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Original Article

A Novel Study of Correlation of Lipid Parameters with Clinical Profile, Staging and Onset of Rhino Orbito Cerebral Mucormycosis in A Covid 19 Pandemic

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ABSTRACT

Objectives: Study was undertaken to Estimate the lipid levels in COVID associated mucormycosis (concurrent and post covid) patients ,To correlate the lipid levels with clinical profile and staging of mucormycosis patients and To correlate the lipid levels with onset of covid associated mucormycosis

Methods: One Hundred and Three patients diagnosed with COVID associated Mucormycosis treated in the Hospitals attached to Bangalore Medical College and Research Institute were studied. Information about systemic health condition with lipid profile and other biochemical parameters were collected. Data was analysed. Descriptive statistics including Chi Square test, Mann Whitney U test,Kruskalwallis test, Spearman's correlation were used and level of significance was kept at 5%. Significance was considered if $p<0.5$.

Results: The age distribution varied from 22yrs to 75yrs with majority being males(83.4%). Most common symptom among all severity stages was nasal block(79.6%) followed by headache(75.7%). Most Common Comorbidity was DM(50.4%) followed by HTN and DM(36.8%) followed by HTN only (6.7%) followed by DM,HTN and IHD(4.8%) followed by IHD(0.9%).

Conclusion: The study showed a positive correlation between serum lipid profile and stage of Mucormycosis and negative correlation with COVID 19 onset to Mucormycosis onset duration. Hence our hypothesis proved that the patients with altered lipid parameters have higher chances to get severe form of the disease and faster onset of Mucormycosis post COVID 19 and therefore serum lipid profile can be used as a prognostic parameter in predicting the severity and prognosis of COVID 19 associated Mucormycosis.

Key Words: *Mucormycosis , lipid profile , Covid*

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INTRODUCTION

Mucormycosis is an angioinvasive disease caused by mold fungi of the genus Rhizopus, Mucor, Rhizomucor, Cunninghamella and Absidia of Order- Mucorales, Class- Zygomycetes [1]. The prevalence of mucormycosis globally varies from 0.005 to 1.7 per million population, while the prevalence is 80 times higher (0.14 per 1000) in India compared to developed countries, in recent estimate of year 2019–2020 [2], [3], [4].

India has very high cases of the mucormycosis in the world. Common Risk factors include Diabetes Mellitus, haematological malignancies, organ transplant and prolonged use of corticosteroids. [5],[6],[7].

This fungus usually resides as a commensal of the nasal mucosa and in conditions of immunosuppression like diabetes, ketoacidosis, solid organ transplant, severe burns, etc. can germinate in the nasal cavity and paranasal sinuses to invade the palate, orbits and brain, often leading to death [8].Coinfection in patients with coronavirus disease 2019 (COVID-19) has been reported on multiple series, being bacterial in origin the most frequent; and fungal infection being reported only in severe cases [9,10,11].

India has reported surge in cases of post COVID 19 Mucormycosis over the past few years due to the increasing frequency of risk factors like corticosteroid therapy, uncontrolled diabetes, diabetic ketoacidosis, neutropenia and obesity

Studies have shown that eukaryote contain cholesterol and fungi contain ergosterol with lanosterol being precursor for both and ergosterol is essential for mitochondrial DNA maintenance in fungi, as cholesterol does in humans. (12)

Thus we conducted a study is to estimate the lipid parameters and correlate the serum lipid parameters with clinical profile, stage of the disease, duration of onset of mucormycosis post covid infection in patients with COVID associated Mucormycosis.

MATERIALS AND METHODS

This was a Cross sectional Study design performed after obtaining institutional ethics committee clearance and written informed consent , the patients fulfilling the inclusion and exclusion criteria were taken up for the study.One hundred and three patients were included in the study. Detailed history was taken including their co-morbid conditions, lipid parameters including other biochemical parameters were collected from all patients and were correlated with parameters such as stage of the disease, duration between onset of mucormycosis after covid infection and Statin use were done.Data was entered in the excel spread sheet. SPSS (Statistical Package for Social Sciences) version 20. was used to perform the statistical analysis. Data was subjected to normalcy test (Shapiro-wilk test). Data showed non normal distribution of lipid profile. Hence non-parametric tests were applied.

Descriptive statistics of the explanatory and outcome variables were calculated by mean, standard deviation, median and interquartile range for quantitative variables, frequency and proportions for qualitative variables. Chi square was applied to test the statistical association between qualitative variables. Mann Whitney U test was applied to test the mean difference between lipid profile and gender, lipid profile and statins use. Kruskalwallis test was applied to test the mean difference between lipid profile and staging of mucormycosis. Spearman's correlation was applied to test the correlation between age, duration of covid onset to mucormycosis onset and lipid profile. The level of significance was set at 5%. Significance was considered if $p<0.5$.

RESULTS and DISCUSSION:

The age distribution varied from 22yrs to 75yrs with majority being males(83.4%), females accounted for (16.6%).Most common symptom among all severity stages was nasal block (79.6%) followed by headache (75.7%), Eye pain (65.0%), Tooth ache (61.2%), Facial pain (60.2%), Opthalmoplegia(54.4%), Nasal discharge(48.5%), Perception of Light-negative(27.2%) other symptoms (24.3%)

Most Common Comorbidity associated was DM only(50.4%), followed by DM with HTN(36.8%) followed by HTN only (6.7%) followed by DM,HTN with IHD (4.8%) followed by IHD only (0.9%).

Lipid Profile among all severities showed positive correlation. The mean Total Cholesterol(TC) , LDL levels, TG levels showed positive correlation (TC was 153.21 in stage 2, 225.51 in stage 3, 225.29 in stage 4, p value <0.5 and LDL was 99.85 in stage 2, 160.98 in stage 3, 147.14 in stage 4, p value <0.5 and TG was 139.45 in stage 2, 192.78 in stage 3, 264.71 in stage 4, p value <0.5) while HDL levels were similar among all stages of severity (29.26 in stage 2, 30.12 in stage 3, 29.57 in stage 4, p value <0.5)

It also showed statistically significant negative correlation between TC, LDL, VLDL, TG levels and COVID 19 onset to mucormycosis onset duration (p value <0.5).

24.27% of patients were on Statins and no statistically significant correlation was found between prior statin use with lipid profile and severity of mucormycosis. (p value >0.5).

Guzman G Et al [16] concluded that Sphingolipids and phosphoinositides plays and crucial role in fluidity of cell membrane and structure and as well as potent signalling molecules involved in phagocytosis and many fungi through unknown mechanisms usurp host lipid metabolism pathways to effectively establish infection.

Xiong Q Et al [17] study conducted a study to determine the effect of cholesterol on growth of Aspergillus fumigatus, they showed that adding serum or cholesterol to the RPM1 growth medium with the sterol biosynthesis inhibitors itraconazole or voriconazole partially rescued the cells from the drug-induced growth inhibition and enhanced the growth of the fungus. They concluded that potency of sterol biosynthesis inhibitors is attenuated by cholesterol by providing a substitute for membrane ergosterol.

Similar study by Nagi et al [18] concluded that in a lipoprotein-deficient serum supplementation of free cholesterol promoted the growth of C.glabrata in a fluconazole treated media where it previously showed no growth in cholesterol free media.

Our study showed direct positive correlation with severity of mucormycosis and negative correlation with time duration to onset of mucormycosis as the total cholesterol, triglycerides level and LDL level increased, highlighting the importance of significance of Lipids for growth of fungi, serving as prognostic marker for severe fungal infections and mortality.

Lipid Profile	GENDER	N	Mean	Std. Dev	Median	IQR	p value*
TOTAL CHOLESTEROL	Male	81	191.23	53.056	201.000	92.000	.457
	Female	22	197.18	52.542	220.000	95.000	
HIGH DENSITY LIPOPROTEIN	Male	81	29.44	8.562	0.229	0.784	0.297
	Female	22	30.59	7.042	0.626	11.000	
LOW DENSITY LIPOPROTEIN	Male	81	131.60	45.446	147.000	76.000	0.784
	Female	22	134.14	46.520	156.000	82.000	
VERY LOW DENSITY LIPOPROTEIN	Male	81	30.75	14.006	28.000	19.000	0.229
	Female	22	32.45	9.787	31.500	20.000	
TRIGLYCERIDE	Male	81	176.09	71.859	168.000	110.000	0.626
	Female	22	163.18	51.510	157.500	112.000	
HDL/LDL	Male	81	.258	.1524	.2000	.1000	0.663
	Female	22	.282	.1708	.2000	.3000	

*Mann whitney U test

Spearman's correlation between age and lipid profile						
Age	TC	HDL	LDL	VLDL	TG	HDL/LDL
r value	-0.214	-.096	-.182	-.117	-.182	.093
p value	.030*	.333	.066	.240	.066	.351
N	103	103	103	103	103	103

*Significant

Stage	N	Age		F value	p value*
		Mean	Std dev		
2	47	50.04	14.933	1.475	0.23
3	49	45.63	12.008		
4	7	44.86	9.477		
Total	103	47.59	13.373		

*ANOVA

Stage	GENDER		Total
	Male	Female	
2	40	7	47
	38.8%	6.8%	45.6%
3	36	13	49
	35.0%	12.6%	47.6%
4	5	2	7
	4.9%	1.9%	6.8%
Total	81	22	103
	78.6%	21.4%	100.0%
Chi square - 2.167			
p value - 0.338			

Co- morbidities	Stage			Total
	2	3	4	
DM	43	45	7	95
	45.3%	47.4%	7.4%	100.0%
HTN	22	26	2	50
	44.0%	52.0%	4.0%	100.0%
IHD	6	0	0	6
	100.0%	0.0%	0.0%	100.0%
DM + HTN	15	26	2	43
	34.9%	60.5%	4.7%	100.0%
DM + HTN + IHD	5	0	0	5
	100.0%	0.0%	0.0%	100.0%

Spearman's correlation between Covid onset to mucor onset duration and lipid profile						
Covid onset to mucor onset duration	TC	HDL	LDL	VLDL	TG	HDL/LDL
r value	-0.534	.041	-0.526	-0.313	-0.416	0.548
p value	.000*	.680	.000*	.001*	.000*	.000*
N	103	103	103	103	103	103

*Significant

Stage	On Statins		Total
	Yes	No	
2	11	36	47
	44.0%	46.2%	45.6%
3	14	35	49
	56.0%	44.9%	47.6%
4	0	7	7
	0.0%	9.0%	6.8%
Total	25	78	103
	100.0%	100.0%	100.0%

Lipid Profile	On statins	N	Mean	Std. Dev	Median	IQR	p value*
TOTAL CHOLESTEROL	Yes	25	190.92	59.873	200	88	0.814
	No	78	193.01	50.666	208.5	93	
HIGH DENSITY LIPOPROTEIN	Yes	25	28.60	10.235	26	16	0.374
	No	78	30.04	7.538	29.5	10	
LOW DENSITY LIPOPROTEIN	Yes	25	132.00	49.328	153	79	0.808
	No	78	132.19	44.486	147.5	77	
VERY LOW DENSITY LIPOPROTEIN	Yes	25	30.32	13.462	26	14	0.617
	No	78	31.37	13.184	29	19	
TRIGLYCERIDE	Yes	25	168.88	64.821	161	111	0.829
	No	78	174.76	69.338	169	108	
HDL/LDL	Yes	25	.256	.1758	0.2	0.1	0.519
	No	78	.265	.1502	0.2	0.1	

*Mann Whitney U test

Lipid Profile	Stage	N	Mean	Std. Dev	Median	IQR	p value
TC(TOTAL CHOLESTEROL)	2	47	153.21	46.401	143	64	0.001#
	3	49	225.51	29.374	229	31	
	4	7	225.29	40.533	239	81	
HDL(HIGH DENSITY LIPOPROTEIN)	2	47	29.26	8.848	27	13	0.001#
	3	49	30.12	8.220	30	11	
	4	7	29.57	3.309	28	4	
LDL(LOW DENSITY LIPOPROTEIN)	2	47	99.85	42.774	90	57	0.001#
	3	49	160.98	23.095	165	25	
	4	7	147.14	40.176	147	67	
VLDL(VERY LOW DENSITY LIPOPROTEIN)	2	47	25.11	8.499	23	11	0.001#
	3	49	34.39	12.349	33	20	
	4	7	48.57	21.439	47	47	
TG(TRIGLYCERIDE)	2	47	139.45	60.197	119	76	0.001#
	3	49	192.78	50.628	196	70	
	4	7	264.71	92.217	251	154	
HDL/LDL	2	47	.349	.1816	0.3	0.2	0.001#
	3	49	.188	.0754	0.2	0.1	
	4	7	.214	.0900	0.2	0	

*Kruskal Wallis test
#Significant

Clinical presentation	Stage			Total	p value *
	2	3	4		
Nasal block	39	39	4	82	0.286
	83.0%	79.6%	57.1%	79.6%	
Nasal discharge	21	26	3	50	0.680
	44.7%	53.1%	42.9%	48.5%	
Facial pain	29	30	3	62	0.624
	61.7%	61.2%	42.9%	60.2%	
Eye pain	21	39	7	67	0.001#
	44.7%	79.6%	100.0%	65.0%	
Ophthalmoplegia	0	49	7	56	NA
	0.0%	100.0%	100.0%	54.4%	
PL Negative	3	19	6	28	0.001#
	6.4%	38.8%	85.7%	27.2%	
Headache	32	42	4	78	0.065
	68.1%	85.7%	57.1%	75.7%	
Toothache	27	31	5	63	0.714
	57.4%	63.3%	71.4%	61.2%	
Other symptoms	15	8	2	25	0.197
	31.9%	16.3%	28.6%	24.3%	

*Chi square test
#Significant

LIMITATIONS:

Since our study was one of the first study correlating lipid levels with severity of Mucor till date at the time of doing this study, further studies are required.

CONCLUSION:

The study showed a positive correlation between serum lipid profile and stage of mucormycosis and negative correlation between lipid levels and COVID 19 onset to mucormycosis onset duration. Hence our hypothesis proved that the patients with deranged lipid parameters have higher chances to get severe form of the disease and faster onset of mucormycosis post COVID 19 infection owing to the increased multiplication of the fungus and therefore serum lipid profile can be used as a prognostic parameter in predicting the severity and prognosis of COVID 19 associated mucormycosis.

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