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Flash Look

Progression in Glaucoma: a snapshot

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ABSTRACT

The main goal of glaucoma management is to slow disease progression, so preserving functional vision as much as possible. Thus, accurate detection of structural and functional progression in glaucoma is essential for an effective patient care and to protect quality of life. However, from a clinical point of view, optimizing this detection remains a challenge for ophthalmologists worldwide. We hereby review concepts and summarize current knowledge about interpreting the different methods to detect disease progression in glaucoma patients.

INTRODUCTION

Glaucoma is a progressive optic neuropathy with a varying degree of deterioration among patients. The main goal of glaucoma management is to slow the disease progression so to preserve functional vision as much as possible. Therefore, it is crucial for physicians to know how to estimate rates of structural and functional progression for an effective patient care and to protect quality of life. However, it still remains a diagnostic challenge.[1]

More than 10 years ago, *The Early Manifest Glaucoma Trial* (EMGT) aimed to determine factors for progression in glaucoma patients, including treatment regimens.[2] To distinguish between progression and normal inter-exam variability or changes do to age and media opacities is not straightforward. Also, despite several methods for structural and functional analyses are used, there is no consensus on the most reliable method to identify a real and significant change. A great number of research papers have been published on the subject but its results are sometimes difficult to translate into clinical practice.[3-6]

The purpose of our review is to summarize the state of the art and enable each physician to better acknowledge and interpret the different methods to detect progression in glaucoma patients.

UNDERSTANDING CONCEPTS

2.1. Trend-based and Event-based Analyses

For progression analysis, most methods - both structural and functional - can be categorized as either *trend--based or event-based*.[1,7,8]

In trend-based analyses (e.g. mean deviation [MD]), a form of regression (most commonly linear) is used to evaluate a series of measurements and estimate statistically significant rates of change. Its main advantage is the fact of taking all measurements into account. However, its peak performance is not achieved before a minimal number of examinations are available.

In event-based analyses (e.g. Humphrey Guided Progression Analysis [GPA]), each new exam is compared with baseline values. Differences are considered statistically significant if superior to expected inter-test variability (i.e. 95% prediction limits are defined as the long-term variability of a global index or at each test location). It has the advantage of being potentially faster than trend-based analyses but it does not allow direct estimation of the rates of visual field (VF) change.[9,10]

2.2. Pointwise vs Global analyses

Each examination - either structural or functional - is composed of a group of individual measurements.[8,10,11]

Pointwise analyses evaluate differences in each point

of the examination, separately. Pattern standard deviation (PSD) is an example of pointwise analysis. It allows detection of highly localized damage but is inherently more variable and it may be difficult to distinguish between normal variability and clinically significant change. Also, pointwise rates of change tend to plateau with disease worsening and may underestimate the rate of damage in more advanced disease when significant visual loss exist and the hill of vision becomes flattened.[3]

In global analysis, an average of all individual measurements is used in a single examination. Mean deviation (MD) and visual field index (VFI) are examples of global indexes and are relatively easy to interpret. However, global analysis is relatively insensitive to highly localized damage, since computing an average of all measurements can mask change in few points.[7,12]

2.3. Defining and interpreting progression

Regardless of the methods and analyses used to evaluate rates of change, defining progression criteria is essential.

It is important to recall that more conservative criteria yield higher specificity and lower sensitivity, and vice-versa. Also, one need to know that the results of statistical tests used are the observed magnitude of change and/or the chance of a meaningful change assuming a null hypothesis of no change. Thus, it is always necessary a subjective interpretation for each value and analysis for them to become clinically significant. For example, if a rate of reduction in retinal nerve fiber layer thickness (RNFLT) of 0.2 μm/year is found ($p < 0.05$), it could mean a small and significant glaucomatous disease progression, an age-related change or even a random finding.

It is important to know each method and its limitations and to understand the usefulness of combining event and trend-based analyses.

FUNCTIONAL PROGRESSION

Various visual field perimetric techniques have been used, being standard achromatic perimetry (SAP) the most frequently used in glaucoma patients.[7] Short wavelenght-automated perimetry (SWAP) has been available for 20 years but recent studies raised questions about its compared sensitivity to SAP.[13]

As previously mentioned, pointwise event-based (e.g. GPA) and trend-based analysis (e.g. MD and VFI) should be considered complementary and useful at different stages of the disease. GPA compares each new test result, point by point, and VF loss is measured as change in pointwise pattern deviation by more than the expected variability. If changes occur in more than 3 points in three consecutive follow-up tests, a "likely progression" flag is raised. However, glaucoma may cause generalized sensitivity loss and GPA may not detect this pattern of change.[14] The MD is the weighed average of total deviation values and VFI is similar but with greater weight given to central than peripheral points, being more resistant to the effects of optical mean opacities than MD.[15,16]

While in early disease an absolute change of -2dB in MD may be insensitive for a highly localized change but recognized on GPA pointwise analyses, in more severe glaucoma global pointwise rates of change reach a plateau and may underestimate rates of change.[7,17] Nevertheless, the physician should bear in mind that in terms of visual-related quality of life (VRQL), a MD below -18dB or a VFI greater than 50% were significantly associated with low VRQL scores.[18]

Based on the *The United Kingdom Glaucoma Treatment Study* (UKGTS), a multicenter randomized clinical trial, visual field (VF) deterioration was based on the GPA pattern deviation maps and defined as, in either eye, at least 3 test points showing significant negative change compared with baseline ($P<0.05$), at the same location in 2 consecutive VFs (tentative deterioration) and deterioration according to the same criteria present in the next 2 VFs (confirmed deterioration).[19] Thus, 4 visual fields are needed to confirm progression. The challenge remains on feasibility based on the limitations of each department and on the cost-effectiveness of each strategy.[20] Some authors suggest a "wait-and--see-approach", clustering VF examinations at baseline and after a 2-year period. It is argued that this strategy reduces the false-positive rate, while increasing sensitivity for detection of disease progression.[21]

In addition, a word should be given to new models, including pointwise trend analyses, and advanced statistical techniques such as Baseyan methods. Overall, these new methods suggest the possibility of an improvement in VF progression detection, allowing more accurate predictions of the future of the disease and thus leading to more efficient follow-up consultations.[7,22-24]

STRUCTURAL PROGRESSION

The evaluation of the optic nerve head (ONH) and peripapillary retinal nerve fiber layer (RNFL) still remains a pillar in glaucoma patients' management.[7] Automated,

quantitative measurements of the ONH and RNFL easily provide potentially useful large amounts of data that need to be interpreted in the context of each individual patient.

Analogous to functional progression evaluation, structural parameters are used in event- and trend-based analyses. However, several studies alert for only fair agreement between structural (e.g. rim area / topography) and functional evaluations.[25-27]

The advent and current routinely use of spectral domain ocular coherence tomography (SD-OCT) has revolutionized the structural characterization of the ONH, RNFL and the macula with fast image acquisition, high resolution and low exam variability.[27,28] Thus, very subtle rates of change can be detected using trend analyses. However, it is important to note that the use of the same device is essential since measurements are not interchangeable.[8,28] Yet, most versions of SD-OCT's currently used have demonstrated good performance for glaucoma detection, but data is not as sharp when evaluating glaucoma progression.[29,30] Also, the number of examination affects the effectiveness of regression analysis. As for visual fields, to best estimate rates of change, the optimal frequency suggested is to perform 6 exams during the first 2 years of follow-up, based on a baseyan analysis approach.[7] However, practical issues commonly limit such recommendations.

As predicted, most eyes present early deterioration in inferior and superior poles of the ONH, where it is believed damage firstly occurs.[31] We should note, however, that significant changes in RNFL thickness and glaucoma progression are not the same thing. Age-related RNFL loss also occurs in healthy subjects and no clearly defined thresholds exist to undoubtedly separate it from true glaucoma progression. Long and expensive studies, such as longitudinal cohorts of control subjects may help enlightening these still imperfect definitions.[32,33] Moreover, it was proposed that macular thickness might be more helpful than RNFL to identify progression in advanced disease states (e.g. MD < -10dB).[30,34]

Since a good structure-function correlation occurs mainly in dramatic cases, a combined approach is desirable to diagnose glaucoma, identify progression and better manage most patients.[35] Table 1 summarizes issues and criteria for both structural and functional evaluations.

Table 1 | Issues related to structural and functional evaluations.

Structural	Functional
Patient-independent (objective)	Patient-dependent (subjective)
Less time consuming	Consumes more time and resources
No fatigue effect	Fatigue hinders repetition
Low variability (~5%)	Higher variability
Variability less related to baseline value	Variability worse with worse baseline value

FUTURE TRENDS

Recently, Burgoyne et al have claimed the use of other ONH variables than rim analysis as potentially clinically useful early markers of glaucomatous change, such as Bruch's membrane opening (BMO), lamina cribrosa (LC) thickness and displacement.[36-38] The LC morphology, in particular the posterior displacement of the anterior LC surface is believed to be a sensitive and reliable marker of glaucomatous damage.[39-42] However, other authors argued that LC is a dynamic structure and that its morphology should not be evaluated using only LC position clinical indexes. They support this theory based on the fact that BMO varies with axial length, age and race.[43] Also, evidence exists that connective tissue components of the ONH change after glaucoma surgery, thus limiting its clinical utility to diagnosis, being currently inadequate for a validated progression evaluation.[44,45]

Recent studies defend the use of *LC shape* (i.e. central ridge characterization) as a probably better predictor of glaucoma progression. Using advanced imaging techniques, it is believed that the deviation of LC shape from its normal saddle shape may be indicative of pathology or a risk factor for glaucoma progression.[6]

Over the last years, it has been studied the potential for using biomarkers in glaucoma to enable physicians for screening high-risk populations, contributing to an earlier diagnosis and eventually a timely medical decision.[46,47] A biomarker has been defined as a biochemical, molecular, or cellular alteration that is measurable in biological media such as tissues, cells, or fluids.[48] Minimally invasive procedures are being developed to identify biomarkers of retinal ischemia. Serum proteins, autoimmunity factors, inflammatory molecules and neurodegenerative biomarkers in glaucoma have been studied and reviewed elsewhere.[49] Notably, for the trabecular meshwork dysfunction, serum amyloid-A, an acute-phase apolipoprotein, and also 3α-hydroxysteroid dehydrogenase, an enzyme that metabolizes steroids have been proposed as potentially useful biomarkers for primary open-angle glaucoma or as risk predictors.[50,51]

Future advances in structural, functional and biochemical analyses would certainly help clinicians to effectively screen populations and provide the best care possible to glaucoma patients. However, as demonstrated, there is no machine or ancillary test which reliably replaces a comprehensive and throughout clinical examination. Each patient should be regarded as unique, by evaluating his/her individual characteristics and disease stage. Further robust studies will keep us on good track, pursuing excellent evidence-based care to glaucoma patients worldwide.

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