REVIEW ARTICLE

Implications of the Unexpected Bioenergetic Role of Melanin in the Physiopathology of Congenital Glaucoma

Arturo Solis Herrera

Department of Research Development and Innovation, Human Photosynthesis® Research Centre, Aguascalientes 20000, Mexico

ABSTRACT

Primary congenital glaucoma is, theoretically, the result of abnormal development of the anterior chamber angle structures. The Barkan membrane, which allegedly covers the trabecular mesh and causes increased intraocular pressure, cannot be demonstrated histologically. Congenital glaucoma has been attempted to correlate with a variety of both local and systemic diseases, including genetic alterations. However, it is surprising that the role of melanin in the pathogenesis of this disease had not been examined although it is the first cause of blindness in the dark-skinned population. The unsuspected intrinsic property of melanin to dissociate the water molecule, like chlorophyll in plants, means that its biological role presupposes a revolution in biology and therefore in medicine since it implies modifying the prevalent patterns of the flow of energy and mass in the eukaryotic cell. Einstein said it's easier to break the atom than a prejudice, so it's not going to be easy to modify the dogma of glucose as a source of energy. But glucose is only the universal precursor of any organic compound of our body, but it is not able to provide the energy that its own metabolism requires. Moreover, on the other hand, now that we know the unsuspected bioenergetic role of melanin, it will be necessary to concatenate the flow of mass and energy so that the diseases are understood differently, but at the same time, it opens a new era in medicine, and in the case of ophthalmology, which represents new therapeutic approaches in chronic diseases such as glaucoma.

Keywords: Melanin, energy, intraocular pressure, water dissociation, glaucoma

BACKGROUND

Glaucoma-induced blindness in children is responsible for almost one-fifth of children in blind institutions and 5% of pediatric blindness worldwide. Males are more affected than females. A minority of cases, about 10%, present an increased frequency in the family, and the remainder (90%) occur sporadically. The disease is presented bilaterally in 75% of cases.

The pathophysiology of congenital glaucoma has been extensively studied due to it is a life-long disease that frequently leads to blindness.

In any system, when the problem is in the generation and distribution of energy, the fault is widespread. And in the case of congenital glaucoma morphologial alterations are widespread, [Figure 1] i.e.,: predisposition to damage of the optic nerve by loss of retinal ganglionar fiber, trabecular dysfunction, dislocation of the crystalline with pupil blockade, increase in the Uveo-scleral resistance, increase in the of aqueous humor outflow resistance which increased intraocular pressure; ruptures in Descemet´s membrane with appearance of corneal opacity and photosensitivity; decreased visual acuity; and progressive and irreversible damage to the visual fields that eventually lead to blindness.

Primary congenital glaucoma is the result of isolated abnormal development of the anterior chamber angle structures; meanwhile, secondary congenital glaucoma is

Address for correspondence:
Arturo Solis Herrera, Human Photosynthesis® Research Centre, Aguascalientes 20000, Mexico. E-mail: comagua2000@yahoo.com

associated with a variety of ocular and systemic syndromes and with surgical aphakia.

INTRODUCTION

The dynamics of aqueous humor is focused on secretion, transit, and resorption. Elevation of IOP is considered the major risk for glaucoma,[1] and thereby, approved clinical strategies are based in suppressing aqueous humor formation or inflow, facilitating aqueous humor drainage or outflow, or the combination of both. However, in spite of valuable efforts of researchers and ophthalmologists, glaucoma, defined as an irreversible neurodegenerative disease of the visual system, is the leading cause of blindness in the world in people with dark skin.[2] The explanation is that exact regulatory mechanisms of aqueous humor circulation and the contributions of imbalanced aqueous humor dynamics to the pathogenesis of ocular hypertension and glaucoma are not fully elucidated.

Another factor of confusion is low-tension glaucoma, whose medical and surgical treatment does not improve the prognosis.[3] The prevalence of low-tension glaucoma is almost equal to primary open-angle glaucoma in the population.[4]

Ophthalmoscopic changes in both primary open-angle glaucoma as in low-tension glaucoma are significantly similar [Figure 2], as the main findings are the progressive increase in the excavation of the optic nerve that is accompanied by loss of peripheral vision, also progressive.

FUNCTIONAL ANATOMY

The anatomical pattern of the eye of mammals can be described as three hollow spheres that fit together but whose histology significantly different from each other sphere or shell, the outermost is the sclera, which contains few cells and abundant collagen, the second sphere is the uveal tract, where one of the highest concentrations of melanin in the body is found, 40% more than in the skin; and at the same time abundant blood vessels; and the innermost sphere corresponds to the retinal tissue formed mainly by nervous tissue and scarce blood vessels compared to the uveal tract [Figure 3].

The aqueous humor flow in humans which is produced at ciliary body follows a circadian rhythm, being higher in the morning than at night, which means a closed sunlight interaction. There are three mechanisms described involving in aqueous humor formation: Diffusion, ultrafiltration, and active secretion. The

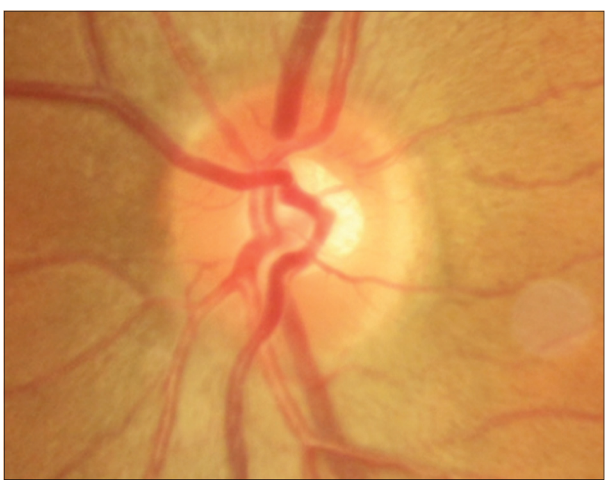

Figure 1: Left optic disc in a normal patient. The blood vessels that enter and leave are of normal characteristics, as well as the layer of axons that come from the ganglion cells of the retina.

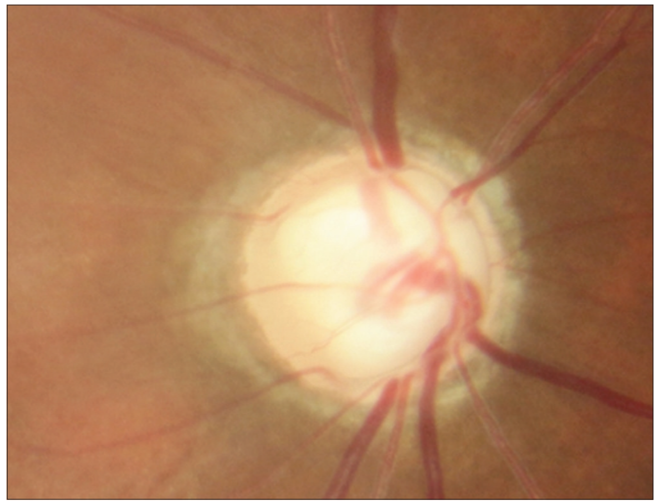

Figure 2: Typical appearance of the optic nerve of a patient with advanced glaucoma. It is characteristic of the progressive loss of the layer of axons and occurs with and without elevated intraocular pressure

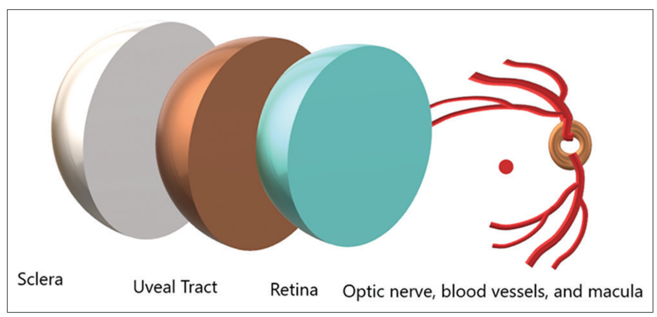

Figure 3: The drawing represents the posterior part of the eye. In the anterior segment of the eye, the spheres are repeated and retain their general histological characteristics, although they are modified enough to make their function significantly different, since in the posterior part of the eye, the image transformation into bioelectric energy is performed inside the retina and then and is transmitted to the occipital lobe and calcarine caesura of the brain, where the image is processed and appears in the consciousness. The optic nerve, retinal blood vessels, and macula are anatomic structures that are immersed within the blue hollow sphere that represents retinal tissue

aqueous humor leaves the eye by passive flow through two ways: The trabecular meshwork and the uveoscleral pathway. In humans, 75% of the resistance to aqueous humor outflow resistance is localized within the trabecular meshwork, and thereby, the uveoscleral pathway outflow is physiologically important but poorly understood. Figure 3 shows the structures involved in this posterior outflow pathway of aqueous humor.

It is remarkable the presence of melanin in all the structures involved in aqueous humor dynamic. At the posterior pole, it is in the uveal tract, and in the anterior segment, we have trabecular meshwork, iris, and ciliary body.

So far, to melanin was attributed to both the body and the eye, the relatively simple function of sunscreen. Inside the eye, it was thought to main function as an absorbent of the excess of light that penetrated to the eye, which allowed a higher optic quality of the images.

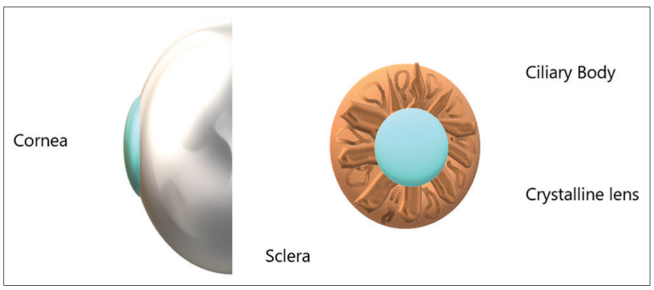

Figure 4: The anatomy of the anterior segment of the eye is also a pattern observed in mammals, fish, birds, and reptiles. However, it presents pigmented structures that provide support to the refractive elements, for example, to the crystalline, and is called ciliary body by the cilia that depart from it and go to the lens to hold it. However, the ciliary body is a dynamic tissue because its movement that is somewhat complex allows to modify the shape of the lens and therefore changes the focus closely and far, which is called accommodation. Another function of the ciliary body is the production of aqueous humor

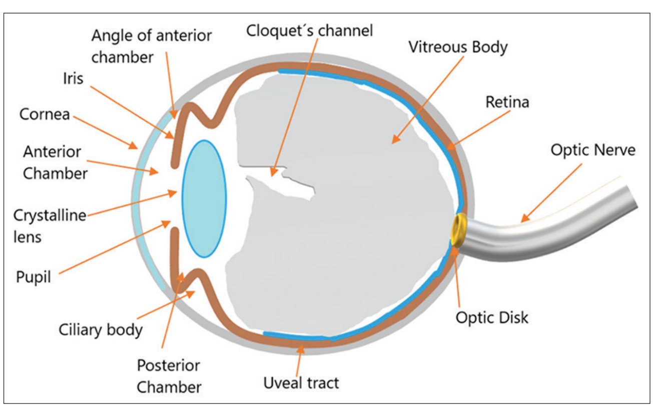

Figure 5: In this drawing, the main anatomical parts of the eyeball have been represented, emphasizing the structures related to the dynamics of aqueous humor

Aqueous Humor Secretion

The anterior part of the eye has contrasting functions, as it projects a clear image on the retina, which is formed through the natural lenses that are the cornea, the crystalline, and to a lesser extent the vitreous body. While performing the function of forming the image, the anterior segment of the eye also fulfills the function of giving structural and metabolic support to tissues whose transparency requires a substantive energy expenditure [Figure 4].

The three mechanisms described that are involved in aqueous humor formation such as diffusion, ultrafiltration, and active secretion are theoretical in their major part. The management of fluids in the body is surprisingly accurate processes, and they are repeated since the beginning of time. The processes of secretion and resorption of fluids in the eye is also very precise, something that is not possible to achieve with passive diffusion. Dynamic

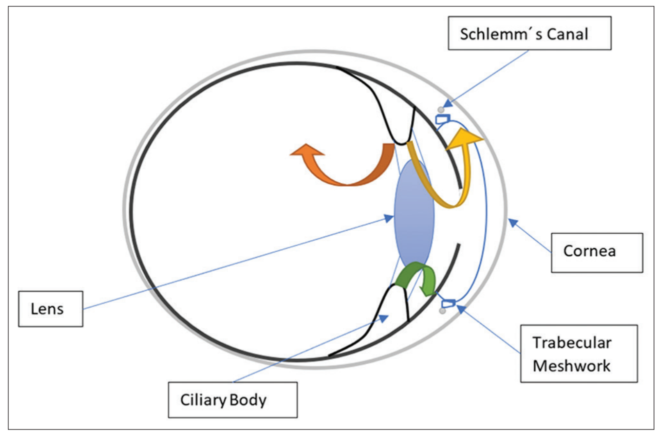

Figure 6: The diagram illustrates the main ways out of aqueous humor and related structures. It should be noted that they are theoretical

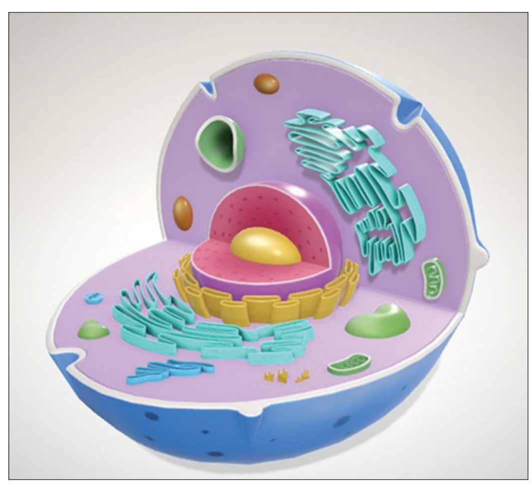

Figure 7: A usual scheme that demonstrates the main structures and organelles of the eukaryotic cell. The melanin granules are not even represented and would be located mainly in the perinuclear space

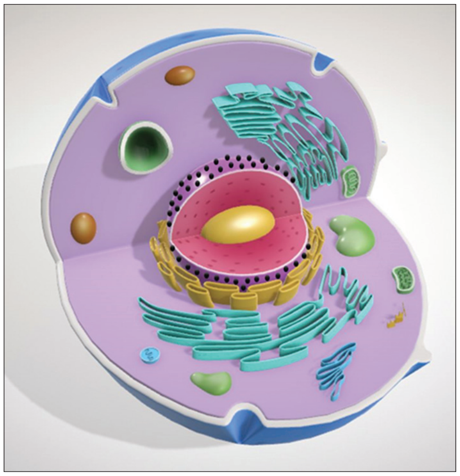

Figure 8: It is necessary to add the granules of melanin (melanosomes) for didactic purposes

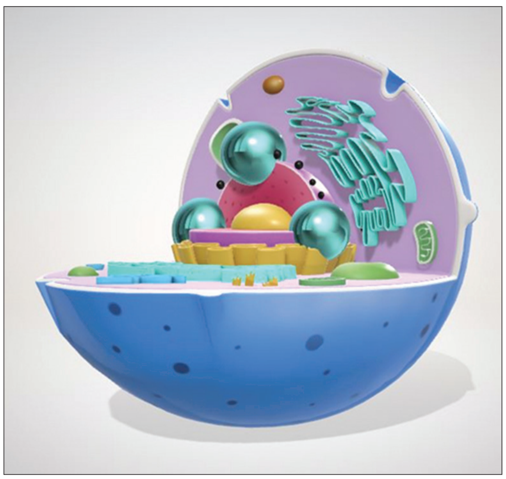

Figure 9: Schematic representation of how it would be the aspect of the growing spheres of energy that releases the granules of melanin and that follows the dictates of the simple diffusion, tending to occupy all the space that surrounds them

Figure 10: Photograph taken at childbirth. Note opacity both the corneas

Figure 11: Details of opacity of both the corneas, at childbirth

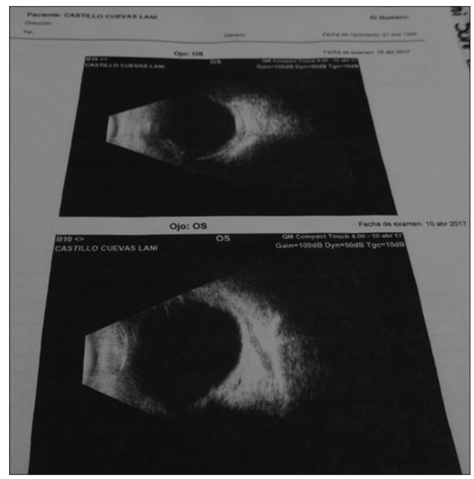

Figure 12: Ultrasonography taken on April 10, 2017, OS

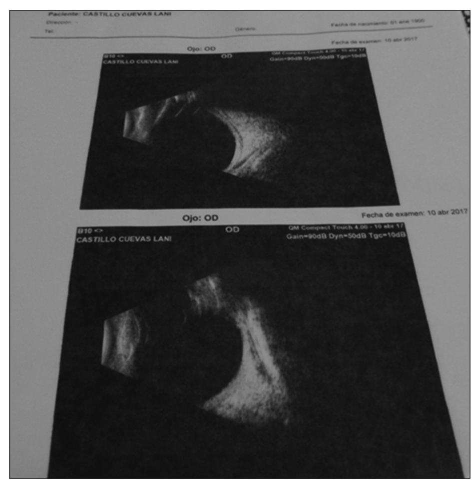

Figure 13: Ultrasonography of the right eye taken on April 10, 2017

of aqueous humor is highly accurate. Such a surprisingly accurate and constant composition cannot come from a passive runoff of the interstitial liquid from adjacent tissues or even from the capillaries in the area. Recall the aqueous humor provides nutrition, removes excretory products from metabolism, transports neurotransmitters, stabilizes the ocular structure, and

Figure 14: Appearance of the patient on January 15, 2018, during the first examination

Figure 15: Photography taken at first examination, January 15, 2018

Figure 16: Appearance of the cloudy corneas

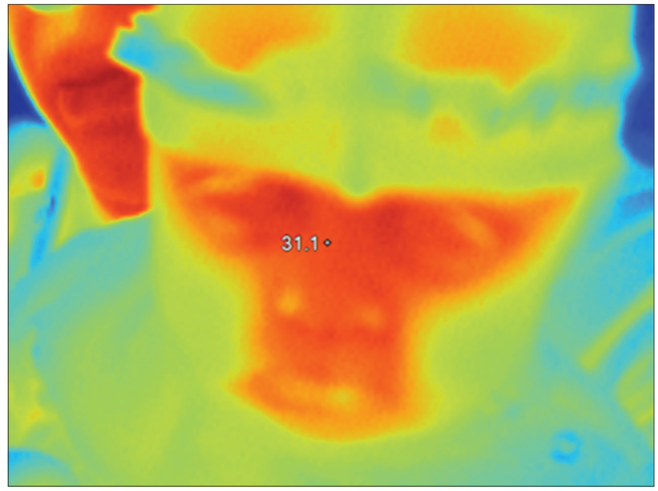

Figure 17: Thermographic image showed 31.1°C on January 10, 2018

Figure 18: The opacity diminished significantly, overall in the left eye

Figure 19: The facial expression is different, compatible with a better visual acuity

Figure 20: The nystagmus presenting during the initial examination has decreased notoriously, probably due to improved vision

Figure 21: No tearing, no photophobia. Ocular hyperemia has decreased considerably. The visual fixation is central

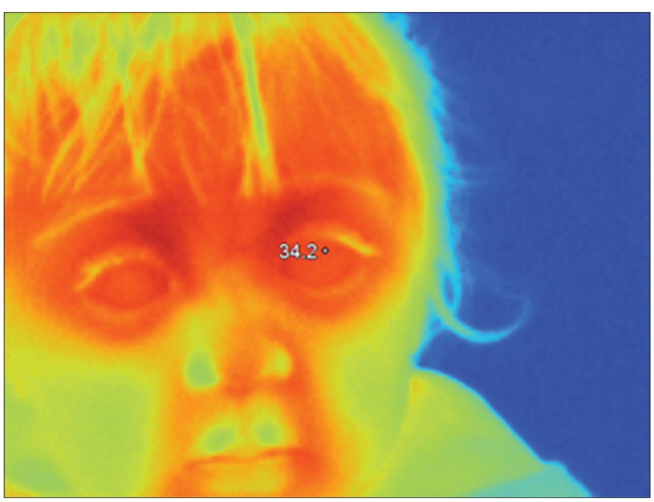

Figure 22: The thermographic image taken on June 2018 shows an increase of about 3°C. The thermal reading of the OI is shown in this image

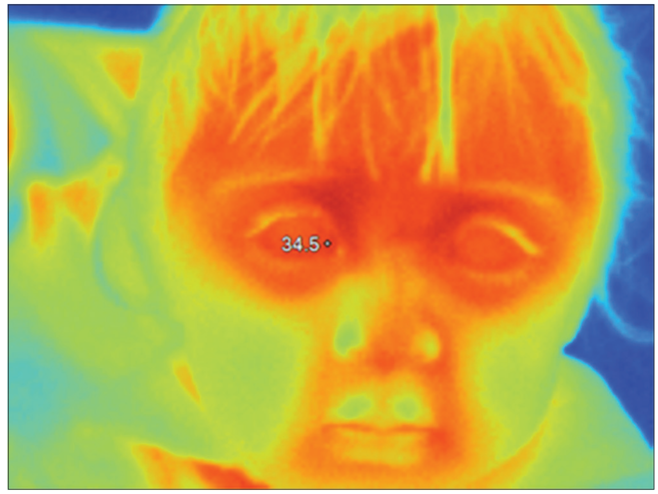

Figure 23: The thermographic image of OD also shows an increase in temperature, compared to the thermal image taken during the first consultation

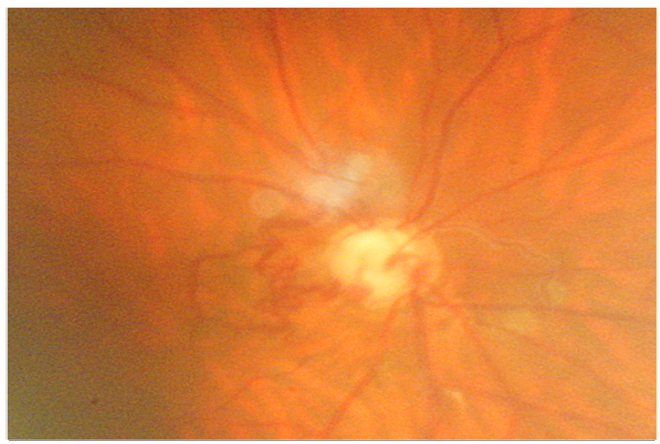

Figure 24: The fundus picture of right eye, shows an excavation of 95%, after several months of treatment with us

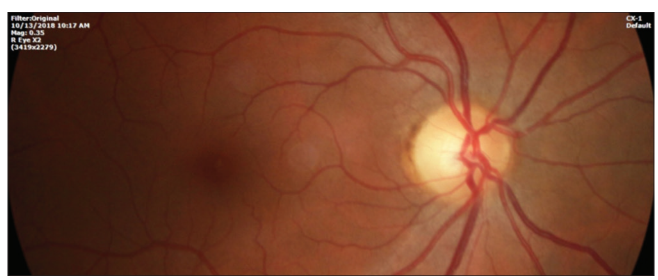

Figure 25: The anatomical characteristics of the retina in general have been preserved in our patient, in this photograph of a healthy patient, we can compare that the anatomy of the retina is maintained; The main difference would be the excavation of the optic nerve

contributes to the regulation of the homeostasis of transparent, opaque, and pigmented tissues of the area.[5]

Thereby, the functions of aqueous humor are complex, precise, surprisingly accurate, and it is not a static liquid but has a constant and precise circulation through which the total aqueous humor is renewed 4–7 times a day. Such a dynamic and accurate processes cannot come from chance.

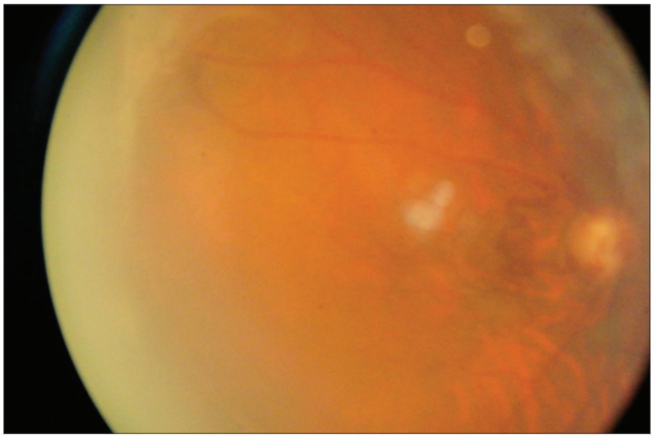

Figure 26: The photograph of the eye fund, RE, shows the excavation, but in general, the retina and choroid are appreciated in good condition. The vitreous is transparent

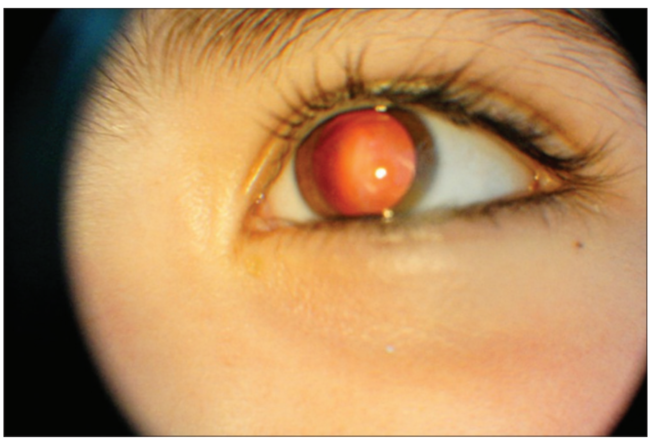

Figure 27: The image shows the left eye, after several months of treatment. We do not have the initial photographs because they did not cooperate to take them

Figure 28: Photo of the left eye fund, taken with much difficulty but we can appreciate an optic nerve of normal characteristics

Figure 29: The Clinical picture, taken at 27/07/2016, shows the absence of photophobia, tearing, nor hyperemic

Figure 30: This clinical picture, taken 1 year later, at September 29, 2017, shows the remarkable absence of symptoms

Figure 31: This clinical picture, taken 1 year later, in June 15, 2018, shows a good tolerance to light. The patient not has tearing, photophobia nor hyperemia

Ultrafiltration as a mechanism of aqueous humor secretion is entirely theoretical. It is so that Gibbs–Donnan equation cannot predict the composition of aqueous humor, and thereby, ultrafiltration can be discarded.

Active secretion of aqueous humor is a good option, however, requires remarkably energy expenditure, and so far, cannot be explained in the basis of glucose and adenosine triphosphate (ATP) as a source of energy.

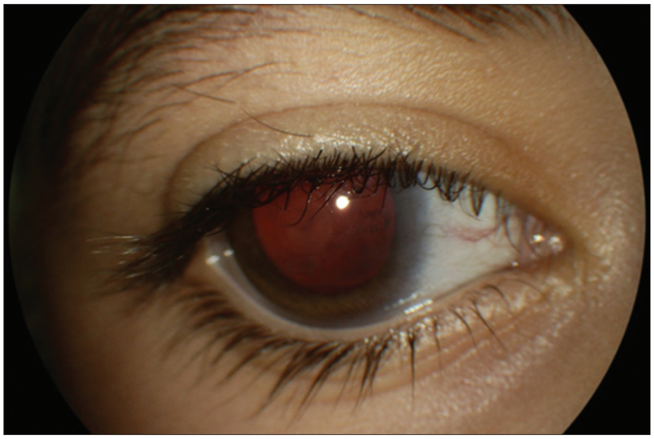

Figure 32: The anterior segment of the right eye, photographed at June 15, 2018, shows an improvement in the corneal transparency

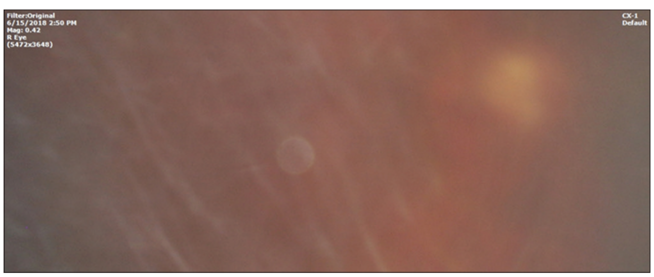

Figure 33: At greater magnification, the ocular fundus of the right eye shows an important excavation, the presence of the eyelashes prevents to see more detail

Aqueous Humor Outflow

The aqueous humor leaves the eye by passive flow (theoretic) through two pathways at the anterior chamber and posterior chambers of the eye. The conventional pathway consists of aqueous humor passing through the trabecular meshwork, across the inner wall of Schlemm's canal, into its lumen, and draining into collector channels, aqueous veins, and episcleral veins.[6] [Figure 5], but this is an ancient dogma that can be tracked back to the past century. It is hard to accept because cannot be explained the mechanisms by which the IOP drops from 15 mm Hg in the anterior chamber in average to less of 3 mm Hg in episcleral veins, and all the involved processes happen in a distance less of 2 or 3 mm.

The processes involved in the inlet and outlet of aqueous humor are very accurate, surprisingly accurate. Therefore, they cannot be passive because they would depend too much on coincidence. In the normal functioning of the body, chance plays a remarkable minimal role.

The so-called non-conventional route is composed (theoretically) of the uveal meshwork and anterior face of the ciliary muscle. Supposedly, the aqueous humor enters the connective tissue between the muscle bundles, through the suprachoroidal space, and out through sclera.[7] However, these deeply rooted concepts cannot be modified since the beginning of the past century. This "passive absorption" of aqueous humor by connective tissue between the muscle bundles of ciliary body cannot explain the astonishing balance between the production and drainage of aqueous humor.

Energy and Aqueous Humor Production and Composition

Energy can be defined as everything that produces a change. However, exact biochemical processes require an accurate amount of energy, and it is a premise which is fulfilled anywhere in the body even in the laboratory. For this reason, most of the biochemical reactions of the body have not been able to be replicated *in vitro*.

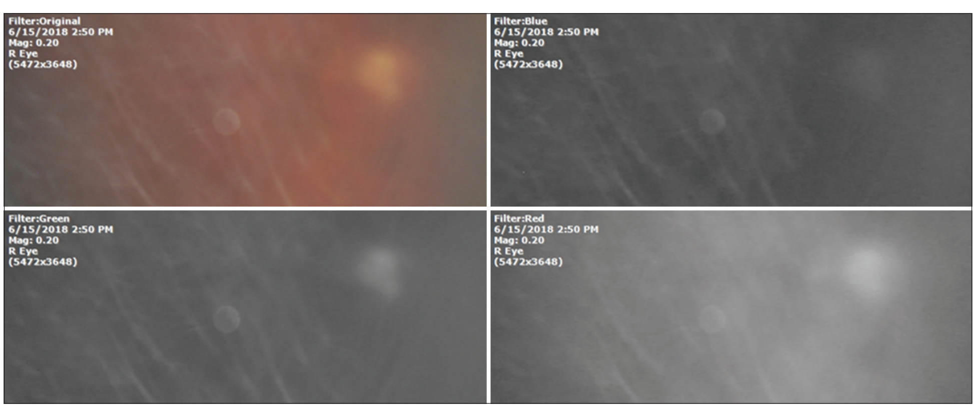

Figure 34: Using different filters to intensify the image, you can see some more details of the optical nerve excavation of the right eye

Three mechanisms are involved in aqueous humor formation: Diffusion, ultrafiltration, and active secretion.[8] Supposedly, the first two processes are passive and do not entail active cellular participation. However, laws of diffusion are quite simple, from the greater concentration to the less concentration.

Theoretically, in the eye, diffusion occurs when the solutes, especially lipid-soluble substances, are transported through the lipid portions of the membrane of the tissues between the capillaries and the posterior chamber, proportional to a concentration gradient across the membrane.[9] However, a gradient concentration across the cell membrane requires energy. Any gradient of concentration in eukaryotic cell or its surroundings occurs by chance.

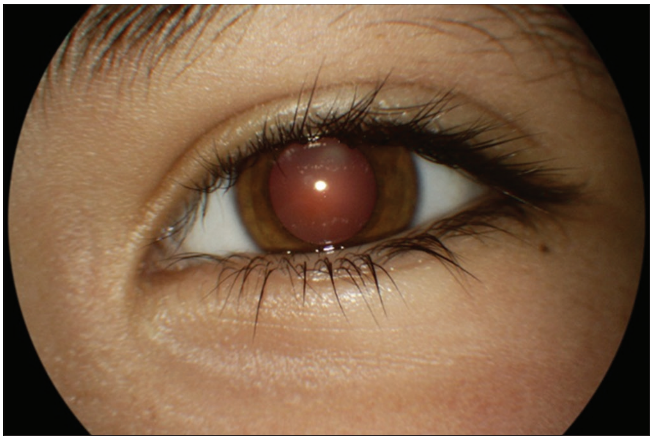

Figure 35: The picture shows the anterior segment of the left eye, which presents normal features. The photograph took on June 15, 2018

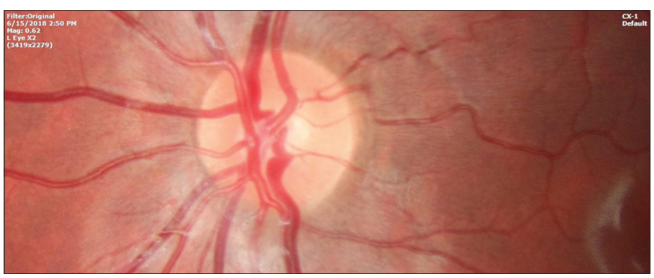

Figure 36: The characteristics of the left optic nerve are within normal limits. Photograph taken on June 15, 2018

Ultrafiltration is the flow of water and water-soluble substances, limited by size and charge, across fenestrated ciliary capillary endothelia into the ciliary stroma, in response to an osmotic gradient or hydrostatic pressure. There are substantial contradictions in this theory because ultrafiltration requires a accurate amount of energy which exert an exact thrust force that expels liquids against fenestrated ciliary capillary endothelia. In regards osmotic gradient or hydrostatic pressure, they are physicochemical processes that require energy also.

Active secretion is thought to be the major contributor to the aqueous formation, responsible for approximately 80%–90% of the total aqueous humor production.[10] Note the expression: you think, which reflects that it is a process that is not understood.

The main site for active transport is believed to be non-pigmented epithelial cells. Theoretically, active transport takes place through selective transcellular movement of anions, cations, and other molecules across a concentration gradient in blood-aqueous barrier. Aquaporins or molecular water channels have shown to contribute to aqueous humor secretion.[11] It can be said that the more selective a process is the more accurate the energy it requires.

Theoretically, the energy required for the transport is generated by hydrolysis of ATP to adenosine diphosphate, which is activated by Na^+ and K^+.[12] However, this relatively old theory has many contradictions. For example, if glucose and, therefore, ATP were a source of energy, then an average human being (70 kg weight) needs to ingest about 180 kg daily of food.[13]

Figure 37: Using different filters, it is corroborated that the structures of the left eye fund have no alteration compatible with pathology.

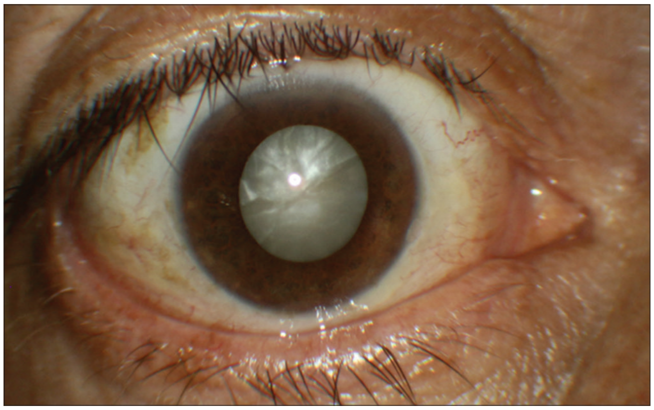

Figure 38: The metabolic processes involved in the transparency of ocular tissues such as the cornea, crystalline, and vitreous body are not well-understood to date. There are many questions about that. Therefore, it is common for the opacity of the transparent media of the eye to be added frequently to other pathologies of both the eye and the body

On the other hand, the flow of energy is very complicated if we start from glucose, as many transformations and numerous enzymes are described, and must keep in mind that every transformation and every enzyme require energy. And to top it off, the way ATP liberates energy from hydrolysis is not known, and there is not even a consensus about it, there are theories and more theories only.

It is interesting that the hydrolysis of ATP requires the presence of Na^+ and K^+, but it would be explained because, in solution, gases move faster than ions. In this case, we talk about the hydrogen that is released by melanin by dissociating the water.

This means that the energy released from melanin is carried on by the molecular hydrogen that moves fastest, causing physical chemical changes in the medium that is reflected in several ways, i.e.,: Ions movement.

The enzyme Na^+ K^+ ATPase can be inhibited by several molecules, including cardiac glycosides, dinitrophenol,[14] vanadate,[15] and possibly acetazolamide.[16] The ASA suffix means that the enzyme does not use ATP as a source of energy to carry out its function and is an enigma that dates back several decades since no one has been able to define the energy it uses. Now, we can think that the energy that emanates from melanin in the form of molecular hydrogen and high energy electrons could be the answer.

Aqueous Humor Outflow

The aqueous humor theoretically exits the eye through both conventional and unconventional pathways. The movement of fluids in the conventional pathway takes place from a pressure gradient from trabecular meshwork into Schlemm's canal [Figure 5] and through the inner wall of Schlemm's canal; but theoretically it is a passive pressure-dependent transcellular mechanism, frequently associated with paracellular routes, such as giant vacuoles and pores acting as one-way valves.[17] It is the main passageway for particulate materials, such as cells, ferritin, and microsphere.[18] The inner wall of Schlemm's canal is a complex tissue poorly understood, and there is still doubt if it influences outflow facility in normal or glaucomatous eyes.[19]

Uveoscleral flow pathway derives mostly from animal experiments and mathematical calculations. This theoretical model has been utilized for many years and views the aqueous outflow as a passive fluid movement down a pressure gradient.[20]

The processes that control aqueous humor dynamics are not linear but are part of a highly complex interactive network, in which an alteration in any component requires a contemporaneous adjustment of numerous other components in an interactive fashion resulting in long-term homeostasis.[21]

THE ROLE OF MELANIN IN THE FORMATION, COMPOSITION, AND OUTFLOW OF AQUEOUS HUMOR

The unsuspected intrinsic property of melanin to transform light into chemical energy by dissociating the water molecule, such as chlorophyll in plants, opens a new chapter in the study and treatment of ophthalmological diseases.[22]

It is not by chance the presence of melanin in important amounts in tissues with a high metabolic rate as choroid and ciliary body, or in adjacent tissues, as is the case of the retina. Its unsuspected bioenergetic role takes an unusual relevance given that current biology, based on glucose as a source of biomass and energy at the same time, it has fallen into numerous contradictions, besides it is being too complex and based on theoretical concepts in about 95%.

The concept that the human body can take energy directly from light implies the creation of a new molecular biology that splits from the fact that the source of energy of the cell is the molecular hydrogen and high-energy electrons coming from the dissociation and reforming of the water molecule by melanin.

The role of melanin as a simple solar filter, it is so deeply rooted in textbooks and researchers and teachers, that it is not even depicted in the usual Eukaryote cell schemas [Figure 6].

The diagrams that are used in cell biology rarely or perhaps never represent the melanosomes that are the granules of melanin wrapped in a double lipid membrane and that are strategically located in the perinuclear space, forming a design that surrounds the cell nucleus in its entirety. The fact that the largest organelle of the cell is covered by a structure like a melanosomes wrapper explains the energy source of this organelle because, as we know, the cell nucleus contains neither mitochondria nor ATP, and their energy needs are substantial. In Figure 7, we draw the melanin granules in their main location: The perinuclear space.

Melanin releases in symmetrical form, in all directions, by the way of increasing spheres of energy that is transported by molecular hydrogen [Figures 8 and 9]. Being the smallest element, it easily permeates by any through it cell structure with ease. As it is not combined with water, molecular hydrogen moves through the water contained in the cellular cytoplasm, following the laws of simple diffusion. During its transit, it is captured by the different chemical reactions and organelles.

The fact that melanin transforms liquid water into its gaseous components (hydrogen and oxygen) in a way so constant and exact, as it has done since and beginning of time, opens an interesting possibility in relation to the physiology of aqueous humor, because in the same places where aqueous humor is produced, it can be reabsorbed, depending on the symmetry of the reaction that depends on the amount of light, temperature, pressure, moisture, etc., like any other chemical reaction.

Thereby, the aqueous humor outflow pathways already described are secondary. Perhaps, the main secondary pathway is the conventional pathway because handle formed elements. The unsuspected intrinsic property of melanin to dissociate the water molecule, as chlorophyll in plants, explains the hypotensive effects of eicosanoids, compounds of 20 carbons; and the proof is the increase in the skin pigmentation and enlargement of lashes.

Thereby, the enhancement of the water dissociation is a new therapeutic target in ophthalmology and cases of congenital glaucoma which we described below prove it.

PRIMARY CONGENITAL GLAUCOMA

Case 1

Female, born on April 4, 2017, borns after complicated pregnancy. The first examination date was January 15, 2018. photo-type V in the Fitzpatrick´s classification.

She was diagnosed with bilateral congenital glaucoma. When she came to consultation, used pilocarpine, dorzolamide, timolol, and latanoprost. Baby has three previous surgeries: OI has a trabeculectomy, OD cyclocryotherapy, and a trabeculoplasty [Figures 10-17].

After informed consent, treatment with QIAPI 1®, an enhancer of water dissociation in human body developed by our team, was started by sublingual way, at a dose of three drops for every 2 h during daytime.

The next photographs were taken 6 months later, in June 25, 2018 [Figures 18-23].

The improvement has been remarkable, and IOP is within normal limits, in accordance with her ophthalmologist. Family members refer that physical and mental performance has also improved, as it does not fall and move safely.

Case 2

Male, born in October 8, 2009, was presented. The date of first examination was May 7, 2014. He was diagnosed with congenital glaucoma, especially in the right eye. At the onset, there were photophobia, tearing, and hyperemia. Their doctors told his family that he did not see anything in the right eye the past week, before consultation at our clinic [Figures 24-29]. He was under treatment at the time of first consultation with carboxymethyl cellulose, Timolol maleate, atropine and eicosianoids; all in ophthalmic drops.

Evolution has been very satisfactory, as the integrity of the eyeballs has been retained, without the need for surgical interventions. The administration of QIAPI 1® has allowed a good evolution. The other drugs were suspended from the beginning [Figures 30-37].

CONCLUSION

Treatment of congenital glaucoma had so far been a formidable challenge, as it often required complicated surgeries, with little likelihood of success. Intensive treatment with antihypertensive medications is of limited utility in cases such as these.

However, the therapeutic approach based on the single elevated intraocular pressure is happening to the second term since it is now possible to conceive the congenital glaucoma as an alteration in the generation and distribution of energy that comes from melanin.

That is why glaucoma is associated with other pathologies, because in any system, when the problem is energy, the fault is widespread. Therefore, it is common for glaucoma to be associated with cataracts [Figure 38] because the transparency of tissues such as cornea, crystalline, and vitreous body implies a significant energy expenditure because transparency is not given by chance.

The separation of metabolism in regards to energy (melanin) and mass (glucose), starting from the unsuspected intrinsic ability of melanin to dissociate the molecule from water, such as chlorophyll in plants; it marks the beginning of a new era in biology as in ophthalmology, allowing the development of new treatments in complicated problems such as congenital glaucoma, which will allow the quality of life of the sick to improve.

ACKNOWLEDGMENT

This work was financed by the Human Photosynthesis(TM) Research Centre.

REFERENCES

1. Ho LC, Conner IP, Do CW, Kim SG, Wu EX, Wollstein G, *et al*. *In vivo* assessment of aqueous humor dynamics upon chronic ocular hypertension and hypotensive drug treatment using gadolinium-enhanced MRI. Invest Ophthalmol Vis Sci 2014;55:3747-57.
2. Kingman S. Glaucoma is second leading cause of blindness globally. Bull World Health Organ 2004;82:887-8.
3. Chumbley LC, Brubaker RF. Low-tension glaucoma. Am J Ophthalmol 1976;81:761-7.
4. Shiose Y. Low-tension glaucoma-prevalence and background factors. In: Gramer E, Kampik A, editors. Pharmakotherapie Am Auge. Berlin, Heidelberg: Springer; 1992.
5. Sires B. Orbital and ocular anatomy. In: Wright Ed, editor. Textbook of Ophthalmology. Baltimore, MD: Williams and Wilkins; 1997.
6. Goldmann H. Minute volume of the aqueous in the anterior chamber of the human eye in normal state and in primary glaucoma. Ophthalmologica 1950;120:19-21.
7. Johnson M, Erickson K. Mechanisms and routes of aqueous humor drainage. In: Albert DM, Jakobiec FA, editors. Principles and Practice of Ophthalmology. Philadelphia, PA: WB Saunders; 2000.
8. Millar C, Kaufman PL. Aqueous humor: Secretion and dynamics. In: Tasman W, Jaeger EA, editors. Duane's Foundations of Clinical Ophthalmology. Philadelphia, PA: Lippincott-Raven; 1995.
9. Civan MM, Macknight AD. The ins and outs of aqueous humour secretion. Exp Eye Res 2004;78:625-31.
10. Mark HH. Aqueous humor dynamics in historical perspective. Surv Ophthalmol 2009;55:89-100.
11. Yamaguchi Y, Watanabe T, Hirakata A, Hida T. Localization and ontogeny of aquaporin-1 and -4 expressions in iris and ciliary epithelial cells in rats. Cell Tissue Res 2006;325:101-9.
12. Cousins SW, McCabe MM, Danielpour D, Streilein JW. Identification of transforming growth factor-beta as an immunosuppressive factor in aqueous humor. Invest Ophthalmol Vis Sci 1991;32:2201-11.
13. Bergman J. ATP: The perfect energy currency for the cell. Creation Res Soc Q 1999;36:1-11.
14. Cole DF. Ocular fluids. In: Davson H, editor. The Eye-Vegetative Physiology and Biochemistry. Orlando: Academic Press; 1984.
15. Becker B. Vanadate and aqueous humor dynamics. Proctor lecture. Invest Ophthalmol Vis Sci 1980;19:1156-65.
16. Maren TH. The rates of movement of Na+, Cl-, and HCO-3 from plasma to posterior chamber: Effect of acetazolamide and relation to the treatment of glaucoma. Invest Ophthalmol 1976;15:356-64.
17. Bill A, Svedbergh B. Scanning electron microscopic studies of the trabecular meshwork and the canal of Schlemm--an attempt to localize the main resistance to outflow of aqueous humor in man. Acta Ophthalmol (Copenh) 1972;50:295-320.
18. Epstein DL, Rohen JW. Morphology of the trabecular meshwork and inner-wall endothelium after cationized ferritin perfusion in the monkey eye. Invest Ophthalmol Vis Sci 1991;32:160-71.
19. Ethier CR. The inner wall of Schlemm's canal. Exp Eye Res 2002;74:161-72.
20. Kupfer C, Ross K. Studies of aqueous humor dynamics in man. I. Measurements in young normal subjects. Invest Ophthalmol 1971;10:518-22.
21. Ingber DE. Mechanical signaling and the cellular response to extracellular matrix in angiogenesis and cardiovascular physiology. Circ Res 2002;91:877-87.
22. Solis-Herrea A. Towards a new ophtalmic biology and physiology: The unsuspected intrinsic property of melanin to dissociate the water molecule. MOJ Cell Sci Rep 2017;4:00084.

How to cite this article: Herrera AS. Implications of the Unexpected Bioenergetic Role of Melanin in the Physiopathology of CongenitalGlaucoma. Clin Res Ophthalmol 2018;1(2):1-11