STUDY OF SERUM TOTAL THIOL LEVELS AND LIPID PEROXIDATION AS INDICATOR OF OXIDATIVE STRESS IN PATIENTS OF ACUTE CENTRAL SEROUS RETINOPATHY

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ABSTRACT

BACKGROUND

''Central Serous Retinopathy (CSCR) is an idiopathic, commonly encountered retinal disease, in which stress has been implicated to play a possible role. Our study aimed to determine the role of oxidative stress in the pathogenesis of the disease by comparing the serum levels of total thiols and TBARS in patients of CSCR and normal controls.''

The aim of this study was to determine the level of plasma total thiol and malondialdehyde (MDA) in patients of central serous chorioretinopathy (CSCR) and compare these parameters with that of normal individuals to evaluate the relevance of oxidative stress in the disease pathogenesis.

MATERIALS AND METHODS

A prospective cross-sectional study was performed that included 30 patients of CSCR and 30 normal patients as controls. Serum total thiol and malondialdehyde levels were measured and compared between the two groups. Correlation between serum total thiol and malondialdehyde with best corrected visual acuity, central minimum macular thickness at the foveola (CMT) and average macular thickness (AMT) was done using Pearson's correlation coefficient.

RESULTS

Serum total thiol levels were lower (370.9+53.34 mM) compared to the control group (761.5+25.44 mM), with $p<0.01$. Serum MDA levels were higher (7.52 + 0.68 μM) than the control group (2.03+0.112 μM), with p value <0.01. In CSCR, correlation analysis tests showed a strong positive correlation ($p<0.05$) between the elevated levels of MDA with CMT ($r = 0.377$) and AMT ($r =0.398$) and a very strong negative correlation ($p<0.01$) between serum total thiol levels with CMT ($r = - 0.834$) and AMT ($r = -0.73$). Regression analysis showed that a decrease in total thiol levels can be a strong predictor (beta -0.811) of increase in CMT in CSCR ($p<0.01$) while increase in MDA levels is not a significant predictor (beta 0.057). The overall model fit was adjusted $R^2 =0.675$ ($p<0.01$).

CONCLUSION

A higher level of total thiol and a lower level of MDA were found in CSCR as compared with normal controls. Total thiols can be useful in the prediction and diagnosis of the severity of CSCR.

KEY WORDS

Central Serous Chorioretinopathy, Total Thiols, Malondialdehyde, Oxidative Stress.

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BACKGROUND

Central Serous Chorio-Retinopathy (CSCR) is a retinal disease, characterized by neurosensory detachment of the retina at the macula, often with pigment epithelial detachments. It predominantly affects males between 20 to 50 years of age, with dimness of vision, metamorphopsia and positive scotoma.[1]

CSCR is said to be acute when the duration of the disease is less than four months or chronic when more than four months.[1,2]

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Mean age adjusted annual incidence of CSCR in a Caucasian population study is 5.8/100, 000.[3] However incidence in an Asian population was much higher at 0.3%.[4] The male: female ratio is 6:1.[5]

Pathogenesis of CSCR has been postulated to be caused by disturbances in the choroidal circulation and changes in the retinal pigment epithelium and Bruch's membrane. Hyperpermeability of choroidal vessels lead to increased hydrostatic pressure disrupting the outer blood retinal barrier function of the retinal pigment epithelium leading to pigment epithelial detachments. Further increase in hydrostatic pressure in the choroidal vessels leads to entry of fluids in the subretinal space.[2]

Of the risk factors implicated in the pathogenesis of CSCR, stress plays a very important role. Psychogenic stress, type A personality and use of psychoactive drugs have all been associated with CSCR.[4,6] Psychogenic stress causes oxidative damage by generating free radicals, often with lipid peroxidation and long-term exposure to psychogenic stress factors can increase the risk of development of many diseases in humans.[7,8,9]

Thiobarbituric acid reactive substances (TBARS) reflect lipid peroxidation due to increased oxidative stress and tissue injury. Assay of TBARS is done by measuring MDA which is a product of polyunsaturated fatty acid peroxidation and free radical production has been linked to overproduction of MDA.[10,11,12] Anti-oxidants are substances present in the body that help combat oxidative stress. Thiols, which are organic compounds containing the sulfhydryl group constitute a major portion of the antioxidants. Total thiols constitute intracellular and extracellular thiol in free form and protein bound form. Oxidative stress with decreased levels of thiols occurs in diabetes mellitus, neurological diseases, cardio vascular diseases, alcoholic cirrhosis and chronic kidney diseases.[13,14,15,16,17]

Many antioxidants have thiols in their structure and thiols contribute to the total antioxidant capacity, hence thiol levels can be a useful measure of oxidative stress.[14]

Oxidative stress can cause endothelial damage and disruption of auto regulation in the choroidal vasculature and apoptosis of retinal pigment epithelium with altered pump function. These changes may contribute to subretinal fluid leakage, characteristic of CSCR.[14,18,19,20]

This study is aimed at evaluating oxidative stress in acute CSCR by assessment of the serum total thiol and MDA. Drugs with native thiol like N acetyl cysteine have been used in psychiatry.[21] The future may hold promise for thiol-based drugs, in CSCR also, to keep thiol levels at normal, thereby improving or reversing the underlying disease process.[14,21]

MATERIALS AND METHODS

The study was designed as a single institutional cross-sectional observational study, conducted by the departments of Biochemistry and Ophthalmology of Bankura Sammilani Medical College and Hospital, a tertiary care government hospital in West Bengal, for a period of six months. The study protocol was approved by the Institutional Ethical Committee and informed consent was taken in duly filled proforma from all the subjects.Thirtypatients of acute onset CSCR, recruited from patients attending Ophthalmology Outpatient Department, formed the study population along with thirty age and sex matched controls

Inclusion Criteria

Patients with newly diagnosed, acute onset CSCR, having duration of less than 4 months.

Exclusion Criteria

1. Patients with chronic CSCR, having disease duration more than 4 months and recurrent CSCR.
2. Patients with other retinal diseases like diabetic retinopathy, hypertensive retinopathy, age related macular degeneration, retinal dystrophies, degenerative myopia, macular hole and chorioretinitis.
3. Patients with other ocular diseases like visually significant cataract and glaucoma.
4. Patients who have undergone any intraocular surgery.

Study Technique

a. Ophthalmological Examination

All patients underwent thorough ophthalmological examination including visual acuity assessment, slit lamp examination of the anterior segment, applanation tonometry and dilated fundus examination by indirect ophthalmoscopy and biomicroscopy with + 90 Dioptre lens.

The diagnosis of CSCR was confirmed by the Spectralis spectral domain optical coherence tomography. (Heidelberg Engineering Inc, Heidelberg, Germany). The 6x6 mm volume scan protocol was used in which, retinal thickness maps centered on the fovea were obtained with the 1, 3, 6 mm ETDRS (Early Treatment Diabetic Retinopathy Study) grid superimposed on it. The macula was divided into 9 regions by three concentric rings centred on the fovea, 1 mm (innermost ring), 3 mm (inner ring) and 6 mm (outermost ring) with the 3 mm and 6 mm rings divided into 4 quadrants each, namely superior, inferior, temporal and nasal. The parameters studied were-

1. Central minimum thickness at the foveola (CMT)
2. Average macular thickness (AMT) measuring the mean of the retinal thickness in the 9 regions of the macula.

These values were determined automatically and analysed by the OCT software.

b. Biochemical Tests

Estimation of serum total thiol was done following the method described by Hu et al.[22] Serum was mixed with TRIS –EDTA buffer, dithio-bis nitrobenzoic acid (DTNB) and absolute methanol, incubated at room temperature, centrifuged and absorbance taken from the supernatant at 412 nm, using UV-VIS Double Beam Spectrophotometer. Total thiol concentration was calculated as absorbance/e x 20 [e = 0.0136 micromol/litre. cm and dilution factor of 20] and expressed in mM concentration.

Estimation of serum Thiobarbituric acid reacting substances (TBARS) was done following the method described by Okhawa et al.[23] Serum was mixed with TCA, sulphuric acid and thiobarbituric acid agent. Upon adding n-butanol, centrifugation and absorbance was taken from the supernatant at 532 nm. TBARS concentration was expressed as µmol/L of malondialdehyde (MDA).

Statistical Analysis

SPSS 20.0 statistical software (SPSS Inc. Chicago, IL) was used to analyse data. Continuous data were presented as mean and standard deviation (SD). After using Shapiro-Wilk test data were found to follow normal distribution. Independent samples t test was done to compare the differences in parameters between two groups. A p value ≤0.05 was considered statistically significant.

Pearson's correlation coefficient was measured to find out correlation among different variables in the patients. Finally, a stepwise multiple regression analysis was done to predict the possible role of oxidative stress in the pathophysiological process

RESULTS

The clinical and laboratory features of CSCR and controls show that the mean age of the patients in the CSCR group was 33.9 ± 7.28 years and that of the control group was 32.3 + 5.18 years (Table-1). Both the subjects and controls included in the study were males. Best corrected visual acuity (BCVA) log MAR was 0.55 + 0.12 in the patient group and 0.133 + 0.12 in the control group, which was statistically significant (p value <0.01).

Similar statistically significant difference was noted in the means of central minimum thickness (CMT) which were 460.87+148.6 microns in the CSCR and 487.73 + 149.63 microns in the control groups respectively (p<0.01). Regarding average macular thickness (AMT), the findings showed mean values of 296.7.82 micron in the CSCR group and and 207.03 + 7.42 microns in the control group respectively (p <0.01). Serum mean MDA values in the CSCR group (7.52 + 0.68 μM) was raised significantly (p value <0.01) than the control Group (2.03 + 0.112 μM). In contrast, serum total thiol levels were found to be decreased in the CSCR group (370.9 + 53.34 mM) as compared to the control group (761.5 + 25.44 mM) This difference was found to be statistically significant (p <0.01).

In Table 2, Pearson's correlation coefficient (r) among different parameters in the CSCR group showed a statistically significant positive (p < 0.05) correlation between the elevated levels of MDA with CMT (r = 0.377) and AMT (r =0.398). As expected, the correlation of serum total thiol levels with CMT ((r = - 0.834) and AMT (r = -0.73) was negative and statistically very significant (p <0.01).

Predictive role of increased MDA and reduced thiol levels on the main retinal parameter indicating severity of leakage i.e. CMT was noted in Table 3, after a multiple regression analysis. It was observed that a decrease in total thiol levels can be a strong predictor (beta -0.811) of increase in CMT of CSCR (p<0.01) but increase in MDA levels was not a significant predictor (beta 0.057). The overall model fit was adjusted R^2 = 0.675 (p<0.01)

Variable	CSCR (Case) (n=30)	Control (n=30)	P value
	Mean ± SD	Mean ± SD	
Age (yrs)	33.97 ± 7.28	32.30 ± 5.18	<0.01
BCVA (logMAR) Best Corrected Visual Acuity	0.55 ± 0.12	0.13 ± 0.12	<0.01
CMT (micron) Central Minimum Thickness	460.87 ± 148.6	207.03 ± 7.42	<0.01
AMT (micron) Average Macular Thickness	487.73 ± 149.63	296.30 ± 7.82	<0.01
Total Thiol in Serum (mM)	370.97 ± 53.34	761.5 ± 25.44	<0.01
MDA in Serum (μM)	7.52 ± 0.68	2.03 ± 0.11	<0.01

Table 1. Clinical and Laboratory Comparison of Patients of CSCR and Control Group using Independent Sample 't' Test

	Age. CSCR	BCVA.CSCR	CMT.CSCR	AMT.CSCR	Thiol. CSCR	MDA. CSCR
Age. CSCR	-	0.15	- 0.126	- 0.031	0.116	- 0.018
BCVA.CSCR		-	0.213	0.099	-0.077	- 0.271
CMT. CSCR			-	0.933**	-0.834**	0.377*
AMT.CSCR				-	-0.730**	0.398*
Thiol. CSCR					-	-0.394*
MDA. CSCR						-

Table 2. Pearson's Correlation Coefficients (r) of Different Parameters in Patients of CSCR

*p value <0.05 **p value <0.01
BCVA: Best Corrected Visual Acuity CMT: Central Minimum Thickness (at the foveola)
AMT: Average Macular Thickness MDA: Malondialdehyde

Contributing Variables	Dependent Variable	R^2	Adjusted R^2	Beta
Thiol. CSCR	CMT. CSCR	0.698	0.675**	-0.811**
MDA. CSCR				0.057

Table 3. Regression Analysis Showing the Role of Thiol and MDA on CMT in Patients of CSCR

*p<0.05 **p <0.01

DISCUSSION

Acute CSCR is a retinal disease affecting young males, the exact pathogenesis of which still remains unknown, despite improvements in diagnostic and therapeutic options.

Oxidative stress has been implicated in its pathogenesis and assessed by a few studies.[14,15]

This study evaluated oxidative stress in acute CSCR by measuring serum total thiols and MDA. The mean serum total thiol was 370.97 ± 53.34 mM in the CSCR patients and 761.50 ± 25.44 mM in the control group, with a p value <than 0.01.

Altinkaynak et al in acute CSCR, showed findings similar to ours, with a mean total thiol level of 364.2 ± 14.1mM in the CSCR group and 441.2 ± 16.3mM in the control group, with a p value of 0.017.[14]

Turkoglu et al found that, total thiol levels in the CSCR group (mean 297.95 ± 50.50 mM) were significantly lower relative to normal group (mean 395.78 ± 29.55mM), with p value of < 0.001.[15] The total thiol values in CSCR in this study, were lower compared to our findings. This could be because this study involved patients of chronic CSCR, while we studied acute CSCR patients.

Ratanasukonet al studied the effect of oxidative stress on the retinal pigment and choroidal abnormalities in CSCR and noted that use of high dose anti-oxidants reduced leakage in the early stages of fundus flurescein angiography, suggesting the role of oxidative stress in the pathogenesis.[24]

Turkcu et al studied parameters like total antioxidant capacity and total oxidant status in CSCR and reached conclusion that the antioxidant system may be inadequate in the disease.[25]

Serum total thiols as a marker of oxidative stress, have been studied in various systemic diseases like ischaemic heart disease, diabetes, pulmonary diseases, Alzheimer's disease, preeclampsia, kidney diseases and alcoholism.[26,27,28,29,30,31,32,33]

Serum thiols have also been studied in ophthalmic diseases like keratoconus, pseudo exfoliation syndrome and cataract.[34,35,36]

As regards thiol levels in CSCR, thorough review of scientific periodicals yielded only two studies in Turkish population, that assessed total thiol in CSCR, of which only one was done in acute CSCR.

Low levels of thiol correlated with increased levels of lipid hydroperoxides.[37] MDA have been studied in senile cataract, age related macular degeneration, dry eye syndrome and corneal pathologies.[38,39,40,41] Kaur et al assessed MDA in senile cataract and found mean values of 4.96 ± 0.89 in the cataract group and 0.76 ± 0.25 in the control group. Totan et al measured MDA levels in Age related macular degeneration and found mean MDA levels of 2.18 micromoles/litre in patients and 1.53 micromoles/litre in controls. Choi et al assessed MDA in dry eye disease and found mean MDA levels of 3.80 ± 1.05 pmol/mg in controls and 13.32 ± 4.03 pmol/mg in patients. Cejkova et al found that MDA was expressed in

corneal diseases and injuries much more frequently than normal corneas.

MDA is therefore very relevant to assess oxidative stress in CSCR. However, review literature is lacking in assessment of MDA in CSCR. In our study, mean value of MDA in CSCR was 7.52 ± 0.68 and mean value in controls was 2.03 ± 0.11, with p value<0.01.

MDA levels had strong positive correlation and total thiol levels had strong negative correlation with CMT and AMT (p value<0.05) (Table-2). Thiol and MDA levels had negative correlation with p value<0.05. Lower levels of thiols correlate with increased levels of MDA, as also observed by Prakash et al.

Low thiol values and high MDA values had significant effect on the subretinal fluid leakage, as measured by the CMT and AMT.

This reinforces the findings of previous studies, where oxidative stress is linked to the pathogenesis of CSCR. From the results of multiple regression analysis (Table-3), a reduction in total thiol levels is established as a strong predictor of CSCR. Therefore, supplementation of antioxidants by diet or medication and use of thiol containing drugs to restore thiol levels, can serve as therapeutic options in addition to the existing treatment modalities available.

CONCLUSION

Decrease in serum total thiols and increase in MDA, establishes the role of oxidative stress in CSCR. However, a larger sample size and measurement of other parameters of oxidative stress like total antioxidant capacity and total oxidant status, would have been helpful in establishing its role as potential biomarkers in the prediction and diagnosis of the severity of CSCR.

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