PERSPECTIVE

# Neurodegeneration in branch retinal vein occlusion

One of the most common forms of visual impairment and reduction in overall visual acuity is branch retinal vein occlusion (BRVO), second only to diabetic retinopathy (Rogers et al., 2010; Sun et al., 2013). Unlike central retinal vein occlusion (CRVO) which is a similar macular disease, BRVO is extremely more prevalent and generally only affects a smaller portion of the retina (Osborne et al., 2004) due to the nature of the disease. While initially the impairment can be extreme, evidence exists that patient visual improvements generally up to 20/40 can be achieved either with or without intervention (Rogers et al., 2010; Alshareef et al., 2016). Unfortunately, the existence of BRVO in patients can lead to further visual complications resulting from the hypoxic stress in the eye. Such examples are cystoid macular edema (CME) as well as inner retinal layer and retinal ganglion cell (RGC) damage. Therefore, improved detection, monitoring, and testing for BRVO not only holds the possibility of reducing this occurrence of macular disease, but also minimizes the occurrence of secondary complications due to the BRVO trauma. Rogers et al. (2010) reported 10% incidence of BRVO in fellow eyes.

In our current research (Alshareef et al., 2016), we have investigated the spectral-domain optical coherence tomography (SD-OCT) of patients with BRVO, as well as their unaffected eye, and control patients exhibiting no BRVO or any other visual impairments. Typically, the analysis of BRVO has centered on investigations of the retinal nerve fibre layer (RNFL) as this has been shown to thin noticeably following BRVO (Kim et al., 2014). However, our previous work (Chhablani et al., 2015), as well as work in the literature (Nouri-Mahdavi et al., 2013), has shown that retinal diseases result in damage to RGC's nuclei and dendrites in the macula. Furthermore, this damage has been shown to occur earlier and more consistently than that observed in the RNFL (Alshareef et al., 2016). However, our research shows for the first time that it may also extend to patients exhibiting BRVO, and could present a better evaluation and diagnostic tool for this common disease.

While our data showed that, regardless of the duration of BRVO onset, both RNFL and ganglion cell inner plexiform layer (GCIPL) exhibit significant thinning when the disease is present, the extent of thinning in the GCIPL is more severe. This was determined by analyzing the average, minimum and sectoral (superotemporal, superior, superonasal, inferonasal, inferior, inferotermporal) GCIPL thicknesses in an elliptical annulus around the fovea. Macular RNFL and outer retinal thickness were analyzed using similar parameters and compared to the normal fellow eyes. RNFL contains RGC axons while both the ganglion cell and inner plexiform layers are made up of RGC nuclei and dendrites. This would suggest that the nuclei and dendrites, more that the axons, of RGCs are the primarily affected areas when a hypoxic-ischemic event occurs. While we recognize that the study has its limitations in terms of the number of patients surveyed and long-term or follow-up investigations into the BRVO patients, the significance of this work cannot be overlooked. Proper BRVO evaluation and treatment should involve the potentially more important investigation of the viability of these retinal cells as well as the photoreceptor integrity and external limiting membrane.

Typically, treatment protocols for BRVO rely on the preservation of inner retinal cells (Sun et al., 2013) and that the photoreceptor integrity and external limiting membrane investigation aids in predicting the final visual acuity outcome. However, the RGC loss due to the BRVO could be dramatically affecting this outcome. Inner retinal layers have been shown to exhibit the highest sensitivity to oxygen starvation events (Janaky et al., 2007). Furthermore, following a hypoxic-ischemic event, vascular endothelial growth factor (VEGF), nitrogen monoxide, free oxygen radicals, glutamate and inflammatory cytokines levels have all shown to increase significantly. Any of these events could trigger the various degradation mechanisms for RGCs such as the disruption of the blood-retinal barrier, excitotoxicity and the build-up of intracellular calcium ions ($Ca^{2+}$) (Alshareef et al., 2016). Furthermore, neurodegeneration is mediated by, amongst other factors such as platelet-derived growth factor and tumor necrosis factors, VEGF. Neuronal degeneration could significantly affect the viability of RGCs due to progressive hypoperfusion. Additionally, the neuron apoptosis could result in an acute input reduction to the inner retina which again would result in a decrease in RGC viability.

Further investigation is required to determine the nature of the RGC status in the GCIPL and RNFL resulting in a significant decrease in thickness when BRVO onset occurs and this status could be used for BRVO diagnosis and treatment.

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