Objective Assessment of Progression after Acute Primary Angle Closure Using HRT and GDx

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Abstract

Irreversible damage to the optic nerve can follow the rapid increase of IOP during an acute primary angle closure (APAC). Despite the development of advanced imaging technology, there is still a lack of good longitudinal studies assessing patients after an acute attack. The aim of this study was to assess the progression of patients using different objective optic nerve head and retinal imaging parameters following APAC.

Twenty patients with a single attack of APAC, were retrospectively assessed in this study. Patients were assessed with the Heidelberg retinal tomography (HRT3) and scanning laser polarimeter (GDx-VCC) as well as Humphrey visual field (HVF) repeatedly up to eighteen months after the acute attack. Progression for each imaging modality was assessed with multiple parameters.

All patients showed retinal nerve fibre layer (RNFL) and optic disc changes over time. At 18 months, 67% of patients showed progression in 4/5 GDx parameters, and 33% in all 5. HRT analysis similarly showed progression in 4/5 parameters in 70% of patients, and 30% in all 5.

This study shows that structural progressive changes to RNFL and ONH occur following APAC confirming that APAC patients need long-term follow-up after the acute attack.

Keywords: Acute primary angle closure; Scanning laser ophthalmoscopy; Scanning laser polarimetry

Introduction

Acute primary angle closure (APAC) is regarded as an ophthalmological emergency and if not promptly treated could lead to irreversible visual loss [1]. It is characterized by a mechanical occlusion of the trabecular meshwork leading to a profound and sight threatening increase in intraocular pressure (IOP). Clinical diagnosis is based on the objective examination. Acute pharmacological IOP lowering therapy and laser treatments such as peripheral iridotomy are crucial to reduce the risk of development of chronic angle closure [2]; irreversible damage to the optic nerve can follow the rapid increase of IOP during APAC. Optic disc pallor associated with oedema is one of the possible features of the acute attack. After IOP normalization it is possible to observe both visual field loss and thinning of the retinal nerve fibre layer (RNFL) [3]. Despite the extensive use of Scanning laser ophthalmoscopy (HRT) and Scanning laser polarimeter (GDX-VCC) for optic nerve assessment in diagnosis and follow up of primary open angle glaucoma, there is a paucity of clinical studies which have objectively assessed the progression of patients following APAC.

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Table 1: Demographic characteristics.
Patients were assessed with HRT34, GDx-VCC5 as well as HVF6 twice, within a month of the acute attack, and at eighteen months post APAC (Figure 1).

Progression for each imaging modality was assessed with multiple parameters and reliability criteria were met accordingly [7,8]. For HRT analysis, we employed: rim area, rim volume, mean RNFL thickness, linear cup-to-disc ratio and GPS. Figure 2a shows one of the HRT printouts and Figure 2b shows the GDx printout. Repeat imaging was performed in all patients.

All mean values for individual HRT and GDx parameters were calculated with standard errors of the mean (SEM). The unpaired t-test was used to evaluate the degree of retinal and ONH modification produced by the acute attack between baseline and follow up visits. Analysis of results was undertaken using GraphPad Prism ver. 5.00 for Microsoft Windows (GraphPad Software, San Diego, CA, USA). P ≤ 0.05 was considered significant.
Figure 2A: HRT and GDx printout. A: HRT printout. Top left shows the reflective image of the patient ONH. Next, the vertical topographic profile of the ONH. Top right shows the graphical representation of the MRA. The mid pictures represents the horizontal topographic profile of the ONH and RNFL thickness respectively. Bottom left table shows the stereometric parameters (patient’s values, changes from baseline exam, and normal ranges). Bottom right picture represent the MRA with 95% confidence intervals.
Results

11 male and 9 female patients were assessed in this study (15 Caucasian subjects, 3 Indian subjects and 2 Asian subjects). Mean age was 54.7 ± 6.8, mean IOP during the acute attack was 45.3 ± 8.1 mmHg, mean IOP at follow up visit was 16.3 ± 2.4 (Table 1). All patients were in good general health status without history of systemic chronic diseases.

Differences in HRT parameters after acute attack

The following parameters were used in the HRT analysis in all 20 patients after APAC attack: rim area, rim volume, mean RNFL thickness, Linear cup-disc ratio, and Glaucoma probability score.

As seen in Table 2, rim volume (0.3 ± 0.033 mm$^3$ vs 0.4 ± 0.03 mm$^3$, p<0.05), mean RNFL thickness (0.18 ± 0.027 mm vs 0.250 ± 0.18 mm, p<0.05) and GPS (0.46 ± 0.05 vs 0.30 ± 0.05, p<0.05) were all significantly altered at 18 months follow up compared to baseline. No significant changes were found for Rim Area (1.28 ± 0.04 mm$^2$ vs 1.4 ± 0.03 mm$^2$, p=0.0557) and C/D Ratio (0.64 ± 0.04 vs 0.52 ± 0.04, p=0.0544) (Table 2 and Figure 3).

Differences in GDx parameters after acute attack

The GDx was used in addition to the HRT to assess the ONH modifications after APAC. TISNT average (46.5 ± 2.6 vs 54 ± 2.5, p<0.05) and Inferior average (43.6 ± 3 vs 53.7 ± 3, p<0.05) were significantly altered at 18 months after the acute attack.
The Venn diagram shows progression of patients with 5/5 parameters of GDx-HRT overlapping with VF. It was interesting to observe that 35% of our patients had the maximum number of altered parameters at both the HRT and GDx parameters. This percentage decreased to 20% when we tried to correlate HRT, GDx, and VF pathological evidences (Figure 5a).

At 18 months after the acute attack, HRT analysis showed progression in 5/5 parameters in 60% of patients, 30% in 4/5 and 10% in 3/5 (Figure 5b). The 3 HRT parameters that were modified in all patients were rim volume, mean RNFL, and GPS which suggests their importance in the assessment of APAC patients.

Similarly, 60% of patients showed progression in 5/5 GDx parameters, 35% in 4/5 and 5% in 3/5 (Figure 5a). The parameters that were modified in all patients were TISNT average, inferior average and NFI. This suggests that these parameters should be chosen when assessing patients after APAC.

**Discussion**

APAC has traditionally been regarded as an acute occurrence but more recently has been found to be part of a chronic process [4,9,10]. This study suggests that progressive changes do occur following APAC, as detected using both HRT and GDx nerve fibre layer analysis [4,9,10]. At 18 months after the acute attack, 60% of patients showed progression in all HRT (rim volume, rim area, mean RNFL, C/D Ratio, and GPS) and GDx (TISNT Average, inferior average, superior average, TISNT SD, and NFI) parameters.

**HRT evidence of damage**

In this study, Rim Area remained stable and within normal limits. This result is in contrast with several studies on APAC patients where a reduction in the neuroretinal rim area was recorded [11,12]. For example, Shen SY et al. have suggested a decrease in rim area 16 weeks after APAC in a predominantly Chinese population [11], accompanied by a reduction in disc area (10%). In this study, however, the ONH assessment was performed using optic disc photography. Similarly, Chai et al., in a case report, documented a reduction in rim area in a 64-year-old man one year after a single episode of APAC (2.15 mm² at 1 week, and 2.08 mm² at 1 year) [12,13]. The discrepancy with the literature could be due to the use of different imaging techniques for ONH assessment and on different study populations. Nevertheless, rim area, by itself or incorporated in the MRA, is one of the most frequently used parameters for glaucoma diagnosis and follow-up [14-17]. Lan et al. have reported that HRT defined-rim area has a good correlation to HVF MD for glaucoma diagnosis [14]. Strouthidis et al. using both the HRT classic and the HRT2 have suggested that rim area is a useful tool for assessing disease progression with good correlation between the two versions of the same instrument [15]. Fayers and co-authors have also proposed an event based analysis of sectorial rim area adjusted for image quality and number of observations for the monitoring of glaucoma progression [16]. Zangwill et al. have suggested that the MRA (which adjusts rim area to disc size) is a useful biomarker for glaucoma diagnosis [17].

Rim volume was significantly reduced following APAC (p<0.05) in this study, suggesting an association between the acute attack and subsequent glaucomatous damage as reported by Chen et al. where visual field modifications were reported after a single episode of APAC18. Rim volume, unlike rim area, takes into account the three-dimensional nature of the ONH rim. Thus rim volume may be
considered a better parameter in assessing subtle ONH rim changes [19,20]. This is in keeping with Chai et al. who suggested that a reduction in rim volume was observed after a single APAC attack [13]. It is partially in keeping with the data provided by Sng CC et al. where a trend of Rim Volume reduction was suggested after a single episode of APAC [21]. The main difference between this study and Sng et al is that the latter was conducted on a small cohort of Chinese population with a mean of 33 months follow up and a large range between inter-individual assessment (range, 11-85 months.) In our study Caucasian patients were assessed for a mean follow up of 18 months. By contrast, Chew et al. in a prospective study, did not demonstrate a change in rim volume after APAC22 during a prospective investigation where APAC eyes were compared to fellow eyes for a shorter period of 12 months. It is important to note that Rim Volume has been shown to be consistently reduced in POAG as reported by Hoffmann et al. [23], Leung et al. [24], and Kamai et al. [25].

Mean RNFL thickness was significantly reduced, suggesting long-term damage to the axons of RGCs. This result is in keeping with Sng et al. where peripapillary loss of RNFL was diagnosed after a single episode of APAC [21]. Furthermore, Chew et al. noted that even if cup to disc ratio did not change, there was significant thinning of the RNFL on HRT analysis 12 months after APAC [22]. It is interesting to note that this was the only change found by the authors after APAC.

GPS was significantly increased in patients in this study going from 0.3 ± 0.05 to 0.5 ± 0.050 (p<0.05). Despite the significant increase the overall score remained in the borderline range. GPS is essentially based on 3 papillary parameters (size of the excavation, excavation depth, and slope of the rim), and 2 RNFL parameters (vertical and horizontal curvature of the RNFL) as documented by Swindale et al., and by Zelefsky et al. [26,27]. The ability of the GPS (which is operator independent) to identify glaucomatous abnormalities was compared with the MRA (which is operator-dependent as it needs a contour-line) by Coops et al. who have documented a mild reduction in sensitivity but higher specificity of the GPS compared to the MRA [28]. The predictive ability of the GPS in identifying glaucomatous eyes was evaluated by Alencar et al. who compared it to subjective evaluation of stereo photos [29]. These authors have suggested that GPS is a powerful tool for predicting glaucoma and has good correlation with stereo disc photography. However, GPS has poor reproducibility for borderline values as documented by Strouthidis et al., therefore values between 0.30 and 0.64 should be interpreted with caution [30]. Thus, GPS should not be used as a unilateral parameter of progression in studies of this kind. Furthermore GPS was designed as a biomarker for glaucoma diagnosis and, to our knowledge; this is the first study that has applied GPS evaluation to APAC follow up.

**GDx evidence of damage**

In this study GDx has been shown to be a helpful tool in assessing progression after APAC. GDx is known to be useful in detecting progressive RNFL thinning in primary open angle glaucoma as highlighted by Grewal et al. [31], Reus et al. [32], Toth et al. [33], and summarised by Da Pozzo et al. in their review of SLP [34]. Similarly, previous findings have reported that GDx is able to highlight superior and inferior RNFL defects 16 weeks after APAC [35]. Aung et al. suggest that RNFL loss after APAC is due to a localized event as they did not find sectorial glaucomatous damage in the nasal and temporal RNFL quadrants.

In our study, significant worsening of the TISNT average was found 18 months after the acute attack (p<0.05). Looking at sectorial parameters, inferior average was the only sectorial parameter that was significantly abnormal at 18 months (p<0.05). This result is partly in keeping with Tsai et al. who have reported a thinning of both superior and inferior average [36]. The main difference between these studies could be attributed to differences in population and numbers of examined patients. The worsening of inferior average is also supported in part by data published by Liu et al who have suggested that each TISNT parameter is altered in patients with primary angle closure glaucoma and GDx alteration is in keeping with VF deterioration [37]. However, Lai et al. have reported that APAC does not produce any GDx damage in patients who had a short lasting attack (less than 48 hours) [5]. The current study was a retrospective investigation and unfortunately no data on the duration of the acute attack were recorded. In the current study, regrettably, the SD-OCT was not yet available at the WEH.

**Agreement between different imaging techniques**

60% of patients showed progression in 5/5 HRT and GDx parameters after APAC. 20% of patients demonstrated HRT (5/5 parameters), GDx (5/5 parameters), and visual field progression, 18 months post the acute attack.

As far as we are aware, this is the first longitudinal study where multiple imaging modalities have been used to provide objective measurements of changes. It confirms that APAC patients need extended follow-up after the acute attack [38].

The use of multiple imaging technologies for the assessment of APAC is crucial since HRT and GDx are designed to analyse different structural features of the back of the eye. The HRT primarily assesses ONH morphology, providing robust structural data for both glaucoma diagnosis and progression. By looking at the birefringence of the microtubules present in the RGCs axons, the GDx provides information on the status of the RNFL. Therefore, the combination of these technologies should improve the detection of ONH and RNFL damage.

Furthermore, recent studies have shown that APAC eyes have thicker choroid in the macula region compared to the fellow eye when examined with enhanced depth imaging OCT [39]. Both these findings suggest how OCT analysis could also be applied to an inter-platform approach to APAC.

Our results showed significant thinning of the inferior RNFL with GDx, and this together with other groups’ findings suggest that sectorial damage is the most likely pattern of RNFL loss after APAC [40]. In fact unlike POAG, which is a chronic multifactorial disease, APAC is a sudden event which produces long term retinal changes. Monitoring changes that occur soon after the onset of the insult could be a useful endpoint in a clinical trial, as this acute event, which is not part of a multifactorial disease, could be a helpful model for studying neuroprotective strategies in glaucoma.

**Correlations between ACG and OAG**

Differences in retinal findings between open angle glaucoma (OAG) and angle closure glaucoma (ACG) have been reported. Zhao et al. have suggested that patients with ACG have larger rim area, smaller cup volume, lower cup depth, reduced cup-to-disc ratio, and cup shape measure within normal limits when compared to patients with OAG [41]. Further studies have demonstrated that ACG patients differ from OAG patients only in cup shape measurements, with more
negative values in ACG [42]. Boland at al. have shown that most HRT stereometric parameters differ between OAG and ACG [43]. Nouri-Mahdavi et al. have proposed that patients with ACG have more sectorial HRT changes when MRA was used, showing the presence of inferotemporal RNFL thinning [40]. However, Ravi et al. could not find any significant difference on HRT between OAG and ACG. They suggested however, that HRT would be less sensitive in identifying early damages in ACG compared to OAG [42].

Chen at al. have suggested that there is no significant difference in GDx parameters between ACG and OAG[44]. However, they propose a different trend of progressive thinning of RNFL over time [44]. On the contrary, other authors have suggested that the GDx-VCC makes it possible to differentiate between OAG and ACG. Lee at al. have demonstrated significant superonasal, supertemporal, inferotemporal, and inferonasal RNFL thinning in OAG which was in agreement with HVF findings, while only inferotemporal and superotemporal thinning were found in ACG [45]. Liu and colleagues have demonstrated different GDx-VCC superior-inferior RNFL symmetry between OAG and ACG [46].

In conclusion, to the knowledge of the authors, this is the first time that a multiparameter approach has been used to assess patients following APAC. This study confirms that RNFL and ONH changes occur after APAC suggesting that long-term follow up, using objective imaging technologies, should be considered in patients following a single acute attack. However, given the retrospective nature of the study and the small sample size, further studies are needed to confirm these findings in larger and multi-ethnic population.

References


