The importance of combining structure and function to measure rates of progression in glaucoma

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Received: 21 March 2018 / Accepted: 22 March 2018 / Published online: 5 April 2018
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Dear editor,

In a cohort of glaucoma patients followed with standard automated perimetry (SAP) and spectral domain optical coherence tomography (sdOCT) for an average of 3.5 years, Zhang et al. [1] investigated the relationship between progression assessed with the visual field guided progression analysis (GPA, Humphrey Field Analyzer, Carl Zeiss Meditec, Inc.) and rates of structural (sdOCT) and functional (SAP) change. In particular, they included a combined index of glaucomatous damage (the retinal ganglion cell [RGC] index), which combines structural and functional information into a single metric based upon an algorithm developed by Medeiros et al. [2, 3].

Monitoring functional change in glaucoma, a chronic, progressive optic neuropathy and a leading cause of irreversible blindness worldwide [4], plays a crucial role in clinical decision-making in order to prevent deterioration of quality of life. Despite the lack of a gold standard to define glaucoma progression, SAP has been the reference technique in clinical practice and randomized clinical trials to monitor functional progression. Notwithstanding its widespread use in clinical and research settings, SAP results can be analyzed in different ways depending on the parameters of interest (e.g., global indices, clusters or pointwise sensitivities) and the type of statistical method used to define significant change (namely, event- and trend-based analyses). The GPA employs a statistical package that enables the analysis of SAP changes based upon different parameters and using both event and trend analyses of these parameters.

In the present study, the authors compared the GPA event-based algorithm with the rates of change of sdOCT-measured retinal nerve fiber layer (RNFL) thickness and the RGC index over time using trend analysis. Regarding the GPA, they

defined significant progression if at least three test locations, repeated in the same points on three consecutive follow-up tests, exceeded the lower limits of test-retest variability from the device's reference database (which is deemed "Likely Progression" by the software's output). These criteria were developed in the Early Manifest Glaucoma Trial [5] and have since been commercially available and largely used to define functional progression. Regarding the trend analysis of RNFL thickness and the RGC index, the authors defined significant change based upon the estimated age-related change obtained from linear regression applied to a subset of healthy eyes. For the RNFL thickness and RGC index, eyes were deemed to have progressed if the slope of change was statistically significant ($P < 0.05$) and faster than that of average age-related loss.

Therefore, Zhang et al. addressed a clinically important question as they investigated potential limitations of what is currently the most widely employed method to detect glaucomatous functional progression by comparing with a structural metric (RNFL thickness) and a new index that combines functional and structural information, which provides an estimate of the number of RGCs. Because glaucoma ultimately leads to RGC death, such comparison provides a valuable insight into the relationship between the GPA output and the phenomena underlying the pathogenesis of glaucoma progression.

The authors found that 11% of eyes progressed based upon the GPA, 16% based upon sdOCT RNFL thickness slopes, and 23% based upon the RGC index slopes. In addition to detecting more progressing eyes, the RGC index detected progression in 15% of eyes that had been missed by the GPA. Of note, eyes that had been missed by the GPA had an average RGC slope of $-28,910$ cells/year, but with rates of change that ranged from two to nine times faster than the expected age-related losses. This is a striking observation as it suggests that by over-relying on the GPA output, clinicians may be missing a substantial number of eyes which have been losing RGCs at a very rapid rate. Simply stated, eyes otherwise

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considered stable based upon visual fields could potentially be losing RGCs at a speed that could result in significant impairment in their lifetime.

The authors should be congratulated for their work and for stressing the importance of combining structural and functional parameters to assess glaucoma progression. The application of the RGC index to measure rates of progression in clinical practice may prove useful to tailor therapy in glaucoma and mitigate the burdens of false-negative results from the GPA—a method which, despite significant limitations, is often considered the reference standard to detect progression in clinical practice.

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