Risk Factors of Central Serous Chorioretinopathy among Nepali Population

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ABSTRACT

Introduction: Central Serous Chorio-retinopathy (CSCR) is a common cause of retinal blindness in Nepal.

Objective: To identify risk factors of Central Serous Chorio-retinopathy (CSCR) in the Nepali population.

Methodology: A case-control study was conducted on patients with CSCR presenting at tertiary eye center of Nepal, from 2019 to 2021. Data on age, gender, ethnicity, stress, axial length, alcohol drinking and other risk factors were collected. Chi-square tests were conducted to find associations between variables and CSCR. Binary logistic regression was utilised to determine the odds of developing CSCR among the cases and to adjust for potential confounders. Wilcoxon Rank Sum test was used to compare means.

Result: The study included 145 eyes from 132 cases of CSCR and 145 age- and sex-matched controls. Young adults in the age group of 31-40 years and male gender were significantly associated with CSCR (p<.05). Tharu ethnicity (adjusted OR= 3.3 95% Confidence Interval=1.890-5.444), shorter axial length (adjusted OR= 1.725; 95% CI=1.271-2.342) and alcohol use (adjusted OR=2.779, 95% CI=1.136-6.799) were significantly associated with CSCR. Smoking, stress, inadequate sleep, and night duties were common among CSCR cases but did not reach statistical significance.

Conclusion: This is first study in Nepal to report higher prevalence of CSCR in tharu ethnic group. Young adult male, alcohol drinking and short axial length are other significant risk factors of CSCR among Nepali population. Although the study does not establish temporal causation, it underscores need to suspect CSCR in tharu patients presenting with relevant symptoms. Further research is warranted to explore why the tharu population is more susceptible to CSCR.

Key words: Central serous chorioretinopathy; ethnicity; risk factors.

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INTRODUCTION

Central serous chorioretinopathy (CSCR) is common retinal disease characterised by serous detachment of the neurosensory retina, often accompanied by detachment of the retinal pigment epithelium (RPE). Although its exact pathogenesis remains unclear, abnormalities in choroidal circulation are widely accepted to play pivotal role. Hyper-permeability of choroidal vessels results in increased tissue hydrostatic pressure which eventually lead to RPE disturbances (La, 2010). Once hydrostatic pressure breaches the RPE, there is accumulation of fluid in the sub-retinal layer which is hallmark of CSCR (Uyama et al., 1999).

Based on this model of pathophysiology, various factors that can cause ischaemia, inflammation and stasis of choroidal circulation have been linked to the disease (Prünte et al., 1996) Disturbance in autonomic function and increased levels of catecholamines and corticosteroids is suggested to lead to altered homeostasis and choroidal hyper-perfusion leading to CSCR (Tewari et al., 2006; Jinghua et al., 2003; La, 1987). This has been used to link CSCR with other risk factors such as increased stress, anxiety, loss of sleep and Type A personalities. Anatomical factors as axial length and choroidal thickness have also been implicated along with infectious pathology like Helicobacter pylori (Semeraro et al., 2019). Cases of familial CSCR had been reported in the literature, but no clear transmission pattern or genotype has been found in association with it (Semeraro et al., 2019).

Interestingly, literature has not been equivocal about these risk factors and significance of many risk factors is debatable. However, it is important to have good understanding about these risk factors as the treatment of CSCR in basically avoidance of these risk factors in early stages. As there are no literatures assessing risk factors for CSCR in Nepali population, this study was conducted to understand the risk factors by comparing CSCR cases with age and sex matched healthy normal population.

METHODOLOGY

This was a case control study. It was conducted in a tertiary eye hospital in Nepal between 2019 January to 2021 September. The study population consisted of 145 CSCR eyes of 132 CSCR cases with no other co-existing ocular morbidities. The authors also recruited 145 age and sex matched healthy subjects to understand the relative frequency of these risk factors in normal population. Case to control ratio was 1:1.1

First objective of the present study was to find association between modifiable risk factors like: alcohol drinking, smoking, stress, inadequate sleep, night duties, hypertension, gastritis and CSCR. The second objective was to find association between non-modifiable risk factors like: age, gender, ethnicity, axial length, pregnancy, and CSCR.

For the inclusion and exclusion criteria, the CSCR cases who were more than 20 years old and attending the hospital during the study period were included. For control group, age and sex matched subjects (hospital staff and patient parties visiting eye hospital with no ocular and no known systemic comorbidity) were included. Cases without Optical Coherence Tomography (OCT) examination and presence of any retinal

diseases other than CSCR were excluded while in control group presence of any eye diseases and any refractive errors other than +1 to -1 Dioptres were excluded. Age and sex matched controls were chosen because young adult and male gender are known risk factors of CSCR and they can act as confounding factors.

For the data collection, risk factors for CSCR were evaluated through a structured questionnaire developed by a team of ophthalmologists based on a previous pilot study conducted in the same hospital. Two ophthalmic assistants were trained to conduct the patient interview. Unaided and best corrected visual acuities (BCVA) were taken using Snellen visual acuity chart for all cases. Anterior and posterior segments of all subjects were evaluated with a slit lamp biomicroscope and Volk 90 D aspheric lens. Heidelberg Spectralis Spectral Domain OCT was used for imaging. Diagnosis of CSCR was made by ophthalmologists based on fundus findings and imaging. For this study, CSCR was classified into three categories, acute when patients presented with their first episode of serous retinal detachment for fewer than four months, persistent where the serous fluid extended beyond four months and recurrent when a new onset of detachment was observed following a documented period of disease resolution in individuals with a prior history of CSCR (Daurich et al., 2015).

Based on the pilot study, where the proportion of exposure of alcohol was 0.2 among controls, and odds ratio was 2.5, sample size was calculated to be 94 by considering a margin of error of 5%, a confidence level of 95% and power of 0.8. SPSS-20 was used to collect and analyse the data. Descriptive statistics were presented as median (interquartile range) for continuous data after testing for normality. Normality was examined with shaphiro-wilk test. Frequencies and percentages were calculated for categorical data Chi-square test was used to find the association of individual risk factors with CSCR. Wilcoxon rank-sum test was used to compare means. Logistic regression was used to calculate adjusted odd's ratio of the risk factors by reducing the effects of confounding factors. Significance levels were set as p-value of less than 0.05.

The research adhered to the principles outlined in the Declaration of Helsinki. Prior to participation, informed consent was obtained from all subjects. Ethical approval for the study was granted by the Nepal Netra Jyoti Sangh's ethical review committee. (Reference number: 07/2021)

Primary outcome of interest was CSCR. Exposures were age, gender, ethnicity, axial length, alcohol use, smoking, stress, inadequate sleep and night duties. Predictors were age, gender, ethnicity, axial length and alcohol abuse. Potential Confounders were age and sex. Effect modifiers were genetic predisposition within the tharu ethnic group and occupational or environmental factors related to night duties or stress levels.

RESULT

This study comprised of 145 eyes from 132 cases of CSCR and age and sex matched 145 controls. Left eye was affected more (60, 41%) than right eye. Both eyes were involved in (13, 9%) of cases. Median age of the cases was 37 (IQR: 33-42) years and control was 36 (IQR: 32-42)

years (Table 1). The highest incidence of CSCR (52.3%) was in the 31-40 years age group and this age group was significantly associated with CSCR (Chi-square test: p <0.05). Male gender was significantly associated with CSCR (p <0.05). Male is to female ratio was 3.1:1 among cases and controls. Most of the patients (99, 75%) had acute CSCR followed by persistent in 25 (18.9%) cases and recurrent in eight (6.1%) cases.

Subfoveal choroidal thickness was increased in both eyes of CSCR among tharu population but was significantly thicker in affected eyes (p <0.05) and axial length was significantly shorter in both eyes of CSCR among Tharu population (p <0.05) (Table 2). Shorter median axial length 22.72 (IQR: 22.13-23.34) mm was seen in the affected eyes and 22.74 (IQR: 22.31-22.52) mm in contralateral eyes of CSCR cases in comparison to controls in which median axial length of 23.17 (IQR: 22.63-23.73) mm and 23.13 (IQR: 22.60-23.76) mm was seen.

Most of the cases of CSCR had normal visual acuity (n=58, 40%) followed by mild and moderate visual impairment (Table 3).

Tharu ethnicity was seen in (84, 64.1%) CSCR cases and was significantly associated with development of CSCR (Chi-square test p <0.05). Inadequate sleep, night duties, untreated hypertension, pregnancy, gastritis were all more common in CSCR cases when compared to controls but they were not significantly associated with CSCR (Table 4). Non-modifiable risk factors, tharu ethnic group and young adults; and modifiable risk factors like alcohol consumption and presence of stress were found to be significantly associated with CSCR using Chi-square test (p <0.05) while doing individual risk factor analysis.

But while adjusting for confounders, using binary logistic regression, increase in stress do not increase odds of developing CSCR. The risk factors that were significantly associated with CSCR were tharu ethnicity (adjusted OR= 3.2; 95% Confidence Interval (CI) =1.808-5.444), shorter axial length (adjusted OR= 1.725; 95% CI=1.271-2.342) and alcohol use (adjusted OR=2.779 95% CI=1.136-6.799) (Table 5). People who smoke have higher odds of developing CSCR but was not clinically significant.

Table 1: Distribution of age and gender among cases and control group.

	CSCR Cases			Control		
Age group	**Male**	**Female**	**Total (Percent)**	**Male**	**Female**	**Total**
21-30	12	2	14 (10.6)	13	3	16
31-40	51	18	69 (52.3)	56	20	76
41-50	34	9	43 (32.5)	37	10	47
51-60	4	2	6 (4.5)	4	2	6
Total	101 (75.0%)	31 (25.0%)	132 (100)	110	35	145

Table 2: Comparison of choroidal thickness and axial length in affected and non-affected eyes of CSCR cases in tharu and non-tharu population.

Parameters		Tharu	Non-Tharu	Independent Sample Test (p-value)
Axial length	Affected eyes	22.68 (IQR:22.14-23.28)	23.19 (IQR:22.56-23.74)	<0.05
	Non-affected eyes	22.68 (IQR:22.12-23.45)	23.17 (IQR:22.70-23.79)	=0.063
Choroidal thickness	Affected eyes	414.5 (IQR:366-493)	392 (IQR:325-479)	<0.05
	Non-affected eyes	398 (IQR:341.25-455.75)	372 (IQR:323-434)	<0.05

Table 3: Visual acuity in cases.

Affected eyes	
Visual impairment	**Frequency (Percent)**
Normal (6/6-6/12)	58 (40)
Mild (<6/12-6/18)	48 (33.1)
Moderate (<6/18-6/60)	33 (22.8)
Severe (<6/60-3/60)	5 (3.4)
Blindness (<3/60)	1 (0.7)
Total	145 (100)

Table 4: Risk factors for development of CSCR on individual risk factor analysis.

Risk Factors	Case Frequency (Percent)	Control Frequency (Percent)	Chi-square test (p-value)
Tharu	84 (64.1)	55 (38)	<.05
Not Tharu	48 (35.9)	90 (62)	
No significant stress	96 (72.7)	127 (87.6)	<.05
Significant stress	36 (26.3)	16 (11.5)	
No night duties/outings	121 (91.7)	139 (95.9)	0.146
Night duties	11 (8.3)	6 (4.2)	
Good uninterrupted sleep	108 (81.8)	128 (88.3)	0.131

Risk Factors	Case Frequency (Percent)	Control Frequency (Percent)	Chi-square test (p-value)
Interrupted+ Poor sleep	24 (17.1)	17 (11.7)	
Gastritis Present	12 (9.1)	13 (9)	0.568
Gastritis Absent	120 (90.9)	132 (91)	
Alcohol abuse	26 (19.7)	12 (8.3)	<0.05
No alcohol abuse	106 (80.3)	133 (91.7)	
Smoking	20 (15.2)	11 (7.6)	<0.05
No history of smoking	112 (84.8)	134 (92.4)	
Untreated Hypertension	9 (6.8)	5 (3.4)	0.201
No uncontrolled hypertension	123 (93.2)	140 (96.6)	
Pregnancy	2 (1.5)	-	0.137
No pregnancy	130 (98.5)	145 (100)	

Table 5: Binary logistic regression analysis for CSCR risk factors.

Variables	B	S.E.	Wald	Df	Sig.	Exp (B)	95 % CI for EXP (B)	
							Lower	Upper
Tharu (Yes/no)	1.006	0.283	12.641	1	0.000	3.208	1.890	5.444
Axial length (Continous)	0.545	0.156	12.233	1	0.000	1.725	1.271	2.342
Stress (Yes/no)	-0.976	0.379	6.621	1	0.010	0.377	0.179	0.792
Night work (Yes/no)	-0.876	0.593	2.184	1	0.139	0.416	0.130	1.331
Adequate sleep (Yes/no)	-0.132	0.431	0.093	1	0.760	0.877	0.377	2.039
Age (Continous)	-0.051	0.020	6.655	1	0.010	0.950	0.914	0.988
Sex (Male/Female)	-0.060	0.329	0.033	1	0.855	0.942	0.494	1.796
Alcohol (Yes/no)	1.022	0.456	5.014	1	0.025	2.779	1.136	6.799
Smoking (Yes/no)	0.777	0.460	2.857	1	0.091	2.175	0.883	5.357
Constant	-15.059	3.751	16.120	1	0.000	0.000		

DISCUSSION

Risk factors for CSCR have not been studied well among Nepali population. This hospital-based study is the largest and most comprehensive study reporting the profile and risk factors of CSCR patients from Nepal.

The current study shows that CSCR is disease predominantly affecting the male patients (75%)

as has been observed in most of other population as well.(Hanumunthadu et al., 2018) The median age of this study patients was 37 (IQR: 33-42) years. Majority (52.3% of CSCR cases) were in the age group of 31-40 years. This finding agrees with most of the international studies which show that this disease is more common in young adults and middle age patients (Daurich et al., 2015). The exact reason for this difference has not been identified but it is believed that androgen hormones might have some role in CSCR (Grieshaber et al., 2007; Manayath et al., 2018). As the level of androgen hormones starts to decrease after 45 years of age, CSCR is seen less commonly in older age groups (Kaye et al., 2020). However, some studies have shown that the disease, especially chronic CSCR can occur in older people (Kitzmann et al., 2008; Tsai et al., 2013; Perkins et al., 2002). Differences in CSCR incidence among various ethnic groups is not properly understood. Few studies have showed a higher frequency of CSCR among Asians, Caucasians and Hispanics as compared to African Americans. (Daurich et al., 2015; Manayath et al., 2018) Asian population are reportedly at increased risk of having CSCR and the disease may be bilateral, multifocal and severe than in other ethnic groups (Daurich et al., 2015; Manayath et al., 2018). In this study, tharu ethinicity had higher odds of developing CSCR. The Tharus, comprising 6.6% of the total Nepali population, primarily live in the Terai region, which spans 20 districts (Central Bureau of stastistics, Nepal, 2021). The Terai is located between the Mahabharat Range and the Indian plains. They comprise of 35.9% of the population in our catchment area. (Central Bureau of stastistics, Nepal, 2021, Gupta et al., 2021) In this study, they represented 64.1% of CSCR cases. In this study, shorter axial length and thicker choroidal thickness was statistically significant finding among affected eyes of tharu population among CSCR cases which might be a reason why tharu population are at increased odds of developing CSCR. Many studies have suggested that shorter axial length and increased choroidal thickness can be a contributing factor to development of CSCR (Yang et al., 2013; Lee et al., 2017). Genetic studies may also be helpful to see if there are any genetic differences leading to increased incidence of CSCR in tharu community, which may help to open up further insights about role of genetic factors in pathophysiology of CSCR. It is well known from previous studies that sickle cell anaemia is more prevalent among tharu population (Gupta et al, 2021). From this study, it can be said that CSCR is also more prevalent in tharu ethnic group.

Anatomically shorter axial length was identified as an independent risk factor for development of CSCR in current study. Some studies agree to this finding whereas others do not find signification association between the two (Gawaecki et al., 2023, Terao et al, 2020). In the study by Terao et al, axial length of the both eyes of CSCR cases was significantly shorter than their control group. This study also showed that shorter axial length is significantly associated with development of CSCR.

This study is in agreement with studies which show that use of alcohol increases the odds of developing CSCR (Karimi et al., 2023; Haimovici et al., 2004). Some studies have reported that smoking is associated with CSCR (Okawa et al., 2021; Karimi et al., 2023). In this study, smoking increased the odds of developing

CSCR but the association did not reach clinical significance.

Some studies have shown stress to be an important risk factor for CSCR (Semeraro et al., 2019; Sesar et al., 2021). Stress hormones namely corticosteroids and catecholamine are thought be involved in the pathophysiology of CSCR. (Semeraro et al., 2019) Increased stress levels in recent past (three months) was found to be associated with CSCR on individual analysis in this study but while adjusting for confounders, stress did not increase the odds of having CSCR. Stress is a very subjective and levels of stress are often difficult to be elucidated in an accurate and reproducible manner between people, different cultures and studies. This causes significant challenges in interpreting the results about association of stress with CSCR as reported in different studies.

Other significant risk factors associated with the occurrence of CSCR were hypertension, *Helicobacter pylori* infection, steroid usage, sleeping disturbances, autoimmune diseases, psycho-pharmacologic medications and Type A behaviour (Sesar et al., 2021). Current or prior pregnancy was also a risk factor.(Daurich et al., 2015; Haimovici et al., 2004) In this study, there was no significant association between inadequate sleep, night duties, untreated hypertension, pregnancy, gastritis, and CSCR. Personality type was not assessed with CSCR and there were only a couple of patients on steroid treatment among this study and control groups.

Identification and management of the risk factors plays a crucial part in management of many CSCR cases as many of the cases will need no further treatment. A smaller subset of cases will need additional treatment options as they can end up with persistent or recurrent disease. Some chronic cases may also develop complications like choroidal neovascularisation (CNV) (Fung et al., 2012; Pang et al., 2015; Inhoffen et al., 2012) Even in these patients, management of risk factors is an essential part of the treatment strategy. As this is the first comparative study analyzing the risk factors for CSCR in Nepali population, the findings of this study will provide a significant evidence for understanding the disease process and formulating treatment plans for CSCR patients in the country.

As a hospital based, non-randomised, case-control study, this research has some inherent limitations inherent to this study design. A community-based study is better suited to evaluate the risk factors of the population. The results might be affected by recall bias or response bias as the study population self-reported their risk factors which allows for possibilities of subjective discrepancies among different respondents. These limitations were partially corrected with presence of the control group in the study. The strength of the study is that age and gender matching case control study was done and data analysis was done using logistic regression to adjust for the confounding factors. The study is first one to study risk factors of CSCR in Nepali population and first one to show that tharu ethnicity is significant risk factor for CSCR.

CONCLUSION

This study showed that male gender, young age adults, tharu ethnicity, shorter axial length,

alcohol use and smoking were the major risk factors for development of CSCR in the Nepali population. Although this study does not establish temporal causation, it emphasises the need to suspect CSCR in Tharu population patients presenting with relevant symptoms. Some of these risk factors are modifiable, thus identification of these risk factors will help in developing treatment plans for CSCR patients. Further studies are recommend to understand the cause of increased risks of CSCR in Tharu population as this may provide further insights into the role of anatomical risk factors or genetics in CSCR.

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