MONITORING GLAUCOMA PROGRESSION

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Glaucoma is a disease of the optic nerve, characterised by a specific pattern of progressive injury to retinal ganglion cells and their axons, which results in the alteration of optic disc topography, commonly known as "cupping", and associated with visual field loss. Glaucoma is, therefore, a disease that is defined, staged, longitudinally assessed, and treated on the basis of structural appearance of the optic nerve and its function[1].

Most glaucoma patients show slow progression of structure and function over many years. However, a subset of glaucoma patients will demonstrate fast progression and are at risk of significant visual disability or blindness. To reduce the probability of visual disability, clinicians after diagnosing glaucoma and initiating treatment, should focus primarily on whether the disease is stable or whether there are progressive changes that require an increase in therapy.

RISK FACTORS FOR PROGRESSION

There are several risk factors for glaucoma progression, including higher intraocular pressure, pseudoexfoliation, older age, lower ocular perfusion pressure, advanced disease at time of presentation and the presence of an optic disc haemorrhage. Cardiovascular disease is an important risk factor for rapid glaucoma disease progression irrespective of IOP control. Patients with significant risk factors for progression should be followed more closely to ensure that the treatment plan is sufficient.

TOOLS FOR DETECTING GLAUCOMA PROGRESSION

European and American guidelines explain progression as a deterioration of structural and/ or functional defects .More detailed definitions of progression however have not yet been established. According to the World Glaucoma Association, both functional and structural testings should be conducted throughout the course of the disease. Previously, it was generally accepted that optic disc changes precede VF damage. However, the Ocular Hypertension Treatment Study (OHTS)[2] and the European Glaucoma Prevention Study (EGPS)[3] have shown that structural and functional damage seldom coincide in patients converting from ocular hypertension (OHT) to glaucoma, and the nonlinear relationship between MD and RGC counts indicates that face value interpretations of rates of MD loss over time can be misleading. It remains unclear why some patients seem to first develop a structural change, while others first change in function. But this could be related to the accuracy of the methods used to evaluate structural and functional changes as well as individual morphology and factors governing susceptibility to damage.

While visual fields and optic disc photography have been considered the gold standard for detecting progression, no one particular test is perfect for detecting progression. Additionally, there is not always agreement among tests or those interpreting the tests.

For decades, clinicians have used standard automated perimetry (SAP) to detect functional progression in glaucoma patients. Despite the subjective nature of the testing and the importance of patient's attention and cognitive abilities, it remains a decisive component of glaucoma testing. Structural progression can be detected using a variety of tools, including optic disc and RNFL photography and OCT.

SAP TO DETECT FUNCTIONAL PROGRESSION IN GLAUCOMA

Criteria from The Collaborative Normal-Tension Glaucoma Study (CNTGS) and The Early Manifest Glaucoma Trial (EMGT)

THE CNTGS

The CNTGS' investigators determined progression using the threshold numbers in full-threshold Humphrey Visual Fields. If 2 or more points within or adjacent to an existing scotoma worsened by at least 10 dB or 3 times the average of the short-term fluctuations, whichever was larger, that field was thought to have progressed after confirmation on 2 subsequent fields. These numbers, however, may not apply to Swedish Interactive Threshold Algorithm (SITA) visual fields for 2 reasons. First, the short-term fluctuation is not measured in the SITA program. Second, a 10-dB change in full threshold may not be equivalent to a 10-dB change in a SITA field.

THE EMGT

The Glaucoma Progression Analysis software (Carl Zeiss Meditec Inc., Dublin, CA) incorporates the EMGT's statistical method for identifying glaucomatous progression. For the indication of likely progression, the Glaucoma Progression Analysis software requires that 3 consecutive visual field tests contain 3 or more identical points that have changed at a statistically significant level.

DETECTION OF PROGRESSION AND ESTIMATION OF RATES OF PROGRESSION

Detection of progression and estimation of rates of disease deterioration are essential in order to evaluate risk of functional impairment and establish treatment strategies.

RATE OF PROGRESSION

Rate of progression provides important information about

the risk of vision loss. SAP is the most commonly used method for assessing rates of visual function loss in glaucoma and estimating risk of impairment from the disease. Glaucoma progression rate varies widely, even among patients under careful management, and risk factors alone cannot accurately predict which patient will progress rapidly versus slowly. While some patients progress very slowly and need only minimal therapy, a minority of treated patients will progress at rate that could rapidly lead to disability, if left unchecked. Therefore, an understanding of each patient's rate of progression is helpful in individualizing treatment and in identifying patient at high risk for progressing to visual disability.

By tradition, rates of change have been measured by SAP using linear regression over time with parameters such as mean deviation (MD) and expressed in units of decibels/year (dB/y).

Progression may have different clinical consequences depending on the age and level of visual field (VF) loss. Progression in an 80-year-old patient with early damage has different implications compared to a 45-year-old with advanced damage. In individual patient, the rate of VF change allows the clinician to predict the possibility of lifetime visual disability by taking into account factors, such as age, life expectancy, and the amount of presenting VF loss. Numerous reports have estimated that the average rate of VF change, in glaucoma patients ranges from 0 to -1.1 dB/y[4]. More recently, Heijl et al. reported a median MD rate of - 0.62 dB/y in patients undergoing routine care[5].

In a recent study, Chauhan and colleagues have suggested that rates of MD change slower than -0.5 dB/y would be unlikely to lead to visual disability. While a patient with early visual field loss (MD=-4dB) and a rapid rate of progression (-2 dB/y), could be expected to develop total (-30 dB) in 13 years[6]. Such reasoning is fundamentally based on the assumption that rates of MD change over time are linear. However, there is very little evidence in the literature to support this notion.

A change of -0.5 dB in MD in early stages of the disease (with initial MD close to 0 dB) would correspond to a loss of approximately 100,000 RGCs. Such loss would actually be greater than the loss of approximately 35,000 cells that would be associated with a 2-dB change in MD for an eye with severe damage and MD of -15dB.

ESTABLISHING A RELIABLE BASELINE

Establishing a reliable baseline is essential for detection of glaucoma progression. Functional assessment requires repeated VF tests to overcome the patient's learning curve. The first documentation of a VF defect should be confirmed as soon as possible on at least 2 additional consecutive examinations. The VF in stable severe glaucoma shows more fluctuations compared to stable mild glaucoma[7]. It should be emphasized that obtaining a representative baseline is foundational to future management decision.

FREQUENCY OF TESTING

In the evaluation of functional defects, the EGS has made recommendations regarding the frequency of VF testing using specific analysis tools. The frequency of testing is to be adapted to the severity of glaucoma damage and the rate of progression.

As per EGS guideline[8] 3 fields per year—including baseline tests—in the first 2 years after initial diagnosis should be done. This amount of testing usually is enough to detect rapidly progressing eyes- those worsening by -2 dB/year or more. The World Glaucoma Association 2011 Consensus Statement on Glaucoma Progression made a similar suggestion. In summary, we need to perform field-testing more frequently in patients with manifest glaucoma and field loss in the first few years after diagnosis, and continue to test yearly for the next 5 years or so. Thereafter, in clearly stable patients and in elderly patients, with mild VF defect and slow rate of progression we may be able to further reduce the number of fields, in some cases perhaps to one field every second year.

MEASUREMENT OF VISUAL FIELD PROGRESSION IN GLAUCOMA

The most extensively available analysis aid for measuring visual field progression is the Humphrey Perimeter's Guided Progression Analysis or GPA. Two commonly used methods to identify change in VF defects over time are the event-based and the trend-based progression analyses. GPA helps doctors identify and quantify VF progression in glaucoma patients, using both event and trend analysis. Event and trend analysis are different but have complementary goals. The goal of event analysis is to assess whether there has been any statistically significant worsening in the VF. The goal of trend analysis is to quantify any observed rate of change, and to help the practitioner measure the risk of future disability associated with that rate. The recently introduced Guided Progression Analysis by the Humphrey VF Analyzer (Carl Zeiss Meditec, Inc. Dublin, CA, USA) provides both an event-based progression analysis and a trend-based analysis on the same printout.

In clinical practice, information from both these analyses is essential, because it is not only adequate to identify VF progression in glaucoma but also to decide the rate of progression (ROP), so that the treatment can be more aggressive in patient with fast rate of progression.

GPA EVENT ANALYSIS

Event-based analysis determines VF progression to be either present or absent depending on a predefined change in the VF parameters. The event-based progression analysis, called the glaucoma progression analysis (GPA), is based on the criteria designed to identify VF progression in the EMGT[9].

GPA offers a plain language event analysis called GPA Alert. GPA Alert will show the message 'Possible Progression' when 3 or more test points show statistically significant deterioration on 2 successive follow- up examinations, compared to a baseline of two field tests. A 'Likely Progression' message will be found when the same 3 or more significantly deteriorated test points appear in at least 3 consecutive follow -up tests.

SYMBOLS USED IN GCMPS

GCPMs use triangle symbols to highlight statistically significant deterioration from a baseline consisting of the average of two chosen tests. Each follow-ups field is compared to that baseline, and open triangles indicate test point locations with deterioration that is statistically significant at the 5% level. Half black triangles indicate test point locations that have shown statistically significant deterioration in 2 consecutive follow-up examinations, and filled-in black triangles designate locations where such deteriorations has been observed in 3 or more consecutive tests[10].

While evaluating GCPMs one can

expect that each test point will have a 5% risk of being falsely flagged simply from random test variability. GCPMs are not calculated for fields having an MD value worse than -20dB.

GPA TREND ANALYSIS

Trend-based analysis provides the actual rate of change of VF parameters and is based on the ROP of the visual function of the eye through a linear regression model using a new global index, VF index (VFI).The goal of trend analysis is to quantify how quickly each patient is changing and thereby to help doctors identify patients who are progressing at rates that threaten to cause considerable visual disability within the patient's expected life time.

This regression analysis is automatically displayed in the GPA summary and the Full GPA reports whenever a sufficient number of visual field tests are available. VFI is a single number that summarizes each patient's VF status as a percentage of the normal age-corrected sensitivity. Therefore, a completely normal VF would have a VFI of 100%, and a perimetrically blind VF would have a VFI of 0%.

LIMITATIONS OF EVENT AND TREND ANALYSIS

Both of these are known to have some limitations. One of the major limitations of the trend-based analysis is the length of the follow-up required to detect progression, which itself is influenced by a number of factors, including examination frequency, media opacities like cataract, underlying rate and type of progression[11]. The ability of the event-based analysis to detect progression is dependent upon the degree of change exceeding test–retest variability of stable glaucoma patients, which is known to be already high for damaged locations[12]. Therefore, the event-based approach is also likely to be less sensitive to smaller changes in the VF parameters. In addition, event-based analyses have also been shown to be vulnerable to threshold variability.

INTERPRETING VFI PROGRESSION RATE

Interpretation of rates of progression can be quite intuitive if one considers the patient's current level of visual function and life-expectancy. Ideally it would be better to prevent all progression, but a minimum goal could be trying to retain at least a VFI of 50% in the better eye. The US Social Security Administration has defined an MD of -22dB as a threshold for visual disability. An MD of -22dB corresponds to a VFI of approximately 30%[13].

ALTERNATIVE ANALYSES

Overview

The overview report puts all of a patient's VF tests into a single report. The Overview also is the preferred standard format in follow-up of diseases other than glaucoma, such as neurological field loss. While this report does not quantify change, it provides a broad qualitative overview of a patient's VF history.

CHANGE ANALYSIS

The Change Analysis report was first offered in the original HFA over 25 years ago and has largely been replaced by the newer GPA report. It contains a linear regression analysis of MD that may be useful in certain situations.

Challenges

One should not assume that all VF progression is due to glaucoma. Patients with glaucoma are generally elderly and either have or can develop other diseases. The practitioner should rule out other causes of a worsening VF such as vascular occlusive disease, age-related macular degeneration, non glaucomatous optic neuropathies, and even central nervous system lesions or strokes. Before changing a patient's management, one should obtain at least 2, preferably 3, confirmatory visual fields-a potentially challenging clinical practice. Without these confirmatory visual fields, physicians may diagnose progression when there is not any. The researchers from the CNTGS and EMGT agree that confirming progression with more than one follow-up field is significant.

OPTIC DISC TO DETECT STRUCTURAL PROGRESSION IN GLAUCOMA

Progressive neuroretinal rim thinning, increased excavation, and diffuse and localized loss of the RNFL are all recognizable features of structural damage in the disease. However, their precise relationship with functional deterioration in patients with glaucoma remains largely unclear.

Stereoscopic photography (ideally simultaneous, with a fixed angle) is the preferred method of qualitative imaging. Images obtained with digital scanning devices are dependent on software for interpretation. Often, 3 images are necessary during the first 18 months to distinguish progression from fluctuation. If colour photography is not available, manual drawings are still useful to provide a record of the optic disc appearance.

Challenges

Regulatory agencies throughout the world generally have not approved structural assessment of the optic nerve as a primary end point in clinical trials of glaucoma drugs and devices. Both the Ocular Hypertension Treatment Study[14] and the European Glaucoma Prevention Study demonstrated that a substantial proportion of patients with ocular hypertension who developed glaucoma showed a change first in optic disc photographs. However, despite being included as end points for glaucoma conversion in these studies, progressive optic disc damage has not yet been demonstrated to translate into worse clinically relevant outcomes for these patients.

Previous investigations have shown that baseline structural measurements predict future development of VF loss in suspected glaucoma suggesting a potential role for these measurements in early detection of the disease. Such evidence comes from studies using cross-sectional grading of optic disc photographs and imaging methods for structural evaluation in glaucoma, including confocal scanning laser ophthalmoscopy, optical coherence tomography, and scanning laser polarimeter. However, measures of predictive ability reported in these studies have generally indicated a low accuracy of cross-sectional structural measures for predicting individual functional outcomes. This is likely due to the wide variation in the appearance of the optic nerve, which makes it difficult to identify early signs of disease at one time.

OCT TO DETECT PROGRESSION IN GLAUCOMA (TD- OCT AND SD-OCT)

OCT is an imaging technique originally developed to provide objective and quantitative estimates of the thickness of the RNFL. OCT RNFL measurements are reproducible and have been shown in cross-sectional studies to be able to discriminate glaucomatous from healthy eyes. Today's spectral

domain (SD-OCT) instruments provide high resolution and highly repeatable images that can be used in the diagnosis of glaucoma and detection of structural progression. More recently, macular imaging with OCT has emerged as an important parameter in the diagnosis of glaucoma. There are several advantages to using macular scans compared to optic nerve and RNFL parameters. At a fundamental level, glaucoma is a disease of retinal ganglion cells. Since the macula contains more than 50% of the ganglion cells of the entire retina, a macular scan will sample the majority of retinal ganglion cells. In addition, while the optic disc and peripapillary region have highly variable structural characteristics among normal and glaucoma patients, there is much less variability in the macular region[15]. Detecting and following glaucoma progression using macular thickness is the newest area of interest, and the research is still emerging.

MEASURING GLAUCOMA PROGRESSION BY OCT

The statistical approaches used in assessing glaucoma progression can be divided into event based and trend based. In event analysis, progression is recognised when a follow-up measurement exceeds a predetermined threshold for change from baseline. It is assumed that any change lower than this threshold is due to natural age-related loss and/or measurement variability, whereas changes exceeding the threshold represent actual progression. The threshold for a change can be determined from an individual subject's variability or from variability in a normal reference group. Event analysis is intended to identify a gradual change over time that eventually crosses a threshold or to detect an acute event that exceeds a threshold. However, a confirmatory test is always recommended, particularly in the latter case, to prevent a measurement produced by an artefact and being labelled as a real event.

A trend analysis identifies progression by monitoring the behaviour of a parameter over time. A regression analysis or mixed effect analysis of a dependent variable (ie, RNFL thickness) is performed on follow-up measurements, providing a rate of progression over time. This method is less sensitive to sudden change and the variability among consecutive tests because it is neutralized by the overall rate of change.

The rates of localized thickness change are shown to have higher discriminating ability between progressing and non-progressing group than the global RNFL thinning rate. Thus, focal RNFL loss may not always result in a detectable change in global RNFL thickness. The inferotemporal (7 o'clock) sector is the most frequent location that showed progression, suggesting that this location is not only important in discriminating glaucomatous from healthy eyes but it should also play an important role in detecting glaucomatous progression.

For the global RNFL thickness, mean rate of change is −0.72 µm/year for progressors and 0.14 µm/year for non-progressors. The rates of change are widely variable among the eyes.

Challenges

The detection of glaucoma progression with OCT remains a challenge because when measuring structural changes over time, it is hard to distinguish between glaucomatous structural damage and measurement variability or age-related structural loss. Studies analysing healthy subjects demonstrated a considerable negative correlation between age and average RNFL thickness of −0.33 µm/year while other studies reported a −0.52µm/year rate of age-related loss of RNFL.

Although the test itself is objective, interpretation is subjective and influenced by clinician's experience. In addition, there are limitations to OCT interpretation, such as: other ocular diseases, signal-to-noise ratio, instrument/image artefacts and the stage of the disease.

The impact of concomitant macular disease renders macular OCT scans ineffective in glaucoma. Other conditions may impact the optic nerve (epiretinal membranes are a common source of artefacts in RNFL scans) and RNFL measurements, as well. The development of posterior vitreous detachment (PVD) also influence RNFL scans, as focal traction at the vitreoretinal interface may cause the RNFL to look thicker. As the PVD advances and the traction are released, the RNFL measurement becomes thinner. Without careful evaluation, this thinning may be misinterpreted as progression. Uveitis can also influence RNFL scan.

OCT IN DIFFERENT DISEASE STAGES

Stage of glaucoma disease has a significant impact on OCT relevance. The RNFL layer contains blood vessels, glial tissue and ganglion cell axons; even in eyes with no light perception due to glaucoma, the RNFL does not fall below 30µm; the floor effect on most commercial instruments is considered to be around 45µm to 50µm. As the RNFL approaches this floor in advanced glaucoma, the thickness is more heavily influenced by other structural components, such as blood vessels, and less by actual RNFL thickness, making progression detection more difficult[16]. Patients with mild to moderate glaucoma may show significant rates of change in both RNFL and macular/ganglion cell layer thickness. In a study of advanced glaucoma patients, however, there may be a significant difference in the rate of change of macular thickness, but not in RNFL thickness, between progressive and non-progressive patients[17].

SUMMARY OF MONITORING PROGRESSION WITH TD-OCT AND SD-OCT[18]

TD-OCT is a sensitive measure of glaucoma progression. Studying both overall average and sectoral RNFL thicknesses is important in detection of progression. SD-OCT with its increased resolution, image registration capabilities, higher reproducibility, and three-dimensional rendering capabilities offers potential advantages over TD-OCT. SD-OCT is a valuable clinical tool for glaucoma diagnosis and detection of progression. RNFL parameters have been demonstrated to provide accurate information for disease diagnosis and sensitive method for disease progression. Initial studies evaluating macular and ONH parameters show encouraging results. The limited agreement between functional and structural tests emphasizes the importance of assessing both structure and function when making clinical decisions regarding glaucoma progression.

FREQUENCY OF TESTING

No fixed guidelines have been developed regarding the frequency of OCT testing. The principle is to obtain scans at roughly the same rate as VF. After 2 years, if the patient appears to be stable, the frequency of testing can be decreased. If progression is assumed, the frequency of examinations can be increased.

When progression is suspected based on OCT, clinicians should take a

systematic approach to make appropriate clinical decisions.

1. Repeat the test. To understand that the suspected change is definite rather than due to artefact.
2. Next, make a decision whether or not the change is typical of glaucomatous change versus a factor of age or due to other disease.
3. If the change appears to be glaucomatous, determine the rate at which the progression has occurred.
4. Calculate the rate of changes and compare it to the patient's life expectancy and stage of the disease. It is important in deciding, on the basis of the rate, how aggressively to treat, or even whether, to modify therapy.
5. Finally, if therapy is increased, revise the baseline for all testing (VF, OCT and photography) so future changes are compared to an appropriate baseline.

CONCLUSION

It is crucial to monitor both the structural and functional change in order to identify glaucoma progression. Creating a reliable baseline is essential to detect progression. Repeated visual field testing with same threshold algorithm is needed to set up a functional baseline. Documentation of the optic disc for structural baseline can be done clinically or with imaging device. The presence of progressive optic disc damage on stereophotographs is a highly predictive factor for future development of functional loss in glaucoma. It is important to realize that these 2 methods are complementary and cannot substitute each other. RNFL thickness is a dominant parameter in the detection of glaucoma progression. However, macular parameters might provide a useful alternative for glaucoma progression assessment. Researchers suggest that the analysis and interpretation of rates of SAP and OCT change over time in glaucoma should depend on the stage of the disease. There is a strong need for approaches combining structural and functional data for detection of progression and estimation of rates of change in the disease.

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