The Relationship between Low Tension Glaucoma, CSF, the Size of the Ventricles, and Neurodegenerative Diseases

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Received: July 15, 2020; Published: July 28, 2020

Abstract

Glaucoma (POAG) is a group of neurodegenerative eye diseases that leads to damage of the optic nerve, being a leading cause of irreversible blindness in the world, almost 80 million in 2020. By other hand, Alzheimer’s disease (AD) is the most common cause of dementia, it is also a neurodegenerative disease and is characterized by specific changes in the brain. Worldwide, 46.8 million people are believed to be living with Alzheimer’s disease or other dementias. Every 3.2 seconds, a new case of dementia occurs somewhere in the world.

Both diseases affect older populations and involve selective loss of certain types of neurons. They are both neurodegenerative, chronic, and progressive diseases that are age-related and cause irreversible neuronal cell loss. There were several populations of AD patients that were examined for the prevalence of glaucoma and it was found that there was almost a two- to three-fold increase in glaucoma diagnosis in these patients. Low tension Glaucoma patients were four times more likely to develop dementia.

Recent data indicated that patients with primary open-angle glaucoma (POAG) have low cerebrospinal fluid (CSF) opening pressure on lumbar puncture compared with a group without glaucoma. Furthermore, lower CSF opening pressure was correlated with a larger cup-to-disc ratio.

Both the CNS and the eyeball share common morphological characteristics, such as melanin, and circulating water. And the mysteries about how CSF and the aqueous humor are produced, how the amount and composition of them is strictly controlled, and how they are absorbed, are questions that have not been answered.

Finally, the melanin of the eyeball was, so far; considered as a simple sunscreen that absorbed excess light that penetrated the eye, allowing better image quality. And in the case of CNS, the neuromelanin of substantia nigra and locus coeruleus was thought to be something of a deposit of the neuron metabolism wastes.

Our discovery of the surprising intrinsic property of melanin to transform visible and invisible light into chemical energy, through the dissociation of water molecule, starts a new era in biology and medicine, as it allows to address in a different and coherent way the study and treatment of various diseases of the CNS.

Keywords: CSF; Ventricles; AD; NOG; Energy; Melanin

Introduction

The optic nerve is composed predominantly of retinal ganglion cells whose cell bodies are located on the retinal surface and whose synaptic terminals are located some 50 mm downstream in the lateral geniculate nucleus of Thalamus. It has been described axoplasmic
flows with different speeds and directions (slow, fast, orthograde, retrograde), supposedly slow flow is needed to transport heavy molecules, e.g. neurotrophins and the fast flow is reserved for small molecules such as adenosine triphosphate (ATP) [1]. Axonal transport decreases in the presence of elevated intraocular pressure [2]. The reduced retrograde axoplasmic flow can stress retinal ganglion cells and cause their death from deprivation of neurotrophic factors such as brain-derived neurotrophic factor [3]. Glial cells in the optic-nerve head (microglia and astrocytes) become activated in response to the elevated intraocular pressure in glaucoma [4]. This activation of glial cells may be the explanation of the pseudo fluorescence observed with the red filter in glaucomatous patients (Figure 1).

**Figure 1:** The photographs are of a patient diagnosed with POAG. In the upper left, illuminated with polychromatic light (white), deep excavation is seen and covering about 60% of the papilla. On the edge of the optical disc, in the meridian from 3 to 6, melanin is observed. Pseudo-fluorescence is detected with the red filter (lower right).

Activated astrocytes synthesize molecules (pseudo-fluorescence) that lead to degradation and remodeling of the extracellular matrix, and these changes can have biomechanical effects on the optic-nerve head that in turn increase stress on retinal ganglion-cell axons [5]. Evidence suggests that glial activation and TNF-α are important mediators of damage to retinal ganglion-cell axons [6]. But the concept of glial activation does not consider the energy required by the glia to behave normally. It is feasible that when the energy that comes from melanin in the form of molecular hydrogen (H₂) and high-energy electrons (e⁻) is not the adequate, the exact one, as it has been since the beginning of time, the mechanisms that we could call glia regulators cannot carry out their normal work, and the glia behaves in an aberrant way.

Three-dimensional histomorphometry studies of primates with experimentally induced glaucoma raised the possibility that one of the early changes in the structure of the optic-nerve head in glaucoma is the thickening - rather than thinning - of prelaminar tissue [7] by apposition of fibrous tissue. This change is accompanied by microglial proliferation [8]. Subsequently, the lamina cribrosa bows posteriorly (Figure 2-4).

The biomechanics of the posterior sclera and lamina cribosa are tightly coupled [9]. The small collagen fibers that make up lamina cribiformis are continued with the collagen fibers of the sclera. The scleral stiffness and scleral collagen fiber organization are determinant factors in the posterior bowing of lamina cribiform, however, their study is particularly difficult so you have to resort to mathematical models, which do not reliably reproduce the continuous random variables characteristic of biological phenomena [10].

Figure 2: In principle, the excavation of the optic disc could resemble the saucer appearance of the coffee dish.

Figure 3: In other patients, the optical disc is observed as when a tablespoon is taken from the center of a gelatin.

These changes in the lamina cribrosa (Figure 5), combined with the eventual loss of prelaminar tissue, make the cup larger and deeper. The biomechanical consequences of these changes are believed to strain retinal ganglion-cell axons, which further compromises their function [11]. There is a loss of gap-junction communication that accompanies astrocyte activation [12]. Clinical observations have indicated that the optic nerve head, and more specifically the lamina cribrosa, is the initial site of glaucomatous damage [13]. However, this

conclusion is skewed by the ease with which sclera’s lamina cribiformis is observed in the living patient, compared to the difficulty of observing other deeper anatomical components of the visual pathway.

Citation: Arturo Solís Herrera., et al. "The Relationship between Low Tension Glaucoma, CSF, the Size of the Ventricles, and Neurodegenerative Diseases". EC Neurology 12.8 (2020): 183-222.
In animal models, and presumably also in human glaucoma, damage to retinal ganglion-cell axons precedes the death of the cells [14], but the site of damage is uncertain because can be of intraocular, intra-orbital, or even of intra-cranial origin. Retinal ganglion cells survive for only about 1 to 2 months after axonal degeneration [15]. Thus, the degradation of the retinal ganglion-cell axon and soma may involve separate mechanisms [16]. In DBA/2 mice, damage to retinal ganglion-cell axons occurs despite the absence of the collagenous lamina cribrosa plates typically found in primates [17], which suggest that lamina cribiformis (Figure 6) cupping role in axons disappearing could be secondary.

Figure 6: Lamina Cribiformis, scanning electron microscopy. The fibers that make up the pial septum are initiated in the lamina cribiformis and inserted into the periphery to the sclera. This delicate tissue that envelops and protects the axons of the optic nerve from the intense movement of the normal eyeball (thousands of times a day) extends from the lamina cribiformis to the anterior third of the optic chiasma, where they gradually disappear. To preserve their shape and function, they require an adequate power supply. When the balance between mass and energy is not suitable, the fibers that make up the pial septum tend to proliferate and soon after to retract; eventually giving rise to a glaucomatous-like excavation. At the head of the optic nerve, the divisions that come from the tissue of the pial septum are smaller, and in the post-region, close to the optic quiasm, the divisions of the pial septum are larger. Image retrieved from: https://www.atlasophthalmology.net/photo.jsf?node=5438&locale=en May 04 2020.

The loss of retinal ganglion cells in the glaucomatous retina occurs through apoptosis [18]. Coupled with thinning and further posterior bowing of the lamina cribrosa, apoptotic loss of the retinal ganglion cells results in a large, deep cup, as seen clinically in advanced glaucoma. The thinning and further posterior bowing of the lamina cribiformis suggests that energy is necessary even to keep its shape (Figure 7).

Glia cells phagocytose cellular debris and initiate a scar response after retinal ganglion-cell death. Inflammation-like glial activity is frequently observed in degenerative disorders of the central nervous system and is referred to as neuroinflammation.

In glaucoma, a major cause of blindness, the ganglion-cell axons that make up the optic nerve are damaged by a variety of factors, only some of which, at best; are poorly understood (Figure 8). The optic-nerve damage in glaucoma, so far; is not yet amenable to direct treatment, physicians provide treatment for the only known risk factor that can be modified, elevated intraocular pressure, but with poor outcome. The proof is that Glaucoma, after 60 years or more, still is the first cause of blindness in sunny countries and third in cold countries.

Vision loss in glaucoma is preceded by disfunction and death of retinal ganglion cells (RGCs). The molecular pathways that finally lead to disappearance of RGCs are not understood, thereby is unclear how or where the RGCs are insulted direct or indirectly. Supposedly, the initial insult to the axons of RGCs is in the lamina cribiformis, where they exit the eye. The lamina cribosa or cribiformis is comprised of perforated sheets or plates of extracellular matrix (ECM, largely collagen) that provide support for the axons as they pass through the posterior wall of the eye [19], protecting the axon bundles from mechanical stress, due to intense movement of the intra-orbital part of the optic nerve that follows the movement of the eyeball. Thereby, this lamina cribiformis starts at the optic nerve, but it is prolonged along all the optic nerve, including intracanalicular portion, and finally disappear gradually in the anterior third of the optic quiasm. One of the dif-

Figure 7: The collagen of any tissue tends to proliferate and retract when there is an imbalance between mass and energy. The pial septum (BLUE) that covers the axons of the optic nerve (Orange), are the right size to protect and promote the function of them. (TOP). When there is an imbalance between mass and energy, the collagen tends to retract itself, which conditions irregular changes in the delicate anatomy of the pial septum (BLUE), causing irregular distortions of progressive nature in the structure and function of the axons (Orange) (bottom).
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Figure 8: Characteristically, the imbalance between mass and energy induces proliferation of fibrous tissue, this is collagen synthesis. Yellow arrows represent the irregular forces that affect the delicate tissue of the optic nerve as a result of the thickening of the fibers that originate in the septum pial that surrounds the optic nerve and gives rise to extensions that penetrate into it, organizing the delicate nerve fibers in bundles, allowing a significantly minor deterioration by the abrupt jolts of the optic nerve induced by the intense daily movement of the eyeballs. The posterior bulging of the lamina cribiformis, that is manifested by an increase in cup-disc ratio; is not a phenomenon located only at the head of the optic nerve but is a trend that extends throughout it.

Differences between the lamina cribiformis at optic nerve and the intracranial part of the optic nerve is that the space between the different pial septum are progressively greater (Figure 9). Alteration of glial support is important factor for neuronal compromise [20] (Figure 10).

The balance between mass and energy of the human body is astonishingly accurate and constant at all levels. When this balance strictly regulated by millions of years of evolution is altered by factors such as contaminated water, shocking air, pesticides, herbicides, fertilizers, solvents, industrial waste, alcohol, addictive drug abuse, emotional stresses, etc. the tissues of the organism begin to disorganize and what we call diseases begin to appear, which do not actually exist as such, because everything comes down to an imbalance between mass and energy.

And glaucoma is no exception. One of the most common tissue alterations when there is imbalance between mass and energy is the proliferation of collagen fibers and their consequent retraction, which explains the posterior bulging or bowing of the lamina cribiformis. Increasing intraocular pressure is not what determines the shape of glaucomatous excavation. The explanation is that the collagen fibers of the cribiformis sheet are continued on the periphery with the collagen fibers of the sclera, and posteriorly, the collagen fibers of the cribiformis sheet form a continuum with the collagen fibers that make up the septum pial, which extends into its anterior portion from the cribiformis sheet of the sclera and then ends, posteriorly; in the anterior third of the optic quiasm where they gradually disappear (Figure 9).

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Figure 9: Mouse optic nerve section stained with anti-GFAP with hematoxylin counter stains (Astrocyte bodies and processes brown, nuclei purple blue). In contrast to the lamina cribrosa of the human optic nerve, the mouse astrocytes do not cover a network of robust collagenous plates [21]. There is some resemblance with the imagen of figure 6.

Figure 10: Normal optic nerve. Cross- section showing collagen strands dividing nerve into fascicles (Masson’s trichrome) [23].

It has been demonstrated significant alterations in the architecture of the laminar and peripapillary scleral connective tissues at the earliest stage of experimental glaucoma (EG) in the monkey eye. In the lamina cribrosa of EG monkey eyes, permanent deformation, and thickening, accompanied by increases in both total connective tissue volume and total number of laminar beams, were observed [22].

It is well established that the first site of neuronal damage may be remote from the site of insult [24]. For example, in transected motor axons, neuromuscular junctions that are many centimeters from the lesion, degenerate first. The axons immediately adjacent to the lesion remain intact for two or three times longer than the distant terminals [25]. Thus, locating the first degenerative changes that finally affect the optic nerve, is not the same as demonstrating that the optic nerve is the solely site of insult in glaucoma, given that an imbalance between mass and energy, could produce a progressive contracture of collagen fibers, in all the body.

In experimental models, it has been found that RGCs degenerate in specific fan-shaped sectors of the retina [26], which is consistent with the injury of specific axon bundles in the optic nerve. The fan-shaped regions of cell loss in mouse are thought to be equivalent to the arcuate scotomas of human glaucoma. Arcuate scotomas resemble fans with a sideways bend and are also suggested to result from an axon injury [27], for example an area along the optic nerve by the anatomical deformation caused by the irregular contracture of the collagen of the pial septum due to the imbalance between mass and energy (Figure 11-13).

**Figure 11:** The blue tubes outline the collagen and glia (Pial Septum) that cover the axons by organizing them into fascicles, which gives it mechanical protection against the intense movement of the optic nerve in its laminar, orbital and intracanal portions.

In glaucoma, it is thought that elevated intraocular pressure (IOP) blocks traffic within the lamina itself, while also causing this connective tissue strut to bow posteriorly. This phenomenon is referred to as optic-nerve cupping. Its cause is the loss of retinal ganglion cell axons, along with supporting glia and vasculature. However, glaucoma-like optic disc-cupping frequently occurs without an elevation of intraocular pressure.

Figure 12: The orange cylinder represents the bundle of axons that are covered by the pial septum, organizing the neuronal tissue into fascicles.

Figure 13: The white ring represents the distortion caused by the retraction of the collagen fibers of the pial septum, and which constitute its main component. In the presence of hypoxia, collagen tends to proliferate and finally to retract, causing irregular constriction, affecting some fascicles more than others, which would explain the fan-shaped alterations. Note: Hypoxia is caused usually by an imbalance between mass and energy.
There is enough evidence that dark skin, older age, elevated intraocular pressure, family history of primary open-angle glaucoma, myopia, and low diastolic perfusion pressure are risk factors for primary open-angle glaucoma [28]. Evidence for other risk factors (diabetes mellitus, elevated systolic blood pressure, and migraine, among others) is less consistent [29].

Elevated intraocular pressure is not part of the clinical definition because primary open-angle glaucoma can occur even when intraocular pressure is normal (typically 10 to 21 mm Hg), currently, it is the only supposedly modifiable causative factor. Thereby, all available current treatments of primary open-angle glaucoma are aimed at reducing intraocular pressure by medical or surgical means, although only about a third of cases are in high intraocular pressure.

The meninges

The meninges arise from neural crest cells and mesenchyme that migrate to surround the developing neural tube. This forms the dura mater, also called the pachymeninx, made up of periosteal, meningeal, and Dural border cell layers. The arachnoid barrier cell layer and the pia on the surface of the central nervous system are the leptomeninges and the naturally occurring space between pia and arachnoid is the subarachnoid space (SAS); the enlarged portions of the SAS are the cisterns.

The pia mater consists of flattened cells with long, equally flattened processes that closely follow all the surface features of the brain and spinal cord [30]. The pia mater is the innermost layer of the meninges. Pial cells form a continuous layer joined by desmosomes and gap junctions, making this layer impermeable to the cerebrospinal fluid. Subpial tissue separates the pial cellular layer from neuroglial cells and contains mainly collagen fibers, a few elastic fibers, amorphous intracellular substances, small vessels, fibroblasts, and macrophages [31].

The pia is separated from the brain surface by a glial basement membrane and by occasional places where pial cells pull away from the brain to form a small subpial space. Pial cells at the brain surface may be arranged in a single layer or in several layers. Single pial cell processes and their subjacent collagen correspond to the pia intima; these closely follow surface features of the brain and spinal cord.

Where small vessels penetrate the surface of the brain and spinal cord, they pull along a small envelope of pial cell processes and extracellular space. These perivascular spaces (Virchow-Robin spaces) extend for varying distances into the parenchyma of the nervous system and may serve as conduits for the movement of extracellular fluid between the subarachnoid space and the minute spaces around neurons and glial cells.

The cerebral cortex lies beneath the pia mater and covers the surface of most of the brain. It contains many folds, or gyri. The cerebral cortex consists of two parts: the neocortex and the limbic cortex. The neocortex covers most of the surface of the cerebrum. The limbic cortex covers the cingulate gyrus, the fold of the cerebrum immediately adjacent to the longitudinal fissure above the corpus callosum [32].

Connective tissue

Connective tissue provides structure and support and is a "space filler" for areas not occupied by other tissue. Connective tissue consists of cells, fibers, and ground substance. The ground substance consisting of glycoproteins and water, and the insoluble protein fibers collectively are called matrix. Connective tissue can be classified as loose or dense. Loose connective tissue has relatively fewer cells and fibers per area than dense connective tissue, in which the cells and fibers are tightly packed. Dense connective tissue can be characterized as regular or irregular based on fiber arrangement [33].

Among the cells that may be found in connective tissue are fibroblasts (flattened cells that produce and maintain the fibers and ground substance), macrophages (phagocytic cells), mast cells (which contain heparin and histamine), glial cells in the case of CNS; and fat cells. Connective tissue composed primarily of fat cells is called adipose tissue.
The fibers found in connective tissue include flexible collagen fibers with high tensile strength, delicate reticular fibers, and elastic fibers, which can undergo extensive stretching. Collagen fibers are a major component of much of the eye’s connective tissue. These fibers are composed of protein macromolecules of tropocollagen that have a coiled helix of three polypeptide chains. The individual polypeptide chains can differ in their amino acid sequences, and the tropocollagen has a banded pattern because of the sequence differences. Collagen is separated into various types based on such differences, and several types are components of ocular connective tissue structures. The amorphous ground substance, in which the cells and fibers are embedded, consists of water bound to glycosaminoglycans and long-chain carbohydrates.

Connective tissue does not consist only of the components described above. Except for cartilage, all connective tissues are vascularized to varying degrees [34]. In general terms, connective tissue that provides support and framework for the body consists of fibrous proteins and nonfibrous ground substance in varying proportions depending on their functions [35].

Cerebrospinal fluid flow

CSF flow is a dynamic process that moves in a to-and-fro motion. The flow of CSF through the aqueduct of Sylvius, basal cisterns, and foramen magnum normally changes direction two or three times per second, with a net slow flow in the superior to inferior direction [36].

Cerebrospinal fluid flows in bulk from sites of production to sites of absorption. Fluid formed in the lateral ventricles flows through the paired interventricular foramina (foramen of Monroe) into the third ventricle, then through the mesencephalic aqueduct (aqueduct of Sylvius) into the fourth ventricle. The majority of CSF exits from the fourth ventricle into the subarachnoid space; a small amount may enter the central canal of the spinal cord. In people, CSF enters the subarachnoid space through the lateral apertures (foramina of Luschka) and the median aperture (foramen of Magendie) of the fourth ventricle [37].

CSF abnormality seems to be related as much to the location of disease as to the cause or the severity of lesion; meningeal and paraventricular diseases generally produce greater abnormalities than deep parenchymal diseases.

When suspended in CSF, a 1500-gm brain weighs only about 50g. So, physical support of neural structures is a main function of CSF. Cerebrospinal fluid also provides a “water jacket” of physical support and buoyancy, protecting of volume changes, for instance of blood during changes associated with posture, respiration and exertion.

The direct transfer of brain metabolites into CSF provides a transport and excretory function, which is important due the brain lacks a lymphatic system, like the eye. The “sink” action of the CSF arises from the restricted access of water-soluble substances to the CSF and the low concentration of these solutes in the CSF. Therefore, solutes entering the brain, as well as those synthesized by the brain, diffuse freely from the brain interstitial fluid into the CSF. Removal may then occur by bulk CSF absorption or, in some cases, by transport across the choroid plexus into the capillaries [38].

CSF formation

Cerebrospinal fluid is formed principally by the choroid plexuses, with a smaller amount formed extra-choroidally. Theoretically, choroidal formation involves two processes: first is a supposed filtration across the choroidal capillary wall, which is fenestrae, like capillaries in the eye’s choroidal layer; and second is secretion by the choroidal epithelium, which in the eye has an equivalent: the pigment epithelium. Within the choroid plexuses, hydrostatic pressure of the choroidal capillaries theoretically initiates the transfer of water and ions to the interstitial fluid and then to the choroidal epithelium. However, the hydrostatic pressure, it is a so random process that lacks the necessary accuracy regarding CSF formation, which is a highly regulated phenomenon. Thereby, each step involved in CSF production is supplied with exact energy in time and form.

The capillary endothelium that forms the blood-brain barrier has a higher number of mitochondria, however, mitochondria is not a source of energy, instead, mitochondria has a main role as temperature regulator. The biochemical processes of the body are astonishingly
accurate, and this since beginning of time. Thereby, accurate biochemical processes also require an exact temperature regulation, and that is the main role of mitochondria. ATP and ADP also have a secondary role as temperature regulators, but mainly regarding control of phosphate levels.

The circumventricular organs, which include the four choroid plexuses, the median eminence, the neural lobe of the hypophysis and other specialized areas, border the brain ventricles and are involved with specific secretory activities that appear to require a direct contact with plasma. The capillaries within these organs are fenestrated, like capillaries in other organs of the body. Overlying each of the organs are specialized epithelial cells joined by intercellular tight junctions at their apical (ventricular) borders. These epithelial cells also are characterized by an abundance of intracellular organelles and lysosomes, which means high energy expenditure, and thereby a significant content of melanosomes, in a similar way to choroid plexuses.

The choroid plexuses are the major source of CSF. They are formed by evaginations of the ependyma and the pial blood vessels into the ventricles, and they consist of a single row of cuboidal, specialized epithelial cells with a high content of melanosomes, located mainly in the perinuclear space; thrown into villi around a core of blood vessels and connective tissue.

The basal and lateral cell surfaces have numerous infoldings. Overall, the structure of these cells resembles other epithelia specialized for fluid transport, which means high energy requirements, such as proximal renal tubular epithelium and pigmented epithelium of the eye (Figure 14). The plexus tissue has excellent blood supply: it was estimated that the rat lateral ventricle CP receives 3 - 4 ml/min/g, which is 10-fold the blood supply when compared to 0.35 - 0.4 ml/min/g in cerebral cortex [39].

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**Figure 14:** Microphotography of the choroid layer of the human eye. Retina pigmented epithelium is located at left, followed by the choriocapillaris, medium and large blood vessel layer. The abundant melanin content (dark) is very noticeable. At right, the collagen fibers (vertically) of the sclera. Solís- Herrera, 2007©.
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The dynamic of CSF is subject to circadian rhythms.

Aqueous humor dynamic

As the CSF, the aqueous humor formation is a biological process subject to circadian rhythms, being higher in the morning than at night. Thereby sunshine has a significant and consistent impact. Supposedly, the two main structures related to aqueous humor dynamics are the ciliary body and the trabecular meshwork. Theoretically three mechanisms are involved in aqueous humor formation: diffusion (sic), ultrafiltration, and active secretion.

It’s hard to believe that simple diffusion can drive the formation of a so exact liquid as aqueous humor. Its composition and volume are strictly regulated. In regards ultrafiltration, Donnan Gibbs balance cannot predict electrolyte composition neither aqueous humor nor CSF, thereby can be discarded. Active secretion seems like the main option; however, literature is silent about the source of energy of this kind of process.

The liquids of the organism are quantized, i.e. they are accurate. But such accuracy involves several factors, being one of the most important that energy is also quantized, that is, accurate. An exact chemical process requires, in other things, an exact amount of energy, in location, extent, time and form.

Supposedly, the aqueous humor leaves the eye by passive flow, mainly by two ways: the trabecular meshwork (TM) and the uveoscleral pathway. The trabecular meshwork is the structure that overpasses the scleral sulcus and converts it into a circular channel, called Schlemm’s canal, that consists of connective tissue surrounded by endothelium. TM can be divided in three components: uveal meshwork, corneoscleral meshwork and juxtacanalicular meshwork [40].

The conventional pathway consists of aqueous humor passing through the trabecular meshwork, across the inner wall of Schlemm’s canal, into its lumen, and into draining collector channels, aqueous veins and episcleral veins [41]. Although it is difficult to explain the pressure changes that occur in a structure that has a thickness of less than two mm; due to normal episcleral venous pressure is 14.1 ± 1.0 cmH₂O, mm Hg. The pressure in Schlemm’s canal is about 14.3 ± 1.0 cm H₂O at spontaneous intraocular pressure (IOP) 19.2 ± 0.9 cmH₂O [42]. The difference between the total outflow resistance and that between the anterior chamber and Schlemm’s canal was about 10% of the total at intraocular pressures below 35 cmH₂O.

The non-conventional route is composed of the uveal meshwork and anterior face of the ciliary muscle. The aqueous humor enters the connective tissue between the muscle bundles, through the suprachoroidal space, and out through the sclera [43]. But such a strictly regulated balance between production and aqueous humor output cannot be explained simply as that aqueous humor simply transmigrates between tissues. Since the flow through trabecular mesh, Schlemm canal, collecting channels and episcleral aqueous veins do not explain the dynamics of the aqueous humor, this is the delicate balance between production and output; then the constant and uniform presence of melanin in one of the two layers of epithelium that upholster the ciliary body (Figure 15) has the answer. The dissociation and re-forming of the water molecule by melanin is an astonishingly accurate process, and the balance between production and exit of aqueous humor is also. In humans, aqueous humor has an excess of hydrogen ions that probably comes from melanin’s water dissociation.

The main function of melanin wherever it is found is to transform sunlight into chemical energy by med from the dissociation of the water molecule, such as plant chlorophyll. When the liquid water molecule dissociates, energy is released, which is transported by molecular gaseous hydrogen as it is the main energy hauler that nature uses in the entire universe. Molecular hydrogen in gaseous form comes from the dissociation of the liquid water molecule.

The constant dissociation and re-forming of the water molecule (liquid/gas/liquid/gas......) regulates quite precisely the amount of water present in the tissues, because as any chemical reaction, can move right or left depending on pressure, temperature, amount of light, amount of water, etc.

Figure 15: Histological cut of the ciliary body. The pigmented epithelium that covers the ciliary body is covered in turn by a single layer of non-pigmented epithelium (H & E, 40X).

Apparently, all biological fluids have a common origin (melanin) since the analysis of graphs resulting from their composition yields an astonishingly regular distribution.

**Melanin, water dissociation and metabolism rate**

It is not by chance the presence of Melanin overall in zones of high metabolic activity. For instance, in eye’s choroid layer, melanin content is around 40% more than the skin, and interesting choroidal circulation constitutes 85% of the blood circulation of the eye, choroidal flow is higher than in tissues like retina and brain, choroidal flow-ranges from 800 to 2000 mL/min/100g of tissue; choroid provides the metabolic requirements of the full retinal thickness mainly in the macular region; in other parts of the eye, the presence of melanin in the pars plicata and pars plana of ciliary body provides the energy that requires a high energy state like transparency of tissues (Vitreous body, crystalline lens and cornea). In embryonic life, choroid serves as an additional site for the erythropoiiesis.

In our opinion, the explanation is given by the unsuspected intrinsic property of melanin to dissociate the water molecule, like chlorophyll in plants. This means that melanin can transform light energy into chemical energy through splitting of $2H_2O$ into $2H_2$ and $O_2$. By the way, molecular Hydrogen ($H_2$) is the energy carrier that Nature uses at most in the entire Universe. Living things cannot be different [44]. Let us look at the energetic role of melanin in the case of CSF.

It was learned through trial and error, that excision of the choroid plexus did not benefit human patients with hydrocephalus. Thereby, the existence of an unknown extra-choroidal source of CSF was inferred. From there onwards, several theories have emerged that could not be verified.

The most invoked theories are: diffusion of brain interstitial fluid across the ependyma or pia mater; formation of the interstitial fluid that theoretically occur by active transport processes (secretion) at the cerebral capillaries, which means energy expenditure; others re-
searchers propose passive permeability of the capillary endothelium and active transport by the surrounding astrocytes [45]. CSF formation is so theoretical that the relative contributions of choroidal and extra-choroidal sources to CSF in normal and pathological conditions are uncertain.

The CSF formation is relatively constant and is closely correlated to the weight of the choroid plexus and varies among species [46]. The rate of CSF formation in human being is 350-370 µl/min [47]. The formation rate directly parallels the rate of sodium exchange, which is linked to the bicarbonate ion, and this in turn to CO₂ level.

The enzyme carbonic anhydrase plays an important role because modulates CO₂ metabolism (Figure 16).

![Figure 16: Scheme of reversible action of the enzyme carbonic anhydrase on CO₂. And this enzyme, like any other, requires energy not only to function but to preserve form. Carbonic anhydrase, in peripheral tissues, favoring the formation of bicarbonate which solubilizes CO₂ and is transported by the blood plasma to the lungs, and in the alveoli, the carbonic anhydrase favored the formation of CO₂ (gas) from the bicarbonate, allowing the lung to expel it outwards, towards the atmosphere.]

Inhibition of carbonic anhydrase slows (but does not abolish) sodium, bicarbonate, and chloride flow, resulting in a reduction of CSF secretion [48]. Paradoxically, studies of chronically hydrocephalic animals have shown a reduction of CSF formation with increasing intraventricular pressure [49]. The ionic composition of the CSF is not as predicted by the Gibbs-Donnan equilibrium for an ultrafiltrate [50].

**CSF circulation**

Cerebrospinal fluid flows in bulk from sites of production to sites of absorption. Fluid formed in the lateral ventricles flows through the paired interventricular foramina (foramen of Monroe) into the third ventricle, then through the mesencephalic aqueduct (aqueduct of Sylvius) into the fourth ventricle. CSF enters the subarachnoid space through the lateral apertures (Foramina of Luschka) and the median aperture (foramen of Magendie) of the fourth ventricle.

Theoretical mechanisms for propelling the CSF along its route include: a) the continuous outpouring of newly formed ventricular fluid, b) the ciliary action of the ventricular ependyma, c) respiratory and vascular pulsations and d) the pressure gradient across the arachnoid villi [51].

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The CSF flow has an order, not only determined by the force of gravity. It is not understood where the energy that drives it or how it is used comes from, but it is known to vary according to the amount of light.

CSF absorption

Absorption of CSF occurs, theoretically; by bulk absorption of the fluid and by absorption or exchange of individual constituents of the fluid (e.g. ions, proteins, drugs). In any case it involves energy expenditure, the origin and destination of which is not understood.

Bulk absorption occurs, theoretically; into the venous system and depends primarily on the CSF hydrostatic pressure, e.g. as the pressure rise, the absorption rate increases. Which is contradictory to clinical findings that the increase of intracranial pressure is accompanied by a decrease in CSF production [49].

If intracranial pressure falls below a critical point, bulk absorption decreases. Theoretically, the primary site of bulk absorption is the arachnoid villi that project into the Dural sinuses. Supposedly, two other routes are through lymphatic channels in the dura and through the perineural sheaths of cranial nerves, particularly the olfactory nerve and spinal nerves.

Absorption through the arachnoid villi occurs, again theoretically; transcellularly through macropinocytotic vesicles and giant intracellular vesicles. Absorption is supposedly unidirectional from the CSF into the venous blood, the villi act like one-way valves. The medical literature is very discrete, event silent about the source of energy involved in CSF absorption.

The choroid plexus also has an absorptive function, acting on specific substances in the CSF rather than by bulk fluid absorption. As usual, researchers avoid the topic of where the energy needed for macropinocytotic vesicles and intracellular giant vesicles to form as well as to move into the cell and in the right direction.

The thorny energy problem in relation to the dynamics of CSF is solved if we include in the scheme the unsuspected intrinsic property of melanin to dissociate the water molecule [52].

Melanin and CSF formation and absorption

Melanin is found in all cells of the body, usually located in the perinuclear space. The amount of melanin depends on the location and function of the cells in question. The association of abundant melanin and numerous blood vessels are observed in the choroid plexuses of the CNS and in the choroid layer of the eye.

Melanin dissociates the water molecule by releasing oxygen and molecular hydrogen, so, usually; oxygen levels in tissues and vessels near the pigment oxygen levels are high. We must keep in mind that the oxygen in the body’s tissues comes mostly from to dissociation of water, through melanin and not from the atmosphere.

Our body does not need to take oxygen from atmosphere because eukaryotic cells produce oxygen at their own through melanin’s water dissociation.

Melanin differs from chlorophyll in the reversibility of water dissociation. This is: melanin dissociates the molecule from water and has the capacity to re-forms it. In chlorophyll the process is irreversible.

The process is outlined as follows: $2\text{H}_2\text{O} \rightarrow 2\text{H}_2 + \text{O}_2 \rightarrow 2\text{H}_2\text{O} + 4\text{e}^-.$

Melanin, in the presence of natural light and water, separates the molecule from water in its gaseous components: hydrogen and oxygen. But melanin can re-form water, for every two water molecules that are reconstituted, 4 high-energy electrons are generated.

The flow of energy that drives the biomass of the CNS and the eyeball, begins with sunlight, which reaches the Earth, passing through the atmosphere, where it undergoes significant changes due to the absorption, reflection and refraction of light; and in tissues it is cap-

tured by melanin, which absorbs all wavelengths, dissipating the notably amount of absorbed energy through the dissociation of the molecule from water (Figure 17).

The evolution of life has followed the same path in relation to the flow of energy and mass since the beginning of time. Therefore, any significant change in these processes results in functional or anatomical alterations.

Visual affectations reported by more of 50% of the crew members of the international Space Station, after long duration exposure to microgravity [53] we add another factor: the difference in light coming from the sun.

The light that reaches astronauts within the space station has significant differences with sunlight reaching the earth’s surface every day. It is therefore not surprising that the physiology of the body is affected substantively, because the difference in energy that melanin absorbs, modifies its chemical energy output plus the per se involvement on tissues. So, we should think that the two main factors that affect astronaut health is the difference in light energy and microgravity.

An indispensable element in life is the flow of water and/or liquids in general, as they are exact processes that require exact energy in time and form. The describe ocular alterations indicate perturbations in flow of water or liquids: optic disc edema, globe flattening, choroidal folds, and hyperopic shift.

MRI findings in postflight astronauts, in whom similarities to idiopathic intracranial hypertension such as posterior globe flattening is found, have implicated elevated intracranial pressure.

**Striking similarities between chemical composition of several fluids of human body**

All the fluids of the body are water-based, which does not attract much attention, because we consider water as the universal solvent. But by including the concentration of other elements, for example: Sodium, Magnesium, Phosphorus, Potassium and Calcium, the similari...

**Figure 17:** *Life originates from three elements of which we really know little: Light, Melanin, and water; in order of abundance in the Universe.*
ties are extraordinarily clear.

The graphs below show the distribution of the elements cited in the blood plasma, in the cerebrospinal fluid (CSF), in the aqueous humor, in the vitreous humor and finally in the amniotic fluid. The surprising similarities point to a common origin (Figure 18-22).

**Figure 18:** Electrolyte composition of blood plasma.

**Figure 19:** Electrolyte composition of cerebrospinal fluid.

_Citation:_ Arturo Solís Herrera, _et al._ “The Relationship between Low Tension Glaucoma, CSF, the Size of the Ventricles, and Neurodegenerative Diseases”. _EC Neurology_ 12.8 (2020): 183-222.
Theories about how bodily biological fluids such as CSF, aqueous humor, plasma, amniotic fluid, and vitreous body occur, argue diffusion, ultrafiltration, and active secretion, although none of these theories have been proven besides that are not possible, for several physical chemical reasons.

Diffusion: Biochemical processes of body are astonishingly accurate, and simple diffusion cannot produce something like that.

Ultrafiltration: It is a purely mechanical process in which some liquid is passed through an ultra-thin mesh. But it requires a lot of energy, of which literature in the respect is silent, in addition the Gibbs-Donnan model does not predict the chemical composition of bodily fluids neither their balance, so it does not happen that way. And a very thin, very thin mesh is susceptible to break and/or plug frequently, so it required to be restored too often.

Active secretion

Active secretion is not free, it requires energy, and not any energy. Because the accuracy in the liquids of the body is constant, it is amazing because it is repeated in the different bodily liquids, therefore if it were an active secretion, it has to be strictly regulated.

The similarity in the composition of various major fluids is accompanied by the omnipresence of melanin in tissues that relate to these bodily fluids. The homogeneity of the composition of these fluids coupled with the constant presence of melanin, leads us to consider a common origin that begins in the unsuspected intricate property of melanin to dissociate and re-form the molecule of water.

Melanin and the dynamics of bodily fluids

The unsuspected intrinsic property of melanin to dissociate and reform the water molecule, explains both the formation of these liquids, their composition, as well as their reabsorption. A feasible proof that melanin of tissues is the main element of the formation and reabsorption of biological liquids, we have it in the composition of these liquids, since the resulting graphs are almost identical for both CSF, plasma, aqueous humor, amniotic fluid, and vitreous body.

If we just look at the graphs, we could not identify which one is which. The resemblance is amazing so we can think that they form in the same way: from the dissociation of water and its consequent reformed, and the only molecule in the human body capable of dissociating and reforming water is melanin.

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So, it is not surprising that when the physicochemical properties of water are modified, the perfect substrate for melanin, all the melamins of the body are veined compromised to a greater or lesser degree depending on several factors. Thus, the alterations in the dynamics of aqueous humor are often associated with alterations in the dynamics of CSF.

**Heavy metals and the choroid plexus (CP)**

Although the CP can remove various metals from the blood, it can be damaged by heavy metals such as Mn, Pb and other metals which may in turn damage the functions of the CP [54]. Redzic, *et al.* had shown both in man and animals that high levels of lead in the environment may lead to the loss of TTR synthesis in the CP and hence disturbances in thyroid uptake by the brain [55]. Melanin is characteristically present in choroid plexus (Figure 23).

![Figure 23: Melanin and choroid plexus.](image)

**Representative clinical cases**

The association between increased excavation of the optical disc and the increase in volume of the cerebral ventricles secondary to a diminished production of CSF is common [56]. Impairments in CSF turnover have been suspected for many years in the etiology of Alzheimer’s Disease. However, there are no noninvasive imaging tools to evaluate CSF clearance.

Impaired CSF clearance is observed in mouse aging [57] and AD [58] models. In rodents and other mammals, CSF is primarily cleared along olfactory nerves that traverse the cribriform plate, draining into lymphatic vessels in the nasal mucosa [59]. Rodent CSF clearance is rapid because radiolabeled albumin [60] and paramagnetic contrast [61] injected into the CSF reach the turbinate within minutes. Researchers usually do not consider the presence of melanin in tissues, attributing the role of a simple sunscreen to it.

Much less is known about human CSF clearance anatomy. Arachnoid granulations arguably considered important human CSF egress sites [62], are not found in the rodent. The only evidence for a human nasal turbinate CSF efflux pathway comes from postmortem studies [63].

The enter and egress of Low-molecular-weight radiotracers in CSF through the choroid plexus and perivascular drainage [64] suggest that the reabsorption of CSF is reducing in AD. But the ability of melanin to dissociate and re-form the water molecule, makes it possible to assume that this pigment is involved in both the production and clearance of CSF.

The separation of liquid water into its gaseous components (H₂ and O₂) is the most expensive energetic part, as the laboratory requires heating the water at two thousand degrees Celsius. Melanin and chlorophyll separate water at room temperature by taking energy from light. The second phase, the re-forming of water, from gas to liquid, requires less energy. It releases heat so it is exergonic. Water dissociation needs energy, absorbing energy.

Reactions are complementary to each other. And the same thing happens during CSF production and clearance. When the difficult part of the process is altered (dissociation), then liquid water tends to accumulate, which explains how the size of the ventricles increases. The first part of the cycle is the most sensitive, so increased ventricles are found in size but with decreased intracranial pressure.

**Clinical case 1:** ALME. Date of birth: August 1953 three-month-long-evolving, constant vertigo. The rest of the interrogation is unimportant to the current condition.

![Figure 24: MRI, case 1; ventricles with moderate volume increase.](image-url)
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Figure 25: Patient photographs in case 1. The excavation is discreetly increased. Attention is striking about the glare seen in the center of the disc, in both eyes, when using the red filter. PIO 16 mm Hg, 17.00 hours.

Clinical case 2: OAAE. Date of birth: April 1932. Memory loss valued by neurologist and angiologist. She was being treated like AD.

Figure 26: Images for case two. Characteristically patients with low tension glaucoma, have decreased CSF production, and are detected by an increase in ventricle volume.

Figure 27: Eye fundus photographs corresponding to case 2. The photographs are somewhat blurred by crystalline nuclear sclerosis, but we can see a marked increase in excavation, especially in the left eye (above), where it reaches 80%. In the right eye, the excavation is lower below, about 70%, compatible with low-tension glaucoma. The IOP was 16 mm and 17 mm Hg, 11.45 am.

Figure 28: The images of nuclear magnetic resonance imaging correspond to case three. The volume of the ventricles increased very significantly.
Clinical case 4: RVJ. Date of birth August 1954. Vertigo, loss of muscle strength in the half right of the body. Partial loss of vision.

Figure 29: Photographs of the retina and optic nerve corresponding to case 3. The excavation of the optic nerve is increased in area and depth. Note the glare at the center of the excavation that is visible with the red filter. The intraocular pressure is 14 mm Hg, at 10.00 am.

Figure 30: Magnetic resonance imaging of case 4. The growth of the ventricles is remarkable.

Figure 31: Magnetic resonance imaging of case 4. The growth of the ventricles is noticeable and subcortical/cortical atrophy is evident.

**Figure 33:** Patient photographs in case 5. The growth of the ventricles is very noticeable.

**Figure 34:** Images of the patient’s optical disc in case 5, the excavation is 70%, note the glare in the center of the disc with the red filter. Intraocular pressure 18 mm Hg, 18.00 hours.


Figure 35: MRI corresponding to case number 6. Increased ventricular volume is moderate.

**Figure 36:** The excavation is marked, about 90%, deep, and with a glow in the center of the optical disc in the red filter image (Case 6).

**Clinical case 7:** JJCV. Date of birth April 1939. Fading, low vision, hearing loss, moderate weakness in lower limbs. Started in 2014.

**Figure 37:** Figures corresponding to case 6. Increased volume of ventricles and subarachnoid space is accompanied by cortical atrophy.
Figure 38: Images of the excavation of the optic nerves, case 6. The excavation covers just over 90% of the surface of the optic nerve in both eyes and is deep.

Figure 39: Images for case number 7. The ventricles and subarachnoid space increased in size. Cortical atrophy zones.

Figure 40: The excavation of the optic nerves in case 7 is increased, is already close to 90% and is deep. IOP 14 mm Hg- 12.00 hour.

Clinical case 9: VCGE. Date of birth: April 1943. Bad vision, the patient forgets everything and repeat things a lot. AD.

Figure 41: The increase in the ventricles is marked in the case of patient 8.
Conclusion

The unsuspected intrinsic property of melanin to dissociate the water molecule, such as chlorophyll in plants, is a solid foundation that allows us to consistently explain clinical observations about the frequent association of optic glaucomatous neuropathy and decreased production of CSF, which is accompanied by growth of the cerebral ventricles and subarachnoid space.

The dissociation and re-forming of water that occurs inside melanin provides a logical explanation of how bodily fluids occur and are reabsorbed. When water is dissociated, that is, when water passes from liquid to gas, then the gases diffuse into the tissues since hydrogen is the smallest atom (7 nanometers). So, the amount of water in the ventricles would decrease. But when the second part of the cycle occurs, when the gas re-forms it, then the volume of water in the ventricles increases. The same reasoning can be applied to the eye, to the amniotic fluid.

And the common origin of bodily fluids is clearly discerned when comparing electrolyte concentration graphs in tissues. Distribution graphs are astonishingly similar (Figure 18-22).

Therefore, patients who have growing of optical disc excavation, also have decreased CSF formation, with the consequent growth of ventricles; this is consistent because factors that affect melanin functions, such as pesticides, herbicides, metals, plastics, solvents, industrial waste, alcohol, drinking water with dissolved oxygen levels less than 2 mg/l, etc. affect the body jointly and rarely a particular area.

Acknowledgment

This work was supported by Human Photosynthesis© Research Centre. Aguascalientes 20000, México.

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