Revisiting the vascular theory of glaucoma using optical coherence tomography angiography

11

Valorization addendum

Relevance of this research

Glaucoma is the leading cause of irreversible blindness world-over, as well as in my country, India. Based on the results of the population based studies conducted in different parts of India till now,[1-5] George et al[6] reported the burden of glaucoma in India to be 11.2 million. Of these, primary open angle glaucoma (POAG) was estimated to be 6.48 million and primary angle closure glaucoma (PACG) was 2.54 million. If we include primary angle closure (PAC) along with PACG, with the idea of estimating the number of people with primary angle closure disease (PACD) that require treatment, the number is 6.6 million, similar to that of POAG.[6] The clinical course and severity of primary glaucoma is not uniform across populations. Angle closure glaucoma in India is different from that seen in other parts of South-east Asia. PACD tends to have a more chronic course and acute angle closures are relatively rare.[7] The burden of glaucoma blindness in India is 1.1 million. PACG on an average produced 2 times the proportion of bilateral blindness than POAG in India.[6] Glaucoma, a disease with such a significant burden on the community, is of great societal significance. Studying the utility of optical coherence tomograpy angiography (OCTA) in PACD, a disease with a high prevalence in India, is of significant relevance to us.

In spite of glaucoma being such a significant disease, the exact pathogenesis of it is not fully understood. Mechanical (IOP related mechanical damage) and vascular (ischemic damage due to reduced blood supply) theories are the two commonly proposed theories to explain its pathogenesis. However, the vascular theory is not studied well because of a lack of simple, non-invasive, accurate and precise method for studying ocular blood flow. Optical coherence tomography angiography (OCTA) came with the hope of fulfilling most of the requirements for an ideal test to evaluate ocular blood flow. Evaluating OCTA therefore was necessary to determine if it was a useful test to quantify the ocular blood supply and to contribute to the pathogenesis of glaucoma.

Two crucial steps in the management of glaucoma are to diagnose the disease early and to prevent disease progression by effective treatment. Early detection

of glaucoma has received great emphasis as the optic nerve damage from glaucoma remains irreversible till date. Evaluating rim area, RNFL thickness and GCC thickness on OCT is one of the preferred method to diagnose glaucoma early. We sought out to evaluate if the OCTA-measured vessel density was able to diagnose glaucoma earlier than the structural measurements of OCT. If so, this could lead to a paradigm shift in the way glaucoma is diagnosed and monitored. In our cross-sectional analysis, we however found that the OCTA-measured vessel densities were inferior to OCT-measured structural parameters in diagnosing glaucoma in early stages.

The primary treatment of glaucoma still revolves around managing the intraocular pressure (IOP) and IOP still remains a primary outcome measure in evaluating the efficacy of various treatments. If OCTA is useful in evaluating the vascular changes in glaucoma, this could possibly open up new ways of evaluating treatment outcomes.

Target groups

Beneficiaries of the results of this dissertation are the clinicians, academic researchers and the industry. The essential theme of the entire thesis was to evaluate the clinical utility of OCTA in glaucoma. The results therefore are straight away applicable to all clinicians. The take home message from the thesis for the clinicians is that OCTA evaluates the blood vessels of the superficial retina precisely. However, the technology still is not equivalent to traditional OCT-measured structural parameters in diagnosing glaucoma and so the technology in its current form is not an essential part of the clinical workup of glaucoma diagnosis. The thesis is also applicable to academic researchers as the results not only give a comprehensive knowledge about OCTA but also gives directions to future research with this technology. For researchers evaluating OCTA in longitudinal studies, the results of the thesis give clear indications of the test-retest variability and the factors other than glaucoma progression that can affect a measurement change. For the industry, the thesis provides a factual update

on the current status of the technology. It demonstrates that there is a definite need for improvements in the technology before it becomes a part of the day to day glaucoma care.

Product

Translating the results of the thesis to meaningful products started early in the course of the research work. The challenges in the currently available quantification algorithms of OCTA have been mentioned in the earlier chapters. Briefly, one of the challenges is that the software considers both the large vessels and capillaries together during quantification. It is quite possible that the vascular changes in glaucoma may be more pronounced in large vessels compared to capillaries, or vice-versa. There is a need to evaluate large vessel and capillary changes separately in glaucoma. We had done some work in this regard and had used fractal analysis based algorithm to quantify the large and small vessels of retina separately.[8] This is an ongoing work. The other important challenge is that the OCTA technology is now available on the OCT devices of multiple manufacturers. Cirrus HD-OCT 5000 (Zeiss Meditec, Inc., Dublin, CA, USA) and Spectralis (Heidelberg Engineering, Heidelberg, Germany) are two SDOCT-based devices that perform angiography. Triton (Topcon, Tokyo, Japan) is a swept-source OCT-based device that performs angiography. However, none of these, like Avanti RTVue-XR (Optovue Inc., Fremont, CA, USA), the device used in the thesis, have commercially available quantification software. We have therefore developed a vessel density analysis software that can be used on the images of any of these devices (device-independent software). This is called “ReVeal” (retinal vessel evaluation algorithm). The software is in the testing phase and would be available to the market soon.

Innovativeness of the research

The innovativeness of the thesis is the fact that the research work was conducted

keeping the clinical perspective in mind so that the results could be translated directly to the clinics. The other most important aspect was the testing of the technology in angle closure glaucoma, which to the best of our knowledge, is not done before. Angle closure glaucoma is a significant problem in India and the results of our study provide useful information about the utility of OCTA in Indian population.

Realization

Steps to take the research work of this thesis further is already underway. The results of the thesis demonstrate that the OCTA technology needs to mature a lot before it can become an essential part of the glaucoma workup. A significant proportion of scans obtained for this research was of poor quality, primarily due to motion artifacts. The new generation of devices performing OCTA therefore come with an eye-tracker so as to nullify the effect of eye movements during scanning. Our work in underway to find out if the repeatability and utility of OCTA improves with the introduction of this eye-tracking technology. The studies related to the current thesis are predominantly cross-sectional in design. Longitudinal studies to validate the results of these studies are also ongoing. One of the primary question that remained unanswered in the thesis was the effect of glaucoma drugs on the OCTA-measured vessel densities. Studies are also underway to evaluate this.

REFERENCES

1. Jacob A, Thomas R, Koshi SP, et al. Prevalence of primary glaucoma in an urban south Indian population. Indian J Ophthalmol 1998;46:81-6.
2. Ramakrishnan R, Nirmalan PK, Krishnadas R, et al. Glaucoma in a rural population of southern India: the Aravind comprehensive eye survey. Ophthalmology 2003;110:1484-90.
3. Vijaya L, George R, Baskaran M, et al. Prevalence of primary open-angle glaucoma in an urban south Indian population and comparison with a rural population. The Chennai Glaucoma Study. Ophthalmology 2008;115:648-54.
4. Vijaya L, George R, Arvind H, et al. Prevalence of primary angle-closure disease in an urban south Indian population and comparison with a rural population. The Chennai Glaucoma Study. Ophthalmology 2008;115:655-60.

5. Garudadri C, Senthil S, Khanna RC, et al. Prevalence and risk factors for primary glaucomas in adult urban and rural populations in the Andhra Pradesh Eye Disease Study. Ophthalmology 2010;117:1352-9.
6. George R, Ve RS, Vijaya L. Glaucoma in India: estimated burden of disease. J Glaucoma 2010;19:391-7.
7. Seah SK, Foster PJ, Chew PT, et al. Incidence of acute primary angle-closure glaucoma in Singapore. An island-wide survey. Arch Ophthalmol 1997;115:1436-40.
8. Kumar RS, Anegondi N, Chandapura RS, et al. Discriminant Function of Optical Coherence Tomography Angiography to Determine Disease Severity in Glaucoma. Invest Ophthalmol Vis Sci 2016;57:6079-88.