

# Cross-Sectional Study of the Retinal Nerve Fiber Layer Thickness at 7 Years After an Acute Episode of Unilateral Primary Acute Angle Closure

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**Abstract:** The purpose of this article is to investigate the long-term retinal nerve fiber layer (RNFL) status and determinants of RNFL thinning after an episode of unilateral primary acute angle closure (AAC).

This cross-sectional study analyzed the medical records of consecutive patients with a single episode of unilateral AAC from 1999 to 2009 in Hong Kong. The peripapillary RNFL thickness was correlated with age, gender, presenting intraocular pressure (IOP), time to laser iridotomy, time to cataract extraction, follow-up duration, as well as the last IOP, vertical cup-to-disc ratio (CDR), and vision. The fellow uninvolved eye was used as a proxy comparison of RNFL loss in the attack eye.

In 40 eligible patients, the mean age was  $68.3 \pm 8.7$  years with a male-to-female ratio of 1:7. The mean presenting IOP was  $49.2 \pm 14.0$  mm Hg and the time from presentation to laser iridotomy was  $6.7 \pm 6.9$  days. Forty percent of subjects received a cataract extraction at  $3.2 \pm 2.9$  years after the attack. The last IOP, CDR, and LogMAR vision were  $16.0 \pm 3.8$  mm Hg,  $0.6 \pm 0.2$ , and  $0.6 \pm 0.6$  LogMAR units, respectively, at  $7.9 \pm 2.4$  years. The RNFL thickness in the attack eye ( $69.2 \pm 19.1 \mu\text{m}$ ) was  $25.2 \pm 17.9\%$  thinner than the fellow eye ( $93.0 \pm 17.8 \mu\text{m}$ ) at  $7.5 \pm 2.9$  years post-AAC. Using univariate analysis, the last vertical CDR (odds ratio [OR] = 17.2,  $P = 0.049$ ) and LogMAR visual acuity (VA) (OR = 6.6,  $P = 0.03$ ) were the only significant predictors for RNFL thinning whereas none of the other covariates showed significant associations ( $P > 0.1$ ).

At 7.5 years following unilateral AAC, the RNFL thickness was 25% thinner than the fellow eye. CDR enlargement and poor VA were the only significant predictors for RNFL loss.

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**Abbreviations:** AAC = acute angle closure, CDR = cup-to-disc ratio, dB = decibel, IOP = intraocular pressure, MD = mean

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deviation, OCT = optical coherence tomography, OR = odds ratio, PSD = pattern standard deviation, RNFL = retinal nerve fiber layer, VA = visual acuity.

## INTRODUCTION

In chronic glaucomatous diseases, severity is often characterized by clinically visible optic disc cupping. However, in primary acute angle closure (AAC), glaucomatous optic neuropathy may develop without any obvious cupping.<sup>1</sup> Although visual field is still the gold standard investigation for glaucoma, its use may be limited in AAC as previous studies have reported high underdetection rates, great variability, and unreliability in glaucomatous optic neuropathy assessment following AAC.<sup>2,3</sup> These shortcomings of the visual field in AAC may be related to the concomitant presence of cataract, atonic mydriasis, and poor eye-hand coordination in advancing age.<sup>4</sup>

Optical coherence tomography (OCT), on the contrary, objectively measures the peripapillary retinal nerve fiber layer (RNFL) thickness with less-stringent cooperative requirements from the patient as compared with the visual field examination. It has been previously reported that changes in RNFL thickness following AAC is an evolving process that takes place anywhere between 2 and 16 weeks after the attack<sup>5</sup> but very few studies have reported the long-term RNFL status as well as the factors associated with RNFL thinning after AAC. The purpose of this study was to investigate the long-term RNFL status and determinants of RNFL thinning after an episode of unilateral AAC.

## PATIENTS AND METHODS

The study was approved by the Institutional Review Board of the Hospital Authority of Hong Kong. No individual patient particulars were disclosed in this study. The authors declare no financial or proprietary interests and this was a nonfunded study.

This cross-sectional study analyzed the medical records of the consecutive patients with the diagnosis of AAC from January 1999 to April 2009 using an electronic medical records database of the Hospital Authority of Hong Kong searching the keyword "acute angle closure glaucoma" (the former terminology for acute angle closure).<sup>6</sup> All patients attended the Caritas Medical Centre, Hong Kong Special Administrative Region, China. The inclusion criteria consisted of patients with a first episode of unilateral acute angle closure defined as an intraocular pressure (IOP)  $\geq 21$  mm Hg, with at least 1 of the following symptoms: ocular pain, headache, nausea, vomiting, and visual blurring, and at least 2 of the following signs: corneal edema, mid-dilated pupil, conjunctival injection, a shallow anterior chamber on slit-lamp examination in the attack eye

via the Van Herrick System grading, or an occludable angle by gonioscopy in the fellow eye ( $\geq 270^\circ$  of grade 0–1 angle on the Shaffer classification).<sup>6</sup> Gonioscopy in the attack eye was often not feasible because of the presence of corneal edema from the acute elevated IOP.<sup>6</sup> The exclusion criteria included those with secondary angle closures (phacomorphic angle closure, subluxed lens, and neovascularization), a history of vitreoretinal or corneal surgery in the attack eye, incomplete clinical data, suboptimal OCT scans, preexisting glaucoma prior to the AAC attack, and follow-up interval  $< 6$  months after the AAC.

Patient demographics, presenting IOP, presenting Snellen visual acuity (VA), time from presentation to definitive laser iridotomy, time from attack to cataract extraction, follow-up interval from the attack, and the last VA, IOP, vertical cup-to-disc ratio (CDR), and peripapillary RNFL thickness were recorded. The RNFL thickness of the fellow uninvolved eye was used as a proxy reference point for the calculation of the amount of RNFL loss in comparison to the eye with the AAC. Snellen VA was converted to LogMAR units for statistical analysis. For nonnumerical VA, the following denotations were used: finger count = 1.7, hand movement = 2.0, light perception = 2.3, and no light perception = 3.0 LogMAR.<sup>7</sup>

### Peripapillary RNFL Thickness Measurement

The Spectralis Spectral Domain OCT (Heidelberg Engineering, Carlsbad, CA) was performed after pharmacological pupil dilation, by a single, imaging technician who was masked to subjects' clinical information. Scans were centered on the optic disc with a scanning diameter of 3.5 mm and 768 A-scans were obtained using the high-speed mode. To improve image quality, automatic real-time function was used to obtain multiple frames during scanning and optimize images by noise reduction. Scans were repeated 3 times and assessed for signal strength and centration. Scans with signal strength quality  $\leq 16$  or poor centration were excluded. RNFL thickness was analyzed with the RNFL Single Exam Report OU with fovea-to-disc technology. The global RNFL thicknesses were recorded in micrometers for both eyes.

### Statistics

The percentage of RNFL thinning in the eye with AAC was correlated with 9 covariates using both univariate and multiple linear regression analyses. The covariates included gender, age, presenting IOP, time from presentation to laser iridotomy, time from attack to cataract extraction, follow-up interval after the attack, as well as IOP, vertical CDR, and VA on last follow-up (Table 1). All the covariates were coded as continuous except for gender, which was binary. A *t* test was used to assess differences in means. Correlations were expressed in coefficient estimates and a *P* value  $\leq 0.05$  was considered statistically significant. All estimates were expressed as mean  $\pm$  standard deviation.

## RESULTS

During the 10-year study period, 40 subjects were eligible for the study. The mean age was  $68.3 \pm 8.7$  years with a male-to-female ratio of 1:7. The mean presenting IOP was  $49.2 \pm 14.0$  mmHg and the mean number of days from presentation to laser iridotomy was  $6.7 \pm 6.9$  days. Forty percent (16/40) of subjects received a cataract extraction in the eye with AAC closure at a mean of  $3.2 \pm 2.9$  years after the attack.

At a mean follow-up period of  $7.9 \pm 2.4$  years after the AAC attack, the mean IOP in the involved eye was  $16.0 \pm 3.8$  mm Hg and the mean vertical CDR was  $0.6 \pm 0.2$ . The mean VA was  $0.6 \pm 0.6$  LogMAR units. The mean RNFL thickness was  $69.2 \pm 19.1$   $\mu\text{m}$  in the eye with AAC and  $93.0 \pm 17.8$   $\mu\text{m}$  in the uninvolved fellow eye. When using the fellow eye as a proxy normative reference, the RNFL in eye with the AAC was  $25.2 \pm 17.9\%$  thinner at a mean of  $7.5 \pm 2.9$  years following the AAC. Only 27/40 (67.5%) of subjects were able to produce reliable visual field examination using the Humphrey Visual Field Analyzer's (Carl Zeiss Meditec AG, Berlin, Germany) 24-2 Swedish interactive thresholding algorithm. Of those that had reliable fields, the mean deviation (MD) and pattern standard deviation (PSD) were  $-10.5 \pm 7.9$  and  $+5.0 \pm 3.2$  decibel (dB), respectively, on last follow-up. Compared with the fellow eye (MD =  $-6.7 \pm 8.4$ ; PSD =  $+4.4 \pm 3.2$  dB), this represented a 56.7 and 13.6% worsening of the MD and PSD, respectively, in the attack eye, although this was short of statistical significance (both  $P > 0.09$ ), probably because of the small number of subjects who were able to produce reliable fields. Because of the incompleteness of visual field parameters, they were not included as covariates in the regression analyses.

Using univariate analysis, the last vertical CDR (odds ratio [OR] = 17.2,  $P = 0.049$ ) and LogMAR VA (OR = 6.6,  $P = 0.03$ ) were the only significant predictor for RNFL thinning whereas none of the other covariates showed significant associations ( $P > 0.1$ ). Using multivariate analysis, again, none of the covariates were significant determinants of RNFL thinning ( $P \geq 0.09$ ) (Table 1).

## DISCUSSION

Similar to open-angle glaucoma, the functional defects from AAC on the visual field often lags behind anatomical defects; in 55% of AAC subjects, it may have normal visual fields whereas 15% may develop optic atrophy without ever developing disc cupping.<sup>1,2</sup> Visual field testing is therefore unreliable during AAC episodes.<sup>8</sup> In our study, 32% of subjects were able to produce a reliable visual field examination after their AAC attack either because of poor VA or poor eye–hand coordination. Similar difficulties have been reported for patients suffering from phacomorphic angle closures.<sup>9</sup>

The OCT, on the contrary, can objectively measure the serial changes following AAC and it has been well described by various authors during the early periods following an acute attack. It is known that RNFL thinning after AAC is not a one-off event but rather one that evolves over time at an accelerated rate compared with the uninvolved fellow eye.<sup>10</sup> Yoles and Schwartz<sup>11</sup> proposed a mechanism whereby healthy neurons bathed in a pool of toxins produced by damaged neurons that may cause the healthy counterparts to undergo accelerated degenerative changes.

When the pre-AAC RNFL baseline is not available, the uninvolved fellow eye can serve as a useful means of comparison for RNFL thinning since under normal circumstances the RNFL should be similar over both the eyes.<sup>8</sup> Fang et al<sup>10</sup> longitudinally measured the RNFL in both the eyes of subjects with unilateral AAC and reported that at 2 weeks, the attack eye had a RNFL that was 31.2% thicker compared to the fellow eye, likely secondary to optic nerve edema. However, by 4 months, the RNFL over the attack eye was 21.8% thinner than the fellow eye.<sup>10</sup> Similarly, Tsai et al<sup>8</sup> observed optic nerve edema at 1 week after an episode of AAC, which subsided by 4 weeks postattack as characterized by a significant RNFL thinning in

**TABLE 1.** Predictors of Retinal Nerve Fiber Layer Thinning After Acute Angle Closure

	Univariate Regression Analysis					Multivariate Regression Analysis				
	Coefficient Estimates	Odds Ratio	95% Confidence Interval		P Value	Coefficient Estimates	Odds Ratio	95% Confidence Interval		P Value
Male gender	16.24	11.85	-7.74	40.22	0.18	70.27	35.05	1.58	138.97	0.09
Age, y	0.46	0.46	-0.47	1.39	0.33	0.67	0.82	-0.94	2.29	0.44
Presenting IOP, mm Hg	0.46	0.28	-0.11	1.03	0.11	0.93	0.74	-0.52	2.39	0.26
Time from presentation to laser iridotomy, d	0.04	0.59	-1.15	1.24	0.95	-0.03	0.80	-1.60	1.53	0.97
Time from attack to cataract extraction, y	2.77	2.14	-1.81	7.35	0.22	3.50	2.71	-1.81	8.81	0.24
Follow-up interval after attack, y	0.36	1.66	-3.00	3.72	0.83	0.86	2.49	-4.01	5.73	0.74
Last IOP, mm Hg	-1.12	1.06	-3.27	1.03	0.30	-2.71	2.17	-6.96	1.54	0.26
Last vertical CDR	-34.87	17.16	-69.60	-0.13	0.049*	49.89	48.21	-44.61	144.38	0.34
Last visual acuity, LogMAR	-14.90	6.59	-27.82	-1.98	0.030*	-9.65	13.74	-36.57	17.27	0.51

CDR = cup-to-disc ratio, IOP = intraocular pressure.

\* Statistically significant.

the average and 4 quadrants measurements. By 12 weeks, however, the RNFL thinning had reached a plateau and there was no significant difference between the 4 and 12-week RNFL thickness.<sup>8</sup>

In our study, the RNFL measured at a mean of  $7.5 \pm 2.9$  years after an episode of unilateral AAC, and was  $25.2 \pm 17.9\%$  thinner in the attack eye as compared to the fellow eye. Based on the reported thinning of 21.8% at 4 months by Fang et al,<sup>10</sup> it seems that the degree of RNFL thinning reaches a plateau from 4 months onward up until years after an AAC attack. This is of course provided that the IOP is well controlled to  $\leq 21$  mm Hg, like in our population that had a mean IOP of  $16.0 \pm 3.8$  mm Hg at  $7.9 \pm 2.4$  years of follow-up. Similarly, Aung et al<sup>5</sup> reported that much of the RNFL loss took place within the first 12–16 weeks after the initial AAC attack. From the visual field, the MD was 56% worse in the attack eye than in the fellow eye on last follow-up, although this did not reach a level of statistical significance ( $P > 0.09$ ) because of the small number of subjects who were able to produce reliable visual fields, again, reiterating the limitations of the visual field examination after acute angle closure.

It has been the understanding that the acute elevation of IOP in AAC focally targets the superior and inferior RNFL.<sup>12,13</sup> With improvements in the management of AAC over the years and the popularity of more effective IOP-lowering treatments such as immediate argon laser peripheral iridoplasty,<sup>14</sup> the duration of AAC attacks and, hence, the association of the acute IOP elevation with the degree of RNFL loss may be variable throughout the literature. Lai et al<sup>15</sup> previously reported that the amount of RNFL thinning was likely associated with the duration of the AAC attack. On the other hand, Aung et al<sup>5</sup> did not find any significant association between RNFL thinning and the duration of AAC. In our study, the duration of AAC from presentation to laser iridotomy was not a significant predictor for RNFL thinning. The only significant associations were an increased vertical CDR (OR = 17.2,  $P = 0.049$ ) and a poor VA (OR = 6.6,  $P = 0.03$ ) from clinical examination, reiterating the importance of a complete ophthalmological examination after an AAC attack.

Thus, it seems that when the IOP is already within a normal range after the attack, there is no evidence to suggest that having an IOP that is the upper range of normal would result in a greater RNFL thinning or vice versa. Thus, the benefits of further lowering the IOP to the lower range of normal may not be substantiated based on the findings from this study. In addition, the timing of cataract extraction after AAC also does not seem to affect the overall RNFL status on a long-term basis, given the IOP was controlled within a normal range.

This study was limited by the nonlongitudinal nature of the RNFL measurements partly because of the lack of availability of the OCT machine during the early years of the study as well as inconsistencies in the model and make of OCT machines used throughout the follow-up interval (a time domain OCT in the earlier years prior the availability of the spectral domain OCT). However, the longitudinal changes during the early post-AAC periods have been well reported by the different authors as described above. What is lacking in the literature at present is the long-term RNFL status after AAC, which has been reported in this study at 7.5 years after an attack. Furthermore, most patients first presented to our center during their acute attack; thus, a preattack baseline RNFL thickness was not available. Instead, we used the uninvolved fellow eye as a proxy reference for comparison on the amount of the RNFL loss derived from the AAC. By comparing with the other eye, we were also able to factor in the amount of RNFL thinning that is lost with normal aging. Having a control group that did not have acute angle closure would be ideal but as our center does not routinely perform RNFL measurements for those without glaucoma, it would be logistically difficult for us to obtain age and sex-matched serial RNFL tracings over a 7-year period. Furthermore, inevitably, inconsistencies and missing information from the medical records did not allow us to accurately comment on information such as the actual duration of the AAC symptoms prior to ophthalmological consultation, which may have had impact on RNFL outcome.

In conclusion, at 7.5 years after an episode of unilateral AAC in a Chinese population, the peripapillary RNFL thickness in the attack eye was 25% thinner than the uninvolved fellow

eye. An enlarged vertical CDR and poor VA were the only significant predictors for the degree of RNFL loss.

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