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Editorial

From glaucoma to neuroglaucoma[☆]

Del glaucoma al neuroglaucoma

The peculiarity of the optic pathway, which is determined by its great extension, the number of neurons involved, the distribution and decussation of the axons and the intense and constant axonal flow, means that any type of lesion is projected and reflected progressively along the entire pathway and can reach the ends of the pathway both anterogradely and retrogradely. This secondary axonal damage or distal neuronal degeneration was already described by Waller¹ in 1850. Wallerian degeneration – so named in his memory – is limited to one neuron, but when it jumps the synapse and extends to another adjacent neuron with which it is related, it is called transynaptic degeneration (TD).²⁻⁴ In the case of the optic pathway, the lesion of the first and second neurons would extend anterogradely to the lateral geniculate ganglion (LGG) and the visual cortex. Likewise, third neuron lesions due to tumours or strokes would extend retrogradely through the second neuron towards the retina, and these changes can be shown in analyses of the ganglion cell layer (GCL) in optical coherence tomography (OCT),⁵ with complete match between the campimetric alteration and the ganglion cell lesion. In our work pending publication on the alteration of the occipital cortex evidenced by magnetic resonance imaging, we found that 25 months after glaucomatous damage a lesion arises in the occipital cortex that can be measured by assessing the increase in the occipitoparietal and calcarine fissure, an increase that would be the expression of a decrease in the volume of the occipital cortex secondary to atrophy.⁶ In another study, also pending publication, we can see how cerebrovascular accidents retrogradely alter microcirculation – both in area and density – of some retinal layers as evidenced by angio-OCT.

Furthermore, with new computer solutions applied to radiological methods such as diffusion tensor tractography, we can evaluate the diffusion movements of water molecules along

axons, which are wider than in the perpendicular direction of their movement due to being limited by the cell membrane and myelin sheath. Using this phenomenon, the predominant direction of axonal bundles at each point in the central nervous system can be studied by MRI and nerve pathways can be identified and assessed.⁷

This opens up a new concept in the case of glaucoma – neuroglaucoma – which would not be limited to the ocular economy, but would have the capacity for potential extension through the optical pathway to the LGG and occipital cortex,⁸ even altering the areas of association of visual information, with a symptomatology that in most cases would go unnoticed by the glaucomatologist. In the same way, retrogradely, it would involve the extension of brain lesions to the GCL and retinal nerve fibre layer (RNFL), making the diagnosis of glaucoma difficult and altering it when mainly based on OCT.

The origin of this damage transferred between neurons of the optic pathway lies in the intense axonal flow, the main purpose of which is to rapidly transport different components from the soma in a rapid manner (mitochondria and vesicles at 1 $\mu\text{m/s}$) and slow manner (cytoskeleton components, 1 mm/day). Paradoxically, neuronal architecture depends on this axoplasmic transport -and vice versa-, which is affected by neuronal or other distantly related neuron injury. The alteration of neuronal dynamics can occur at different levels, from damage to motors (dynein and kinesin), rails (microtubules), loads (whose purpose is to couple the motors) or the fuel used⁹ (mitochondrial ATP). Progressive neuronal degeneration would start with axonal dysfunction called diaschisis that would give way to structural damage or progressive gliosis in several phases. Initially, physical degradation of the axon and myelin sheath would occur and lipids would be generated. These lipids would be phagocytized, causing the disappearance of most of the myelin. In the final phase, generalised

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gliosis would structurally and functionally disorganise the damaged axon.¹⁰

The repercussions of TD are manifold in daily clinical practice. In anterograde TD, atrophy localised in the occipital cortex, that would originate in an ocular lesion, could produce symptomatology derived from the lesion in the area of association of visual information. In retrograde TD, alterations in the RNFL and GCL may hinder and confuse the diagnosis of glaucomatous disease in patients suspected of this pathology. Furthermore, diaschisis due to compression of the optic pathway by mainly selar tumours could lead to earlier surgical treatment in those patients without campimetric lesions, but with a lesion of the GCL in development that can be evidenced by OCT. This opens up interesting fields of clinical and research collaboration with disciplines such as radiology, neurology, neurophysiology, endocrinology and neurosurgery.

In conclusion, despite the increasing sub-specialisation of ophthalmology, the unitary concept of eye disease and its cerebral repercussions and vice versa is evidence that we must take said concept into account in order to avoid misdiagnosis and inadequate medical-surgical approaches, as well as to establish new lines of research to shed light on the vast environment of the brain which, from the first neuron of the optic pathway to the occipital cortex, is constituted as a unit.

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