Original Article

Low incidence of pachydrusen in central serous chorioretinopathy in an Indian cohort

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Purpose: The aim of this study is to report the prevalence, clinical and swept-source optical coherence tomography (SS-OCT) characteristics of pachydrusen in eyes with central serous chorioretinopathy (CSCR) and their fellow eyes. **Methods:** A total of 264 eyes of 132 patients with a diagnosis of CSCR (acute/persistent/recurrent/chronic/inactive) in atleast one eye, were analyzed in this retrospective, cross-sectional study. SS-OCT parameters including choroidal thickness (CT), large choroidal vessel layer thickness (LCVT) at fovea and the site of pachydrusen were recorded. Paired *t* test and analysis of variance (ANOVA) was used to compare CT in eyes with CSCR (subfoveal and site of pachydrusen) and multiple groups respectively. **Results:** The mean age of the study patients was 42.9 ± 9.5 years with 119 males (90.15%). Bilateral CSCR was present in 31 patients. Nine eyes (chronic, 4; persistent, 2; and inactive/resolved CSCR, 3) showed presence of pachydrusen with an overall prevalence of 6.82% (9 eyes of 9 patients out of 132 patients). There was no significant difference of subfoveal CT (SFCT) in eyes with CSCR (422.4 ± 107.8 μ) vs fellow eyes (407.0 ± 96.5 μ) and eyes with CSCR associated with pachydrusen (413.7 ± 101.5 μ) vs fellow eyes of CSCR eyes with pachydrusen (431.6 ± 188.8 μ) ($P = 0.71$). LCVT as a percentage of CT was higher at the site of pachydrusen compared to SFCT (69.8% vs. 50.8%). **Conclusion:** CSCR can be associated with pachydrusen with a lower prevalence rate than previously reported. Whether the thickened large choroidal vessels at site of pachydrusen play any role in formation in pachydrusen needs further evaluation.

Key words: Central serous chorioretinoapthy, choroidal thickness, large choroidal vessel layer thickness, optical coherence tomography, pachydrusen, pachychoroid pigment epitheliopathy

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Drusen have been described extensively in age related macular degeneration (AMD) and are histologically shown to be hyaline excrescences with deposit at sub-retinal pigment epithelium (RPE) level between RPE and Bruch's membrane.[1-3] Based on morphological (fundus photography and imaging including optical coherence tomography, OCT) and histo-pathological description, drusen have been classified in hard, soft, pseudodrusen and cuticular drusen.[1-3] However, drusen are rare in other chorioretinal pathologies.

Originally described by Spaide, pachydrusen are characterized by large drusen associated with increased choroidal thickness (CT) which are distinctly different from drusen reported in AMD.[4] Various authors have described this pathologic entity in multiple disease states including AMD, polypoidal choroidal vasculopathy (PCV), central serous chorioretinopathy (CSCR), pachychoroid pigment epitheliopathy (PPE), pachychoroid neovasculopathy (PNV) since the first description.[4-9] However, PPE, CSCR, PNV and PCV are considered a part of pachychoroid spectrum and characterized by increased CT, whereas AMD is known to be associated with reduced CT especially in the advanced stages of AMD.[10,11] In the subset of eyes with pachydrusen, CT is higher compared to eyes with soft drusen and pseudodrusen. The presence of pachydrusen in both these types of chorioretinal disorders could suggest a common pathophysiology in the formation of pachydrusen.

We earlier published the analysis of pachydrusen in cases with AMD and PCV in Indian eyes and reported a prevalence rate of 8.4% and 14.14%, respectively.[9] The previous studies based on Caucasian, Chinese and Korean population showed the prevalence of pachydrusen in AMD and PCV as 8.4-25% and 50% respectively.[6-8] The location of pachydrusen at site of pachyvessels (dilated, outer choroidal vessels) and correlation with site of loss of choriocapillaris and hyperfluorescence suggest a role of choroidal vessel in the formation of these deposits.[5,12] This bears significance as CSCR and PCV are part of the pachychoroid spectrum and have an association with thickened choroid. Previous studies have evaluated the pachydrusen in CSCR and provided few insights regarding

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the presence of pathogenesis and morphological changes in the choroid.[5,12]

In this study, we report the prevalence of pachydrusen and their imaging characteristics in CSCR and their fellow eyes in Indian population and compare the prevalence with previous studies.

Methods

The study was a retrospective chart review and included the patients diagnosed with CSCR (either acute or chronic) in at least one eye during the study period of July 2017 to June 2018. Local ethics committee approval (LEC 02-18-044) was obtained and the study protocols conformed to the tenets of declaration of Helsinki. A written consent form was obtained from all the study patients.

CSCR was defined as presence of neurosensory detachment (NSD) and/or pigment epithelial detachment (PED) with or without retinal pigment epithelial (RPE) changes. CSCR was further classified in acute, persistent, recurrent, chronic or inactive CSCR based on a previous description.[13] Persistent CSCR was defined as subretinal fluid (SRF) lasting 4 months or longer in a case of acute CSCR, whereas SRF which lasted 6 months or beyond was categorized as chronic CSCR.[13-15] PPE was defined as presence of RPE changes in fundus photography or autofluorescence without any history of SRF.[16] Patients with coexisting chorioretinal pathologies such as diabetic retinopathy, high myopia, history of prior vitreoretinal surgery, or retinal detachment, media opacities, OCT images with poor signal strength were also excluded from the analysis. The eyes with scans not passing through suspicious pachydrusen areas were also excluded.

Relevant ocular and systemic history was elicited. Visual acuity was recorded in Snellen visual acuity chart and converted to logarithm of minimum angle of resolution (logMAR) for statistical analysis. Ocular examination involved detailed slit lamp examination, fundus evaluation using indirect ophthalmoscopy and +90 diopter (D), intraocular pressure using Goldmann applanation tonometer. Fundus photography was done using (Zeiss Visupac® FF4 and FF450-plus, Carl Zeiss, Dublin, CA). OCT measurements were done using swept source optical coherence tomography (SS-OCT; Topcon DRI OCT Triton® plus). Fluorescein angiography and indocyanine angiography (HRA-II; Heidelberg Engineering, Dossenheim, Germany, Zeiss Visupac® FF4 and FF450-plus, Carl Zeiss, Dublin, CA) were done as per the discretion of the treating physician in case with diagnostic dilemmas or to plan appropriate therapy.

SS-OCT B scans of length 12 mm passing through the fovea were captured in both horizontal and vertical meridian. We also reviewed the volume date to obtain the specific line scan passing through the area of interest through the pachydrusen. Qualitative and quantitative description of OCT parameters was done. Central macular thickness (CMT), CT, and large choroidal vessel layer thickness (LCVT) at the subfoveal level and site of pachydrusen were evaluated. Choroidal thickness measurements were done from Bruch's membrane till the choroidoscleral interface (CSI). LCVT was defined as the linear dimension from inner boundary of a large choroidal vessel of minimum diameter of ≥100 μ to CSI.[17] Percentage contribution of LCVT to CT was calculated.

Pachydrusen was defined as sub RPE deposits on OCT which corresponded with the yellowish deposits on fundus photographs. These have been differentiated from the typical drusen seen in AMD by their complex outer border shape, posterior pole distribution and arrangement pattern (either isolated or in groups).[4,8] Multiple descriptors involving pachydrusen were analyzed which included the location and arrangement pattern, CT and LCVT at site of pachydrusen. Moreover, the number of pachydrusen were counted and tabulated. The images were analyzed by two independent graders (RC, JC) and intraclass correlation coefficient (ICC) was calculated. In case of any discrepancy, decision was arrived after mutual consensus.

All the statistical analysis was done using SPSS software (SPSS for Windows; version 23; SPSS Inc., Chicago, Illinois). Statistical tests including unpaired, paired *t* test and one way analysis of variance (ANOVA) was used to compare the retinal and choroidal quantifiable parameters between two and multiple groups respectively. Tukey *post hoc* test was used if ANOVA showed significant difference. A *P* value ≤0.05 was considered statistically significant.

Results

A total of 132 patients (264 eyes) were included in the analysis. The mean (±SD) age of the study cohort was 42.9 ± 9.5 years with a predominantly male gender distribution (119 males). Mean age of patients with and without pachydrusen was 55.4 ± 7.83 and 42.0 ± 9.01 years, respectively, with a statistically significant difference (P = 0.0001). History of steroid administration was elicited from 3 patients (2.27%). Past history of CSCR with a prior history of treatment for CSCR was present in 27 patients (20.4%).

Among the entire cohort, 31 patients (62 eyes) had presence of bilateral CSCR while 101 patients had presence of unilateral CSCR. Among unilateral CSCR cases, 95 fellow eyes had normal fundus with presence of PPE in the remaining 6 fellow eyes. Chronic CSCR (86 eyes) was the most common subtype of CSCR in 163 eyes with CSCR. Inactive/resolved (25), persistent (18), recurrent (12), and acute subtypes (22) formed the rest of CSCR cohort. The mean duration of disease was 15.7 ± 25.5 months as shown in Table 1. Baseline BCVA was 0.26 ± 0.35 logMAR in all eyes with CSCR whereas fellow eyes of unilateral CSCR had BCVA of 0.05 ± 0.17 logMAR. The overall mean spherical refractive error was -0.67 ± 0.9 D.

Table 1: Shows the baseline parameters in the study cohort of eyes with central serous chorioretinopathy (CSCR) and associated pachydrusen

Baseline parameters	Number (*n*)
Total number of eyes	264 (132 patients)
CSCR (bilateral)	62 eyes (31 patients)
CSCR (unilateral)	101 eyes
Fellow eyes	101 (95, normal; 6, PPE)
Age (mean±SD)	42.9±9.5 years
Gender	Males, 119; females, 13
Duration of disease (mean±SD)	15.7±25.5 months

SD=Standard deviation; PPE=Pachychoroid pigment epitheliopathy

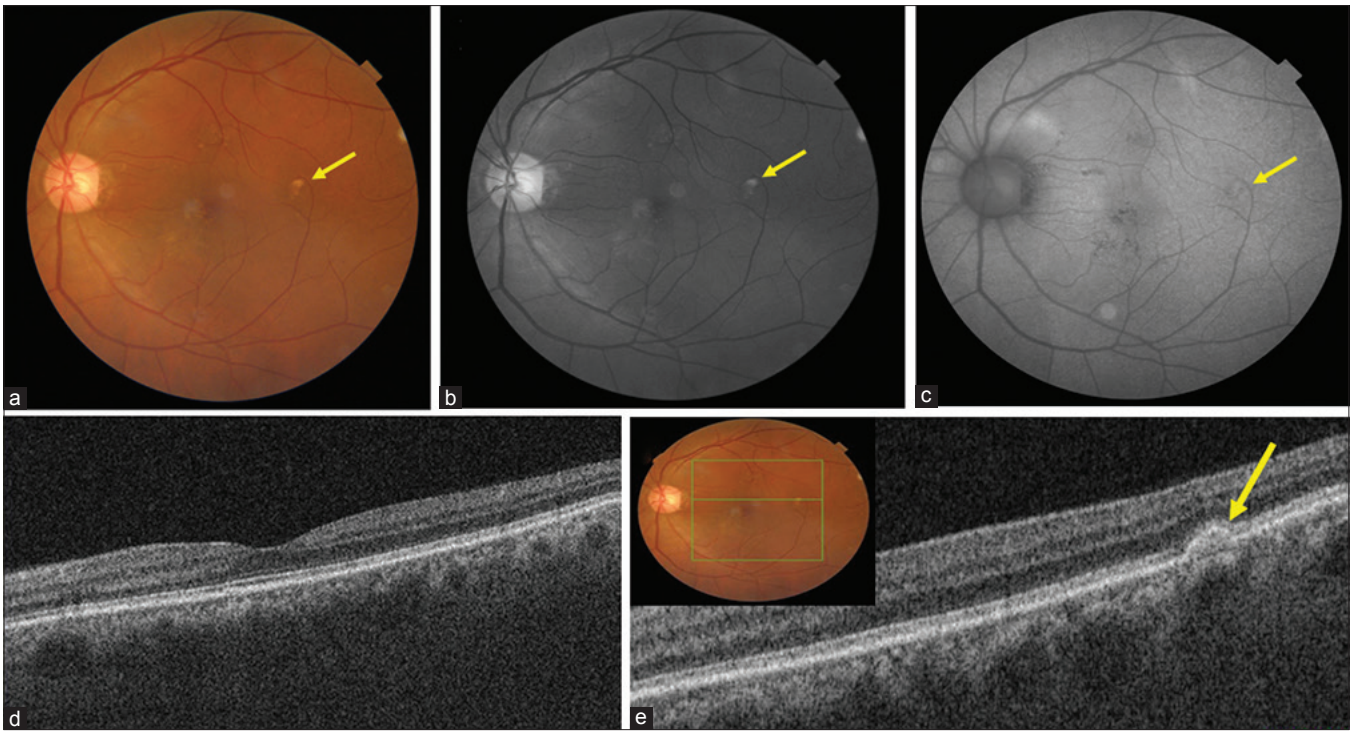

Figure 1: Colour fundus, red-free and autofluorescence (AF) images (a-c) of a 56 years old male with resolved central serous chorioretinopathy (CSCR) in left eye, showing presence of pachydrusen temporal to fovea (arrow). AF shows presence of hypoautofluoroscence areas suggestive of previous episodes of CSCR. Horizontal OCT scan of the left eye (d) shows normal foveal contour. SS-OCT line scan through temporal macula (inset) (e) showing presence of homogenous deposits below the RPE suggestive of pachydrusen (arrow)

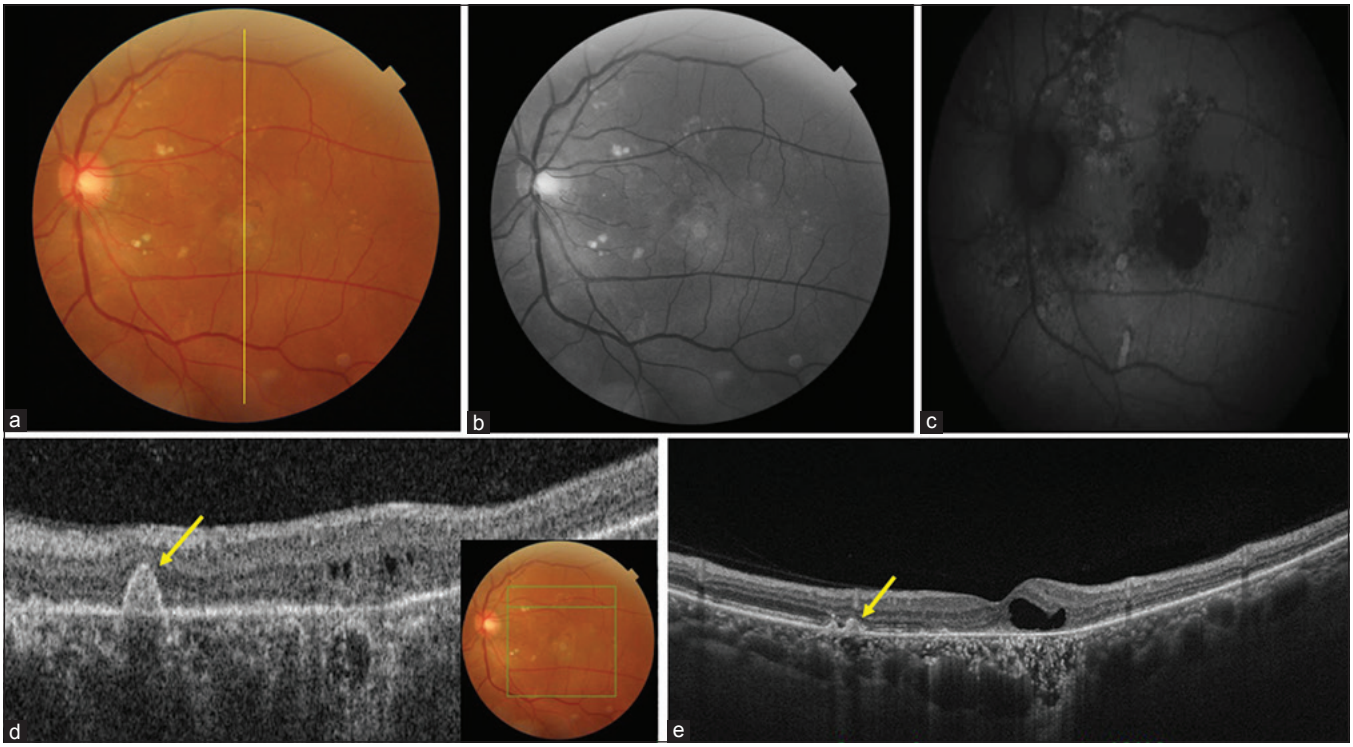

Figure 2: Colour fundus, red-free and autofluorescence (AF) images (a-c) of a 51 years old male with chronic CSCR and a visual acuity of 20/60 in left eye, showing RPE changes and hypoAF areas suggestive of chronicity along with clustered peripapillary pachydrusen near the vascular arcades. Horizontal SS-OCT scan superior to fovea and vertical scan (vertical line in fig a) through the fovea shows RPE deposits suggestive of pachydrusen (arrow, d and e). Also note the presence of large choroidal vessels, degenerated cystoid spaces, loss of outer retinal layers (e)

Table 2: Shows OCT characteristics of eyes with central serous chorioretinopathy (CSCR) and eyes with CSCR and associated pachydrusen

	CSCR	CSCR with pachydrusen	*P*
Number of eyes	154	9	
Baseline BCVA (logMAR)	0.26±0.35	0.44±0.38	0.14
Fellow eyes (logMAR)	0.05±0.17	0.14±0.26	0.15
Duration of disease (months)	15.7±25.5	30.6±40.2	0.11
OCT characteristics			
Central macular thickness (CMT (μ)	346.2±166.1	259±76.6	0.12
NSD height (μ)	165.3±168.1	103.5±64.4	0.27
Subfoveal			
CT (μ)	422.4±107.8	413.7±101.5 μ	0.81
LCVT (μ)	212.0±78.9	210.1±61.6 μ	0.94

OCT=Optical coherence tomography; BCVA=Best corrected visual acuity; SD=Standard deviation; logMAR=Logarithm of minimum angle of resolution; NSD=Neurosensory detachment; CT=Choroidal thickness; LCVT=Large choroidal vessel layer thickness

Eyes with pachydrusen

A total of 9 eyes of 9 patients had presence of pachydrusen among the 264 eyes (including both CSCR and their fellow eyes). These included chronic (4 eyes), persistent (2 eyes), and resolved CSCR (3 eyes). The overall prevalence of pachydrusen in CSCR eyes was 6.82% (9 eyes of 9 patients among 132 patients). The mean age of eyes with pachydrusen was 55.4 ± 7.8 years with a mean BCVA of 0.44 ± 0.38 logMAR. Most common location of pachydrusen was at the macular area (5 eyes, 55.6%) followed by vascular arcades (4 eyes, 44.4%), whereas analysis of distribution pattern revealed a varying arrangement of pachydrusen – clustered (5 eyes, 55.6%), solitary (3 eyes, 33.3%) and scattered (1 eye, 9.9%). The mean ± SD of the number of pachydrusen was 2.1 ± 1.5 per eye. ICC between the two observers was 0.97.

Mean SFCT in CSCR eyes (422.4 ± 107.8 μ), fellow eyes of CSCR (407.0 ± 96.5 μ), eyes with pachydrusen (413.7 ± 101.5 μ) and fellow eyes with pachydrusen (431.6 ± 188.8 μ) was not significantly different (P = 0.71). Mean CMT and height of neurosensory detachment (NSD) in eyes with CSCR was 346.2 ± 166.1 μ and 165.3 ± 168.1 μ respectively whereas mean CMT and height of NSD in eyes with CSCR and associated pachydrusen was 259 ± 76.6 μ (P = 0.12) and 103.5 ± 64.4 μ (P = 0.27), respectively [Table 2].

CT and LCVT at the site of pachydrusen were 344.1 ± 61.7 μ and 240.2 ± 59.9 μ respectively. The comparison of CT at the subfoveal and the site of pachydrusen showed a weak positive correlation and did not yield significant difference (413.7 ± 101.5 μ vs. 344.1 ± 61.7 μ; R = 0.14; P = 0.09). Similarly, LCVT comparison at subfoveal level and site of pachydrusen showed no significant difference (210.1 ± 61.6 μ vs. 240.2 ± 59.9 μ; P = 0.31).

Fellow eyes with pachydrusen were normal in 3 patients while 3, 2 and 1 patient had chronic, persistent and resolved CSCR. Mean CMT and SFCT in the fellow eyes were 431.6 ± 188.4 μ and 253.5 ± 77.0 μ, respectively. The comparison of SFCT in eyes with pachydrusen and their fellow eyes was not significant (413.7 ± 101.5 μ vs. 431.6 ± 188.4 μ; P = 0.81), though the number of eyes were very small in both groups.

All the 9 eyes with CSCR and associated pachydrusen had SFCT >300 μ, whereas 7 eyes (77.8%) had CT >300 μ at the site of pachydrusen. In comparison, overall 92.02% (150/163) of CSCR eyes had SFCT of more than 300 μ. The contribution of LCVT at subfoveal area and the site of pachydrusen was 50.8% and 69.8% respectively suggestive of thickened large choroidal vessel layer (Haller layer) at the site of pachydrusen. Representative cases are shown as Figs.1 and 2.

Discussion

In this study, we analyzed the eyes with CSCR and found that prevalence of pachydrusen was 6.81% in patients with CSCR (9 eyes of 9 patients among 132 patients). Various groups including ours have reported the prevalence of pachydrusen in AMD, PCV, CSCR, PPE and PNV.[4-7,9] Results show that there is a wide ethnic and geographical variation of prevalence of pachydrusen with rates ranging from 8.4-25% in AMD to 14.14-49.3% in PCV.[5-9] A striking difference in this study compared to the previous publications has been the low prevalence rate of pachydrusen in CSCR eyes (6.8% vs. 27.2%).[12] We have reported marginally higher prevalence rates of pachydrusen in Indian eyes with AMD (8.4%) and PCV (14.1%) in our previous publications.[9,18]

Pachydrusen is a recent description coined by Spaide and includes drusen other than the previously studied soft drusen and pseudodrusen in AMD.[4] These are not found to be associated with overlying pigment unlike other types of drusen and have a complex shape with ovoid outer border. Lee *et al*. in their study of eyes of PCV with pachydrusen have reported high prevalence rate of 50% and also demonstrated a tendency of bilateral distribution.[7] We could not identify any patients with bilateral pachydrusen in our study cohort, in spite of 31 patients having bilateral disease. The mean number of pachydrusen in our sample was 2.1 ± 1.5 suggestive of the fact that these soft drusen or pseudodrusen appear dissimilar to drusen seen in AMD which are usually multiple in number.

We compared SFCT in CSCR, their fellow eyes, and cases of CSCR with pachydrusen and their fellow eyes. There was no statistical significant difference of CT among these four groups (P = 0.71). Among the 9 eyes with pachydrusen in our study cohort, pachydrusen was associated with different subtypes of CSCR such as chronic, persistent and resolved. Interestingly, we did not find pachydrusen in any of the acute cases of CSCR. In eyes with AMD, different subtypes of drusen are associated with a variable risk of progression to neovascular

AMD. In this context, the relation of pachydrusen to disease activity or its role in alteration of natural history of CSCR is not known at present due to lack of longitudinal studies.

The composition of drusen is known to vary in eyes with AMD. No histopathological correlation elaborating the nature of deposits in pachydrusen in eyes with AMD, CSCR or PCV is available at present. In eyes with CSCR, the underlying pathology of pachychoroid i.e., pachyvessels pressing the inner choroid and choriocapillaris lead to ischemia of choriocapillaris. The site of pachydrusen tends to correlate with the distribution of pachyvessels and the presence of delayed choriocapillaris filling as shown in ICGA based studies.[5,12] This probably lead to altered metabolism of RPE which along with chronic irritation of RPE due to fluid in subretinal and sub-RPE space may lead to formation of these pachydrusen over time. The observation that none of the eyes with pachydrusen had acute CSCR supports this hypothesis. On the contrary, there was no significant difference of choroidal parameters such as SFCT and subfoveal LCVT in eyes with pachydrusen and non-pachydrusen in patients of CSCR. In eyes with pachydrusen, CT at the site of pachydrusen was lesser compared to the subfoveal CT. This appears consistent with the observation that the subfoveal location has the highest choroidal thickness.[19,20] However, it is contrary to the observation reported by Baek *et al*. where they reported a higher CT at pachydrusen site compared to SFCT.[5]

Patients with pachydrusen had a higher mean age of 61.4 ± 11.7 years in the study by Matsumoto *et al*. when compared to our subgroup of pachydrusen (55.4 ± 7.83 years).[12] Hypothetically, older age and longer duration of disease may be associated with a higher prevalence of pachydrusen and these factors apart from ethnic variation may be partly responsible for the low prevalence rate of pachydrusen in our study.

This study has certain limitations. This was a retrospective, cross-sectional study with limited number of patients with even a smaller number of eyes with pachydrusen. Patients with other disease pathologies including PPE and PNV were not studied. The data obtained is from a hospital based cohort and the prevalence rates may not be representative of a population. The terminologies used such as pachychoroid, pachydrusen, and PPE have been recently described with no clear consensus on their definition and their usage is not in much common in clinical practice. We did not relate the presence of pachydrusen with extent of RPE involvement, extent or duration of the disease.

Conclusion

In conclusion, pachydrusen was distributed among all subtypes of CSCR except acute cases with a prevalence of 6.8% and a tendency towards chronic CSCR. However, any generalization is difficult due to the lower number of eyes in each subgroup. This study adds to the limited literature available about pachydrusen. Further studies based on a longitudinal follow up with an inclusion of diverse age groups may provide more information about the progression, natural history and choroidal changes in these eyes.

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Conflicts of interest

There are no conflicts of interest.

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