Editorial

The retina as a biological marker of neuronal damage

La retina como marcador biológico de daño neuronal

Manuscripts dated 1700 BC attest to the fact that the brain has been an obsession for mankind throughout its history. Since ancient Egypt to the past century, the study of the Central Nervous System (CNS) in live humans was restricted to rudimentary neurosurgery approaches and indirect study through signs and symptoms of dysfunctions. However, October 1, 1971 was a turning point in CNS approaches as on that date the first Computerized Tomography (CT) was obtained. Six years later, technological developments produced Magnetic Resonances (MR). Since then, MR has evolved from conventional MR to the numerous varieties available at present.

Since the mid-nineteenth century we are able to observe the retina and optic nerve directly with the Helmholtz primitive ophthalmoscope. In 1917, Vogt described the Retina Nervous Fiber Layer (RNFL) which he observed using a light beam with long (red) waves filtered. However, this discovery was not applied to ophthalmological photography until 1965. Ten years later, Frisen and Hoyt were the first to describe RNFL defects in multiple sclerosis patients.

However, ocular fundus exploration with ophthalmoscope, such as observation of the RNFL with single color photographs are qualitative techniques highly dependent on the observer and his or her experience. For this reason, the adaptation of digital imaging diagnostic techniques to ophthalmology, such as Optic Coherence Tomography (OCT) and laser polarimetry (GDx), were turning points in the exploration of these structures. The possibility of obtaining measurements of the optic nerve and RNFL in an objective, precise and reproducible manner allowed researchers to address greater challenges. The initial applications focused on the study of ocular and mainly retinal pathologies, but at an early stage it was proposed to utilize the information obtained about axonal damage in the optic nerve to other neurological diseases.

RNFL, as part of the CNS, exhibits characteristics which make it unique and different from other structures. The physiological absence of myelin allows the specific study of isolated axonal damage. On the other hand, it is obviously the only point in which it is possible to observe directly a part of the CNS.

The neurological disease which most benefited from RNFL observation as regards physiopathology is, without a doubt, multiple sclerosis (MS). MS is characterized by the degeneration of neurons and axons both in the white and grey matter of the CNS, in association with an inflammatory process having self-immune characteristics. The first to apply this technology to the disease was Parisi in 1999 who, with quantitative measures obtained with OCT, demonstrated the existence of damages in the retina ganglionary cells in patients with optic neuritis and that these measures correlated with P-ERG.1 Subsequently, OCT confirmed that optic neuritis was not the only cause of optic nerve damage in MS patients because patients without known inflammatory events in the optic nerve exhibited RNFL thicknesses significantly lower than those of healthy controls paired by age and sex.2,3 Since then, many papers have contributed to a better understanding of the physiopathology of optic neuritis and MS. It seems that optic neuritis accelerates and worsens an insidious chronic neuronal damage process occurring in MS throughout the CNS and more specifically in the optic nerve, in the same way as any other focal demyelinating inflammatory process in other parts of the CNS. It is known that brain axonal damage is the cause of functional disability in MS patients. The correlation between disability measured with the Expanded Disability Status Scale (EDSS) and the RNFL atrophy supports the association between the optic nerve damage and damages on other CNS locations. In addition, it is known that the primary progressive and secondary progressive types exhibit a greater axonal damage than the relapsing-remitting type and that in most cases the temporal sector is the first to suffer damage.

Post-mortem studies on Alzheimer disease patients had detected neuronal degeneration in the optic nerve, with selective damage of retina ganglionary cells. In the RNFL this damage was also determined with black-white photographs and subsequently with OCT and confocal scan laser.4,5
Retinal abnormalities such as thinning of retinal veins and reduced venous flow have been observed in early stages of the disease. However, the presence of defects in the RNFL is discussed in the initial phases thereof.6 In advanced stages, all studies demonstrate the existence of anomalies and it seems that the macular volume is related to the cognitive deterioration measure with the mini-mental7 test.

Even though retina dopamine level reductions had already been observed in Parkinson patients, the appearance of the above mentioned new technologies allowed to determine in 2004 the thinning of the RNFL in these patients, more markedly in the inferior and infero-temporal sectors.8 A few years later, the correlation between the macular thickness and the global-motor deterioration secondary to the disease was described.9

In the light of the above observations, the following question is required: Is the retina in fact a “window to the brain”? The first approach aimed at confirming that the mean thickness reduction with OCT corresponds exclusively to axonal losses. This was confirmed by Trip et al when referring that the RNFL thickness correlates better with the width of visual evoked potentials wave P100 (which reflects axonal integrity) than the latency thereof (which reflects the integrity of the myelin sheath). In second place, it aimed at determining that the axonal loss, measured at the level of the optic nerve, is related directly to neuronal damage in other locations. This assumption seems to be likewise confirmed by the good correlation observed between the RNFL measures and the brain atrophy fraction in MS patients without optic neuritis history.10 In patients having such history, focal inflammatory events added to the chronic damage explain the lack of correlation.

The possibility of using retina ganglionary cells as a biological marker for brain axon damage points to multiple applications in the future. Firstly, we trust it will allow for a substantial increase of the current knowledge about the pathogeny of CNS diseases and secondary neuronal damage. In a second phase, after validating the observations of the retina as a sample of what is happening in other CNS locations, we would have a simple and accessible biological marker for quantitatively monitoring neurodegeneration, neuroprotection and neuroregeneration, a challenge yet to be met. Also awaiting confirmation is the ability to use these instruments in a reliable manner to assess responses to the treatments being applied.

For the time being we are in the initial phase, trying to confirm that we are actually capable of inferring the presence of brain axonal damage on the basis of what we detect in the RNFL. In the short term we will be able to search for sub-clinical damages in patients with known risk factors, determine new and potentially damaging agents for the CNS or, on the contrary, repairing agents. Whatever may emerge, it all seems to indicate that the new retina and optic nerve imaging digital analysis tools constitute a useful method for analyzing neuronal damages and their management.

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REFERENCES