Original Article

Pachydrusen in Indian population: A hospital-based study

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Purpose: To report the prevalence of pachydrusen in Indian population and their characteristics in relation to subfoveal choroidal thickness (SFCT), choroidal vascularity index (CVI) in comparison to eyes with soft drusen and subretinal drusenoid deposits (SDD) in age-related macular degeneration (AMD). **Methods:** The study was a retrospective, cross-sectional study involving patients with a diagnosis of dry AMD in at least one eye. The diagnosis of soft drusen, SDD, and pachydrusen was made on the basis of color fundus photograph and optical coherence tomography (OCT). SFCT and CVI was calculated and compared among the different subtypes of drusen. **Results:** A total of 169 eyes (143 dry and 26 wet AMD) of 85 patients with a mean age of 67.67 ± 9.57 years were included. In eyes with dry AMD, pachydrusen were seen in 12 eyes (8.4%) with a mean (±SD) SFCT of 289.66 ± 91.01 µ. The difference in SFCT was statistically significant ($P = 0.001$) using analysis of variance (ANOVA) test. The eyes with pachydrusen had significantly thickened choroid compared to the eyes with SDD (30 eyes; 21.0%) or combination of soft drusen and SDD (29 eyes; 20.3%) but not soft drusen (72 eyes; 50.3%). The difference of CVI in different subgroups was significant ($P = 0.03$). One eye in wet AMD group had concurrent pachydrusen. Comparison of SFCT and CVI in wet AMD and fellow dry AMD eyes were not significant. **Conclusion:** In Indian eyes with dry AMD, prevalence of pachydrusen (8.4%) is slightly lower compared to western literature (11.7%) and is associated with thicker choroid and higher CVI.

Key words: Age-related macular degeneration, fluorescein angiography, optical coherence tomography, pachydrusen, soft drusen, subretinal drusenoid deposits

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Age-related macular degeneration (AMD) is one of the leading causes of irreversible loss of vision.[1] Although, described extensively in western population, its increasing incidence in the aging population in Indian subcontinent and other Asian countries have also been reported.[2] The prevalence of AMD in Indian population has been found to vary from 1.8–4.7% in different studies.[3-6]

Drusen are presumed to play a key role in pathogenesis of AMD although they can be seen in normal-aged individuals as well.[7] They are essentially composed of extracellular debris located between the basal lamina of retinal pigment epithelium (RPE) and inner layer of the Bruch's membrane.[7,8] Based on morphology and location, various types of drusen including hard, soft, cuticular, subretinal drusenoid deposits (SDD), or reticular pseudodrusen have been described.[9] Pachydrusen is a recently described subtype of drusen seen in patients with thickened choroid, has >125 µ size, and differs from soft drusen of AMD in terms of appearance and pattern of distribution.[10]

The subfoveal choroidal thickness (SFCT) has been studied in various types of drusen patterns.[10,11] SFCT in Indian subjects has been reported to be lesser as compared to different ethnicities in various studies while other studies with a higher mean age of study population have shown contrasting results.[12–16] As reported before, the incidence of polypoidal choroidal vasculopathy (PCV) is higher in Asian including Indian subjects.[17,18] The choroidal changes in dry AMD has been studied in great detail in the past in the western and Indian population as well.[19,20]

Whether the differences in choroidal thickness, varied incidence of PCV play a role in determining the morphological and distribution pattern of drusen especially pachydrusen in Indian population is still unknown. Present study intends to study the characteristics of various types of drusen including pachydrusen and associated changes in choroid in Indian population.

Methods

The study was a retrospective, observational study and included consecutive patients of dry AMD with presence of soft drusen, SDD, or pachydrusen in at least one eye. The study was conducted at a tertiary eye institute based in South India from June 2016 to June 2017. Prior approval was taken from

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the Institutional Review Board (IRB) and study conformed to the tenets of Declaration of Helsinki.

We analyzed data record of a total of 169 eyes (85 patients) with a diagnosis of dry AMD in at least one eye. The diagnosed cases of PCV were excluded from the study. PCV was defined as the presence of serosanguinous pigment epithelial detachments (PED), double layer sign in optical coherence tomography (OCT) and polyps, branching vascular network seen in indocyanine angiography (ICG) if available. Eyes with unavailable OCT scan or scans with poor demarcation of outer choroidal borders were excluded. The patients with uveitis, media opacity like cataract precluding fundus view, myopia more than 6D, or a history of prior vitreoretinal surgery or laser were also excluded.

The data on demographic profile including age and sex were collected. A comprehensive ophthalmological examination was done including best-corrected visual acuity (BCVA) in logarithm of minimum angle of resolution (logMAR), slit-lamp evaluation, intraocular pressure (IOP) assessment by the Goldmann applanation tonometry, indirect ophthalmoscopy, fundus photography (Zeiss Visupac® FF4 and FF450-plus, Carl Zeiss, Dublin, CA), enhanced depth imaging-OCT (EDI-OCT; Carl Zeiss Meditec Cirrus HD-OCT), or swept source-OCT [SS-OCT; Topcon DRI OCT Triton® (plus)]. A total of 104 eyes, 65 eyes had CT measurements done using the SS-OCT and SD-OCT, respectively. As reported previously in literature, there is a difference of SFCT measurements between SD-OCT and SS-OCT machines ranging from (6.3–13.6 μ) which originates due to the differences in the wavelengths employed for image acquisition and variability in identification of choroid-scleral interface.[21–23] These studies have shown increased CT measurements with SS-OCT, however, the results have not been consistent. These differences in CT were adjusted in the OCT measurements in the study eyes. A correction factor of 9.1 μ (calculating the mean of the differences in the previous studies)[21–23] was added to the eyes undergoing CT measurements with SD-OCT. Fundus photograph and OCT images were analyzed to characterize the deposits as drusen (soft, SDD, or pachydrusen) by two masked observers (Sashwanthi Mohan and Avadhesh Oli). In case of discrepancy, the final decision was made by a senior author (Jay K. Chhablani). Morphologically, hard drusen was defined as hyperreflective sub-RPE deposits usually <63 micron and was not included in the study. Soft drusen were defined as sub-RPE deposits located in the macular region with corresponding confluent yellowish deposits in fundus photography as well. SDD were seen as small mounds of ≥10 sub-retinal deposits in OCT with whitish appearance. Pachydrusen was identified by its large size (>125 μ) with ill-defined margins and was noted in peripapillary region or scattered near the posterior pole without clustering. SFCT was measured at the subfoveal level from outer border of RPE to the sclerochoroidal interface. The delineation of choroidal boundaries and image binarization was done using previously reported automated software to calculate choroid vascularity index (CVI) (ratio of luminal area to total choroid area).[24]

The data were tabulated and the mean with standard deviation (SD) were calculated using the SPSS software (version 22; IBM Corp., New York, NY). The variation of SFCT and CVI was also compared in the various groups of dry and wet AMD using analysis of variance (ANOVA) test. *P* value ≤ 0.05 was considered statistically significant.

Results

A total of 169 eyes of 85 patients were included in the analysis. One eye was not included because of the poor quality of images. The mean (±SD) age of patients was 67.67 ± 9.57 years. The genderwise distribution showed 41 males and 44 females. A total of 143 eyes of dry AMD and 26 eyes of wet AMD with varied distribution of different drusen were analyzed [Table 1].

The mean (±SD) choroidal thickness in the total study population was 228.71 ± 90.7 μ. Among the 143 eyes with dry AMD; soft drusen, SDD, and a combination of soft drusen and SDD were found in 72 eyes (50.3%), 30 eyes (21.0%), and 29 eyes (20.3%), respectively. Pachydrusen were found in 12 eyes (8.4%). The agreement between the two observers as shown by intraclass correlation coefficient (ICC) was excellent (kappa = 0.92). Figs. 1–3 show the representative cases of different types of drusen.

The SFCT comparison in the different groups was also done. The mean SFCT in soft drusen (245.93 ± 89.52 μ), SDD (202.03 ± 85.78 μ), soft/SDD (190.0 ± 93.45 μ), and pachydrusen (289.66 ± 91.01 μ) were compared (*P* = 0.001). The Tukey's post-hoc test showed significant difference between SDD and pachydrusen (*P* = 0.02); soft/SDD and pachydrusen (*P* = 0.008). Mean CVI in soft (0.42 ± 0.04), SDD (0.41 ± 0.04), and soft/SDD group was (0.40 ± 0.04), whereas CVI in pachydrusen group was 0.43 ± 0.02 [Table 2]. CVI comparison across the different groups using one-way ANOVA [F (3,149) = 3.03, *P* = 0.03] was statistically significant. The Tukey's post-hoc test, however, did not reveal significant differences in the pairwise comparison.

Table 1: Showing distribution of different types of drusen in non-exudative (dry) and exudative (wet) AMD eyes

Dry AMD	No of eyes (*n*=143) (%)	Wet AMD	No of eyes (*n*=26) (%)
Soft	72 (50.3)	Only CNVM*	21 (80.8)
SDD†	30 (21.0)	Plus soft	2 (7.7)
Soft/SDD	29 (20.3)	Plus SDD	1 (3.8)
Pachydrusen	12 (8.4)	Plus soft and SDD	1 (3.8)
		Plus pachydrusen	1 (3.8)

*CNVM: Choroidal neovascular membrane; †SDD: Subretinal drusenoid deposits; AMD: Age-related macular degeneration

Table 2: Comparison of SFCT and CVI in different types of drusen in eyes with dry AMD

Type of drusen	No of eyes	SFCT (μ)±SD*	CVI±SD
Soft	72	245.93±89.52	0.42±0.04
SDD†	30	202.03±85.78	0.41±0.04
Soft/SDD	29	190.0±93.45	0.40±0.04
Pachydrusen	12	289.66±91.01	0.43±0.02
	143	228.71±90.7	0.42±0.04

*SD: Standard deviation; †SDD: Subretinal drusenoid deposits; SFCT: Subfoveal choroidal thickness; CVI: Choroidal vascularity index; AMD: Age-related macular degeneration

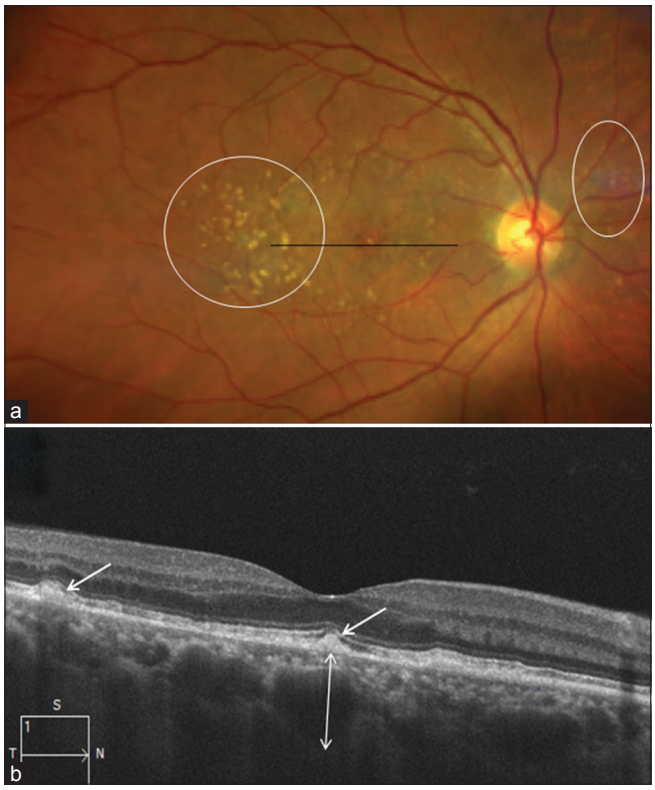

Figure 1: Fundus photograph of a 57-year-old patient with dry age-related macular degeneration showing presence of pachydrusen in macular and peripapillary distribution (white circles) (a). Line scan (black color) using an enhanced depth imaging optical coherence tomography shows the presence of pachydrusen subfoveally and temporal to fovea (white arrows; b). Subfoveal choroidal thickness was 375 μ

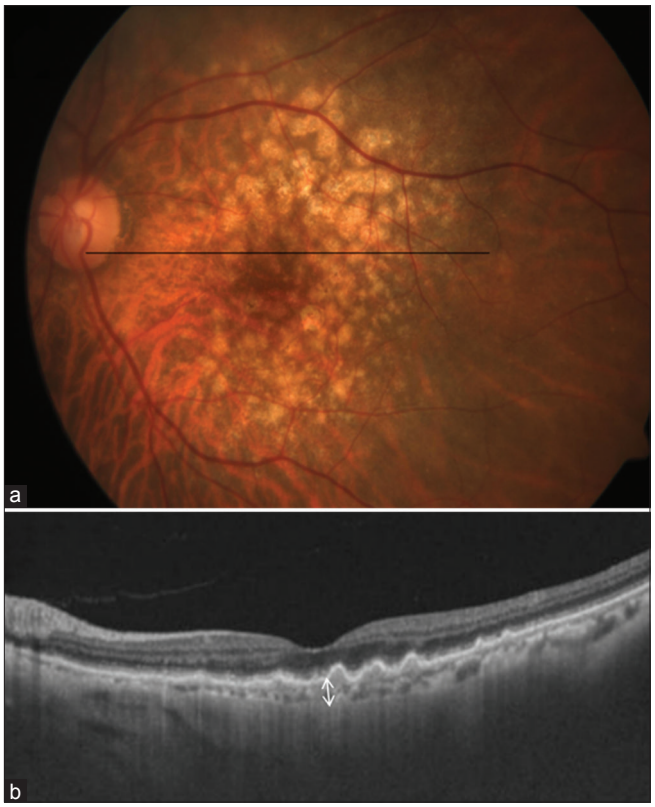

Figure 2: Shows the fundus photograph (a) and swept source optical coherence tomography line scan (black color) (b) of a 72-year-old patient showing presence of multiple soft drusen concentrated near fovea. The subfoveal choroidal thickness was 115 μ

In the subgroup of exudative AMD, 26 eyes among the study population of 169 eyes had presence of choroidal neovascular membrane (CNVM). Along with CNVM, presence of soft drusen (two eyes), SDD (one eye), combination of soft drusen/SDD (one eye) and pachydrusen (one eye) were noted. The mean SFCT and CVI in exudative AMD subgroup was 226.85 ± 73.26 μ and 0.42 ± 0.03, respectively. The fellow eyes of wet AMD were also analyzed. Among the fellow eyes, most commonly associated drusen was soft (11 eyes) followed by SDD (6 eyes) and a combination of soft drusen and SDD (7 eyes). Two eyes had presence of pachydrusen. The mean SFCT in the fellow eye of wet AMD was 246.5 ± 104.6 μ and mean CVI was 0.41 ± 0.04. The comparison of SFCT ($P = 0.44$) and CVI ($P = 0.31$) between the wet and dry AMD eyes was not statistically significant.

Discussion

We studied the prevalence of different types of drusen in AMD (including the patients with at least one eye with dry AMD) in Indian cohort. Among the 143 eyes in dry AMD, 12 eyes (8.4%) had presence of pachydrusen, while in wet AMD group (26 eyes), 1 eye had pachydrusen. In the 12 eyes with pachydrusen in dry AMD group, 5 eyes had presence of only pachydrusen, whereas 5 eyes had presence of combination of both pachydrusen and soft drusen and 2 eyes had combination of pachydrusen, soft drusen, and SDD. This suggests that rather than several distinct pathologies, these drusen subtypes are different manifestations of the same disease spectrum, which may have a correlation with choroidal thickness.

We also attempted to correlate the SFCT changes and observed that though SFCT was thickest in pachydrusen group, other groups such as soft drusen, soft/SDD, and SDD had comparable SFCT. We also analyzed the fellow eyes of wet AMD and found 2 eyes to have pachydrusen with higher prevalence of soft drusen (11 eyes) in these eyes.

The prevalence of pachydrusen in our study was 8.4% (12/143 eyes). Spaide reported a prevalence of 11.7% (11 eyes out of 94 eyes). The mean SFCT in their study was 419 μ as compared to 289.66 μ in our study.[10] The author has explained that expression of different manifestations of drusen, the nature and morphology of drusen, or drusenoid deposits in dry AMD varied with SFCT. The SFCT in increasing order was seen with SDD, soft drusen, and pachydrusen.[10] Whether the change in SFCT was an association or the causative physiological change leading to the above observation needs further elucidation.

Our previous publication studied SFCT (280.1 ± 46.5 μ) in normal Indian eyes with a mean age of 42.8 years.[12] As CT is known to reduce with progression of age, SFCT in the age group of 60–69 years (237.6 ± 61.3 μ) was lesser compared to the overall mean SFCT.[12] In our study, the mean SFCT of the eyes with pachydrusen is higher compared to normal individuals of similar age group. These SFCT values fit in the definition of pachychoroid based on the previous publications.[25,26] The

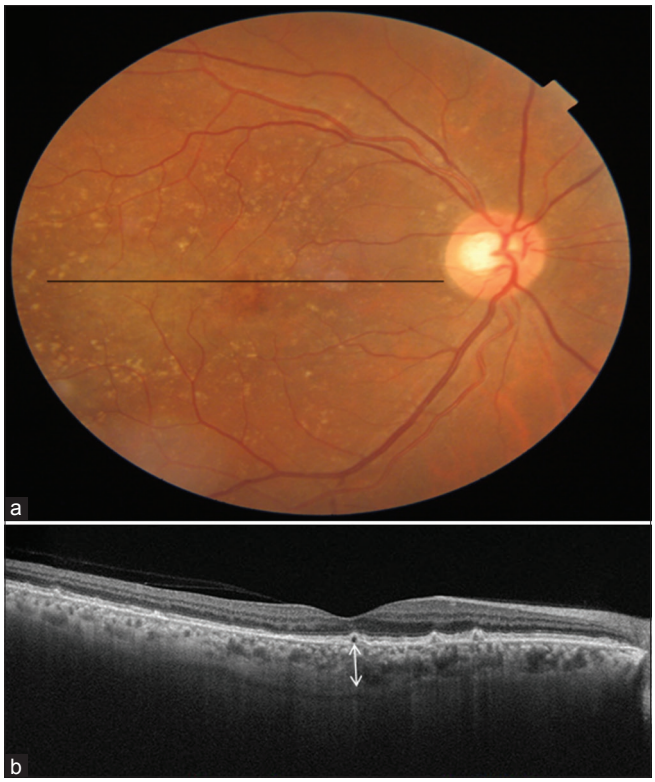

Figure 3: Shows the fundus photograph (a) of a 66-year-old patient with presence of multiple subretinal drusenoid deposits distributed throughout the macula. Swept source optical coherence tomography (b) through the fovea (black color) shows presence of subretinal drusenoid deposits. The subfoveal choroidal thickness was 279 μ

definition of pachychoroid is not yet clearly defined in the literature. Miyake *et al.* and Dansingani *et al.* have used cut-off points such as CT >200 μ or >270 μ with a mean CT of 310 ± 53 μ and 381 ± 141 μ, respectively, in their publication.[25,26] These arbitrarily set cut-off values lead to difficulties in defining the eyes with pachychoroid.

Lee and Byeon have focused on the prevalence of soft drusen, SDD, and pachydrusen in patients of PCV.[11] They reported that in patients of PCV, SFCT with pachydrusen was twice compared to those with soft drusen or SDD. They found a prevalence of 70% for the pachydrusen in the treatment naïve PCV.[11] However, in our study, we excluded PCV patients as they form a different phenotype, which needs a further exploration in an Indian cohort.

The vast difference in distribution pattern of pachydrusen in different studies (including ours) ranging from 7 to 70% gives an impression that characterization of the morphological patterns of drusen in AMD has significant variability among observers. Similarly, geographical distribution and variability of AMD in different population also needs to be taken into account.[2,10,11] While Spaide and Lee and Byeon have described pachydrusen in Caucasian and Korean population, respectively, our study was focused primarily on Indian population.[10,11]

We compared CVI in different subtypes of drusen and found CVI to vary significantly among the groups ($P = 0.03$). However, analysis using the post-hoc test did not reveal significant differences between pachydrusen and other groups. The probable reason for no significant difference could be the role of choriocapillaris in drusen formation, which still cannot be evaluated separately using CVI. CVI in AMD (including both dry and wet variants) in Indian cohort has been reported to vary from 57.10–69.97% with a mean (±SD) of 64.04 ± 2.43%. Though CVI varied in both wet (mean ± SD: 64.42 ± 2.51%) and dry variants (63.75 ± 2.37%), the difference was not significant ($P = 0.29$).[27]

SDD and soft drusen are known to be associated with wet AMD. Similarly, pachychoroid also is associated with CNVM and PCV.[28] Whether the pachydrusen also are harbinger of severe disease with progression to CNVM in AMD eyes or precursor lesion in PCV is still not known. Our data had limited number of patients with pachydrusen in either group, therefore, the exact correlation cannot be identified.

The study has certain limitations. The study sample is hospital based rather than population based which could have provided a more robust outlook of the prevalence of the pachydrusen in the general population. We excluded the eyes with PCV and the possibility that the incidence of pachydrusen is much more in PCV as described earlier cannot be overlooked. The retrospective and cross-sectional nature of the study with no longitudinal follow up does not give information about the incidence rates and prognostic significance of the pachydrusen.

Conclusion

Overall, our study provides first study on pachydrusen in Indian population with AMD. The prevalence rates are slightly lower in comparison to western population as reported previously. Future studies focused on this entity in AMD and other diseases including PCV with a longitudinal follow up can provide more information on this entity.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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