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On the Relationship between Ocular and Ventricular Fluid Dynamics. Advancing a Joint Classification and a Pilot Study in Patients Suffering from Nonocclusive Hydrocephalus

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Abstract Similarity in embryological development, anatomical and structural organization as well as chemical physical properties of organs and apparatus makes them common targets for specific pathological events. Such multi-involvement could well be the case of the cerebrospinal and aqueous circulatory systems, respectively in the brain ventricles and in the anterior and posterior chamber of the eye. After having described the resemblances in secretion, circulation, absorption and composition of the ventricular cerebrospinal fluid and of the ocular aqueous humor, a joint classification of their pathological involvement, namely hydrocephalus and glaucoma, is advanced. Finally, based on our preliminary results, morpho-functional alterations of the ventricular fluid dynamics leading to communicant hydrocephalus is suggested to affect to a certain extent the ocular hydrodynamics as well, predisposing the eye to ocular hypertension.

Keywords: *ventricles, anterior chamber, posterior chamber, aqueous humor, cerebrospinal fluid, hydrocephalus, glaucoma, ocular hypertension*

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1. Introduction

Since the chore of the embryologic development of a living organism is its progressive differentiation into different tissues from a totipotent cellular pool, anatomical and histological structures that are similar but form different apparatus can share chemical, biochemical, physical as well as physiological properties. Consider for example the buccal, genital, bronchial, and conjunctival mucosa: these are tissues histologically similar, derived from embryological common substrates. Yet, they are in charge of different functions and in some cases work in far different environmental conditions.

And yet, anatomical tissues sharing common features but having different functions can be equally vulnerable to the same pathological event: an event able to undermine them histologically as well as biochemically. Sjogren Disease or Vogt-Koyanagi-Harada syndrome can be taken as examples.

The considerations we have mentioned are valid even for the production, circulation and excretion of fluids in a system made of close cavities: as a matter of fact, such peculiar hydrodynamic systems are proper of different districts of the organism: for example the intra-articular spaces and related synovial fluid, the pleural space and related pleural fluid, the eye and aqueous humor or the cerebral ventricles filled with cerebrospinal fluid. Within these anatomical cavities the corresponding fluids allow nutrition and oxygenation of their walls, maintenance of their correct relationship, and in some cases reduce reciprocal friction.

Now, the two cavity systems we intend to consider are the anterior chamber of the eyeball filled with aqueous humor (AH) and the cerebral ventricular system filled with cerebrospinal fluid (CSF).

Fluids and their dynamics play a crucial role in keeping stable spatial relationships between the dioptric media in the eye and in providing nutrition and homeostasis to the surrounding anatomical structures in both eye and periventricular brain. So, abnormal fluid turnover at an ocular and cerebral level may cause severe alterations: namely glaucoma and hydrocephalus.

On the light of these premises it is worthwhile recalling and highlighting the striking anatomical, histological as

well as embryological correspondence between the two systems. Such analogies would provide a theoretical basis to evaluate if pathological circulation of the brain can affect the aqueous turnover of the eye.

AH and CSF, indeed, show noticeably similar secretive, circulatory and excretive patterns.

At the ocular level, in fact, AH produced by the ciliary body fills the posterior chamber, passes through the iridolenticular space and reaches the anterior chamber. Here, via the iridocorneal angle, it filters through the trabecular meshwork, flows into the Schlemm's canal, then, first via Sondermann's vessels and after via the laminar veins reaches the anterior ciliary veins; thereafter, it finally flows into the systemic venous circulation.

At a cerebral level the choroid plexus is the source of about 80% of the CSF. The blood vessels in the subependymal regions and the pia contribute to CSF al well, and some substances enter the CSF as readily from the meninx as from the choroid plexus.

The CSF fills the cerebral ventricles, then passes through Magendie and Luschka foramens to the perimidullary and perispinal subarachnoid spaces, thence up over the brainstem to the cisternae basales and ambiens and finally to the superior and lateral surfaces of the cerebral hemispheres, where it is absorbed into the venous sinus of the dura mater through the arachnoid granulations; from here it finally reaches the systemic venous circulatory system (Figure 1 and Figure 2).

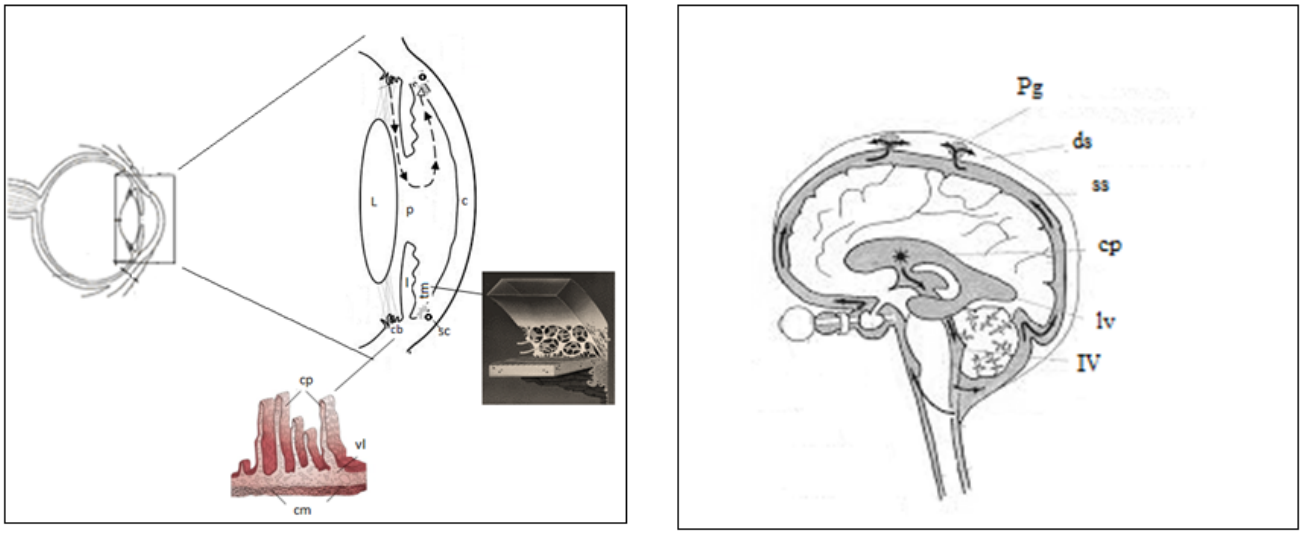

Figure 1. Upper panel: aqueous circulation. The ciliary processes and trabecular meshwork are highlighted. C: cornea cb: ciliary body, L: lens, p: pupil, sc: Schlemm's canal, tm: trabecular meshwork, cp: ciliary processes, cm: ciliary muscular layer, vl: ciliary vascular layer. Lower panel: cerebral ventricular circulation. Pg: Pacchionan granulations, ds: dural sinus, ss: subarachnoid space, cp: choroid plexus, lv: lateral ventricle, IV: IV ventricle. The asterisk marks the site of cerebrospinal fluid production

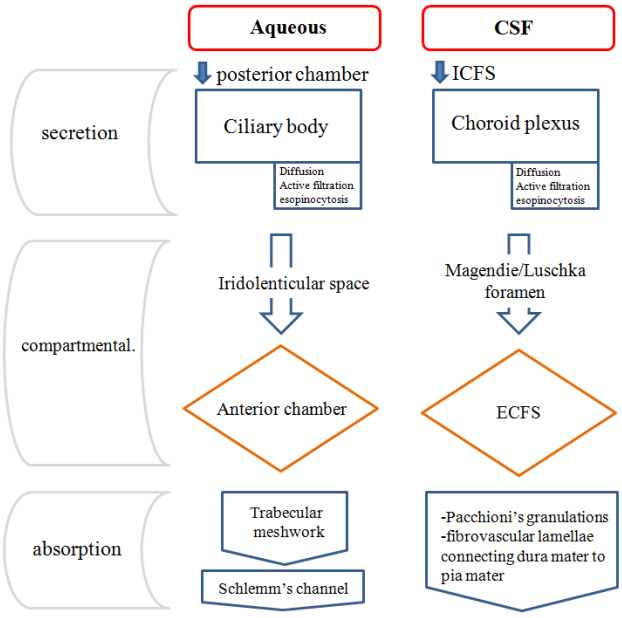

Figure 2. Aqueous and cerebral ventricular circulation. Schematization

Both fluids are localized into a closed anatomical space. The corneal-scleral wall is made of fibrous tissue, with low extensibility. To be noted that the sclera in newborn and young children is more extensible, so that raise of intraocular pressure (IOP) at the early stage of the bulbar development causes bulbar distension. Such phenomenon is comparable to the widening of the fontanels in the newborn with hydrocephalus.

At a cerebral level the anatomo-physiological conditions are very similar: the brainpan, covered with dura mater in its inner surface, encompasses an almost inextensible anatomical space.

Based upon these premises, let us consider more specifically the fundamental characteristic of the ocular and cerebroventricular fluid circulation, highlighting the analogies between the two systems.

1.1. Secretion

In the eye the ciliary processes are responsible for aqueous secretion by joint mechanisms of diffusion, active filtration and esopinocytosis.

In the brain the choroid plexus is responsible for CSF secretion according to the same physiological modalities described for the aqueous production.

The ciliary processes are made of a glomerular vascular structure covered on its inner surface by a double epithelial layer. The vascular meshwork looks dense, especially close to the epithelium where it is structured in a tight meshwork of capillaries, sometimes fenestrated, made of a single layer of endothelial cells. A thin

connective structure rich of nerve endings localizes between the capillary meshwork and the underlying epithelial layer.

The choroid plexus, too, consist of tufts of vessels of different size and up to 2-3 mm long, derived from vascular vegetations of the pia mater and protruding in the ventricles. They are made of capillary arteries, capillary veins and sinusoidal capillaries, many of which are fenestrated. These vessels are embedded in thin connective tissue.

The ciliary body is vascularized by the anterior ciliary arteries, derived from the ophthalmic artery.

The choroid plexus are supplied with blood by the posterior and anterior cerebellar artery as well as the posterior cerebral arteries and choroid arteries.

The double epithelial cover of the ciliary processes is made by an external single layer of dark cells whose melanin granules are prevalently localized in the peripheral cytoplasm, corresponding to the retinal pigmented epithelium, and by an internal tapetum made of clear cells, stemming from metaplastic modification of the retinal neuroepithelium. Clear cells are roughly cubic in shape with their convex apical face show oval nucleus, well developed Golgi apparatus, beta-cytomembranes and a great amount of mitochondria. Mitochondria, indeed, are necessary to the clear epithelial cells for their active secretion of the AH in the posterior chamber of the eye. The effect is accomplished by means of ATP-dependent mechanism acting on the fluid that percolates from the glomerular capillaries.

The clear cells are joined via gap junctions and tight junctions [1,2].

The choroid plexus are covered by a thin epithelial layer made of cubic cells rich in mitochondria and beta-cytomembranes belonging to the ependymal lamina and strictly similar to the clear cubic cells of the ciliary epithelium. The cubic cells of the choroid plexus are joined via tight junctions.

Embriologically, both the ciliary and choroid vascular complex are mesodermal, while the ciliary epithelium and the ependymal lamina is neuroectodermal.

Aqueous humor production is about 2.2 - 0.37 mm^3/min (i.e 0.0022- 0.0003 ml/min) at a constant rate [2]. It involves passive and active mechanisms. Passive mechanisms (diffusion, dialysis, and ultrafiltration) are responsible for about 25-30% of the aqueous secretion. Such passive mechanisms rely on semi-permeable membranes (the vessel wall and the ciliary epithelium) and on the hydrostatic pressure in the blood vessels.

Diffusion, allowed by difference in salt concentration between blood and aqueous humor is preponderant at the level of the ciliary epithelial boundary and acts on the fluid percolated through the blood vessels.

Active mechanisms are responsible for the remaining 70-75% of the aqueous secretion. Their effect is suggested by the higher concentration in the aqueous compared to the blood of sodium, chlorine, ascorbic and lactic acid, as well as by the electrical potential difference between stroma and epithelium in the ciliary cells: these elements, in fact, denote considerable expense of energy, provided by redox reactions and ATP-depended processes.

Na+ enters the clear epithelial cells of the ciliary body by exchange with H+ ions derived from the redox reaction CO2+H2O=HCO3+H+, catalyzed by carbonic anhydrase. Na+ and HCO3- are rapidly dismissed from the cell via Na-ATP-ase related mechanisms and fill the intercellular space, attracting water molecules for osmolarity. Such “protoaqueous”, enriched with different substances, gathers in the posterior chamber.

An additional active process due to beta-cytomembranes, that is pinocytosis, helps transfer interstitial fluid micelles into the posterior chamber.

CSF production is about 500-800 ml per day (i.e. 0.347-0.550 ml/min [3], or 0.4 mm/min [4] with a constant rate, but it tends to fade with age. It involves filtration and diffusion with a complete turnover every 6 hours. Still, also selective dialysis seems to be involved, acting via active secretion of Na+ by the epithelial cells. Na+ ions are therefore followed by water molecules from the choroid capillaries. Active transport is indirectly demonstrated by high concentrations of carbonic anhydrase in the cubic cells of the ependymal lamina, so tightly adjoined as to make an almost impenetrable barrier (the ematoliquoral barrier) to blood molecules. However, small quantities of proteins as well as glucose (at 70% of the plasmatic concentration) are present in the CSF, maybe transported by carriers [5] or transferred by the epithelial cells of the choroid plexus via pinocytosis.

Schematic summary of aqueous humor and cerebrospinal fluid secretion similarities is reported in Table 1.

Table 1. Analogies – secretion

CILIARY PROCESSES	*CHOROID PLEXUS*
Vascular glomerular complex at the level of the posterior chamber	Complex of vascular tufts abutting into the ventricles
Capillaries, often fenestrated	Sinusoidal capillaries, often fenestrated
Vascular network separated from the underlying epithelial layer by a thin connective lamina	Vessels embedded in connective tissue
Blood vessels of the ciliary body originating from the internal carotid artery	Blood vessels of the choroid plexus originated from the internal carotid artery
Vascular network of the ciliary body covered on the inner surface with a double epithelial layer	Choroid plexus covered with a thin epithelial layer belonging to the ependymal lamina
Clear epithelial cells: cube-shaped	Epithelial cells: cube-shaped
Epithelial cells provided with many mitochondria and beta-cytomembranes	Epithelial cells provided with many mitochondria and beta-cytomembranes
Epithelial cells joined via nexus and tight junctions	Epithelial cells joined via nexus and tight junctions
Embryological derivation of the vascular ciliary complex: mesodermal	Embryological derivation of the vascular choroid complex: mesodermal
Embryological derivation of the ciliary epithelium: neuroectodermal	Embryological derivation of the ependymal lamina: neuroectodermal
Average aqueous secretion:0.0022 ml/min at a constant rate	Average CSF secretion: 0.44 ml/die at a constant rate
Aqueous secretion due to passive mechanisms (diffusion, dialysis and ultrafiltration) and ATPase/carbonic anhydrase-dependent active mechanisms	CSF secretion due to passive mechanisms (diffusion and ultrafiltration) and ATPase/carbonic anhydrase-dependent active mechanisms

1.2. Compartmentalization

Far from being stagnant, both aqueous and CSF flow constantly into, respectively, the anterior chamber and the ventricular system.

Aqueous production takes place in the posterior chamber, the CSF in the ventricular cavities (or *internal cerebrospinal fluid space*, ICFS). The lateral ventricular cavities communicate with the third ventricle through the Monro foramen and the latter via the Sylvian aqueduct to the fourth ventricle.

From the posterior chamber the aqueous flows into the anterior chamber passing through the iridolenticular space.

From the ventricular cavities the CSF flows into the subarachnoid space (external cerebrospinal fluid space, ECFS) through the Magendie and Luschka foramens.

Absorption takes place, respectively, by aqueous filtering at the level of the trabecular meshwork of the iridocorneal angle in the eye, and at the level of the Pacchioni granulations and of the subarachnoid space in the brain.

It is evident the anatomical correspondence between the ocular posterior chamber and the ICFS, as well as the anterior chamber of the eye+iridocorneal angle and the ECFS. The iridolenticular space is comparable to the Magendie and Luschka foramens.

In addition, endothelial corneal cells and ependymal cells are histologically similar: like the endothelial cells of the cornea, ependymal cells, too, are joined by adherens and occludens junctions and provided with cilia on their endoluminal surface. This latter element suggests their potential role in regulating pressure and chemical composition of the CSF. Due to such resemblances, ventricular space would match the posterior and the anterior chamber of the eye, and the subarachnoid space would correspond to the iridocorneal angle.

The anterior chamber begins to develop about the 5th month of pregnancy, maybe originating from the confluence of lacunae formed in the primitive mesodermal streak or from the cleavage of the two mesodermal layers that would later differentiate into the iris and corneal endothelium. It should be considered, however, that according to some studies the undifferentiated lens tissue would not be mesodermal but neuroectodermal, stemming from the neural crest [2]. About at the 8th month pupillary membrane absorption completes the communication between anterior and posterior chamber.

The ventricular development occurs gradually, resulting from progressive reduction of the internal liquor space as a consequence of the volumetric development of the cerebral matter.

Meninx originates as a fibro-connective mesodermal formation that differentiates into two meningeal layers: the outer one is the dura mater, the other is the leptomeninx. From the cleavage of the leptomeninx originate pia and arachnoid mater. The progressive separation of these two layers, (that remain joined by thin trabeculae so as to form a spongy network) gives rise to the subarachnoid space.

Like the undifferentiated tissue of the lens, at least in inferior invertebrates the leptomeninx is believed to be not mesodermal but neuroectodermal, originating from the neural crest.

Schematic summary of aqueous humor and cerebrospinal fluid compartmentalization similarities is reported in Table 2.

Table 2. Analogies-compartmentalization

OCULAR HYDRODINAMICS DISTRICS	*VENTRICULAR HYDRODINAMICS DISTRICTS*
Posterior chamber	Internal liquor space (ventricles)
Irido-lenticular foramen	Magendie and Luschka foramens
Anterior chamber	External liquor space (subarachnoid space)
Iridocorneal angle	Subarachnoid space
Anterior chamber development: 5th month	Ventricles development: 1st month
Anterior chamber formation: cleavage of the two mesodermal layers, further differentiating as iris and corneal endhotelium	Subarachnoid space formation: cleavage of the leptomeninx
Embryological derivation of the anterior chamber: neuroectodermal	Embryological derivation of the subarachnoid space: neuroectodermal
Anterior and posterior chamber completed at the 8th month (development of the irido-lenticular space)	Development of the cerebral ventricles completed at the 9th month

1.3. Absorption

At the level of the iridocorneal angle, fully developed at the 6th month of intrauterine life, the aqueous leaves the eye passing through the trabecular meshwork. Perfect balance between ocular inflow (secretion) and outflow (absorption) is required in order to keep intraocular pressure at a constant level.

The trabecular meshwork is sort of spongy tissue made of connective lamellae forming pores. It is made of three different layers: the uveal trabecular meshwork (the innermost layer), the corneoscleral meshwork and the cribriform meshwork (the outermost layer), in contact with the endothelial cells of the Schlemm's canal. Through the trabecular meshwork the aqueous is drained into the Schlemm's canal. Outflow resistance increases gradually due to the progressive narrowing of the trabecular pores. These structures are recognizable starting from the 3rd week of intrauterine life.

The Schlemm's canal is an elliptical tubular structure at the sclerocorneal limbus. Its walls develop at the 4th month of intrauterine life from mesodermal tissue.

CSF is drained mainly at the subarachnoid level via filtration through capillaries embedded in the fibrovascular lamellae connecting dura and pia mater.

The meningeal Pacchioni granulations contribute, too, to the draining function. Pacchionian granulations are sort of arachnoid mushroom-like protuberances made of a trabecular complex covered by a mesothelial layer and protruding into the venous sinus, especially in the superior longitudinal sinus and in the lateral venous lacunae. Pacchionan granulations are also present at the base of the brain and around the spinal nerve roots, and penetrate the meningeal veins and the dural sinus wall. Their

embryological origin, like the trabecular meshwork, is mesodermal.

Pacchioni granulations are well visible after the 39th week of intrauterine life [6], stemming from a membrane (the arachnoid membrane) forming small pouches into the venous sinus. Then, connective and mesothelial tissue grow from the pouches toward the dura mater, making up the inner wall of the venous sinus. Clusters of arachnoid cells derived from the arachnoid membrane finally form granulations the size of a seed of millet.

The collagen fibers making up the trabeculae delimit channels communicating with the subarachnoid space. Such channels, filled with CSF, are similar to the trabecular holes of the iridocorneal angle.

After passing through the Schlemm's canal, the aqueous flows into the aqueous veins, thence into the anterior ciliary veins and finally reaches the episcleral venous circulation. The brain analogous structures are the venous sinus of the dura mater.

Glycosaminoglycans play an important role in regulating the fluid movements through the connective tissues of the trabecular meshwork and of the arachnoid [7]. In fact, both trabecular meshwork and arachnoid contain ialuronic and chondroitin sulfuric acid, creating highly viscous compounds acting as a biochemically selective draining system. These substances could play a role in maintaining the unidirectional characteristics of the aqueous and CSF outflow.

CSF absorption rate depends on the intracranial pressure. The same effect is found at the ocular level.

A schematic summary of the similarities between the absorption of aqueous humor and cerebrospinal fluid is reported in Table 3.

Table 3. Analogies-absorption

OCULAR HYDRODINAMICS	*CEREBRAL HYDRODINAMICS*
Trabecular meshwork: connective laminae that, starting from the Dollinger ring, fill the internal scleral sulcus and abut beyond the scleral spur, merging in the uveal tissue	Subarachnoid space: fibrovascular trabeculae that extend from dura mater to pia mater. Pacchioni's granulations: tufts made of arachnoid trabeculae covered with mesothelial tissue and abutting into the venus sinus
Trabecular holes: elliptical shaped, bounded by the connectival laminae making up the trabecular meshwork	Intertrabecular channels resembling the trabecular holes, communicating with the subarachnoid space and bounded by connective tissue
Draining through the aqueous veins into the venous episcleral circulation	Draining into the venous sinus of the dura mater
Trabecular meshwork: mesodermal derivation	Pacchioni's granulations: mesodermal derivation
Ialuronic acid and chondroitin sulfate acid making highly viscous solutions, working as selective biochemical draining systems	Ialuronic acid and chondroitin sulfate acid making highly viscous solutions, working as selective biochemical draining systems
Aqueous absorption rate as a linear function of the intraocular pressure	CSF absorption rate as a linear function of the ventricular pressure

1.4. Physical-chemical Characteristics

At a physical-chemical level, too, the similarity between aqueous and CSF is striking: both fluids have specific weight of 1006-1008, Ph 7.3, anionic concentration higher than plasma, proteins and glucose to a certain amount. In the cerebrospinal fluid protein concentration is 15 to 40 mg/dl [8], of which about 85% is derived from the blood [9]. Glucose concentration is 45-80 mg/dl [10]. In the aqueous humor protein concentration is 12.4±2 mg/dl [11], while glucose (in patients with cataract) is 3.2 millimoles (i.e. 57 mg/dl [12]).

Cells are very rare or absent (liquor concentration: 0.5 cells per square mm).

CSF is isotonic compared with plasma. It is made of water by 99%, with 1-2% of organic substances and 8-9 grams of salts. Aqueous is made of 98-98.5% water and 1-1.3% salt, with traces of protein.

Intraocular pressure is 10-21 mmHg [13], while liquor pressure is less than 7.3 mmHg at the foramen of Monro. It is up to 14 mmHg at the level of the occipital pole (in the recumbent position [14], or, in the sitting position, below 10 mmHg [15] (5-15 mmHg according to Nathan [13]). In a more recent study liquoral pressure in two normal samples was 12.7±3.9, and 11.5±3.3 mmHg [16].

Both intraocular and liquoral pressure are suitable to temporary physiological variations after abdominal muscle contraction, Valsalva maneuver, Queckenstett maneuver (jugular compression), and even after postural changes. Moreover, both intraocular and ventricular pressure rise as a consequence of respiratory acidosis [17].

Finally, fluctuation synchronous with the systo-diastolic rhythm takes place in both cases.

Finally, aqueous and CSF show similar coagulative properties [18].

Table 4. Physical-chemical characteristics

	AQUEOUS HUMOR	*CSF*
SPECIFIC WEIGTH	1008-1009	1006-1008
PH	7,3	7,3
WATER	98-98,5%	99%
SALTS	1-1,3%	8-9g
ANIONS	Higher concentration compared to plasma	Higher concentration compared to plasma
PROTEINS	Lower concentration compared to plasma.(12.4±2 mg/dl)	Lower concentration compared to plasma (15 to 40 mg/dl)
GLUCOSE	Lower concentration compared to plasma (57 mg/dl)	Lower concentration compared to plasma (45-80 mg/dl)
CELLS	Sporadic or absent	0,5 cells per mm^2
COAGULATIVE PROPERTIES	Same as the CSF	Same as the aqueous
PRESSURE	15± 6 mmHg	5-15 mmH_g
TEMPORARY CHANGES OF PRESSURE	Increase due to abdominal contraction, Valsalva and Queckenstett maneuver Synchronous fluctuations with sistolic and diastolic cardiac phases	Increase due to abdominal contraction, Valsalva and Queckenstett.maneuver Synchronous fluctuations with sistolic and diastolic cardiac phases

What comes out from these data is that ocular and ventricular cerebral hydrodynamics share many aspects. Such histological, embryological and chemical-physical common properties lead to believe the two systems may be subjected to the same etiopathogenetic factors. Indeed, even in the pathological field strict resemblances can be spotted between glaucoma and hydrocephalus.

A schematic summary of the physical-chemical characteristics of aqueous humor and cerebrospinal fluid is reported in Table 4.

1.5. Therapeutic Traits-d-union

In many respects, the pharmacological as well as surgical treatment of many types of CSF hypertension does not differ from the guidelines followed to treat ocular hypertones.

Actually, treatment for communicant hydrocephalus, other than steroids, consists of acetazolamide and furosemide as well as of hyperosmolar solutions like mannitol. Moreover, beta-blocker, a main drug used to treat ocular hypertension, is found to lower intracranial pressure [19].

In a surgical perspective valve implants are long since employed to treat hydrocephalus: similar techniques, indeed, are used in case of malignant glaucoma or glaucoma resistant to any pharmacological treatment, by implantation of a unidirectional valve connecting the anterior chamber to the subconjunctival space.

A schematic summary of the therapeutic options to treat ocular and ventricular hypertension is reported in Table 5.

Table 5. Therapeutical analogies

TREATMENT OF OCULAR HYPERTENSION	*TREATMENT OF VENTRICULAR HYPERTENSION*
Acetazolamide	Acetazolamide+ Furosemide
Mannitol	Mannitol
Beta-blockers (timolol)	Beta-blockers
Steroids (neovascular glaucoma)	Steroids
Implant of unidirectional valves	Inplant of unidirectional valves

1.6. A Joint Classification of the Ocular and Ventricular Forms of Hypertone

Both glaucoma and hydrocephalus depend on factors affecting fluid secretion or outflow.

The classification of the hydrocephalus has been recently discussed [20,21,22,23,24].

Etiologically, hydrocephalus can be classified as:

-Hypersecretive hydrocephalus: rare condition occurring with secreting tumors originating from the choroid plexus.

-Obstructive or non-communicating hydrocephalus: caused by tumors or congenital malformations obstructing the communication between the ventricular compartments.

-Non obstructive or communicating hydrocephalus, i.e. hydrocephalus due to reduced outflow, as a consequence of increased venous pressure like thrombosis/occlusion at the level of the cerebral sinus, severe congestive heart insufficiency or obstruction/alteration at the level of Pacchioni granulations.

Based on the age of onset, hydrocephalus can classified as congenital (caused by a birth defect or genetic disorders) or acquired.

Based on the evolution rate, it can classified as:

-acute: when a sudden rise of intracranial pressure takes place, with ventricle dilatation and fast progression of symptoms till to coma.

-chronic: when the rise of intracranial pressure is more gradual and symptoms encompass visual disturbances, cranial nerve palsy and cognitive involution.

Finally, Based on the level of obstruction, hydrocephalus can be:

-communicant: when the obstacle to the normal CSF is at the level of the subarachnoid space.

-obstructive or non-communicant: when the obstacle is between the ventricles and the subarachnoid space.

The classification of glaucoma may rely on the presence or absence of causal secondary events (primary open angle glaucoma or secondary glaucoma), upon the sudden or progressive onset (i.e. acute or chronic), upon the age of onset (congenital or acquired), on the width of the iridocorneal angle (open, narrow or closed angle glaucoma), or, finally, on the site of the obstruction [2].

In order to devise a common classification for ocular and ventricular forms of hypertone, this latter criterion seems the most suitable.

Based on the site of the obstruction to the aqueous draining, primary glaucoma can be subdivided into:

-glaucoma due to intrascleral block

-glaucoma due to trabecular block (primary open angle glaucoma or POAG)

-glaucoma due to goniotrabecular block (congenital glaucoma)

-glaucoma due to angular closure (irritative glaucoma).

Secondary glaucoma, in turn, can be subdivided as:

-glaucoma secondary to increased episcleral venous pressure

-glaucoma secondary to trabecular block

-glaucoma secondary to angular block

-glaucoma secondary to pupillary block

-glaucoma secondary to ciliary (or posterior) block.

Finally, a rare and controversial clinical entity is glaucoma due to aqueous hypersecretion.

Our purpose of a joined classification of the ocular and ventricular forms of hypertension admits two main classes:

1-forms of hypertension with no mechanical obstacle

2-forms of hypertension with mechanical obstacle.

The first group includes hypertensive conditions in absence of mechanical obstructions along the outflow pathways: hypertension in this case would depend on defective absorption at the draining level (trabecular meshwork in the eye, Pacchioni granulations and subarachnoid space in the ventricles).

The second group is made of hypertensive conditions depending on mechanical obstruction along the outflow pathways (in the eye, for example, pupillary block).

The first group can be further divided in three subclasses, according to whether the draining system is defective per se (hypertone with intrinsic obstruction: HIO) or if it is affected by alterations of the nearby structures (hypertone with extrinsic obstruction: HEO) or, finally, if the hypertone depends on raised venous blood pressure after the draining site (hemodinamyc hypertone: HH).

In the eye, HIO would include primary open angle glaucoma (the cause of increased intraocular pressure is believed to rely on a structural alteration of the trabecular meshwork), congenital glaucoma (a cellophane-like membrane, covering the trabecular meshwork, hampers

aqueous outflow) and glaucoma secondary to iridocyclitis (determining "trabeculitis", that is inflammation of the trabecular meshwork). In the brain HIO would include the so called "communicant obstructive hydrocephalus", that show absorption defect at the level of the Pacchioni granulations, turned impervious to filtration after diffuse arachnoid infections.

In the eye HEO would include hypertension due to neovascular angular proliferation (neovascular glaucoma) and secondary cicatrizial postuveitic glaucoma (without pupillary block). Also pigmentary and pseudoexfoliation glaucoma would belong to this group.

In the brain HEO would comprehend communicant hydrocephalus secondary to adhesive (hemorrhagic or inflammatory) meningeal processes, able to impair the draining function of the subarachnoid space.

Finally, in the brain HH would take place in case of artero-venous fistula or tromboflebitis of the superior longitudinal sinus that act raising the venous pressure at that level. The increased venous pressure, in turn, lowers the transmural pressure gradient across the capillaries, reducing CSF draining.

A similar condition would occur at the ocular level in case of low flow carotid-cavernous fistula, cavernous sinus trombophlebitis or episcleral venous congestion.

The second group (forms of hypertension with mechanical obstacle) can be further classified topographically based on to the site the mechanical obstruction takes place.

If the mechanical obstruction occurs in the posterior chamber of the eyeball or in the internal liquor space (ventricular level), we will define the resulting hypertone as *hypertone with juxtasecretive obstacle (HJO).*

If it occurs in the anterior chamber of the eyeball or in the external liquor space, we can define the resulting hypertone as *hypertone with telesecretive obstacle (HTO).*

Evidently, by using this terminology we refer to pathological conditions in which the obstruction is localized respectively close or far from the secretory anatomical structures.

So, cerebral HJO would include the obstructive hydrocephalus with obstruction localized at the internal liquoral space (i.e. in the ventricles) and the congenital hydrocephalus due to sylvian aqueduct atresy.

In turn, the principal form of ocular HJO would be hypertone caused by posterior (or ciliary) block, as it occurs in case of ciliary body congestion (malignant glaucoma).

Cerebral HTO would encompass communicant hydrocephalus due to neoplasms at the level of the subarachnoid space and obstructive hydrocephalus as a consequence of closure of the Magendie or Luscka foramens. Also congenital hydrocephalus due to atresy of Magendie or Luscka foramens (Dandy-Walker and Arnold-Chiari malformations) would belong to this class.

Ocular HTO would include primary and secondary closure angle glaucoma and glaucoma secondary to pupillary block (Table 6).

Table 6. The advanced joint-classification of the ocular and ventricular hypertone

Hypertone with no obstacle		
	Aqueous	**CSF**
HIO	-Primary Open Angle Glaucoma (POAG)	-communicant hydrocephalus
	-congenital glaucoma	
	-glaucoma secondary to iridociclytis	
HEO	-neovascular glaucoma -pigmentary glaucoma -pseudoesfoliative glaucoma -cicatrizial postuveitic glaucoma	-communicant hydrocephalus secondary to adhaesive meningeal processes
HH	-glaucoma secondary to low-flow carotid-cavernous fistula -glaucoma secondary to cavernous sinus trombophlebitis -episcleral block glaucoma	-communicant hydrocephalus secondary to artero-venous fistula -communicant hydrocephalus secondary to trombophlebitis of the superior longitudinal sinus
Hypertone with obstacle		
HJO	Posterior block glaucoma	-obstructive hydrocephalus with obstruction at the internal liquor space -congenital hydrocephalus due to sylvian aqueduct atresy
HTO	-primary closed angle glaucoma -secondary closed angle glaucoma -glaucoma secondary to pupillary block	-communicant hydrocephalus due to neoplasms at the level of the subarachnoid space -obstructive hydrocephalus due to closure of the Magendie/Luschka foramens -congenital hydrocephalus due to Magendie/Luschka atresy

It should be noted that this speculative joint-classification, based on topographic criteria, can fail to highlight the resemblance of some clinical manifestations of ventricular and ocular hypertension; for example, in newborns and infants early ocular hypertone leads to bulbar dilation (buftalmus) that is somehow comparable to the bombèe fontanel in the child suffering from congenital hydrocephalus. Yet, congenital glaucoma and congenital hydrocephalus are placed in two different classes since in the two pathological conditions the draining impairment takes place at different anatomical sites. Nonetheless, the main scope of our model is to draw the attention on the analogy of the mechanism of damage in the two circulatory systems. It suggests possible correlations between ocular and ventricular fluid dynamics, so that pathological events acting on the anatomical and histological structures in charge of the ocular outflow could affect to some extent even the ventricular draining system and vice versa. More specifically, considered the noticeable anatomical and biochemical resemblance between the subarachnoid complex in the brain and the trabecular meshwork in the eye, structural abnormalities of the former leading to hydrocephalus could match with corresponding subclinical alterations in the latter, determining glaucoma. In the ophthalmological field, such perspective could broaden the idea of glaucoma, turning it from exclusive ophthalmological condition to a single aspect of a wider pathological involvement.

Indeed, liquor pressure in subjects affected by ocular hypertone is found to be higher compared to a age-matched control group [16,25].

Now, it remains to investigate the reverse condition: that is if patients suffering from essential idrocephalus show ocular characteristics that predispose their eyes to ocular hypertone.

Some years ago we provided our contribution in addressing this topic by performing a pilot study on a small sample of hydrocephalic patients.

2. Methods

Nine subjects suffering from communicating (normal tension) hydrocephalus (7 males, 2 females, mean age 68,77 ±3,3 years) participated the study. Exclusion criteria were the presence of glaucoma or diagnosed ocular hypertension (suspected glaucoma), other ophthalmological pathologies, myopia/ hyperopia> 3D, astigmatism > 2D, as well as pharmacological treatments other than those required by their neurological condition.

For each eye mean intraocular pressure (IOP), iridocorneal angle width and anterior chamber depth were evaluated and compared to the normative values as measured in a small age-matched control group (2 males and 5 females).

More specifically, each subject underwent applanation tonometry (average value from 3 different measurements at 8.30, 9.30 and 11.30 AM), gonioscopy (iridocorneal angle width graded according to the classification of Scheie [26]: Table 7) and peripheral depth of the anterior chamber (graded according to the technique of Van Herick [27].

Table 7. Scheie's grading of the width of the iridocorneal angle

Iridocorneal angle width (degrees)	*grade*	*Visible angular structures*
30 - 40	wide	All structures visible
30- 20	I	Iris root visible, difficult to see over iris root into recess
20	II	Narrow ciliary band
10	III	Only anterior trabeculum visible, posterior trabeculum obscured
0	IV	Only Schwalbe's line visible = closed angle

The method of Van Herick makes use of the corneal thickness in the periphery of the anterior chamber to judge its depth (Table 8).

Table 8. Van Herick's grading of the anterior chamber depth

Peripheral anterior chamber depth (PACD) compared to the corneal thickness (CT)	*Grade*
PACD ≥ CT	IV
PACD <CT and >1/2CT	III
PACD between ½ and ¼ CT	II
PACD < ¼ CT	I
PACD =split	I-S
PACD=0	0

The experiment was conducted according to a masking design.

3. Results

In Figure 3 the results obtained from the two samples are summarized. Even if still within the normal range in both groups, mean IOP is slightly higher in the hydrocephalic sample, being such difference statistically significant (15.78 mmHg ± 1.63 vs 13.71 mmHg ± 1.54, t-test: p=.001). In turn, in average the iridocorneal angle turned out to be narrower and the anterior chamber less deep in the pathological sample compared to the control group (Scheie grade: 0.53 ± 0.51 vs 0.11 ± 0.24; p = .007; Van Herick grade: 3.32 ± 0.66 vs 3.9 ± 0.32, p=.003).

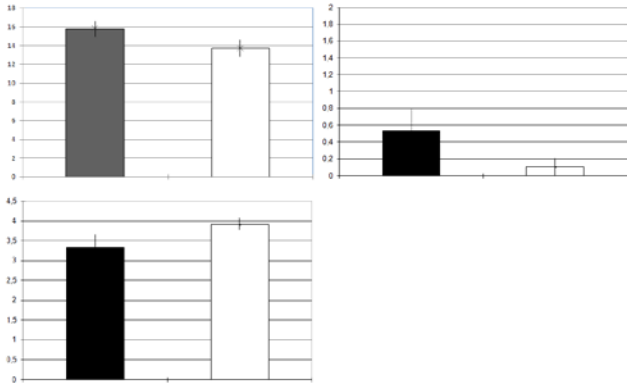

Figure 3. Upper left panel: average IOP; upper right panel: iridocorneal angle width based on Scheie grading (the higher the value, the narrower the angle); lower panel: anterior chamber depth based on Van Herick grading. Black: hydrocephalic sample, white: normal sample. Bars refer to IC 95%

4. Conclusion

Investigating possible etiological relationships between a given clinical condition and anatomo-pathological alterations not directly related to the former will hardly provide persuasive evidence. As a matter of fact, in the medical field variables are umpteen. The aim of this article is to call the attention to the possible existence of a link between brain ventricular pressure on the one side and intraocular pressure/aqueous draining structures on the other side. Indeed, the theoretical premises, exposed in the introduction, seem sound enough to support the existence of a trait-d'union between ventricular and ocular fluid circulation. Moreover, the results obtained in our preliminary experimentation provide interesting hints in this direction.

It is worth recalling previous studies have suggested glaucoma to be associated with lower CSFP. In two retrospective case-control surveys, in fact, average cerebrospinal fluid pressure of patients with primary open angle glaucoma turned out to be 33% lower compared to normal subjects (9.2±2.9 mmHg vs 13.0 ±4.2 mmHg: 9. 6 ±3.1 mmHg vs 12.7 ±3.9 mmHg [16,25]. In a subsequent paper Ren et al confirmed this trend [28]. In line, Bayer found consistent reduction of cerebrospinal fluid production in patients affected by Alzheimer disease, who in turn show higher prevalence of glaucoma compared to the normal population (25.9% vs 5.2% [29]).

The explanation provided for such results relies on the so-called translaminar gradient, i.e. on the difference of pressure between the anterior and the posterior side of the lamina cribrosa. Low liquor pressure compared to intraocular pressure would lead to progressive cupping of the optic disc, thereby predisposing to the development of glaucoma [16,25,30].

An interesting aspect is that in one of the abovementioned studies patients affected by ocular hypertension (therefore with no optic disc cupping

appearance nor visual field defects but with higher than normal intraocular pressure) showed higher cerebrospinal fluid pressure compared to a control group (13.2±3.8 mmHg vs 11.5 ±3.3) [16]. Similar results have been obtained 3 years later by Ren et al [31], who found higher cerebrospinal fluid pressure in a group of subjects affected by ocular hypertension compared to a control sample (16±2.5 mmHg vs 12.9±1.9 mmHg). In addition, he demonstrated significant correlation between IOP and CSF pressure (CSFP) not only in the first group but also in the normal sample.

Elevated cerebrospinal fluid pressure in ocular hypertension is advanced to have a protective effect by counterbalancing the abnormally high intraocular pressure [16]: this way the translaminar gradient would be reduced, so that the papillary cupping, thereby the development of glaucoma, would be prevented.

The abovementioned experiments compared CSFP of patients suffering from glaucoma or ocular hypertension with CSFP of normal subjects.

Indeed, in our pilot study the approach was opposite: we compared IOP of patients affected by communicating hydrocephalus with the average IOP of a control group. The working hypothesis is that anatomopathological elements of the cerebrospinal fluid circulation in the ventricles and of the aqueous circulation in the eye, sharing so many anatomical, histological, biochemical as well as physical features, are likely to be related: it would follow that the structural alterations and consequent possible pathological outcome of the ventricular fluid dynamics are expected to reflect themselves on the ocular hydrodynamics. In our case traces of ventricular outflow impairment leading to essential hydrocephalus (namely diminished CSF absorption at the arachnoid villi) should be found even in the eye as reduced capability of aqueous draining at the level of the iridocorneal angle. As a matter of fact, the peripheral depth of the anterior chamber has been found lower and the iridocorneal angle narrower in our group of patients with communicating hydrocephalus.

Given the embryological similarity between anterior chamber/iridocorneal angle on one side, external liquoral space/subarachnoid space on the other, both could be susceptible to a common developmental disorder. So, the pathological factor responsible for the raise of ventricular pressure could well act, albeit at a subclinical level, in the anterior chamber of the eye. In presence of such (para)physiological variables, as expected, the neurological group showed higher average IOP compared to the control sample. In sum, it is possible that this above-average IOP makes hydrocephalic subjects more liable to develop ocular hypertone, thereby glaucoma in the long term. In effect, our conclusion is supported by the 3-fold greater prevalence of glaucoma in patients suffering from normal pressure hydrocephalus compared to a control group, as reported by Chang & Singh [32].

Evidently, the experimental part of this study suffers from a number of shortcomings: in particular measured IOP values were not corrected for central corneal thickness; moreover, individual measurement of CSF pressure both in normals and controls has not been provided (for ethical reasons, since a non invasive technique is still missing). Finally, the size of the recruited samples was small, so that further studies involving a larger number of participants are necessary to confirm and deepen such preliminary finding.

Above all, the main intent of this preponderantly speculative paper is to recall attention on the importantce of a more interdisciplinary clinical approach in the neuro-ophthalmological field.

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