

● PERSPECTIVE

Glaucoma and amyotrophic lateral sclerosis, two kindred diseases?

Amyotrophic lateral sclerosis (ALS), a predominantly sporadic disease with unknown etiology and pathogeny, is a member of a group known as motor neuron diseases (MND). The heterogeneity of the clinical presentation of the disease is a fundamental aspect of ALS and is determined by the variable engagement of its upper motor neuron (UMN) and lower motor neuron (LMN) components (Ravits and La Spada, 2009).

Glaucomas are a group of diseases with different clinical manifestations in which a common pathological mechanism is assumed to be responsible for neuronal death. Based on this common mechanism, the use of the singular term, glaucoma, is common practice. Glaucoma is a mainly sporadic disease. Known genetic association in glaucoma is estimated at 2–5% at the most. Nevertheless, a percentage of researchers in the field include glaucoma among the “occult” degenerative neuropathies (Gupta and Yücel, 2007). In glaucoma, the neurodegenerative hypothesis is partially superseding the ischemic and mechanic alternatives that prevailed throughout the past century.

A new alternative paradigm attributes a capital role to astrocytes. As neurons as well as astrocytes are lost in the optic nerve head in glaucoma, and following the metabolic dependency of neurons on astrocytes, neural damage is preceded by an astrocyte insult. According to the hypothesis, the aqueous humor (AH) is diverted towards the optic nerve head and, due to its low calcium content, exposes astrocytes to ionic stress. The result is the induction of apoptosis in astrocytes *via* a mechanism known as anoikis (Carreras, 2014).

Calcium, universal messenger for biological signaling, modulates vital cell aspects from impregnation to cell death (apoptosis) (Carafoli, 2007). Due to the peculiarities of the visual organ, glaucoma is possibly a single disease, but because of a similarity between AH and Cerebrospinal Fluid (CSF), both equally calcium-depleted, other neural diseases may follow the same paradigm. These fluids are commonly referred to here as central-nervous-system fluids (CNSF), with the exclusion of blood and interstitial fluid.

At present, then, we can compare glaucoma and ALS as having a mainly sporadic form of manifestation associated with aging, and a similar subgroup of patients with a clear genetic component ranging from 5% to 10%. Much, or even all, of what is mentioned here might also apply to other members of the MND group. For the sake of simplicity, this perspective article deals with the striking similarities between glaucoma and ALS, when glaucoma is examined from the perspective of the aqueous-deviation paradigm.

What kind of disease is ALS? No specific test is available for ALS, meaning that diagnosis is a process of elimina-

tion. As a disease found more commonly in older people, the incidence of ALS will continue to rise. This could be due to more accurate diagnosis as well as to the longer life expectancy in the general population. ALS can affect any adult at any age, with the highest incidence occurring between the ages of 50 and 70. Men are affected more often than women. An individual's lifetime risk of developing MND has risen to 1 in 300–400. Life expectancy from the moment of diagnosis is 2 to 5 years. It kills a third of its victims within a year, and more than half within 2 years after diagnosis.

There is no consensus regarding the pathology and origin of ALS. Much debate persists on the effect that known genetic pedigrees may have on the classification of ALS as a degenerative disease, *i.e.*, with a hidden genomic defect that leads to neuronal death.

What kind of disease is glaucoma? No specific laboratory test exists for diagnosing glaucoma diagnosis or tracking its progression. The disease is diagnosed and monitored on clinical grounds, mainly through direct observation of the optic nerve head and psychophysical tests. With regard to the pathology, it is essential to delineate here the complete sequence of events leading to retinal ganglion cell (RGCs) loss in glaucoma. In so doing, we will find an overlap between glaucoma and ALS based on anatomical, histological, and physiological similarities. Conversely, we will also comment on the differences.

In brief, the new hypothesis concerning the pathogenesis of glaucoma cites not raised intraocular pressure, but the misdirection of the flow of AH towards the posterior pole of the eye as the main cause of cell loss (Carreras, 2014) (**Figure 1**). The core of the hypothesis is the ionic composition of AH, which is significantly poor in calcium in relation to plasma and interstitial fluids. The intraocular optic nerve has a limited ability to transfer excess fluids from the vitreous cavity into the glial perivascular sheet. This fact, along with the lack of tight junctions between the astrocytes, makes the optic nerve surface permeable to fluids from the vitreous cavity. The presence in the prelaminar astrocytes of a signal system, zonulae adherents (ZA), is critical to the maintenance of the tissue structure. This signal system is composed of, among other molecules, N-cadherin, or neural calcium–adherin. Because of this, survival of the astrocytes in the tissue depends on adequate levels of calcium ions (as first messenger). A loss of astrocytes *via* anoikis results in axonal focalized destruction in the prelaminar tissue due to lack of metabolic support (Carreras, 2014) (**Figure 1C**).

Working hypothesis: Based on the similarities between the organs, tissues, physiology, and pathological evidence from the eye suffering glaucoma, on the one hand, and the spinal cord suffering ALS, on the other, we conclude that glaucoma and ALS may share a common pathogenetic mechanism, namely a misdirection in CNSF flow.

Like the AH, responsible for glaucoma, the CNSF is poor in calcium (2.9 mEq/L compared to 5.2 mEq/L in

plasma) (Schain, 1964). If we assume that there are no impenetrable barriers (*i.e.*, there are no tight junctions among the ependymal lining of the central spinal canal) between CSF and interstitial fluid, because of the “to and fro” circulation of the CSF (Orešković and Klarica, 2014), perfusion of CSF into the gray central matter from the ependymal canal is a hazard (Figure 2A). Axons from the pyramidal tract are naked on the myelin sheath when they meet the somas of the lower motor neurons in the lateral gray horns of the spinal cord and brain stem. The distal axonal segments of UMN as well as the somas and proximal segments of LMN axons are surrounded by a neuropil, formed by astrocytic expansions that connect the neurons to the capillaries. Spinal-cord astrocytes also display ZA. The sequence of the effect of low calcium should follow the same pattern described above for glaucoma. Astrocyte anoikis would be followed by early apoptosis of the LMN somas, compartmentalized axonal destruction of the axons of the UMN, and subsequent apoptosis of the somas (Figure 2B).

Common and diverging aspects of Glaucoma and ALS:

For its developmental origin, the eye resembles a CNS ventricle, including the production of an adaptation of the CSF (namely the AH) by a modified choroidal plexus, which, due to the inversion of the optic cup during eye development in mammals, flows outside the ependymal duct. The circulation of the AH can be related to CSF circulation, and hypertensive, normotensive, and hypotensive states are common to both systems.

Histologically, the crucial prelaminar region of the optic nerve, formed by the curved axons of RGCs, is also rich in astrocytes (Figure 1B), while the optic tract is also a common myelinated tract of the CNS similar to those of the spinal cord. In the spinal cord, astrocytes are abundant in the central gray substance where bare descending motor axons make synaptic connections with dendrites from the LMN. Astrocytes typically show two types of structural connections between them: gap junctions (GJ) and adherens junctions, or zonulae adherens (ZA). Through the GJ junctions astrocytes share glucose and most, importantly, lactate, to nourish the axons. Through ZA the astrocytes inform the nucleus of the correct relationships with neighbor cells *via* a signaling system. The ON astrocytes make up Elschnig’s inner lamina, a permeable sheet of astrocytic expansions that lack the only impermeable type of junction: the zonulae occludentes (ZO). A similar feature is to be found in the ependymal lining of the central canal. ZO are present only in the choroidal plexuses, while they are conspicuously absent in the remaining ependymal lining, making it fluid-permeable.

In ALS, meanwhile, mainly the motor tract is affected, which is presumably a result of the shorter distance between the central canal and the surrounding CSF in the anterior part of the spinal cord, due to the presence of the anterior median fissure. In some cases the development of the disease also includes sensorial pathways, a phenomenon easily explained by this hypothesis due to progression by contiguity. In glaucoma, only a sensorial tract comprises the ON. In both diseases, the vessels may play opposite

roles: initially protective in glaucoma (Carreras, 2014), and as a promoter of misdirected flow in ALS. Vessels, in ALS, could predetermine preferential flow routes (Figure 2A).

One of the most striking facts is that neuronal loss in ALS is an extremely orderly process that actively propagates in a contiguous manner from a localized starting focus (Ravits and La Spada, 2009). In glaucoma, contiguous progression along the borders of the central excavation is a feature that can be reproduced in a computer model of the optic pathways (Carreras et al., 2011).

Toxic activity by reactive astrocytes has been proposed as a contributing factor in neuronal death both in glaucoma (Nikolskaya et al., 2009) and ALS (Haidet-Phillips et al., 2011), as well as in other neurodegenerative diseases of the CNS. Here, rather than a toxic function, the essential role of astrocytes in nurturing neurons is interrupted by the detachment of the zonula adherens and the induction of anoikis in the astrocyte (Carreras, 2014).

ALS has recently been separated from neurodegenerative diseases in a very clear, bold manner:

in ALS, neurons do not degenerate, they are killed (Ravits and La Spada, 2009). It is an expression that finds its equivalent in glaucoma: RGCs are healthy until they disappear (Carreras, 2014). Although much effort has traditionally been devoted to explaining why neural cells disappear, less emphasis has been placed on the concomitant loss of astrocytes. As neurons depend on astrocytes for their survival, while the opposite is untrue, a logical sequence of events can be explained by the early disappearance of the astrocyte support from which the demise of the neuron follows. Both processes can be triggered by the perfusion of the intercellular clefts by calcium-poor CNSF.

Translational research: If, as proposed here, glaucoma and ALS share a common mechanism, it would open the door to an etiological approach to therapeutics. Two pathogenetic approaches to therapy are envisaged: either a) the deviation of flow is halted; or b) the levels of calcium ion are equaled to those of interstitial fluid/plasma.

If the analysis presented here is corroborated, the implications for clinical applications would be huge, both in the glaucoma and ALS fields. The hypothesis posed would directly advise exploring the safety of increasing Ca^{2+} levels in CNSF. This would be the most direct therapy.

The fundament of the low calcium levels in CNSF is a crucial point to address. The fact that both AH and LCR are low in calcium could be a) an adaptation to specific tissue needs in the CNS; or b) a side effect of the three mechanisms involved in aqueous humor formation: diffusion, ultrafiltration, and active secretion (Goel et al., 2010). Bito (1970) showed that AH calcium levels nearly matched those of a plasma dialysate in mammals, a process that is temperature-dependent. It then needs to be investigated whether low calcium levels are essential to normal CNSF function, or only circumstantial. Nevertheless, the question arises: is it safe to compensate the calcium relative deficiency? This latter option would offer the

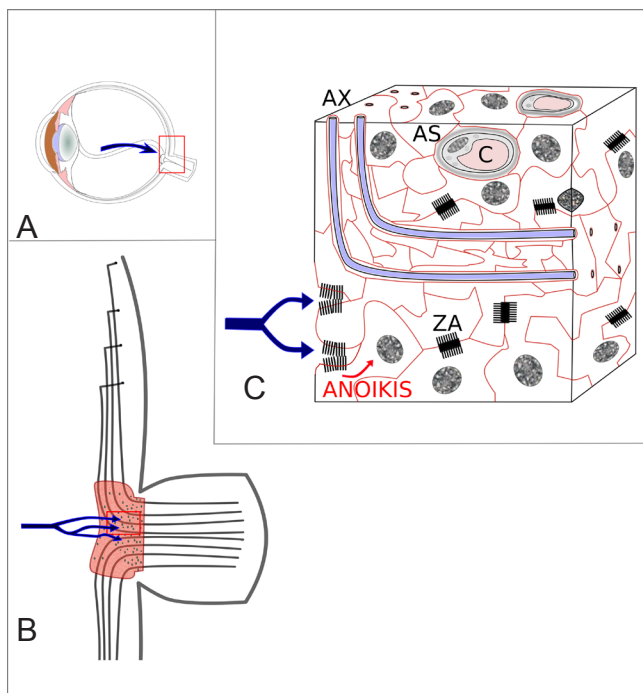


Figure 1 Schematic representation of the pathogenetic sequence in glaucoma and lateral amyotrophic sclerosis.

(A) Posterior deviation of aqueous humor is not impeded. (B) Astrocytes populate the lamina and prelaminar regions of the intraocular portion of the optic nerve. Only the retinal ganglion cells and the nerve-fiber layer are depicted (vessels not represented). (C) Diverted aqueous humor can permeate the prelaminar tissue, release the zonular adherents and trigger anoikis in the astrocyte. Axonal destruction and RGC apoptosis would follow. AS: Astrocyte; AX: axons (unmyelinated); C: capillary; ZA: zonula adherens.

greatest opportunity for treatment, but fortunately not the only one. Impediment to outflow from the ependymal canal is the other direct alternative. Finally, the question is: will the hypothesis resist further scrutiny?

Francisco Javier Carreras*

Surgery Department, Faculty of Medicine, University of Granada, Granada, Spain

*Correspondence to: Francisco Javier Carreras, M.D., Ph.D., fcarrera@ugr.es.

Accepted: 2016-07-26

orcid: 0000-0002-8961-1291 (Francisco Javier Carreras)

doi: 10.4103/1673-5374.191211

How to cite this article: Carreras FJ (2016) Glaucoma and amyotrophic lateral sclerosis, two kindred diseases? *Neural Regen Res* 11(9):1415-1417.

References

- Bito LZ (1970) Intraocular fluid dynamics. *Exp Eye Res* 10:102-116.
 Carafoli E (2007) The unusual history and unique properties of the calcium signal. Chap 1 in Krebs J, Michalak M (Eds) *Calcium: A matter of life or death*. 1st ed. Amsterdam, Oxford: Elsevier. *New comprehensive biochemistry* 41:60.
 Carreras FJ (2014) Pathogenesis of glaucoma: how to prevent ganglion cell from axonal destruction? *Neural Regen Res* 9:2046-2047.

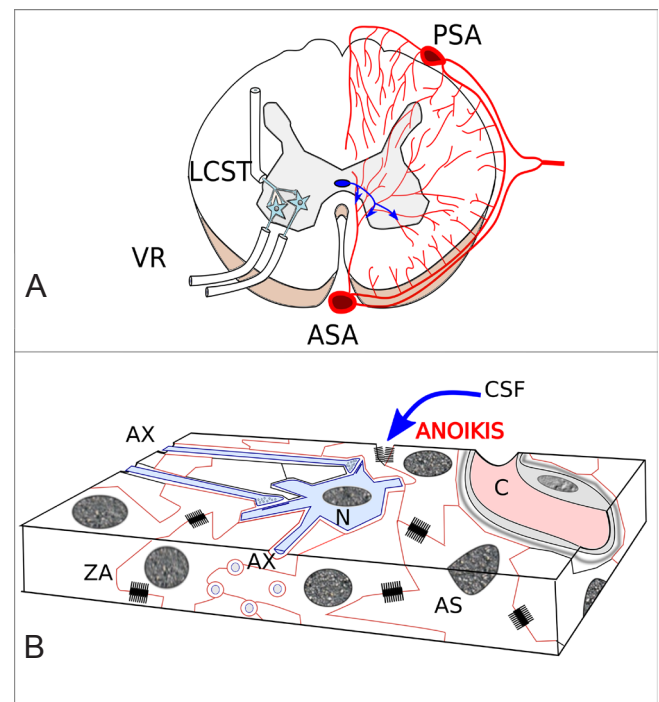


Figure 2 Schematic representation of the proposed pathogenetic sequence in amyotrophic lateral sclerosis.

(A) Section of the spinal cord showing a myelinated axon from the upper motor neurons entering the gray lateral horn and becoming naked. Axons form UMN contact, through synapses, with dendrites from lower motor neurons. Leakage of CSF would follow a preferential anterior route, following the vessels (blue arrows). (B) Lower motor neurons are in close contact with the nurturing astrocytes and through them with the capillaries. The presence of the zonulae adherentes in the astrocytes makes this tissue prone to triggering anoikis in case of permeation of CSF from the central ependymal canal, facilitated by the absence of tight junctions. AS: Astrocyte; ASA: anterior spinal artery; AX: axons (unmyelinated); C: capillary; CST: lateral corticospinal tract; CSF: cerebrospinal fluid; PSA: posterior spinal artery; VR: ventral root; ZA: zonula adherens; N: neuron.

- Carreras FJ, Rica R, Delgado AV (2011) Modeling the patterns of visual field loss in glaucoma. *Optom Vis Sci* 88:E63-79.
 Goel M, Picciani RG, Lee RK, Bhattacharya SK (2010) Aqueous humor dynamics: a review. *Open Ophthalmol J* 4:52-59.
 Haidet-Phillips AM, Hester ME, Miranda CJ, Meyer K, Braun L, Frakes A, Song S, Likhite S, Murtha MJ, Foust KD, Rao M, Eagle A, Kammesheidt A, Christensen A, Mendell JR, Burghes AH, Kaspar BK (2011) Astrocytes from familial and sporadic ALS patients are toxic to motor neurons. *Nat Biotechnol* 29:824-828.
 Nikolskaya T, Nikolsky Y, Serebryiskaya T, Zvereva S, Sviridov E, Dezso Z, Rahkmatulin E, Brennan RJ, Yankovsky N, Bhattacharya SK, Agapova O, Hernandez MR, Shestopalov VI (2009) Network analysis of human glaucomatous optic nerve head astrocytes. *BMC Med Genomics* 2:24.
 Orešković D, Klarica M (2014) To and fro: a new look at cerebrospinal fluid movement. *Fluids Barriers CNS* 11:16.
 Ravits JM, La Spada AR (2009) ALS motor phenotype heterogeneity, focality, and spread: deconstructing motor neuron degeneration. *Neurology* 73:805-811.
 Schain R J (1964) Cerebrospinal fluid and serum cation levels. *Arch Neurol* 11:330-333.