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Original Article

Ophthalmology Section

Clinical Profile and Risk Factors of Exudative Age-related Macular Degeneration: A Hospital Based Case-control Study

APARNA RAVI[1], SIMON GEORGE[2]

ABSTRACT

Introduction: Age-Related Macular Degeneration (ARMD) is one of the leading causes of vision loss in the elderly population. ARMD is characterised by progressive degeneration of the retinal pigment epithelial complex and photoreceptors primarily in the macular region of the retina. The prevalence of ARMD in India ranges from 39.5% to 0.3%, as reported in population-based studies. Numerous risk factors, both modifiable and non-modifiable, have been identified for this condition.

Aim: To determine the clinical profile and risk factors associated with exudative ARMD.

Materials and Methods: This is a case-control study conducted in a tertiary eye care hospital in South Kerala from June 2011 to June 2012. The cases were patients attending the Outpatient Department (OPD) and Retina clinic who were diagnosed with wet ARMD. The corresponding control is the next patient seen after the case who is of the same sex and comparable age. Data were analysed using the Statistical Package for Social Sciences (SPSS) version 17.0. Chi-square test was used to elucidate the association between the presence of ARMD and diet, educational status, occupation, smoking, alcoholism, hypertension, diabetes mellitus, cardiovascular disease, obesity, hyperlipidemia, history of cataract surgery, and cataract. Multivariate logistic regression analysis was used to assess these risk factors for cases and controls.

Results: A total of 130 subjects consisting of 65 cases and 65 controls participated in the study. The majority of patients were in the age group of 60-69 years. History of hyperlipidemia (Odds Ratio [OR]: 1.649, Confidence Interval [CI]: 0.524-5.191, p=0.042) was significantly associated with the development of exudative ARMD. Hypertension (OR: 1.398, CI: 0.694-2.815, p=0.051), cardiovascular disease (OR: 1.770, CI: 0.274-5.064, p=0.188), Body Mass Index (BMI) >25 (OR: 0.537, CI: 0.254-1.133, p=0.075), dietary factors (OR: 1.351, CI: 0.461-3.961, p=0.609), smoking (OR: 1.400, CI: 0.484-4.051, p=0.593), alcoholism (OR: 1.400, CI: 0.484-4.051, p=0.593), history of cataract surgery (OR: 1.160, CI: 0.411-3.279, p=0.456), cataract (OR: 1.618, CI: 0.692-3.782, p=0.149) were not found to be significant. The results may vary in the present scenario due to changes that have occurred over the years, especially in the case of smoking and alcoholism, as the prevalence of which has increased. The majority (88.75%) of study subjects have classic Choroidal Neovascular Membrane (CNVM).

Conclusion: ARMD was found to have a significant association with hyperlipidemia. Those with hypertension, cardiovascular disease, cataract, smokers, and alcoholics have a higher risk of developing exudative ARMD. By controlling modifiable risk factors like hyperlipidemia and by avoiding smoking and alcoholism, the authors can prevent this potentially blinding condition to some extent.

Keywords: Choroidal neovascular membrane, Hyperlipidemia, Macula

INTRODUCTION

The ARMD is one of the important causes of visual loss in the elderly population. ARMD is characterised by progressive degeneration of the retinal pigment epithelial complex and photoreceptors primarily in the macular region of the retina [1]. It commonly occurs in the sixth decade of life and is commonly bilateral [2]. In a population-based study in India, the prevalence of ARMD was significantly higher in those 60 years of age or older [3]. The prevalence of severe visual loss increases as age advances. It ranks third among the global causes of visual impairment [4]. It is estimated that about 30-50 million people are suffering from ARMD worldwide [5]. The prevalence of ARMD in India ranges from 39.5% to 0.3% as reported in population-based studies [6]. It is a major challenge in the new millennium as the size of the elderly population continues to increase due to the availability of better medical facilities and an increase in life expectancy [7].

ARMD is divided into two types: dry and wet ARMD. Dry ARMD is characterised by the presence of drusen. Wet ARMD is a vision-threatening disease that leads to CNVM formation. Macular degeneration leads to the loss of central vision needed for activities requiring fine vision such as reading, performing jobs like driving, stitching, and artwork. Central vision loss impairs proficiency in performing most activities of daily living and can make it more difficult for people to live independent lives [8].

ARMD is a multifactorial disease and it has been associated with numerous systemic, genetic, and ocular risk factors [9]. Many epidemiological studies have been done worldwide to identify the risk factors of ARMD [10]. But there are many controversial results in these studies. Diabetes mellitus has been reported as a significant risk factor for ARMD in a few studies, whereas a few others have reported diabetes as a protective factor [11,12]. Severe visual loss can be prevented in some cases by public education and modification of risk factors like dietary habits, environmental factors, cigarette smoking, etc. [13].

To prevent age-related macular changes and to enhance the functioning of this segment of the population, knowledge of the epidemiology and risk factors of ARMD is important. There are only a few studies available in Kerala about the risk factors of ARMD; hence, the authors have undertaken this study [14]. This study aims to analyse the clinical profile and risk factors associated with exudative ARMD.

MATERIALS AND METHODS

This is a case-control study conducted in a tertiary eye care center in South Kerala for a period of one year from June 2011.

Ethical clearance to conduct this research was obtained from the Institutional Research and Ethics committees (IEC No: 05/25/2011/MCT). Informed consent was taken from each participant.

Sample size calculation: The sample size was calculated using the formula:

$$N=\frac{(Z_{\alpha/2}+Z_{\beta})^2\ pq(r+1)}{r(p_1-p_2)^2}$$

Where:

$Z_{\alpha/2}$=standard normal deviate for a two-tailed test based on the alpha level=1.96

Z_{β}=standard normal deviate for a one-tailed test based on the beta level=0.84,

r=ratio of controls to cases=1

p_1=proportion of patients in group 1 with a history of hypertension=53,

p_2=proportion of patients in group 2 with a history of hypertension=29,

p=average percentage of the characteristic i.e., history of hypertension=

$$\frac{(p_1+p_2)}{2} \text{ and } q=1-p$$

From the study done by Fraser-Bell S et al., [15], assuming that 53% of the subjects in the population had a history of hypertension, the study would require a sample size of 65 subjects for each group (i.e., a total sample size of 130, assuming equal group sizes) to achieve a power of 80% for detecting a difference in proportions of 0.24 between the two groups at a two-sided p-value of 0.05. A total of 130 subjects, including 65 cases and 65 controls, participated in the study.

Inclusion criteria: The study included patients ≥50 years of age attending the OPD and Retina clinic who were diagnosed with exudative ARMD. The corresponding control is the next patient seen after the case who is of the same sex and of comparable age (plus or minus 5 years).

Exclusion criteria: Patients with other retinopathies involving the macula, other causes for choroidal neovascularisation, severe mental or physical disability, and advanced ocular media opacity obscuring the view of the retina were excluded.

Procedure

Patient data, including name, age, sex, address, educational status, diet, and occupation, were noted. Presenting complaint, history of type 2 diabetes mellitus and its duration, systemic hypertension and its duration, cardiovascular disease, hyperlipidemia, and history of cataract surgery were asked for. History of smoking and alcoholism was also noted. In all patients, a general examination which includes Body Mass Index (BMI), pulse rate, and blood pressure was done. The subjects were grouped as normal weight (BMI 18.5-24.9 kg/m^2) and overweight (BMI 25-29.9 kg/m^2) [16].

The diagnosis of exudative ARMD was confirmed through a detailed ocular examination, including measurements of Snellen visual acuity, Amsler grid testing, near vision, and anterior segment examination by slit lamp biomicroscope. Lens opacities were graded using slit lamp examination after pupil dilation with tropicamide and phenylephrine eye drops. Fundus examination, fundus photography, fluorescein angiography, and Optical Coherence Tomography (OCT) were performed in each case. Control subjects were also examined to rule out any retinal changes.

On fluorescein angiogram, the classic CNVM was diagnosed by the appearance of hyperfluorescence detected as a lacy network filling currently with background choroidal fluorescence and increasing in area and intensity in the mid and late phases of angiography. Occult CNVM was diagnosed by the presence of fibrovascular Pigment Epithelial Detachment (PED), stippled hyperfluorescent pigmented dots on the surface of irregularly elevated Retinal Pigment Epithelium (RPE), or as late phase leakage from an undetermined source. The size of CNVM, presence or absence of subretinal fluid, exudates, and subretinal haemorrhage were also noted. Small size lesions were defined as lesions of 1-2 disc diameter, and large lesions as lesions of 2-3 disc diameter.

STATISTICAL ANALYSIS

The risk factors were compared in cases and controls. Data analysis was done using the SPSS software 17.0. Data was expressed in terms of frequency, percentage, mean, and standard deviation. Chi-square test was used as a non-parametric test to elucidate the association and comparison between different parameters. Multivariate logistic regression analysis was performed to assess the risk factors (OR) of each group. A two-tailed probability value less than 0.05 was considered significant for all statistical evaluations.

RESULTS

A total of 130 subjects, consisting of 65 cases and 65 controls, participated in the study. There were 75 males (57.70%) and 55 females (42.30%). The mean age of the subjects with exudative ARMD was 65.55 years, and that of controls was 65.42 years. A higher proportion of subjects in both study groups were in the age group 60-69 years; cases 31 (47.7%), controls 30 (46.2%). Systemic hypertension was not found to be significantly associated with exudative ARMD (Chi-square: 3.78, p=0.051, OR: 1.398) [Table/Fig-1,2]. Out of 65 cases, 34 (52.31%) were hypertensive, whereas 23 (35.4%) controls had hypertension. Among those cases and controls with hypertension, 12 (39%) cases and 13 (50%) controls had hypertension for >5 years, respectively. This is not statistically significant (Chi-square: 1.909, p=0.591).

Variables	Group		Chi-square value	p-value
	Cases (N=65)	Controls (N=65)		
Age (years)				
50-59	11 (16.9)	12 (18.5)	0.061	0.970
60-69	31 (47.7)	30 (46.2)		
≥70	23 (35.4)	23 (35.4)		
Gender				
Male	38 (58.5)	37 (56.9)	0.032	0.858
Female	27 (41.5)	28 (43.1)		
Education				
Illiterate	7 (10.8)	11 (16.9)	2.371	0.667
Informal	21 (32.3)	19 (29.2)		
Primary	22 (33.8)	25 (38.5)		
Secondary	13 (20)	8 (12.3)		
Graduate	2 (3.1)	2 (3.1)		
Occupation				
Unemployed	9 (13.8)	13 (20)	2.844	0.584
Housewife	20 (30.8)	22 (33.8)		
Manual labourer	16 (24.6)	17(26.2)		
Skilled labourer	13 (20)	10 (15.4)		
Professional	7 (10.8)	3 (4.6)		
Diet				
Vegetarian	10 (15.4)	7 (10.8)	0.609	0.609
Non-vegetarian	55 (84.6)	58 (89.2)		
Smoking				
Yes	9 (13.8)	7 (10.8)	0.285	0.593
No	56 (86.2)	58 (89.2)		
Alcoholism				
Yes	9 (13.8)	7 (10.8)	0.285	0.593
No	56 (86.2)	58 (89.2)		

Hypertension				
Yes	34 (52.3)	23 (35.4)	3.78	0.051
No	31 (47.7)	42 (64.6)		
Duration of hypertension	N=31	N=26		
≤1 year	4 (12.9)	1 (3.8)	1.909	0.591
1-5 years	15 (48.4)	12 (46.2)		
5-10 years	10 (32.3)	10 (38.5)		
>10 years	2 (6.5)	3 (11.5)		
Diabetes mellitus				
Yes	20 (30.8)	22 (33.8)	0.141	0.707
No	45 (69.2)	43 (66.2)		
Duration of diabetes mellitus	N=20	N=22		
≤1 year	1(5)	1 (4.5)	6.553	0.087
1-5 years	4 (20)	8 (36.4)		
5-10 years	8 (40)	12 (54.5)		
>10 years	7 (35)	1 (4.5)		
CVD				
Yes	7 (10.8)	3 (4.6)	1.733	0.188
No	58 (89.2)	62 (95.4)		
Hyperlipidemia				
Yes	13 (20)	5 (7.7)	4.127	**0.042***
No	52 (80)	60 (92.3)		
History of cataract surgery				
Yes	11 (16.9)	8 (12.3)	0.555	0.456
No	54 (83.1)	57 (87.7)		
Cataract				
Yes	19 (29.2)	12 (18.5)	2.076	0.149
No	46 (70.8)	53 (81.5)		
BMI				
18-24 kg/m^2	33 (50.8)	43 (66.2)	3.168	0.075
25-29 kg/m^2	32 (49.2)	22 (33.8)		

[Table/Fig-1]: Risk factors of ARMD.
*Statistically significant; CVD: Cardiovascular disease; BMI: Body mass index; Chi-square test

Parameters	B	S.E.	Odds Ratio (OR)	95.0% CI	
				Lower	Higher
Age	-0.116	0.263	0.890	0.532	1.489
Gender	-0.210	0.412	0.811	0.362	1.817
Education	0.090	0.255	1.094	0.664	1.804
Occupation	-0.323	0.237	0.724	0.455	1.152
Diet	0.301	0.549	1.351	0.461	3.961
Alcoholism	0.336	0.542	1.400	0.484	4.051
Hypertension	0.335	0.357	1.398	0.694	2.815
Duration of hypertension	1.067	0.758	2.908	0.658	12.858
Duration of DM	-1.580	0.887	0.206	0.036	1.173
CVD	0.163	0.744	1.770	0.274	5.064
Hyperlipidemia	0.500	0.585	1.649	0.524	5.191
Smoking	0.336	0.542	1.400	0.484	4.051
History of cataract surgery	0.149	0.530	1.160	0.411	3.279
BMI	-0.622	0.381	0.537	0.254	1.133
Cataract	0.481	0.433	1.618	0.692	3.782

[Table/Fig-2]: Odds Ratio (OR) of risk factors.
DM: Diabetes mellitus; CVD: Cardiovascular disease; CI: Confidence interval
Logistic regression analysis

A total of 20 (30.8%) cases and 22 (33.8%) controls were diabetic, which is not statistically significant (Chi-square: 0.141, p=0.707). Additionally, there was no statistically significant difference in the duration of diabetes mellitus between cases and controls. A total of 15 (75%) cases had diabetes mellitus for >5 years compared to 13 (59%) controls (Chi-square: 6.553, p=0.087).

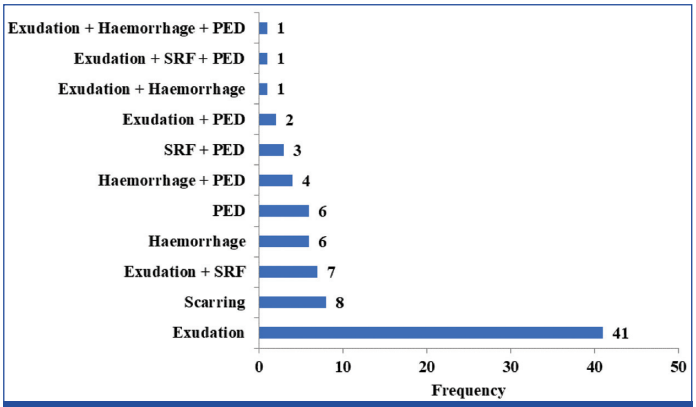
Seven (10.7%) cases and 3 (4.6%) controls had a history of cardiovascular disease, which is not statistically significant (Chi-square: 1.733, p=0.188, OR: 1.770). Hyperlipidemia was found to be significantly associated with exudative ARMD (Chi-square: 4.127; p=0.042, OR: 1.649). Out of 65 cases, 13 (20%) had a history of hyperlipidemia compared to 5 (7.69%) controls.

Lens opacities were not significantly associated with exudative ARMD (Chi-square: 2.076; p=0.149, OR: 1.618), and a history of cataract surgery showed no significant association (Chi-square: 0.555; p=0.456). Lens opacities were present in 19 (29.2%) cases and 12 (18.5%) controls.

A total of 32 (49.2%) patients with exudative ARMD were overweight (BMI 25-29 Kg/m^2) compared to 22 (33.8%) controls. This difference is not statistically significant (Chi-square: 3.168, p=0.075, OR: 0.537). A total of 55 (84.6%) patients with ARMD and 58 (89%) controls were non-vegetarians. There is no statistically significant difference (Chi-square: 0.609, p=0.609).

In this study, it was found that there is no statistically significant difference in smoking or alcoholism between both groups [Table/Fig-1] Socio-demographic factors like education and occupational status were also not found to have a significant difference in this study.

Out of 65 subjects with ARMD, 50 had unilateral disease and 15 had bilateral disease. So a total of 80 eyes were studied, out of which 71 (88.75%) had classic CNVM. Occult CNVM was present in 9 (11.25%) eyes. A total of 55 (68.75%) eyes had smaller lesions, with a size between 1-2 DD (disc diameters), and 25 (31.25%) had larger lesions between 2-3 DD. Out of 80 eyes studied, CNVM was associated with exudation in 41 (51%) eyes, haemorrhage in 6 (7.5%), Pigment Epithelial Detachment (PED) in 6 (7.5%), scarring in 8 (10%), and subretinal fluid in 7 (8.75%) [Table/Fig-3].



[Table/Fig-3]: OCT characteristics of CNVM.
X-axis-number of eyes, Y-axis- OCT characteristics; PED: Pigment epithelial detachment; SRF: Subretinal fluid

DISCUSSION

In the present study, 65 diagnosed cases of exudative ARMD were compared with 65 age and sex-matched controls. The majority of patients with exudative ARMD were in the age group of 60-69 years, which constituted 47.7% of the cases, followed by the ≥70 years age group. The mean age of the cases was 65.55 years, and that of the controls was 65.42 years. Males (58.5%) were found to dominate over females.

Systemic hypertension was found in 52% of cases and 35% of controls, which was not statistically significant (p=0.051). Hypertensive individuals had 1.398 times more risk of developing ARMD than those without hypertension (OR: 1.398, CI: 0.694-2.815). However, no association was found between the duration of hypertension and an increased risk of ARMD. In a case-control study by Chaine G et al., hypertension was significantly associated with ARMD in the total population, but it was not identified as a risk factor in the exudative stage of the disease. [17].

A total of 30.8% of cases and 33.8% of controls were diabetic, and the difference was not statistically significant (p=0.707). There was also no statistically significant difference in the duration of diabetes mellitus between cases and controls (p=0.087). In a study by Bhatnagar K et al., no statistically significant relationship was found between Diabetes Mellitus and ARMD. Out of 76 patients, diabetes mellitus was present in 26.67% of cases [11]. The EUREYE study found increased odds for diabetes mellitus in subjects with neovascular AMD compared with controls, but no association was found between diabetes mellitus and geographic atrophy [12].

A history of cardiovascular disease was not found to have a significant association with exudative ARMD (p=0.188). However, individuals with cardiovascular disease had 1.7 times more risk of developing ARMD than those without the disease (OR: 1.770, 95% CI: 0.274-5.064). In a study by Chaine G et al., [Table/Fig-4], a strong relationship was found between coronary artery disease and advanced forms of AMD. The OR was 3.30 in patients with geographic atrophy, while in patients with exudative disease, the OR was 1.5 [17]. The Singapore Indian Eye Study also found a significant relation between cardiovascular disease and ARMD (OR: 1.68, 95% CI: 1.11-2.54) [18].

This study found a significant association between hyperlipidemia and exudative ARMD (p=0.042, OR=1.649, 95% CI: 0.524-5.191). Wang Y et al., discovered that higher levels of HDL cholesterol were significantly associated with the risk of early AMD (p=0.007, RR=1.18) [19]. Moon BG et al., also reported that a history of hyperlipidemia was associated with the development of early AMD, although serum lipid data were not significantly linked to early AMD [20].

The presence of cataract did not show a significant association with exudative ARMD (p=0.149). Additionally, this study did not find a statistically significant relationship between a history of cataract surgery and exudative ARMD (p=0.456). Lens opacities were present in 29.2% of cases and 18.5% of controls. The study found that individuals with cataract had a 1.6 times higher risk of developing ARMD (OR=1.618, 95% CI: 0.692-3.782). Chakravarthy U et al., discovered a significant association between previous cataract surgery and the development of ARMD (RR=3.05, CI: 2.05-4.55) [9].

Regarding overweight individuals, 49.2% of cases and 33.8% of controls were in the overweight range (BMI: 25-29 Kg/m^2). However, this difference was not statistically significant (p=0.075). In the AREDS study [21], a significant association was observed between higher BMI and Geographic atrophy (OR=1.93, 95% CI: 1.25-2.65). Moeini HA, found no significant difference in BMI between the case and control groups. The mean BMI was 25.38 Kg/m^2 and 30.24 Kg/m^2 in the case and control groups, respectively (p>0.05) [22].

Educational status, occupation, and dietary factors were not found to be associated with a higher risk of ARMD. Zerbib J et al., previously studied the association between dietary factors and ARMD, and their findings indicated that the use of cooking oil rich in omega-3 fatty acids (OR=0.55, p=0.006) and high consumption of fruits (OR=0.60, p=0.04) reduced the risk of exudative ARMD [23].

In this study, 14% of cases were smokers compared to 11% of controls. Smokers had a 1.4 times higher risk of developing ARMD than non-smokers (OR=1.4, 95% CI: 0.484-4.051). However, this study did not find a statistically significant association between smoking and exudative ARMD (p=0.593). Similar results were obtained in a study by Kulkarni S et al., in Maharashtra (OR=0.93, 95% CI: 0.40-2.4) [24]. Patel D et al., found that smokers had a 1.17 times increased risk of developing ARMD compared to non-smokers (p<0.001) [Table/Fig-4] [25]. [Table/Fig-4] depicts comparison of previous studies on risk factors of ARMD [2,3,10,11,12,17,18,20,24,25].

In this study, a history of alcoholism was found in 14% of cases compared to 11% of controls. Alcoholics had a 1.4 times higher risk of developing ARMD than non-alcoholics (OR=1.4, 95% CI: 0.484-4.051). However, no statistically significant association was found between alcoholism and exudative ARMD (p=0.593). In the Andhra Pradesh Eye Disease Study (APEDS), the prevalence of AMD was significantly lower in light alcohol drinkers compared to non-drinkers (OR=0.43, 95% CI: 0.21-0.92) [3].

Author's name (Reference no.)	Place and year of the study	Age group taken	Total N	Significant risk factors (having OR more than 1 or p<0.05
Chaine G et al., 1998 [17]	Paris, France 1998	50-85 years	1844 cases and 1844 controls	Coronary artery disease, hypermetropia, lens opacities or previous cataract surgery
Krishnaiah S et al., 2005 [3]	Andhra Pradesh 1996-2000	≥55 years	3723	Age, smoking, cataract, prior cataract surgery
Topouzis et al., EUREYE study 2009 [12]	Europe	≥65 years	4247	Diabetes mellitus
Moon BG et al., 2012 [20]	Korea 2010	≥50 years	322 cases and 10,127 controls	Age, male gender, smoking, hyperlipidemia, working outdoors, residence in rural areas
Kulkarni S et al., 2013 [24]	Maharashtra 2006-2009	≥50 years	19140	Age, male gender, smoking
Bhatnagar K et al., 2015 [11]	Maharashtra 2011-2013	>55 years	5000	Age, male gender, smoking, sun exposure
Foo VHX et al., 2018 [18]	Singapore 2007-2015	18-90 years	2105	Cardiovascular disease, underweight BMI, Alcoholism
Patel D et al., 2018 [25]	Assam	49-85 years	50 cases and 50 controls	BMI, Waist circumference, smoking
Otabor-Olubor O et al., 2021 [2]	Nigeria 2015-2016	≥50 years	120 cases and 120 controls	Age, female gender, increased body weight, myopia
Mehta K et al., 2022 [10]	Wardha	>45 years	130 cases and 130 controls	Age, diastolic BP, smoking, BMI, sun exposure

[Table/Fig-4]: Previous studies on risk factors of ARMD [2,3,10,11,12,17,18,20,24,25].

Risk factors such as hyperlipidemia, smoking, and alcoholism, which were found to be associated with ARMD in this study, are modifiable. Health education can be provided to the general population regarding the importance of controlling hyperlipidemia, measures to manage obesity, and the need to avoid smoking and alcoholism. This study also highlights the importance of routine eye examinations for individuals over 50 years of age.

Limitation(s)

As this study did not include follow-up, the effect of risk factors on disease progression was not assessed. Additionally, since this was a hospital-based study, the results may not be generalised to the entire population. Therefore, more population-based studies are needed to further investigate the risk factors of ARMD.

CONCLUSION(S)

A history of hyperlipidemia was significantly associated with the development of exudative ARMD. Individuals with hypertension, cardiovascular disease, cataract, smokers, and alcoholics are at a higher risk of developing exudative ARMD. By controlling modifiable risk factors such as hyperlipidemia and avoiding smoking and alcoholism, it is possible to prevent this potentially blinding condition to some extent.

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PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Ophthalmology, Government Medical College, Kozhikode, Kerala, India.
2. Associate Professor, Department of Ophthalmology, Government Medical College, Thiruvananthapuram, Kerala, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Aparna Ravi,
Saketham, ARA 57, Aithady Road, Thuruvickal PO, Ulloor,
Thiruvananthapuram-695011, Kerala, India.
E-mail: aparnaophthal@gmail.com

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