromes.
* Mixed vertiginous syndrome.
* Systemic arterial hypertension and Arteriosclerosis.

Despite visual impairment and CNS disorders, XY did not exhibit signs of clinical depression or multi-infarct dementia. Therefore, XY was allowed to initiate IPLD treatment while maintaining previously-prescribed medication after confirming the existence of good social/family support.

RESULTS

Six months post-IPLD treatment (Time Ⅰ)

XY presented a more stable gait and decreased tremor, a confirmed single event of transitory color vision (not a hallucination) occurred. XY described "seeing better", BCVA remained stable in OU (OD: 20/100 + 1; OS: 20/60 + 2) and PH-BCVA improved 1 line in the left eye (OS: 20/50 + 3), lenses appeared clearer and scarce vacuoles could be observed in OS, IOP decreased in OU (OS: 19 mm Hg; the right eye (OD): 20 mm Hg). ERG changes included previously unrecordable oscillatory potentials (OPs), decreased cone b-wave implicit time, increased mixed rod and cone b-wave implicit time, and increased photopic and scotopic a-and b-wave amplitude (Table 1). OF and FRG showed mobilization of drusen and structural changes (Figures. 3 ~ 4). MRIs appeared unchanged.

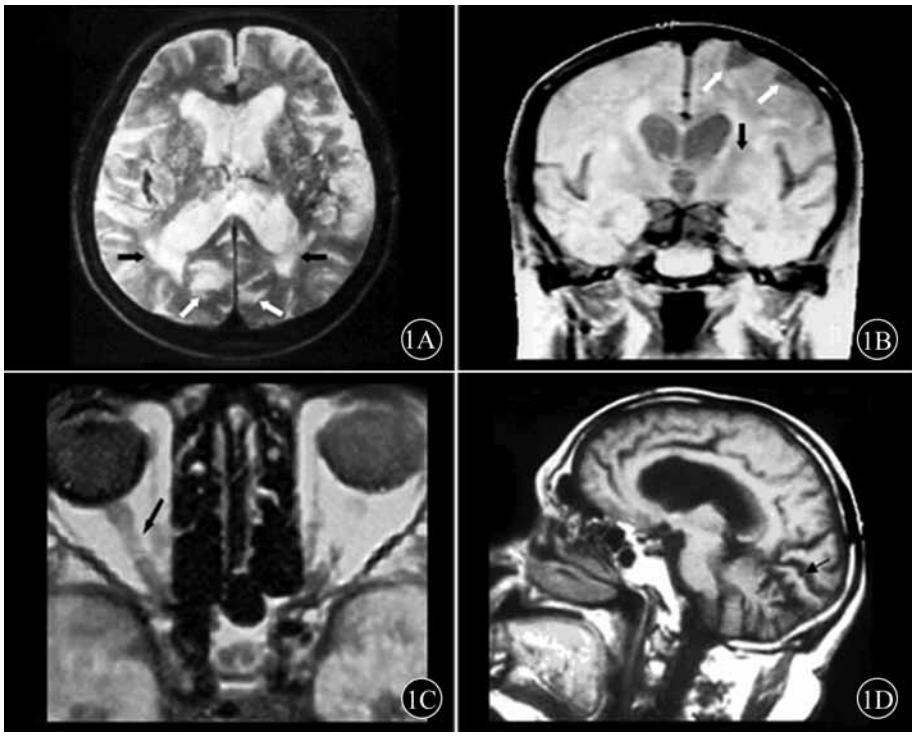

Figure 1 Cerebral magnetic resonance images of 86-year-old patient. (1A) Axial T2. Cortical and central hyperintensities related to multiple infarcts. Bilateral periventricular hyperintensities suggest subcortical arteriosclerotic microangiopathy. White arrows illustrate old bilateral occipital infarcts. Black arrows show cortical atrophy and ventricular dilatation, notorious in occipital prolongations. (1B) Coronal proton density image. White arrows show hypointensities on the left parietal lobe consistent with cortical infarcts. Black arrow points to a hyperintense rim surrounding infarct of the basal ganglia and left lenticular nucleus consistent with a gliotic edge. (1C) Axial T1 image of the optic nerves. Black arrow shows a segment near the middle third of the right optic nerve, which appears thinned. (1D) Sagittal T1-weighted image showing cerebral and cerebelar atrophy and ventricular enlargement. Black arrow shows a markedly dilated calcarine fissure.

Fourteen months post-IPLD treatment latter (Time Ⅱ)

One month after a stroke, XY presented left hemiparesis, larger bilateral central scotomas, BCVA deteriorated in OU (OD: FC. 50 cm; OS: FC. 25 cm), and dense opacities were present in both lenses, but IOP continued to decrease slightly (OU: 19 mm Hg) and ERG recordings continued to improve (Table 1).

DISCUSSION

It is improbable that a deleterious IPLD effect caused deterioration at Time Ⅱ since treatment characteristics preclude photo-thermal or photo-chemical damage. Indeed, far from producing ischemia, low-energy NIR lasers dilate arterioles and increase microcirculation[3]. And the treatment studied has been found to be clinically safe in the long term[2]. Hence, adverse changes in Time Ⅱ are most likely explained by acute hypoxia caused by severe arteriosclerosis and systemic hypertension. In contrast, it is unlikely that positive post-treatment findings may be explained solely by the natural history of the disease, bias, technical error, chance, drugs or a potential placebo effect. Instead, IPLD-effects via the PIPBM mechanism may explain changes as follows.

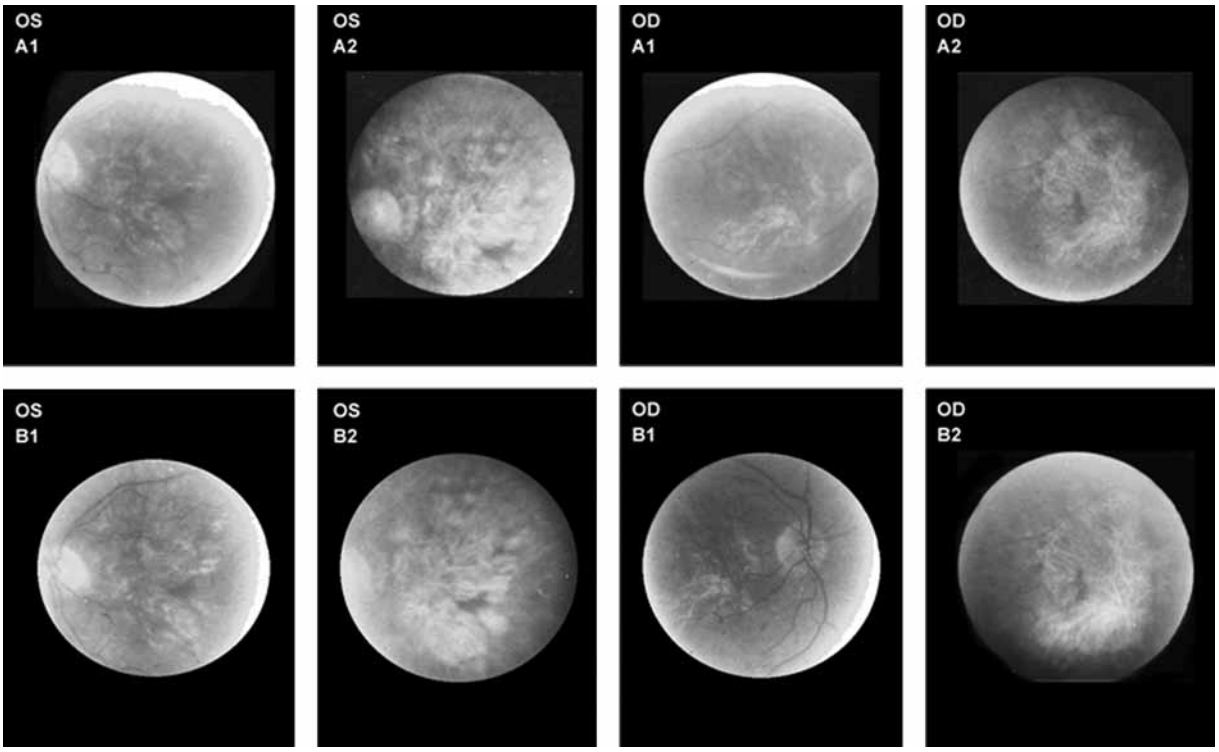

Figure 2 Fluoresceinography. Patient with bilateral ga-AMD. OD = Right eye; OS = Left eye; 1 = Initial phase; 2 = Late-phase. A (Pre-IPLD treatment): 1: The early phase of the FRG demonstrated diffuse hyperfluorescence-caused by pigment epithelium defects (window defects) limited to areas with geographic atrophy in OD and OS. 2: The late phase showed choroidal circulation. There were no areas of abnormal hyperfluorescence or leakage suggesting a neovascular membrane in OD and OS. No signs of intra or sub-retinal blood and central islands of apparently preserved foveal tissue remained relatively hypofluorescent compared to neighboring areas in OD and OS. B (Six months post-IPLD treatment): 1 and 2: Apparent asymmetric atrophy evolution (Stability in OD and progression in OS) can be observed. No apparent progression to the neovascular form (there were no areas of abnormal hyperfluorescence or leakage suggesting a neovascular membrane in OU No signs of intra or sub-retinal blood). Hypo-fluorescence of previously spared zones was maintained in OD and OS.

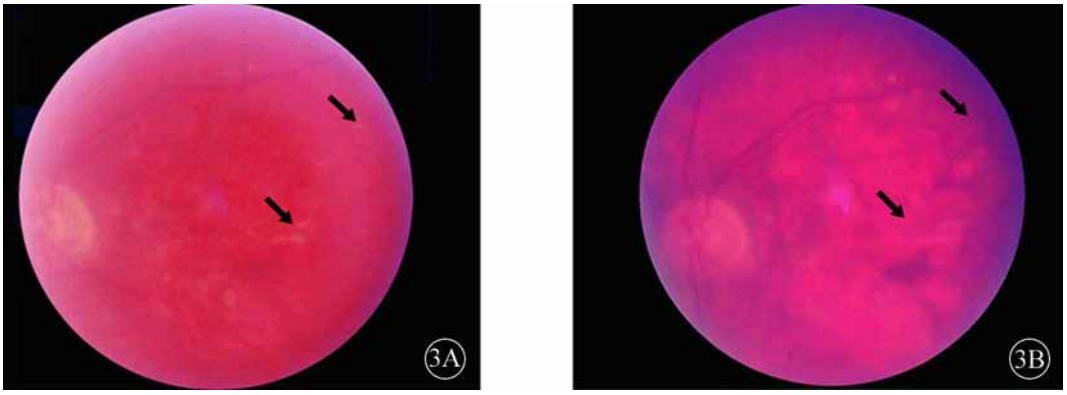

Figure 3 Fundus photographs. Patient with gaAMD. Left eye (OS). A = Pre-IPLD treatment. B = 6 months post-IPLD treatment: A better image of retinal structures can be observed due to diminished lens opacity (errors in the photographic technique can be discarded based on the characteristics of the lens opacity). Arrows show drusen mobilization.

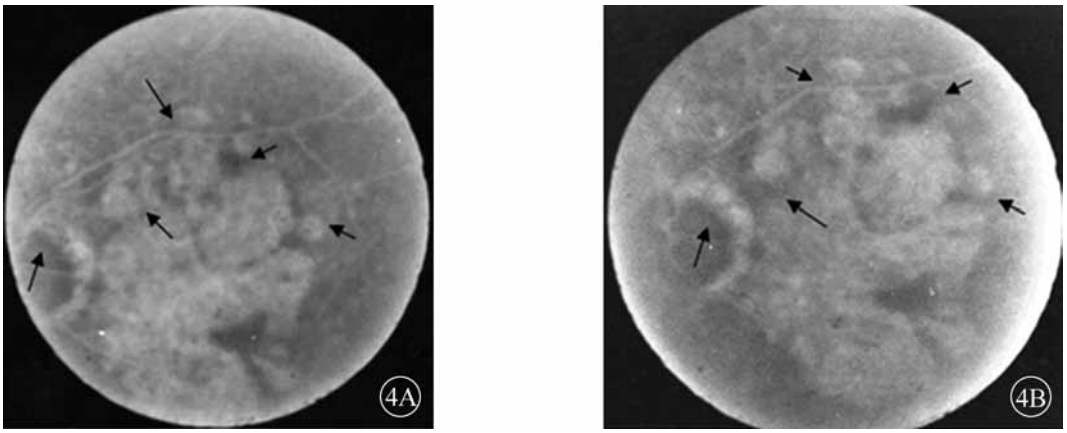

Figure 4 Fluoresceinography (late-phase). Patient with gaAMD. Left eye (OS). A = Pre-IPLD treatment. B = 6 months post-IPLD treatment. Show structural changes: There appears to be a slight increase in atrophic areas. Drusen appeared denser, with better-defined edges; surrounding hypofluorescent areas appear spared and slightly enlarged. Arrows point to examples.

Table 1 Clinical full field electroretinogram measurements

Eye	ERG Phase	Time 0	Time I	Time II	Normal Mean Values ± 2 SD (range)
	Photopic (30 Hz flicker)				
OD	Cone b-wave amplitude	16 μV	32 μV	48 μV	193.9 ± 57.2 (136.7 ~ 251.1)
	Cone b-wave implicit time	39.5 ms	35 ms	30 ms	29.8 ± 1.8 (28 ~ 31.6)
OS	Cone b-wave amplitude	76 μV	20 μV	64 μV	193.9 ± 57.2 (136.7 ~ 251.1)
	Cone b-wave implicit time	41 ms	34.5 ms	35 ms	29.8 ± 1.8 (28 ~ 31.6)
	Scotopic (white single flash)				
OD	Mixed rod and cone a-wave amplitude	−40 μV	−88 μV	−76 μV	285.6 ± 73.2 (212.4 ~ 358.8)
	Mixed rod and cone b-wave amplitude	150 μV	156 μV	180 μV	470 ± 111.6 (358.4 ~ 581.6)
	Mixed rod and cone b-wave implicit time	40 ms	55 ms	56 ms	45.8 ± 8.3 (37.5 ~ 54.1)
	Oscillatory potentials	nonrecordable	recordable	recordable	>75 μV
OS	Mixed rod and cone a-wave amplitude	−108 μV	−76 μV	−80 μV	285.6 ± 73.2 (212.4 ~ 358.8)
	Mixed rod and cone b-wave amplitude	180 μV	180 μV	204 μV	470 ± 111.6 (358.4 ~ 581.6)
	Mixed rod and cone b-wave implicit time	46 ms	56 ms	56 ms	45.8 ± 8.3 (37.5 ~ 54.1)
	Oscillatory potentials	nonrecordable	recordable	recordable	>75 μV

Note: ERG = Electroretinogram; μV = microvolt; ms = millisecond; Time 0 = pre-Infrared Pulsed Laser Device (IPLD) treatment; Time I = 6 months post-IPLD treatment; Time II = 14 months post-IPLD treatment.

VA: Most territories of the visual pathway were diffusely affected in XY, resulting in poorly spared macular vision. In addition to ametropia, three fundamental problems affected VA: cataracts, gaAMD and neurodegeneration-variables complexly influenced by the IPLD. Firstly, the IPLD affects heat shock proteins, enzymes of the anti-oxidative system, Na^+-K^+-ATPase, Ca^{2+}-ATPase, aquaporins (AQPs), and ion pumps[1], which may explain improved lens transparency at Time I. The IPLD may also act on lens mitochon-

dria[1], whose metabolic function is linked to optical lens properties[4]. Secondly, it has been argued that foveal cone misalignment may be perceived as blurring, distortion and decreased VA[5]. Hence, XY's subjective experience of "seeing better" could be partly related to improved photoreceptor alignment (Stiles-Crawford effect) through IPLD effects over cytoskeleton dynamics[6]. Thirdly, the IPLD supplies energy to metabolically fragile photoreceptors extant in the patient's macula, presumably offsetting local energy depletion thought to trigger photoreceptor death[1,5] in accord with studies suggesting light-induced modulation of apoptosis and necrosis[7]. Interestingly, light may also contribute to the regulation of stem cells through the modulation of physiological activities of NO and Ca^{2+}, which are involved in the activation and maintenance of neural activities, the recruitment of stem and progenitor cells, and the activation of signaling pathways that are essential for dendritic development, neural survival, and synaptic plasticity[8]. Reported photo-activation of actin filament in lamellipodia of dendrites[9] and up-regulation of calcitonin gene-related peptide (CGRP) mRNA in axotomized neurons support this possibility[10]. The IPLD also stimulates intra-and inter-molecular energy transfer via water dynamics, modulating the regulating activity of the inositol phosphate group[1], and through it, coincidence detection, long-term potentiation, INS (1,4,5) P3 receptors, and basal polymerization of lamellidopodia[1,9]. These mechanisms-added to objective ERG changes, lens modifications and neurological response discussed below-indicate that the evolution of VA concurs with the possibility of an IPLD-induced enhancement of physiologically-reparative mechanisms in the visual pathway of both eyes.

ERG: Results suggest a global deterministic* post-IPLD-treatment tendency towards a normal ERG pattern. Oscillatory potentials recorded in OU at Times I and II demonstrate increased retinal oxygenation in agreement with recent data showing greater central retina artery blood flow in humans following low-level laser therapy (LLLT)[11]. An IPLD synergic effect over vessel-dilating medication cannot be ruled out and should be investigated. In addition, the IPLD can stimulate and/or substitute ATP production[1], which is vital for activation and inactivation kinetics in photo-transduction. Light can further modulate factors that may contribute to the dramatic slowing of inactivation kinetics found in late AMD by limiting delivery of 11-cis RAL to opsin[12]. These factors include ROS[13], cell attachment[14], immune function[15], drusen mobilization and enzymatic activity[1]. The IPLD also increases the synthesis of biopolymers, particularly biological liquid crystals, e. g., lipid membranes, which play essential roles in photo-transduction and hence photo-vision[16]. Significant recovery of photoreceptors-mediated retinal signals has been reported in ERG of LED-treated rats[17]. Thus, the global deterministic* tendency toward a normal ERG pattern suggest be the result of physiologically-reparative IPLD effects.

Drusen: Drusen mobilization in OF and structural changes in the FRG (Figures 3 ~ 4) at Time I appear consistent with a deterministic* effect, suggesting partial lipid transport/mobilization. We propose this occurs at raft-caveolae of the vascular endothelium and by anti-inflammatory and immune effects[1,15]. Integrin, a drusen constituent[18], serves as a mechanical transductor of low-frequency electric fields[19]. Thus, while drusen can reabsorb spontaneously[20], our results may reflect effects that match local and/or remote drusen regression following laser photo-coagulation after the same post-treatment period (6 months)[20].

Atrophy: Apparent atrophy stability in OD at Time I could fall within the natural-history rate of enlargement of the disease[21]. However, asymmetry observed with progression of atrophy in OS contradicts the high concordance between the enlargement rate in both eyes of patients with bilateral GA[21], suggesting a deterministic* IPLD effect. The response in OD seems important because slowing progression of atrophy in AMD can have a significant positive impact on visual function, even when there is already a large central scotoma[22]. The lack of apparent progression to the neovascular form (as supported by the absence of abnormal hyperfluorescence, lack of signs of intra or sub-retinal blood or sudden loss of vision) suggests a blockage of pathological angiogenesis following IPLD treatment as previously described[1], and it is indicative of IPLD-modulation of oxidative stress[1,13] and inflammation[1,15],

which are correlated to atrophy and neovascularization in AMD.

IOP: Pulsed light can influence IOP as follows: 1-increasing membrane permeability and modulating aquaporin water channels[1] (strongly expressed in endothelial cells in the trabecular meshwork and Schlemm's canal) regulating trabecular endothelial volume; 2-directly and indirectly affecting the cytoskeleton[1,5] (which plays a key role in fluid outflow); 3-modulating cell attachment via NO synthesis[1,14] (a determinant of fluid outflow through the trabecular meshwork) and; 4-up regulating calcitonin gene-related peptide mRNA[10] (*i. e.*, stimulation of unmyelinated axons with NO and of myofibroblast-like scleral spur cells with calcitonin gene-related peptide increases aqueous outflow facility[23]). IOP results at Times I and II also coincide with statistically-significant, non-published data from the phase I trial of the IPLD[2].

Neurological Symptoms: The improvement in neurological symptoms is consistent with the evolution of 2 patients during the phase I trial of the IPLD[2] and with data from other authors.

Indeed, light can stimulates neural plasticity[8], which is essential to regaining motor function, and LLLT can improve neurological function after acute stroke[24]. Infrared-laser effects on the energy metabolism of the rat brain can increase tissue ATP content in cerebral cortex by 19% compared to non-treated brain area[25]. In addition, the IPLD modulates tumor-necrosis factor-alpha (TNF-alpha)[15], which participates in non-infectious (e. g. acute brain insult such as ischemic stroke), immune, and neurodegenerative diseases. By modulating TNF-alpha levels, glias participate in the homeostatic activity-dependent regulation of synaptic connectivity. Thus, IPLD effects may be important for both energy supplementation and neuroprotection, two keys to increase plasticity and reduce the intrinsic vulnerability of neurons in ischemic stroke injury[26].

Color vision: Central achromatopsia associated to an altered pattern of lens absorption and acquired dyschromatopsia (common in macular degeneration and optic nerve injuries) complicate the interpretation of the confirmed, single, non-hallucinatory event of transitory color vision reported. However, said event could be explained as IPLD-induced improvement of neural transduction of information encoded in color-opponent signals from the retina based on the following findings: a-reduced lens opacity; b-positive ERG changes (including OPs that indicate improved oxygenation in the retina[11] and possibly in the brain[27]); c-mobilization of drusen (linked to changes in color contrast sensitivity and other visual deficits[28]); and d-potential activation of neural plasticity by enhanced synaptic transmission, myelinization, and immune protection and supplementation of energy for metabolic processes of the retina and cortex[1,29]. To see an image with colors other than red (*i. e.*, erythropsia), XY must have experienced a brief "window" of spatiotemporal activation and synchronization of biological processes responsible for color vision[30]. We propose such "window" was induced and/or favored by IPLD activation and synchronization of biophysical, biochemical, and biomechanical oscillators[30] as supported by findings herein discussed and by the PIPBM mechanism[1].

Based on the above, we conclude that reasons other than chance, natural history of the disease and/or technical errors were responsible for positive clinical outcomes reported. Indeed, since cellular work depends on energy, the PIPBM may enhance physiologically-reparative mechanisms that span the path from the genotype to phenotype. Thus, weak pulsed light, alone or in combination with other treatments, might be a viable therapeutic approach for complex ophthalmic and neurological diseases with few or no known effective treatments such as early AMD and gaAMD. Additional experimental and clinical investigation is warranted.

NOTE

* Determinism indicates predictability on the basis of the initial conditions of a system. Chaotic systems may still be completely deterministic in that any future state of the system depends only on the initial conditions and the equations describing the change of the system with time. It may, however, require arbitrarily high precision to actually calculate a future state.

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(Editor Alice)