Review Article

ASSESSMENT OF GLAUCOMA PROGRESSION: IMPORTANCE AND CHALLENGES

Nazrina Hassan[1,2], Norshamsiah Md Din[2], Seng Fai Tang[2], Ropilah Abdul Rahman*[2,3]

[1]Department of Surgery, Universiti Malaysia Sabah, Jalan UMS, 88400 Kota Kinabalu, Sabah, Malaysia.
[2]Department of Ophthalmology, Faculty of Medicine, University Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Kuala Lumpur, Malaysia.
[3]Kulliyyah of Medicine & Health Sciences, Universiti Islam Antarabangsa Sultan Abdul Halim Mua'dzam Shah, 09300 Kuala Ketil, Kedah, Malaysia.

ARTICLE INFO

Corresponding author:
Prof. Dr. Ropilah Abdul Rahman

Email address:
drropilah@unishams.edu.my

Received:
April 2020
Accepted for publication:
June 2020

Keywords:

Glaucoma
progressive optic neuropathy
automated visual field progression

ABSTRACT

Rate of progression is a clinically important parameter yet difficult to measure in glaucoma management. An accurate indication of rate of progression of glaucomatous disease would allow clinicians to identify patients who are at most risk of suffering a significant decline in their quality of vision. A major issue that affects accurate measurements of glaucoma disease progression is that it is hidden by the short term and long term variability that is inherent in visual field testing. The purpose of this paper is to review the current understanding of the relationship of systemic and ocular risk factors with glaucoma disease progression, hence the basis for early intervention and tighter comorbids control to slow down the progression.

INTRODUCTION

Glaucoma is a chronic disease. It causes progressive optic neuropathy characterized by morphological changes of the optic nerve head and retinal nerve fiber layer resulting in corresponding visual field defect [1]. It may be associated with or without high intraocular pressure. Glaucoma is broadly classified into open angle and angle closure based on iridocorneal angle configuration.

Epidemiologically, glaucoma is the second leading cause of blindness worldwide. In 2010, it is estimated that there is 60.5 million people with open and angle closure glaucoma and this figure was projected to increase to 79.6 million by 2020 [2]. Primary Open Angle Glaucoma (POAG) is the predominant glaucoma subtype, followed by Primary Angle Closure Glaucoma (PACG) and secondary glaucoma.(2) In Malaysia, the 2014 National Eye Survey II showed an estimated prevalence of blindness in those aged 50 and above was at 1.2%, of which 6.6% was caused by glaucoma [3].

A number of theories have been postulated regarding the factors responsible for the glaucoma progression as well as the pathogenesis of the disease. The most widely known is the mechanical theory, whereby high intraocular pressure (IOP) deforms the lamina cribosa, which distorts the nerves fibres running through it and disrupts axoplasmic flow [4,5]. This theory explains the association of intraocular pressure factors such as raised IOP, IOP fluctuation, central corneal thickness (CCT), and corneal stiffness to glaucoma progression [6-23]. However the theory does not explain why most patients with high IOP do not develop glaucoma and some patients worsen despite adequate IOP control [24].

A less IOP-centric view is suggested by the vascular theory, whereby glaucoma is caused by decreased ocular perfusion pressure which affects ganglion cells at the optic nerve head. Disease progression is then enhanced following this primary insult by impaired vascular autoregulation and dysfunctional neurovascular coupling [25]. Evidence supporting this theory has been mixed, with systemic hypotension, nocturnal blood pressure dipping, low diastolic perfusion pressure and low ocular perfusion pressure being implicated in rapid disease progressors, especially in normal tension glaucoma [7,26,27]. However, other systemic contributors to decreased blood flow such as hypertension; use of antihypertensive medications; atherosclerosis; and vasospastic phenomenon such as migraines, chilblains and Raynauds phenomenon; have not been reliably associated with rapid progression [7,9,28-30]. Furthermore, vascular diseases such as diabetes and cardiovascular disease (CVD) has not

been consistently shown to be correlated with rapid disease progression [7-14,29,31-33].

ASSESSMENT OF GLAUCOMATOUS VISUAL FIELD PROGRESSION

Assessment of glaucoma progression can be based on changes of the optic disc, visual field, peripapillary retinal nerve fiber bundle atrophy, and more recently on retinal nerve fiber layer thickness [34-40]. Visual field progression is mostly through assessment of Standard Automated Perimetry (SAP) as the functional endpoint [41-43].

Glaucoma progression can be divided into event-based analysis using parameters that reflect global or hemifield progression (i.e whether VF progression has occurred or not); and trend analysis of the rate of disease progression [44-47]. Event analyses compare baseline measurements and future follow-up measurements to see whether those measurements are significantly worse; whereas trend analyses uses serial measurements to determine rate of progression. Although event analysis methods are useful in determining whether patients are progressing, they do not provide information about the velocity of visual loss or whether there is significant risk that these rates of loss will affect their vision-related quality of life. Thus much focus is given on rates of glaucomatous progression measured using trend analysis [34].

Trend analyses using visual fields involve linear regression analysis of summary statistics such as Mean Deviation (MD) and, more recently, the Visual Field Index (VFI). Trend analysis with point-wise linear progression (PLR) presents the rate of loss in decibels per year (dB/year) to describe localized points tested in the Humphrey VF that are actively progressing. It has the advantage over event-based analysis for being more accurate in quantifying true disease progression. The use of software programs that perform objective and automated analyses are available [47]. The limitation on this method is that despite the fact that rates of VF worsening are not necessarily constant over time (e.g. treatment intensity and adherence could change), rates of visual field loss are typically expressed as linear rates of change in dB/year [34].

DEFINING RAPID AND SLOW PROGRESSORS

Recently many studies focus on glaucoma progression by categorizing progressions into rapid and slow progressor. Heijl et al conducted a study in 2012 to investigate rates of visual field progression and factors associated with progression rate in open-angle glaucoma. They found that progression rates rapid enough to influence quality of life were common [35]. The mean MD slope was −0.80 dB/year (SD ± 0.82, median, −0.62), and slopes ranged from −5.58 to +1.24 dB/year with a negatively skewed distribution [35].

Kirwan et al explored visual field (VF) progression in a cohort of secondary care-treated glaucoma and ocular hypertensive (OHT) patients. PROGRESSOR software was used to search the Portsmouth VF database for patients with five or more SITA Fast VFs. Patients were divided into groups by the rate of progression. The group progressing at more than 2 dB/year(ie, the MD was decreasing by more than 2 dB/year) was deemed ‘fast progressors’[36].

Chan T et al. in 2017 studied 48 rapidly progressing eyes and 486 non-rapidly progressing. He grouped the rapidly progressing eyes that demonstrates progression of ≥1 dB mean deviation [MD]/year while the non-rapidly progressing eyes that demonstrates progression of <1 dB MD/year [37].

Kim HJ et al conducted a study to identify baseline and longitudinal risk factors for fast visual field decay in open angle glaucoma patients. In this cohort, older age, peak IOP, pseudoexfoliative glaucoma, and baseline MD were associated with the rate of glaucomatous VF worsening. Fast progressors had a higher peak IOP than non-fast progressors [38].

FACTORS AFFECTING GLAUCOMA PROGRESSION

Randomized clinical trials and large cohort studies, have evaluated risk factors for glaucoma progression, revealing a range of systemic and ocular risk factors for glaucoma progression [39-43, 47-49]. Heijl et al found older age, higher mean IOP, and more intensive treatment were associated with faster progression, while pseudoexfoliation glaucoma and IOP fluctuation were not, after adjusting for treatment intensity.

Agreeing with this, Chan TW et al found rapid progressors were older, had significantly lower CCT and baseline IOPs, and were more likely to have pseudoexfoliation, disc haemorrhages, ocular medication changes, and IOP-lowering surgery. They also had significantly higher rates of cardiovascular disease and hypotension, with slightly more than 2-fold increase in risk of rapid progression among those with cardiovascular disease despite significantly lower mean and baseline IOPs [37].

CONCLUSION

Visual field progression in manifest glaucoma with visual field loss in ordinary clinical care varies among patients. Progression rate can be rapid enough to influence the quality of life. Identification of risk factors associated with rapid deterioration in glaucoma patients is important because it helps guide the appropriate use of resources to improve outcome in patients at high risk for visual disability [38]. Detecting the type of progression will enable patient directed care to minimise glaucoma progression.

REFERENCES

1. EGS-European Glaucoma Society. Terminology and guidelines for glaucoma (4th edition). Publicomm srl, editor. 2014.
2. Quigley HA. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol. 2006 Mar 1;90(3):262–7.
3. Clinical Practice Guidelines - Management of Glaucoma (2nd Edition). Malaysian Health Technology Assessment Section; 2017.
4. Ahmad SS. Controversies in the vascular theory of glaucomatous optic nerve degeneration. Taiwan J Ophthalmol. 2016;6(4):182–6.
5. Weinreb RN, Aung T, Medeiros FA. The Pathophysiology and Treatment of Glaucoma. JAMA. 2014 May 14;311(18):1901–11.
6. Blumberg D, Skaat A, Liebmann JM. Emerging risk factors for glaucoma onset and progression. Prog Brain Res. 2015;221:81–101.
7. Leske MC, Heijl A, Hyman L, Bengtsson B, Dong L, Yang Z, et al. Predictors of long-term progression in the early manifest glaucoma trial. Ophthalmology. 2007 Nov;114(11):1965–72.
8. The AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 12. Baseline risk factors for sustained loss of visual field and visual acuity in patients with advanced glaucoma. Am J Ophthalmol. 2002 Oct;134 (4):499–512.
9. Collaborative Normal-Tension Glaucoma Study Group. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. Collaborative Normal-Tension Glaucoma Study Group. Am J Ophthalmol. 1998 Oct;126(4):498–505.
10. Bengtsson B, Leske MC, Hyman L, Heijl A, Early Manifest Glaucoma Trial Group. Fluctuation of intraocular pressure and glaucoma progression in the early manifest glaucoma trial. Ophthalmology. 2007 Feb;114(2):205–9.
11. Lazaro C, Garcia-Feijoo J, Castillo A, Perea J, Martinez-Casa JM, Garcia-Sanchez J. Impact of intraocular pressure after filtration surgery on visual field progression in primary open-angle glaucoma. Eur J Ophthalmol. 2007 Jun;17(3):357–62.
12. Lee PP, Walt JW, Rosenblatt LC, Siegartel LR, Stern LS, Glaucoma Care Study Group. Association between intraocular pressure variation and glaucoma progression: data from a United States chart review. Am J Ophthalmol. 2007 Dec;144(6):901–7.
13. Hong S, Seong GJ, Hong YJ. Long-term intraocular pressure fluctuation and progressive visual field deterioration in patients with glaucoma and low intraocular pressures after a triple procedure. Arch Ophthalmol Chic Ill 1960. 2007 Aug;125(8):1010–3.
14. Nouri-Mahdavi K, Hoffman D, Coleman AL, Liu G, Li G, Gaasterland D, et al. Predictive factors for glaucomatous visual field progression in the Advanced Glaucoma Intervention Study. Ophthalmology. 2004 Sep;111(9):1627–35.
15. Medeiros FA, Sample PA, Zangwill LM, Bowd C, Aihara M, Weinreb RN. Corneal thickness as a risk factor for visual field loss in patients with preperimetric glaucomatous optic neuropathy. Am J Ophthalmol. 2003 Nov;136(5):805–13.
16. Chauhan BC, Hutchison DM, LeBlanc RP, Artes PH, Nicolela MT. Central corneal thickness and progression of the visual field and optic disc in glaucoma. Br J Ophthalmol. 2005 Aug;89 (8):1008–12.
17. Fernandez-Bahamonde J, Roman-Rodriguez C, Fernandez-Ruiz M. Central Corneal Thickness as a Predictor of Visual Field Loss in Primary Open Angle Glaucoma for a Hispanic Population. Semin Ophthalmol. 2011 Jan;26(1):28–32.
18. Francis BA, Varma R, Chopra V, Lai M-Y, Shtir C, Azen SP. Intraocular Pressure, Central Corneal Thickness, and Prevalence of Open-Angle Glaucoma: The Los Angeles Latino Eye Study. Am J Ophthalmol. 2008 Nov;146(5):741–6.
19. Manni G, Oddone F, Parisi V, Tosto A, Centofanti M. Intraocular pressure and central corneal thickness. Prog Brain Res. 2008;173:25–30.
20. De Moraes CVG, Hill V, Tello C, Liebmann JM, Ritch R. Lower corneal hysteresis is associated with more rapid glaucomatous visual field progression. J Glaucoma. 2012 May;21(4):209–13.
21. Congdon NG, Broman AT, Bandeen-Roche K, Grover D, Quigley HA. Central corneal thickness and corneal hysteresis associated with glaucoma damage. Am J Ophthalmol. 2006 May;141(5):868–75.
22. Chee R-I, Silva FQ, Ehrlich JR, Radcliffe NM. Agreement of flicker chronoscopy for structural glaucomatous progression detection and factors associated with progression. Am J Ophthalmol. 2013 Jun;155(6):983-990.e1.
23. Medeiros FA, Meira-Freitas D, Lisboa R, Kuang T-M, Zangwill LM, Weinreb RN. Corneal hysteresis as a risk factor for glaucoma progression: a prospective longitudinal study. Ophthalmology. 2013 Aug;120(8):1533–40.
24. Cioffi GA. ISCHEMIC MODEL OF OPTIC NERVE INJURY. Trans Am Ophthalmol Soc. 2005 Dec;103:592–613.
25. Cherecheanu AP, Garhofer G, Schmidl D, Werkmeister R, Schmetterer L. Ocular perfusion pressure and ocular blood flow in glaucoma. Curr Opin Pharmacol. 2013 Feb;13(1):36–42.
26. Charlson ME, de Moraes CG, Link A, Wells MT, Harmon G, Peterson JC, et al. Nocturnal systemic hypotension increases the risk of glaucoma progression. Ophthalmology. 2014 Oct;121 (10):2004–12.
27. Krupin T, Liebmann JM, Greenfield DS, Rosenberg LF, Ritch R, Yang JW, et al. The Low-pressure Glaucoma Treatment Study (LoGTS) study design and baseline characteristics of enrolled patients. Ophthalmology. 2005 Mar;112 (3):376–85.
28. The AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. Am J Ophthalmol. 2000 Oct;130(4):429–40.

29. De Moraes CG, Liebmann JM, Greenfield DS, Gardiner SK, Ritch R, Krupin T, et al. Risk factors for visual field progression in the low-pressure glaucoma treatment study. Am J Ophthalmol. 2012 Oct;154(4):702–11.
30. Ernest PJ, Schouten JS, Beckers HJ, Hendrikse F, Prins MH, Webers CA. An evidence-based review of prognostic factors for glaucomatous visual field progression. Ophthalmology. 2013 Mar;120(3):512–9.
31. Drance S, Anderson DR, Schulzer M, Collaborative Normal-Tension Glaucoma Study Group. Risk factors for progression of visual field abnormalities in normal-tension glaucoma. Am J Ophthalmol. 2001 Jun;131(6):699–708.
32. Wesselink C, Marcus MW, Jansonius NM. Risk factors for visual field progression in the groningen longitudinal glaucoma study: a comparison of different statistical approaches. J Glaucoma. 2012 Dec;21(9):579–85.
33. Leske MC, Heijl A, Hussein M, Bengtsson B, Hyman L, Komaroff E, et al. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. Arch Ophthalmol Chic Ill 1960. 2003 Jan;121(1):48–56.
34. Saunders LJ, Medeiros FA, Weinreb RN, Zangwill LM. What rates of glaucoma progression are clinically significant? Expert Rev Ophthalmol. 2016;11(3):227–34.
35. Heijl A, Buchholz P, Norrgren G, Bengtsson B. Rates of visual field progression in clinical glaucoma care. Acta Ophthalmol (Copenh). 2013 Aug;91(5):406–12.
36. Kirwan JF, Hustler A, Bobat H, Toms L, Crabb DP, McNaught AI. Portsmouth visual field database: an audit of glaucoma progression. Eye Lond Engl. 2014 Aug;28(8):974–9.
37. Chan TCW, Bala C, Siu A, Wan F, White A. Risk Factors for Rapid Glaucoma Disease Progression. Am J Ophthalmol. 2017 Aug;180:151–7.
38. Kim JH, Rabiolo A, Morales E, Yu F, Afifi AA, Nouri-Mahdavi K, et al. Risk Factors for Fast Visual Field Progression in Glaucoma. Am J Ophthalmol. 2019;207:268–78.
39. Jonas JB, Bergua A, Schmitz-Valckenberg P, Papastathopoulos KI, Budde WM. Ranking of optic disc variables for detection of glaucomatous optic nerve damage. Invest Ophthalmol Vis Sci. 2000 Jun;41(7):1764–73.
40. Chauhan BC, Drance SM, Douglas GR. The use of visual field indices in detecting changes in the visual field in glaucoma. Invest Ophthalmol Vis Sci. 1990 Mar 1;31(3):512–20.
41. Quigley HA, Katz J, Derick RJ, Gilbert D, Sommer A. An evaluation of optic disc and nerve fiber layer examinations in monitoring progression of early glaucoma damage. Ophthalmology. 1992 Jan;99(1):19–28.
42. Zangwill LM, Williams J, Berry CC, Knauer S, Weinreb RN. A comparison of optical coherence tomography and retinal nerve fiber layer photography for detection of nerve fiber layer damage in glaucoma. Ophthalmology. 2000 Jul;107 (7):1309–15.
43. Furuichi M, Kashiwagi K, Furuichi Y, Tsukahara S. Comparison of the Effectiveness of Scanning Laser Polarimetry and Optical Coherence Tomography for Estimating Optic Nerve Fibre Layer Thickness in Patients with Glaucoma. Ophthalmologica. 2002;216(3):168–74.
44. Advanced Glaucoma Intervention Study. 2. Visual field test scoring and reliability. Ophthalmology. 1994 Aug;101(8):1445–55.
45. Folgar FA, de Moraes CGV, Prata TS, Teng CC, Tello C, Ritch R, et al. Glaucoma surgery decreases the rates of localized and global visual field progression. Am J Ophthalmol. 2010 Feb;149(2):258-264.e2.
46. Smith SD, Katz J, Quigley HA. Analysis of progressive change in automated visual fields in glaucoma. Invest Ophthalmol Vis Sci. 1996 Jun;37(7):1419–28.
47. Chauhan BC, Garway-Heath DF, Goñi FJ, Rossetti L, Bengtsson B, Viswanathan AC, et al. Practical recommendations for measuring rates of visual field change in glaucoma. Br J Ophthalmol. 2008 Apr;92(4):569–73.
48. Leung CK, Cheung CYL, Weinreb RN, Qiu K, Liu S, Li H, et al. Evaluation of Retinal Nerve Fiber Layer Progression in Glaucoma: A Study on Optical Coherence Tomography Guided Progression Analysis. Invest Ophthalmol Vis Sci. 2010 Jan 1;51(1):217–22.
49. Grewal DS, Tanna AP. Diagnosis of glaucoma and detection of glaucoma progression using spectral domain optical coherence tomography. Curr Opin Ophthalmol. 2013 Mar;24(2):150–61.