Unveiling Glaucoma Progression

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Abstract

Glaucoma progression is primarily assessed through functional deterioration, most commonly measured by changes in the visual field (VF). This article focuses on the analysis of glaucoma progression using standard automated perimetry (SAP), which remains the gold standard for monitoring functional loss. We review key methods for detecting VF progression, including event-based and trend-based analyses, with particular attention to tools such as Guided Progression Analysis (GPA) and pointwise linear regression (PLR). The strengths and limitations of global indices like Mean Deviation (MD) and Visual Field Index (VFI) are discussed, along with the impact of test variability, learning effects, and the influence of disease stage. Emerging techniques, including machine learning models and deep learning approaches, are evaluated for their potential to enhance sensitivity and specificity in early detection of VF deterioration. This article aims to provide clinicians and researchers with a detailed overview of current strategies and future directions in visual field-based glaucoma progression analysis.

Key words : Glaucoma progression analysis, Humphrey visual field analysis, mean deviation, visual field index.

Introduction

Glaucoma is a group of eye disorders characterised by chronic progressive optic neuropathy with characteristic optic nerve head and corresponding visual field changes; in which intra ocular pressure is the most important modifiable risk factor. Glaucoma is classified into primary (without any underlying ocular pathology) or secondary (with ocular pathology such as neovascularization, pigment dispersion, pseudoexfoliation). Furthermore, it can be associated with open or closed angle of anterior chamber.[1]

An article published in 2010 estimated that there are approximately 11.2 million persons aged 40 years and older with glaucoma in India. Primary open angle glaucoma is estimated to affect 6.48 million persons. The estimated number with primary angle-closure glaucoma is 2.54 million. Most of disease burden is undetected due to the insidious nature of the disease and there exist major challenges in detecting and treating those with disease.[2]

Amongst the array of diagnostic tests available for glaucoma detection visual field analysis or perimetryis considered as the gold standard. Automated static perimetry is the most advanced and commonly used perimetric test at present. Two popular field Analysers being Octopus 900 model and Humphrey Field Analyzer providing comprehensive visual field analysis and detection of glaucomatous damage.

But a major drawback of perimetry is that it is a subjective test requiring a certain level of understanding and cooperation from the patient, which is often difficult to achieve, most glaucoma patients being in the older age group. Reliability of a single printout depends on several factors and test-retest variability is moderate amongst published literature. Statistically Inter observer agreement is only fairly moderate when interpreting the same visual fields and a certain level of clinical acumen and sound understanding of fields is a prerequisite to understand progression of glaucoma so as to plan additional interventions or treatment to halt further loss.

Thus, detection of glaucomatous damage especially progression is a challenging task for most ophthalmologists.

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This article aims to simplify the interpretation of multiple visual field analysis to uncover progression with specific emphasis on guided progression analysis available with the Humphrey visual field analyser.[3] We sincerely hope this information will prove useful and important to enhance the management of glaucoma patients.

Various Methods Employed to Assess Progression

Glaucoma progression can be assessed by a number of methods. One of the most common methods used by the clinicians today in busy OPD settings can be simple comparison of the scotoma over a period from multiple single test printouts of Humphrey or octopus. Both the size and depth of the scotoma is compared. But the accuracy of this method is poor due to a due to several factors like learning curve, test-retest variability, generalised media opacities like attract. Interobserver variability is also very high in this method. Hence this method is not advisable to assess glaucoma progression.

Another method to assess progression has been proposed by Hodapp and Parrish in the book named clinical decisions in glaucoma published in 1993 where they have described a very complicated way toassessglaucoma progression. Progression can be either the appearance of a new scotoma or the deepening of a previously existing scotoma. For the detection of a new scotoma the following criteria must be fulfilled. A cluster of 3 or more non edge points each of which declines by 5 or more decibels or a single non edge point declines by 10 or more decibels or a cluster of 3 or more non edge points each of which declines at P less than 5% level. This new defect detected must be present on 2 consecutive fields to be considered significant. For deepening of a preexisting defect, the following criteria is required. a cluster of 3 or more non edge points or 3 points which are part of the same scotoma each of which declines by 5 decibels with P less than 5% level or a cluster of 3 or more non edge points each of which declines by 10 decibel or more on 2 consecutive fields. This method too is limitedby the fact that whether it's true progression or test-retest variability cannot be certainly ascertained.[4]

A study conducted by Anders et al which included 51 patients with varying degree of glaucoma who were tested 4 times over the duration of 4 week found that in areas with moderate loss of sensitivity variation in the follow up ranged from normal sensitivity to absolute defect with little variation on the distance from fixation. Thus,the sensitivity of a point in a scotoma area can range widely with high test-retest variability. Points with normal sensitivity if located add the centre of the visual field towards fixation showed little variation in sensitivity over a few tests whereas points with normal sensitivity located towards periphery showed great variation insensitivity from test to test. They also documented the influence of mean deviation in influencing variability. Depressed points in a generally depressed field with high mean deviation show more test-retest fluctuation than similarly depressed points in otherwise normal fields.[5] Thus three variables effect the fluctuation namely the sensitivity of tested point, the location of the point and generalised sensitivity that is mean deviation.

The glaucoma change probability maps in Humphrey's visual field analysis is based on the above example. Visual fields were plotted from a large number of glaucoma patients as well as general population for formulation of the age matched normative database. In perimetry, probability maps are visual representations of how often specific visual field findings are observed in a normal population. They help interpret visual field results, particularly in identifying significant deviations from normal and detecting changes over time. Probability Maps compares the sensitivity of a point tested to that of a Normal Database. Each point in the visual field is assigned a probability value, reflecting how likely that level of vision is seen in a normal individual. This is often represented as a grey scale map with shades of increasing darkness ($P > 0.1$), ($P < 0.05$), ($P < 0.01$), ($P < 0.001$)indicating increasing significance of likely damage. Probability maps can also be used to track changes in visual field over time by comparing the results of multiple tests and analysing the changes in probability values at each point in the grey scale. Pattern Deviation Probability Map is the most sensitive map in detecting glaucomatous damage as it removes the generalised depression in field caused by media opacity such as cataract and focuses on the localised specific defect. In essence, probability maps translate raw perimetry data into a visual representation for both detection of glaucoma and monitoring progression[6].

Another study conducted on standard automated perimetry test-retest variability shows that points which sensitivity threshold near 30 decibels show variability of only 3 decibels whereas points with sensitivity near 10 decibels can show widetest-retest variability ranging near 15 decibels[7].

Similarly, a study conducted to assess reliability of standard automated perimetry in regions of glaucomatous damage concluded that visual field testing is unreliable when points have reduced sensitivity approximately 15 to 19 decibels. Thus, detecting progression in Moderate to severely depressed visual fields can be a challenge due to greater test-retestvariable.[8]

Methods described above for detecting progression are thus having certain limitations. Assessment of progression as well as rate of progression is the new standard in glaucoma management. Today glaucoma progression is documented based on event analysis and trend analysis. As the name suggests event analysis informs us whether progression is present or not compact to the previous fields and trend analysis reveals the rate or velocity of progression over time.

Event Analysis

Event analysis determines whether progression (event) is present or not. This is done by comparing the results of a given visual field test to the average of two baseline tests. Progression is present if worsening is there in each point of visual field and if this change persists over multiple visual field tests. Event analysis includes glaucoma change probability maps described above and glaucoma progression analysis (GPA).[9,10]

Guided Progression Analysis

This is a point wise event analysis programme based on pattern deviation data from full threshold tests or Swedish interactive thresholding algorithm tests. it is based on Early manifest glaucoma trial progression criteria. To establish a baseline the procedure averages the patients first 2 reliable visual fields. The GPA compares each consecutive test to this baseline point by point to find any points that deviate beyond the 95% confidence interval for expected test-retest variability obtained from a group of stable glaucoma patients. If 3 or more locations show worsening in the pattern deviation data over 2 consecutive tests the GP outcome is possible progression and if 3 or more points show worsening over 3 consecutive tests the outcome is likely progression. Studies conducted show that possible progression criteria has a sensitivity and specificity of 93% and 95% Respectively. Because changes persistent over multiple tests are considered this helps us to distinguish true pathological change from test retest variability. [11,12]

Worsening of a point from the baseline for the first time is represented by a white triangle while for second time it is represented as a half black triangle and 3rd time as a black triangle. As GPA uses pattern deviation probability plots it is not influenced by cataract. At times in the GPS analysis map certain points are marked with X this indicates that the sensitivity of those points are too depressed to be measured and can't be assessed further. When mean deviation of a field test is-20 decibel or more GPA cannot be calculated further.[13]

Advantage of event based analysis is that it requires fewer visual fields and less time to produce results and detect deterioration more quickly than trend analysis. Also detects local changes in the visual field.

Trend Analysis

As mentioned earlier trend analysis detects the rate or velocity of progression. Trend analysis can be based on mean deviation and visual field index in Humphrey visual field analyser. Octopus 900 offers mean deviation, square root loss variance, diffuse defect and local defect.[14]

Progressor software can also be used for trend analysis based on point wise linear regression. Most glaucoma patients tested overtime will show progression if followed up long enough. It is important to determine the velocity of the disease progression. [leske] rate of glaucoma progression varies widely among the patients and the rate of progression is the strongest predictive factor for further progression in a patient. Assessing rate of progression is essential to understand if the patient has a risk of becoming visually impaired in his lifetime. Linear regression graph is applied to mean deviation and visual field index to calculate progression. All visual fields are considered in this regard.[15]

Mean Deviation

For Humphrey field analysis first 2 reliable fields are considered as baseline and mean deviation average by computers and compared with subsequent fields and plotted overtime to provide a slope of change in mean deviation overtime called the mean deviation slope. The gentle the slope slower is the progression and vice versa. Software compute and provides us the value of the slope. Mean deviation worsening at the rate of one decibel per year(95% confidence interval) is acceptable if it is more than that treatment needs to be stepped up.[16]

Drawback of this method is that mean deviation in the field is affected by generalised opacities such as cataract. Also, it cannot assess localised spatial information within the field i.e insensitive to early localised defects and does not consider the fact that different regions in the visual field may deteriorate at different rates. Requires multiple fields to assess progression and is time consuming.

The octopus can similarly plot mean deviation slope to assess progression in glaucoma patients. Moreover, it has coloured indicators to depict worsening or improvement at p value less than 5% or 1%. Octopus also provides regression analysis for square root loss variance diffuse defects and localised defects

Visual Field Index

Trend analysis using visual field index (VFI) has the advantage that it is calculated from the pattern deviation data hence not affected by cataract. Also, VFI gives more importance to centrally located points as compared to peripheral points. Visual field index derived from multiple visual field tests overtime can be plotted to obtain the slope of glaucoma progression. Software calculate and provides a value for the slope. Accepted rate of progression using VFI should be less than-3 decibel per year (95% confidence interval), If higher treatment must be stepped up to prevent visual impairment during lifetime.[17]

A study conducted by Bengtsson at al. for prediction of visual field loss by extrapolation of linear trend analysis showed that short term rate of progression can predict long term visual outcome.11 visual field tests were performed over 8 years, and the rate of progression was calculated separately from initial 5 fields and using all the 11 fields and compared. It was found that progression rate predicted from initial 5 fields was like overall progression rate. 70 % of patients had predicted final VFI within ±10 % of the estimated final VFI. The conclusion was linear extrapolation based on 5 initial visual field test results was a reliable predictor of future field loss in most patients.[18]

A change in visual field index at the rate of 1% per year corresponds to change in mean deviation by 0.3 decibel per year. Progression is greater than 3% VFI per year or mean deviation by-1 decibel per year can lead to significant loss of quality of life at any age.

To conclude both event analysis and trend analysis has a definitive role to play while event analysis is easier to establish with fewer visual fields and time trend analysis takes longer duration to predict progression but has higher diagnostic sensitivity than event analysis.

Cluster Analysis

to reduce test retest variability the visual field can be divided into clusters and monitor progression based on the average sensitivity of test location within the cluster. Octopus 900 is equipped to provide cluster trend analysis. This detects 2.9 times more progression as compared to event analysis.[19]

Multiple studies have divided the visual field into multiple clusters like 10 or 23 and assessed reduced overall sensitivity in this clusters to detect progression.

Progressor Software

Progressor software provides pointwise linear regression based on absolute sensitivity of individual points. Each point is represented by multiple bar and each bar represents one test. The length of the bar represents the depth of the defect longer bar means lower sensitivity. The colour of bar relates to P value of the regression slope. Undamaged locations are represented by series of short grey bars. Damaged but stable locations are represented by series of long Gray bars. Progressing locations represented by progressively longing bars which change colour according to the regression slope.

The software assesses each point individually and a slope steeper than-1 decibel per year for inner points and a slope steeper than-2 decibel per year for edge points with the p value less than 0.1 is considered progression. This method has the drawback that it does not provide true progression only assessing individual points[14].

Peridata Software

This software imports information of individual field test from various machines and can analyse them for progression.

Conclusion

While being able to identify glaucomatous visual field progression is critical the lack of a gold standard test poses a significant challenge. Multiple methods have been developed to assess progression, but each has their own drawback. Both event and trend analysis must be deployed to assess progression. Everyday newer techniques and software are being developed to ease the process. It is hoped that the information provided in this article will be useful to clinicians concerned with the management of glaucoma patients.

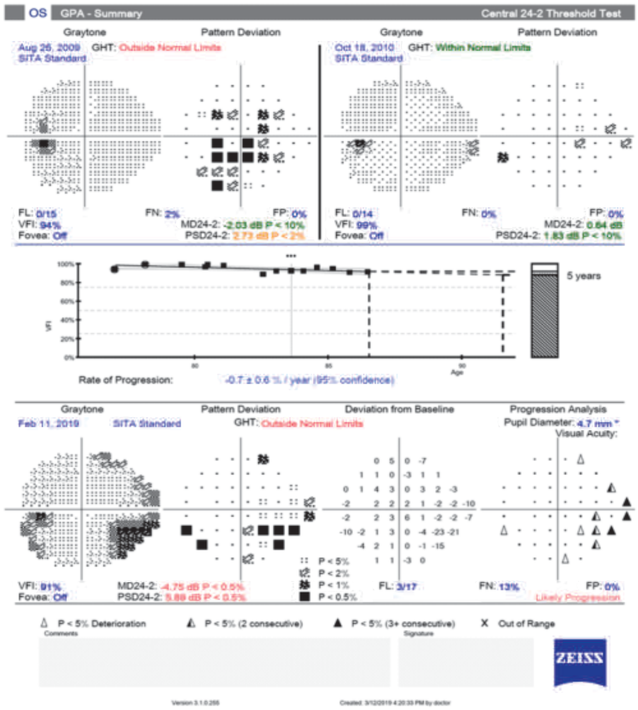

Figure 1 : The GPA Report

The GPA report (Figure 1) shows the two baseline tests above and below the present test values. Multiple triangles in white (first time depression), half white (second time) and three triangles in black (third time) are represented. Thus it is likely progression (three points depressed over three tests)

Second focus on VFI slope it is gentle with rate of progression -0.7 %/ year and no threat to significant impairment of vision in the lifetime. Thus this GPA represents though progression is present it is very slow and management is appropriate no step up or change in treatment regimen required.

Figure 2 : The Progressor Analyser

The progressor analyser (Figure 2) has colour coded values for different rate of progression with p values. Each individual test point is assessed. Multiple coloured points with elongating bars means progression.

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