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Major review

Management of advanced glaucoma: Characterization and monitoring

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ABSTRACT

Recent advances in glaucoma diagnosis focus on diagnosing the disease in early stages. Despite the importance of such efforts, a meaningful proportion of patients present in advanced stages. The cost for treatment and monitoring of advanced glaucoma often exceeds that with earlier disease, not to mention the significant effect of visual impairment on quality of life. Moreover, structural and functional tests used to monitor changes encounter technical limitations in advanced cases that can delay detection of true progression. New technologies and methods to analyze longitudinal data may prove helpful for monitoring patients with advanced glaucoma and reduce the burdens of the disease.

1. Introduction

The main goal of glaucoma therapy is to halt or slow the loss of visual function and to preserve quality of life.[130,131] With acceleration of retinal ganglion cell apoptosis from individuals with no vision impairment to statutory blindness, glaucoma follows a continuum, with detection occurring at any point along it. Given the importance of early detection as a means to prevent visual impairment and blindness,[90,99,110] there have been concerted efforts during recent decades to develop technologies aimed at helping clinicians detect mild to moderate disease with improved sensitivity and specificity.

Modern technologies such as standard achromatic perimetry (SAP), optic disc photography, and optical coherence tomography (OCT), for instance, are now valuable tools to diagnose glaucoma and monitor changes among patients with mild to moderate disease. For monitoring patients with advanced glaucoma, these technologies have only limited usefulness. From a public health perspective, these limitations are concerning because a clinician's ability to monitor

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and treat advanced glaucoma is highly compromised at the stages when the risk of blindness is greatest. We review the challenges for accurate monitoring of advanced glaucoma and propose some methods to overcome or mitigate them.

2. Definition of advanced glaucoma

There is currently no consensus on a glaucoma classification based on severity. Although SAP is known to have a relatively low sensitivity to detect early glaucomatous damage,[49,50,92,107] most classification criteria use this technology using a 30-2 or 24-2 strategy to define severity once measurable functional loss exists.[10,85]

Although structural damage of the optic nerve (glaucomatous optic neuropathy) often can be detected before SAP functional impairment, there are numerous advantages of using SAP results to rank glaucoma severity, despite its limitations. Global metrics derived from this technology, such as mean deviation (MD) and visual field index, are statistically correlated with measures of vision-related quality of life, despite the wide distribution of residuals of tested models.[72,87,123] Moreover, studies have shown that this correlation may not be linear, showing poor correlation in early visual field loss, but becoming more linear and significant in advanced disease (Fig. 1). For example, in later stages of glaucoma, a 1-dB change in the 24-2 MD is associated with approximately 1 unit change in the composite score of the National Eye Institute Visual Function Questionnaire–25.[72,87,114] Of note, this relationship tends to be stronger in better than worse seeing eyes.

As an alternative to SAP, recent studies have shown that OCT-measured retinal nerve fiber layer (RNFL) thinning is also correlated with worsening of National Eye Institute Visual Function Questionnaire–25 scores.[38,44] When using longitudinal data, each 1-μm/year loss of RNFL thickness was associated with a decrease of 1.3 units per year in National Eye Institute Visual Function Questionnaire–25 scores.[38] Nevertheless, to date, there is no glaucoma severity classification system that uses OCT RNFL as its main metric. One of the potential reasons is the poor performance of OCT (and other objective imaging technologies) in discriminating moderate from severe stages of the disease, in part due to the floor effect.[75,79,135] Another advantage of using SAP results to define glaucoma severity is that many randomized clinical trials investigating the effect of treatment in glaucoma and ocular hypertension use SAP (alone or in combination with structural evaluation) as the main outcome measure.[3,54,65,83] Therefore, our current understanding of the relationship between intraocular pressure lowering and glaucoma onset or progression translates to the effect of each mm Hg intraocular pressure reduction on the development or progression of visual field loss. The same concept holds when comparing the results of clinical trials assessing different types of intervention on glaucoma outcomes.

In October, 2011, the American Academy of Ophthalmology reported a new International Classification of Diseases–9/10 codes that allow staging of glaucoma into mild, moderate, and severe disease based on the analysis of the visual field printout of the patient's worse seeing eye (Table 1). Given the great variability in costs of care and resource utilization among glaucoma patients, such a unified classification system may soon be used to establish value-based modifiers.[26]

One limitation of the International Classification of Diseases system is that it lacks details on how loss is defined. Most researchers and clinicians define "loss" based on how age-corrected sensitivities fall within the normative database distribution in total or pattern deviation plots. In this review we define advanced glaucoma based on the visual field staging system described by Hoddap, Parrish, and Anderson criteria using 30-2 SAP and extended to the 24-2 strategy (Table 2).[45] Based on the Hoddap, Parrish, and Anderson criteria, advanced glaucomatous visual fields have 1) an MD worse than −12 dB, 2) at least 50% of the points depressed at $P < 5\%$ (i.e. falling within the lowest fifth percentile of a Gaussian distribution of healthy controls) or 20% at $P < 1\%$ in the (corrected) pattern deviation plot, 3) at least 1 point in the central 5° with a sensitivity of 0 dB, or 4) points within the central 5° with sensitivity <15 dB in both hemifields. Note that 2 remarkable features of these criteria are the use of an objective, continuous variable (MD) and the extent of damage to the central field. These criteria are based on reliable visual field

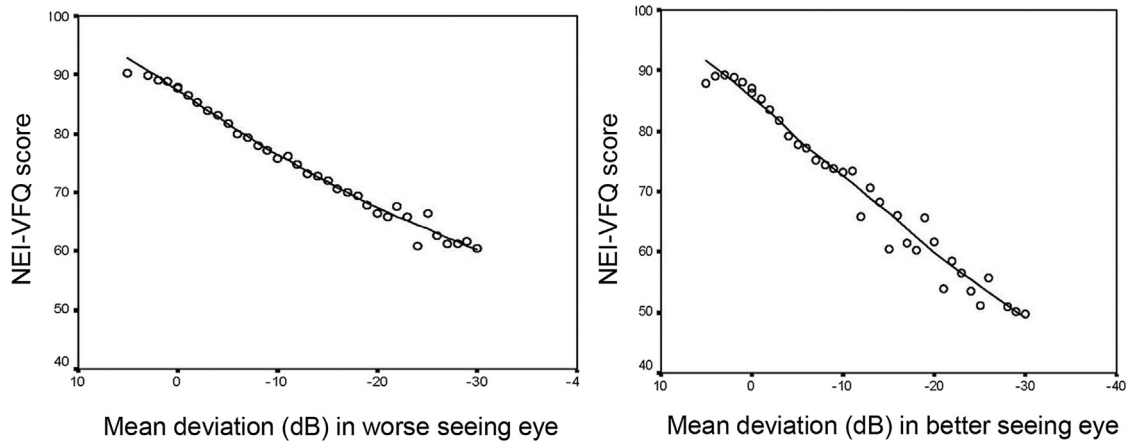

Fig. 1 – Linear regression plot of NEI-VFQ-25 composite scores and visual field loss (mean deviation scores in decibels) in worse and better seeing eyes.[71] NEI-VFQ = National Eye Institute Visual Function Questionnaire.