Association of Longitudinal Changes in Drusen Characteristics and Retinal Layer Volumes with Subsequent Subtype of Choroidal Neovascularisation

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Keywords

Age-related macular degeneration · Choroidal neovascularisation type · Drusen load · Retinal layer volumes · Imaging biomarkers

Abstract

Aim: To investigate the longitudinal correlation between drusen characteristics and retinal layer volumes pre conversion and subsequent type of choroidal neovascularisation (CNV). **Methods:** This was a single-centre retrospective study. The study participants were patients with wet age-related macular degeneration (AMD) in one eye who developed wet AMD in the contralateral eye, with at least 2 years of follow-up prior to conversion. The Moorfields Eye Hospital database was searched for eligible patients and their data were recorded. Eyes were classified as occult or classic based on fundus fluorescein angiography. Optical coherence tomography (OCT) images were analysed for drusen characteristics and retinal layer volumes were analysed over time using automated software (Topcon 3D OCT-2000 and Orion, Voxeleron LLC, respectively). All values were obtained at

baseline as well as year 1 and year 2 before conversion to wet AMD. **Results:** Fifty-one eyes with bilateral CNV showed high correlation of type of CNV between eyes (kappa statistic 0.89). A total of 49 wet AMD eyes (29 occult, 20 classic) were analysed for drusen parameters. Two patients with retinal angiomatous proliferation were excluded. Drusen count, area, and volume did not differ by CNV type, but the rates of change of drusen area ($p = 0.046$) and drusen volume (0.022) were higher in the occult group in the year preceding CNV development. Of the 49 eyes, 17 (10 occult, 7 classic) with available good quality OCT were analysed for retinal layer volumes. There was a progressive reduction in outer nuclear layer (ONL) volume ($p = 0.002$) and an expansion in outer plexiform layer volume ($p = 0.015$) in eyes that developed occult CNV. **Conclusion:** Our study shows that rate of increase in drusen load and reduction in ONL are significant features seen in eyes developing occult CNV, highlighting new imaging markers that need to be replicated in larger studies. These markers provide insight into the pathogenesis of CNV and may serve as prognostic indicators, as classic CNV carries a poorer prognosis compared to occult CNV.

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Introduction

Age-related macular degeneration (AMD) is a leading cause of severe vision loss in people over the age of 50 years in developed countries [1, 2]. There are two main forms of the disease: the dry form (including early and intermediate AMD and an advanced form termed geographic atrophy) and the wet form. Wet AMD develops when new choroidal blood vessels grow and break through Bruch's membrane (BM) and/or the retinal pigment epithelium (RPE). This phenomenon is defined as choroidal neovascularisation (CNV). CNV occurs in approximately 10–15% of all AMD cases, and these eyes are at high risk of severe visual loss because it often results in elevation or penetration through the RPE with adjacent sub- and intraretinal fluid and haemorrhage [3]. CNV can be classified based on fluorescence angiography into occult, classic, or mixed lesion types [4]. Classic lesions are often aggressive with early and severe loss of vision, while occult lesions are often stable with less visual loss [5].

It is important to distinguish between occult and classic CNV lesions because the natural course of the disease and its prognosis and benefit from certain treatments vary between different types of CNV [6, 7]. This was specifically realised when photodynamic therapy or laser treatment were the first lines of treatment. Photodynamic therapy has been established only for those lesions that are predominantly classic CNV [8], while laser photocoagulation has been used mainly for those lesions that have some evidence of classic CNV [4]. Furthermore, the importance of classifying CNV lesions as classic or occult has also been used recently reported in the anti-VEGF era in the MARINA and ANCHOR trials that assessed ranibizumab as intravitreal treatment of CNV secondary to AMD. The MARINA trial was for occult CNV [9], whereas the ANCHOR trial was for predominantly classic lesions [10]. Currently, the clinical relevance of CNV classification in wet AMD eyes is uncertain. This is because anti-VEGF agents were found to be effective in treating CNV regardless of its type [11]. However, classic CNV is associated with poor prognosis, risk of atrophy, and fibrosis after anti-VEGF therapy compared to occult CNV (CATT). New trials to test novel therapies also specify the CNV type among their inclusion criteria [12, 13]. Thus, CNV classification will allow for more effective trials as prognosis and treatment may vary based on CNV type.

The risk of developing occult CNV in the second eye of patients with unilateral occult CNV has been found to be high [14]. Various studies on patients with unilateral CNV secondary to AMD have identified important risk

factors for CNV development in the fellow eye [15–18]. The characteristics of drusen of the fellow eye are correlated with the type of CNV in the affected eye [19–21]. For example, occult CNV is more likely to be associated with intermediate drusen than pure classic CNV that may occur in eyes with no or small drusen [21]. However, very few studies have investigated the correlation between clinical characteristics such as drusen load preceding CNV development in the same eye. We reported that the mean change in macular drusen load in eyes that converted to wet AMD increased a year before conversion to wet AMD [22].

In this study we investigated a cohort of patients who underwent treatment for unilateral CNV and developed CNV in the fellow eye at the end of the 2-year study period. In the fellow eye, automated drusen and retinal layer quantification measurements were obtained from spectral-domain optical coherence tomography (OCT) scans prior to conversion onset. The aim of this study was to investigate whether any correlation existed between these parameters and the subsequent CNV type in the same eye (i.e., fellow eyes). We also investigated the correlation in CNV type between the two eyes in these patients as it is known that drusen phenotypes are similar between eyes. Thus, we hypothesised that certain drusen or retinal layer quantification parameters may indeed better explain the symmetry of type of bilateral CNV.

Materials and Methods

Data Collection

Consecutive fluorescein angiography (FA) and OCT images of patients with unilateral wet AMD were reviewed from the database of Moorfields Eye Hospital. For inclusion in this study, patients were required to have CNV in one eye as evidenced by FA and to have developed a CNV lesion in the fellow eye with at least 2 years of follow-up before developing the lesion. We excluded all patients with polypoidal choroidal vasculopathy, subfoveal fibrosis, or ungradable CNV due to haemorrhage or poor imaging quality. Eyes with CNV secondary to other causes rather than AMD or without available FA images were also excluded.

Image Grading

CNV lesions were classified independently by two ophthalmologists (A.L. and A.E.N.) for each patient on the basis of early, mid, and late frames of FA. The CNV type was classified based on FA as occult, classic, or retinal angiomatous proliferation (RAP). Mixed lesions were classified as classic CNV. Any discrepancies between the two ophthalmologists were resolved by a third expert consultant (S.S.).

The drusen characteristics in the fellow eye of each patient were determined using the drusen quantification software available on the Topcon 3D OCT-2000 device (Topcon, Tokyo, Japan). Drusen

measurements including drusen count, area, and volume were collected retrospectively at baseline, year 1, and year 2.

Macular OCT images were acquired from the fellow eyes using a 6 × 6 mm macular cube scan (3D OCT, Topcon). Each fellow eye was part of a 3 scans/2 years protocol (baseline, year 1, and year 2). Macular layer volumes were derived for circles of 3 and 6 mm diameter around the foveal centre using an automated layer segmentation software (Orion, Voxeleron LLC). The following layer volumes were derived: retinal nerve fibre layer, ganglion cell-inner plexiform layer, inner nuclear layer (INL), outer nuclear layer (ONL), photoreceptors, RPE-BM, and total retinal volume.

Statistical Analysis

Statistical analysis was performed using SPSS software version 24. Normality was tested by the Shapiro-Wilk test. As the data were not normally distributed, nonparametric *t* tests (Mann-Whitney U and Wilcoxon signed-rank test) were used to compare the differences in drusen parameters and retinal layer volumes between the classic and occult types. Agreement of CNV type between the two eyes in cases where the fellow eye developed CNV was quantified with the kappa statistic. *p* values ≤ 0.05 were considered statistically significant.

Results

Demographic Features of the Participants

A total of 209 patients with unilateral wet AMD and available FA were identified. Seventy patients met the inclusion criteria. Of these 70 patients, 19 were excluded due to absence of FA in the fellow eye. In the remaining 51 patients' fellow eyes, 29 were classified with occult CNV, 20 with classic CNV, and 2 with RAP type. As RAP lesions were rare, we only compared the differences in the quantifications of drusen load and retinal layer volume between the classic and occult types.

For drusen load quantifications, the whole cohort of 29 occult CNVs and 20 classic CNVs were included in the study. For occult lesion participants, the mean (SD) age of 22 females (75%) and 7 males (25%) was 75.7 (7.5) years, ranging from 60 to 88 years. For classic lesion participants, the mean (SD) age of 14 females (70%) and 6 males (30%) was 75.8 (6.5) years, ranging from 65 to 85 years.

For retinal layer segmentation analysis, only 17 participants were included (10 occult and 7 classic). The other participants were excluded because their macular OCT images of the 2-year protocol were not available. For occult lesion participants, the mean (SD) age of 7 females (70%) and 3 males (30%) was 82.4 (7.6) years, ranging from 71 to 93 years. For classic lesion participants, the mean (SD) age of 4 females (57%) and 3 males (43%) was 80.2 (7.5) years, ranging from 71 to 91 years.

Table 1. Drusen parameters in AMD eyes prior to conversion to either occult (*n* = 29) or classic (*n* = 20) CNV

Drusen parameter	Occult	Classic	<i>p</i> value
Drusen count			
Baseline	9.93 (8)	8.50 (5.7)	0.729
Year 1	11.48 (7.8)	9.85 (6)	0.561
Year 2	11.69 (8.8)	11.65 (7)	0.791
Drusen area, mm ²			
Baseline	1.49 (1.2)	1.77 (1.38)	0.483
Year 1	1.84 (1.48)	2.21 (1.7)	0.528
Year 2	2.63 (1.8)	2.46 (1.8)	0.707
Drusen volume, mm ³			
Baseline	0.070 (0.07)	0.078 (0.06)	0.464
Year 1	0.085 (0.089)	0.104 (0.084)	0.309
Year 2	0.131 (0.114)	0.118 (0.1)	0.640
Change in drusen area, mm ²			
Baseline to year 1	0.354 (0.61)	0.44 (0.89)	0.855
Year 1 to year 2	0.788 (0.8)	0.252 (0.7)	0.046
Change in drusen volume, mm ³			
Baseline to year 1	0.014 (0.02)	0.026 (0.04)	0.784
Year 1 to year 2	0.046 (0.04)	0.013 (0.03)	0.022

Values for occult and classic CNV are presented as mean (SD).

Drusen Load prior to CNV Development

Table 1 shows the means and SDs of drusen load including count, area, and volume at baseline, year 1, and year 2 and longitudinal change in drusen area and volume from baseline to year 1 and from year 1 to year 2. While drusen parameters (count, area, volume) were alike in both CNV groups, the rates of change of drusen area and drusen volume were higher in the occult group in the year preceding CNV development.

Retinal Layer Volumes prior to CNV Development

Table 2 shows the means and SDs for the various layer volumes for 17 participants preceding CNV development. There were statistically significant differences between eyes with the two CNV types in mean ONL volume (3 mm). The ONL volume was thinner in eyes preceding classic CNV than occult CNV at baseline and year 1, indicating early decrease in photoreceptor volume in eyes that progress to classic CNV type. Otherwise, no significant differences were found between the two CNV lesions in volumes of other retinal layers.

Table 3 shows the longitudinal change of retinal layer volumes at 3 and 6 mm from baseline to year 1 and from year 1 to year 2 in occult and classic CNV lesions. From baseline to year 1, no differences were found between the

Table 2. Mean retinal layer volumes at 3 and 6 mm in AMD eyes prior to conversion to either occult ($n = 10$) or classic ($n = 7$) CNV

Retinal layer	Time line	Mean retinal layer volume at 3 mm			Mean retinal layer volume at 6 mm		
		occult	classic	<i>p</i> value	occult	classic	<i>p</i> value
TRV	baseline	2.19 (0.19)	2.07 (0.12)	0.118	8.32 (0.65)	7.92 (0.48)	0.283
	year 1	2.17 (0.18)	2.03 (0.12)	0.118	8.24 (0.62)	7.85 (0.54)	0.283
	year 2	2.17 (0.18)	2.03 (0.12)	0.172	8.27 (0.62)	7.88 (0.54)	0.283
RNFL	baseline	0.215 (0.03)	0.200 (0.02)	0.205	1.19 (0.17)	1.11 (0.23)	0.283
	year 1	0.206 (0.04)	0.196 (0.02)	0.770	1.16 (0.19)	1.06 (0.22)	0.495
	year 2	0.217 (0.02)	0.196 (0.03)	0.283	1.15 (0.14)	1.05 (0.31)	0.495
GCIPL	baseline	0.508 (0.07)	0.511 (0.04)	0.845	1.75 (0.24)	1.76 (0.13)	0.558
	year 1	0.508 (0.08)	0.498 (0.04)	1	1.73 (0.18)	1.73 (0.13)	0.922
	year 2	0.526 (0.07)	0.500 (0.07)	0.558	1.82 (0.20)	1.74 (0.17)	0.283
INL	baseline	0.301 (0.03)	0.278 (0.02)	0.143	1 (0.08)	0.90 (0.06)	0.435
	year 1	0.301 (0.03)	0.269 (0.02)	0.143	1 (0.08)	0.96 (0.09)	0.696
	year 2	0.288 (0.03)	0.270 (0.02)	0.380	0.99 (0.09)	0.96 (0.07)	0.696
OPL	baseline	0.161 (0.04)	0.183 (0.04)	0.380	0.592 (0.13)	0.623 (0.11)	0.626
	year 1	0.156 (0.03)	0.190 (0.06)	0.435	0.577 (0.10)	0.627 (0.11)	0.380
	year 2	0.186 (0.04)	0.182 (0.04)	0.922	0.648 (0.12)	0.624 (0.11)	0.696
ONL	baseline	0.689 (0.06)	0.589 (0.06)	0.011	2.47 (0.24)	2.21 (0.23)	0.064
	year 1	0.686 (0.08)	0.576 (0.07)	0.015	2.48 (0.27)	2.24 (0.24)	0.079
	year 2	0.626 (0.08)	0.584 (0.08)	0.495	2.34 (0.28)	2.27 (0.28)	0.558
PR	baseline	0.318 (0.02)	0.306 (0.02)	0.495	1.29 (0.11)	1.23 (0.10)	0.435
	year 1	0.316 (0.02)	0.304 (0.02)	0.380	1.28 (0.09)	1.21 (0.09)	0.172
	year 2	0.325 (0.03)	0.302 (0.02)	0.172	1.30 (0.09)	1.22 (0.09)	0.172
RPE-BM	baseline	0.047 (0.02)	0.048 (0.06)	0.329	0.137 (0.03)	0.157 (0.07)	0.696
	year 1	0.048 (0.02)	0.054 (0.06)	0.495	0.135 (0.04)	0.171 (0.08)	0.283
	year 2	0.067 (0.04)	0.068 (0.05)	0.845	0.152 (0.05)	0.200 (0.07)	0.172

Values for occult and classic mean retinal layer volume are presented as mean (SD). GCIPL, ganglion cell-inner plexiform layer; INL, inner nuclear layer; ONL, outer nuclear layer; OPL, outer plexiform layer; PR, photoreceptors; RNFL, retinal nerve fibre layer; RPE-BM, retinal pigment epithelium-Bruch's membrane; TRV, total retinal volume.

two CNV types or even within each CNV group. From year 1 to year 2, most of the retinal layer volume changes were observed in the outer retina, particularly in the occult group. There were significant differences between the two CNV groups in longitudinal ONL (3 and 6 mm) and outer plexiform layer (OPL) volume (3 mm). There was a progressive reduction in ONL volume and an expansion in OPL volume in eyes that developed occult CNV.

In the occult CNV group, INL (3 mm) and ONL volumes (3 and 6 mm) decreased significantly from year 1 to year 2. In contrast, there were significant increases in mean OPL (3 and 6 mm) and RPE-BM (3 mm) volumes

from year 1 to year 2. In the classic CNV group, only RPE-BM volume (6 mm) increased significantly from year 1 to year 2.

Correlation in CNV Type between the Two Eyes

Table 4 summarises CNV types in patients with bilateral CNV. Of the 51 patients with bilateral CNV, 48 (94%) had similar CNV types in both eyes: 27 patients had occult CNV in both eyes, 19 had classic lesions in both eyes, and 2 had RAP lesions in both eyes. The kappa statistic was 0.89 (95% CI 0.76–1.0), indicating a strong level of agreement between the two eyes.

Table 3. Longitudinal change in retinal layer volumes at 3 and 6 mm in AMD eyes prior to conversion to either occult ($n = 10$) or classic ($n = 7$) CNV

Retinal layer volume	CNV subtype	Year 1 volume change			Year 2 volume change		
		mean (mm ³)	<i>p</i> value ^a	<i>p</i> value ^b	mean (mm ³)	<i>p</i> value ^a	<i>p</i> value ^b
Circle diameter 3 mm							
TRV	occult classic	−0.0189 −0.0357	0.059 0.128	0.380	−0.048 0.03	0.721 0.735	0.626
RNFL	occult classic	−0.089 −0.042	0.203 0.612	1	0.011 0.008	0.285 1	0.770
GCIPL	occult classic	−0.004 −0.0134	0.878 0.499	0.696	0.017 0.02	0.333 0.612	0.329
INL	occult classic	0.007 −0.091	0.646 0.176	0.118	−0.0131 0.01	0.037 0.866	0.143
OPL	occult classic	−0.052 0.06	0.333 0.866	0.770	0.029 −0.077	0.07 1	0.015
ONL	occult classic	−0.029 −0.0130	0.959 0.176	0.435	−0.0599 0.08	0.05 0.499	0.02
PR	occult classic	−0.021 −0.020	0.721 0.735	0.770	0.09 −0.023	0.646 0.499	0.435
RPE-BM	occult classic	0.007 0.05	0.241 0.063	1	0.018 0.014	0.07 0.063	0.495
Circle diameter 6 mm							
TRV	occult classic	−0.0845 −0.0667	0.093 0.237	0.845	0.0269 0.0299	0.721 0.735	0.922
RNFL	occult classic	−0.0337 −0.0466	0.445 0.237	0.770	−0.024 −0.099	0.575 0.735	0.845
GCIPL	occult classic	−0.0283 −0.0311	0.333 0.237	0.922	0.0907 0.067	0.114 0.735	0.205
INL	occult classic	−0.041 −0.073	0.646 1	0.696	−0.0136 0.00	0.241 0.735	0.435
OPL	occult classic	−0.0147 0.048	0.139 0.866	0.558	0.0714 −0.033	0.028 0.866	0.118
ONL	occult classic	0.071 0.0311	0.646 0.310	0.495	−0.1417 0.0298	0.013 0.499	0.025
PR	occult classic	−0.0109 −0.0175	0.333 0.176	0.626	0.0225 0.066	0.878 1	1
RPE-BM	occult classic	−0.010 0.0143	0.575 0.091	0.283	0.0166 0.0287	0.074 0.043	0.558

GCIPL, ganglion cell-inner plexiform layer; INL, inner nuclear layer; ONL, outer nuclear layer; OPL, outer plexiform layer; PR, photoreceptors; RNFL, retinal nerve fibre layer; RPE-BM, retinal pigment epithelium-Bruch's membrane; TRV, total retinal volume. ^a Wilcoxon signed-rank test for paired volume measurements, year 1 (baseline vs. year 1) and year 2 (year 1 vs. year 2). ^b Mann-Whitney U test, occult versus classic.

Table 4. CNV types in patients with bilateral CNV

CNV type in first eye	CNV type in fellow eye			Total
	occult	classic	RAP	
Occult	27	1	0	28
Classic	2	19	0	21
RAP	0	0	2	2
Total	29	20	2	51

RAP, retinal angiomatous proliferation.

Discussion

In this study we compared the 2-year change in drusen load and retinal layer volumes between eyes that developed occult and classic CNV lesions at the end of the 2-year follow-up period. When comparing drusen load between the two CNV types, there were significant increases in drusen area and volume in the preceding 12 months prior to development of occult CNV, whereas no significant differences were found in means of drusen count, area, or volume at baseline, year 1, or year 2 in the classic CNV eyes. When comparing retinal layer volumes between the two CNV types, thinning of baseline ONL was found in the classic CNV groups, and significant differences in volume changes of ONL and OPL were found between the two CNV groups in year 2 only (no differences between the two CNVs were found in year 1). In occult CNVs, ONL and INL volumes were found to be reduced, whereas OPL and RPE-BM volumes were found to be expanded from year 1 to year 2. In classic CNVs, only RPE-BM volume increased from year 1 to year 2. We also investigated, in the same cohort, the agreement between CNV type in second eyes developing CNV and the first CNV eye. Agreement was high (kappa statistic 0.89).

The drusen load findings of our study support findings reported previously in the literature. It has been reported that the clinical features in the fellow eye correlate with the type of CNV in the affected eye in AMD patients with unilateral CNV using colour fundus photography [21, 23]. Abugreen et al. [21] found that the fellow eyes of occult CNV have significantly more severe AMD features compared to eyes with classic CNV. Similarly, Sivaprasad et al. [23] showed that this kind of association between the CNV type in the affected eye and the severity of the disease in the fellow eye can only be applied on Caucasians, compared to Chinese patients who did not show a similar disease pattern.

It is important to notice that the present study longitudinally investigated the correlation between prior drusen load quantifications using spectral-domain OCT and subsequent CNV type in the same eye. Our data showed that a greater increase in OCT drusen area and volume can be seen in the year before developing occult CNV compared to other eyes that developed classic CNV. As these drusen quantifications were measured by spectral-domain OCT, the scans only detected soft drusen, and no other type of drusen such as reticular pseudodrusen could be quantified. Thus, our findings of no significant differences between the two CNV groups by means of OCT drusen count, area, and volume at baseline, year 1, or year 2 are consistent with the recent work of Marsiglia et al. [19], who showed that soft drusen on colour photographs in one eye are not associated with CNV type in the other eye.

Our study demonstrated significant baseline thinning of the ONL in eyes that developed classic CNV. Thinning of the ONL in AMD eyes has been reported in recent studies using OCT that showed ONL thinning in eyes with intermediate AMD [24–26]. We also reported in a recent study that the ONL is either not affected at early AMD stages or the amount of damage is not significant to be detected at earlier stages of the disease [27]. Our finding suggests that the ONL degenerates earlier in eyes that will develop classic CNV type than occult one, but does not visibly worsen over time. Additional findings in this study support this hypothesis, which is a significant reduction in ONL volume in the eyes that developed occult CNV. Another notable observation in this study was that the OPL increased in volume in the occult type. OPL thickening with age and in AMD has been reported recently [27, 28]. This increase in OPL volume may represent a compensatory expansion as a consequence of ONL thinning.

Finally, the observed symmetry in CNV types between the two eyes was high, and this may give us an idea of the likelihood symmetry between the two eyes when trying to predict the CNV type that will most likely develop in a fellow eye of a patient with unilateral wet AMD. The symmetry of CNV type between eyes of AMD patients has been reported previously in a study of 115 patients, which showed that patients with unilateral occult CNV have a high risk of developing occult CNV in the fellow eye [14]. However, a recent study reported poor agreement (kappa statistic 0.16) in the symmetry of CNV between the two eyes in patients with bilateral wet AMD [29]. It is possible that methodological differences explain the disagreement with the present study.

To our knowledge, this is the first study to longitudinally investigate the difference in retinal layer volumes and drusen load between occult and classic CNV in order to identify imaging biomarkers. These biomarkers may aid in predicting the CNV type in AMD eyes before it develops. This will allow for more individualised patient care and more effective trials because prognosis and treatment may vary based on CNV type.

The limitations of this study include its retrospective nature; there was a possible ascertainment bias as we only included patients with active CNV undergoing treatment. Further longitudinal studies involving other factors such as subretinal drusenoid deposits, pigmentary changes, and choroidal thickness may enable the development of a risk score based on weight of evidence of each imaging marker.

In summary, the association between simple automated quantification of drusen and retinal layer volumes using the method described and subsequent CNV type would suggest that different pathogenetic mechanisms explain the development of occult or classic CNV. This hypothesis might have to be tested by further studies on larger patient cohorts. The observations of the present study provide imaging biomarkers that may help in predicting the type of CNV. Also, the strong agreement between CNV types with bilateral CNV is consistent with distinct pathogenetic mechanisms or patient-specific modifiers, with some patients being more at risk of one type than another, which may support separating these subgroups in future trials of novel therapies or treatment regimens.

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Statement of Ethics

This study was approved by the Ethical Review Board of Moorfields Eye Hospital and adhered to the principles of the Declaration of Helsinki.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A. Lamin designed the study, collected and analysed the data, and took the writing lead. A. El Nokrashy collected and analysed the data. S. Chandra analysed the data and edited the manuscript. Prof. S. Sivaprasad designed and directed the study. All authors discussed the results and commented on the manuscript.

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