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Research Article

HbA1C – A VIGILANT SCREENING TOOL IN EARLY DETECTION OF COVID ASSOCIATED MUCORMYCOSIS

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ABSTRACT

Aim: To study the outcome of covid associated mucormycosis (CAM) patients on the basis of HbA1c levels

Objectives: To correlate severity of disease and mortality of CAM, based on HbA1c levels irrespective of diabetic status of patient at admission

Methodology: Patients with proven Covid associated mucormycosis were evaluated using HbA1c levels. Grade of involvement by the fungus based on involvement of organs was correlated. Factors other than HbA1c including blood sugar levels, steroids, oxygen usage noted and analysed. Mortality was analysed based on mean HbA1c levels.

Results: Around 50% of the 90 patients were known diabetics at admission.

Undiagnosed diabetes mellitus was found in Mean HbA1c levels were 9.1%. Higher grades that is Grade 3 & 4 were associated with HbA1c levels with mean of 9.61 & 9.26 respectively while lower grades had lower mean HbA1c. Complications of mucormycosis led to death in 7 cases, the mean HbA1c in these patients was high i.e. 9.1 % as compared to that in survived cases 8.83%.

Conclusion: HbA1c should be used as a screening tool in covid patients, to keep high suspicion for occurrence of mucormycosis. These patients can be warned regarding symptoms of mucor and evaluated at regular intervals doing nasal endoscopy, as rhinoorbital mucormycosis being the commonest presenting type.

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INTRODUCTION

A global COVID 19 pandemic was declared by WHO on March 11, 2020, as it rose a public health emergency of international concern.¹ An unpredicted sudden rise of life threatening mucormycosis was seen in patients recovering from COVID 19, especially in the second wave caused by delta variant.^{2,3,4,5} Several studies carried out concluded poorly controlled diabetes mellitus and diabetic ketoacidosis as a predominant risk factor in majority of almost 70% covid associated mucormycosis(CAM) patients.^{2,5,6,7,8,9}

Diagnosis of Diabetes mellitus is usually done using fasting plasma glucose and oral glucose tolerance tests.¹⁰ The importance of HbA1c in diagnosing Diabetes was established by Diabetes Control and Complications Trial and recommended by the International Expert Committee.¹¹ Detection of diabetes mellitus using HbA1C has advantage over other methods, as it doesn't need patient preparation like fasting, or fasting after taking oral glucose, prior to blood collection and can be performed any time of the day.¹²

Also it avoids the problem of day to day variability of glucose levels.¹³ Hence the test can be conveniently carried out instantly, even in emergency settings or community based and hard to reach setups.¹⁴ Also HbA1c levels are average plasma glucose of 8- 12weeks of blood sugar, and are not affected by pre-analytical variations like acute illness or food ingestion.^{15,16}

Factors affecting HbA1c and its measurements are -iron or vitamin B12 deficiency anemias, erythropoiesis, alcoholism, chronic renal failure, splenectomy, haemoglobinopathies, decreased erythrocyte lifespan, hyperbilirubinaemia, aspirin.^{15,17} The International Committee of Experts has set levels of HbA1c > 6.5% as indicating diagnosis of diabetes.^{10,11} The same was concluded by WHO expert consultation in 2009, which also stated that stringent quality assurance & assays be standardised to criteria aligning the reference values, with no conditions present altering its value, which certainly is also

applicable to other tests . The American Diabetes Association also supported the use of HbA1c and introduced a category of “Pre diabetes” with HbA1c 5.7-6.4% identified as high risk groups.^{18,19} Diabetes being the major and most common factor associated in CAM, our study aims to correlate the HbA1c levels with the severity and outcome of this disease.

MATERIAL & METHODS

A prospective descriptive study was conducted in 90 patients admitted in our department, suffering from covid associated mucormycosis (CAM), from March 2021 to September 2021.

Patients with clinical suspicion of invasive fungal sinusitis were evaluated using KOH mount of nasal crusts and fungal culture. Those with positive reports were taken into the study.

Patients were investigated by doing blood investigations, including Glycated Hemoglobin (HbA1c), Random blood sugar and other routine investigations. The extent of involvement was noted on Diagnostic nasal endoscopy & CT scan and MRI of paranasal sinuses, orbit & brain (Figure 2,3). The grading of fungal sinusitis followed by us was as follows- Grade I- Nasal cavity, Grade II – Paranasal sinuses, Grade III- Orbit involvement, Grade IV- Intracranial involvement.

Inclusion criteria:

1. History of Covid 19 positive test
2. Patients with negative RT PCR incovid like symptoms with raised inflammatory markers
3. Positive KOH mount or fungal culture or histopathological examination

Exclusion criteria:

1. Patients with immune compromised status such as HIV/AIDS, Organ transplant patients or on chemotherapy
2. Haematological or other malignancies
3. Longterm immunosuppressive therapy
4. Altered HbA1C as seen in iron deficiency anaemia, Vitamin B12

deficiency, reticulocytosis, altered haemoglobin

5. Cases of recent blood transfusion or haemolytic anaemia

Medical therapy was started immediately for all patients with Injection Amphoterecin B (Liposomal/ Conventional) or Voriconazole/Posaconazole. Patients with orbital involvement without vision impairment were given retroorbital Amphoterecin injections. Patients were posted for endoscopic debridement of nasal cavity and paranasal sinuses (Figure.1) with orbital decompression or orbital enucleation as per ophthalmologists opinion. Patients with palatal perforation (Figure.4) were treated surgically and were given palatal prosthesis after complete cure. Patients with intracranial abscess underwent drainage by neurosurgery. Those with extensive intracranial involvement or large vessel thrombosis or those not willing for surgery were treated conservatively.

Postoperative Liposomal Amphoterecin B 3-5 mg/kg was given for 14 days. The disease was monitored post operatively by repeat endoscopy after 1 week & 2 weeks, residual disease if any was removed. Suspicious tissue if any was sent for KOH/Histopathological examination Repeat imaging after 1 week was used for confirmation of clearance of disease and to rule out recurrence.

In cases with improvement treatment was step down to Posaconazole 400mg twice a day, same was the treatment for patient not tolerating Amphoterecin B. The severity by grading and outcome by cure or mortality was analysed statistically on the basis of HbA1c levels of the patients.

RESULTS

Demography

In our study, 90 patients diagnosed with covid associated mucormycosis ranged between the age of 18-73 years, with mean age of $49.6 \pm$

12.6. Out of which, 69 (76.7%) were males while 21(23.3%) were females.

Covid Association

Out of 90 patients of mucormycosis in our study, 84 were covid positive either before or during diagnosis. Rest of the 6 patients were declared RT PCR negative covid associated mucormycosis based upon symptoms and raised inflammatory markers.

The duration between positive RT PCR for covid 19 to diagnosis of mucormycosis ranged from 0-97 days with median of 24.5 days. Some patients were RT PCR positive at admission to mucor ward.

Association with Diabetes

Known diabetics in our study were 45(50%), while the other 50% did not have history of diabetes.

The HbA1c levels had excellent control in 14(15.6%) cases, a good control in 36(40%) cases, while 40(44.4%) cases had poor control with HbA1c > 9.0.

The mean Random blood sugar levels were 217.5 ± 108.87 , ranging between 80-800mg/dl. While, mean HbA1c levels were 9.1 ± 2.2 , ranging between 4.5 - 14.3.

Mucormycosis

Based on grading as mentioned before, 2 (2.2%) cases were grade I. Grade II disease was seen in 29(32.2%) cases, Grade III in 35(38.9%) cases and Grade IV in 24(26.7%) cases.

Medication history

Out of the 90 cases, 54(60%) were given steroids during the treatment for covid 19 and 41(45.6%) received oxygen therapy.

Injection Amphotericin B was given in 84(93.3%) cases either in conventional or liposomal forms.

Outcome

Total of 83(92.2%) patients were discharged disease free after check scopy or imaging, whereas, 7(7.8%) patients died of the complications due to mucormycosis.

Outcome		
Outcome	No. of cases	%
Discharged	83	92.2
Deaths	7	7.8
Total	90	100

Correlating mucormycosis grade with HbA1c levels

The table below mentions the distribution of HbA1c levels of cases in each grade of

mucormycosis. With maximum number of cases with poor control of HbA1c levels (i.e. more than 9.0) seen in cases with Grade 3 & 4 mucormycosis.

Grade of mucormycosis in relation to HbA1c levels						
Grade	HbA1c					
	Excellent		Good		Poor	
	No.	%	No.	%	No.	%
Gr 1	0	0.0	1	2.8	1	2.5
Gr 2	8	57.1	10	27.8	11	27.5
Gr 3	2	14.3	16	44.4	17	42.5
Gr 4	4	28.6	9	25.0	11	27.5
Total	14	100.0	36	100.0	40	100.0

$\chi^2 = 6.24, P = 0.40, NS$

Also, mean levels of HbA1c were found to be at higher levels in higher grade of mucormycosis. Cases with grade 3 & Grade

4 mucormycosis had mean HbA1c levels of 9.61 & 9.26 respectively as shown in the table below.

Average HbA1c levels Grade of mucor			
Mucor Grade	No. of cases	HbA1c	
		Mean	SD
Gr 1	2	8.20	1.27
Gr 2	29	8.33	2.15
Gr 3	35	9.61	2.02
Gr 4	24	9.26	2.38
Total	90	9.07	2.19

One Way ANOVA, $F = 2.04, P = 0.12, NS$

Outcome Analysis

The following table shows outcome of cases in relation to HbA1c levels, with 6 out of 7 deaths occurred in cases with HbA1c levels > 7. Also the mean HbA1c level in death cases was higher (9.1) as compared to the survived cases

(8.83). Also prognostic value of HbA1c test if calculated with cut-off levels of 8.0, shows 71.4% of moribund cases in group with higher HbA1c(>8.0).

Outcome inrelation to HbA1c levels						
Outcome	HbA1c					
	Excellent		Good		Poor	
	No.	%	No.	%	No.	%
Death	1	7.1	4	11.1	2	5.0
Survived	13	92.9	32	88.9	38	95.0
Total	14	100	36	100.0	40	100.0

$X^2 = 1.00, P = 0.61, NS$

Prognostic value of HbA1c associated with Outcome			
HbA1c	Outcome		Total
	Death	Survived	
> 8.0	5(71.4%)	57(68.7%)	62
< 8.0	2(28.6%)	26(31.3%)	28
Total	7(100%)	83(100%)	90

$X^2 = 0.02, P = 0.85, NS$

Figure 1: Endoscopic picture of debridement in Rhinorbitalmucormycosis

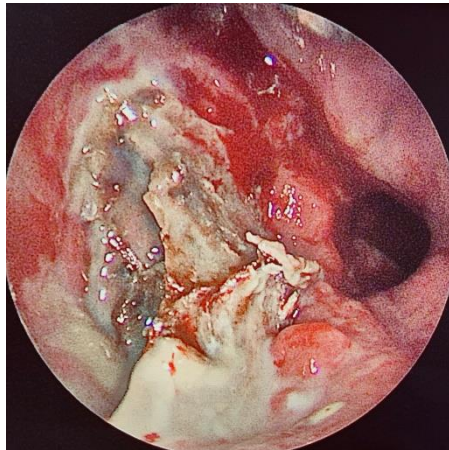


Figure 2: MRI of PNS, Orbit and Brain showing Grade IV disease

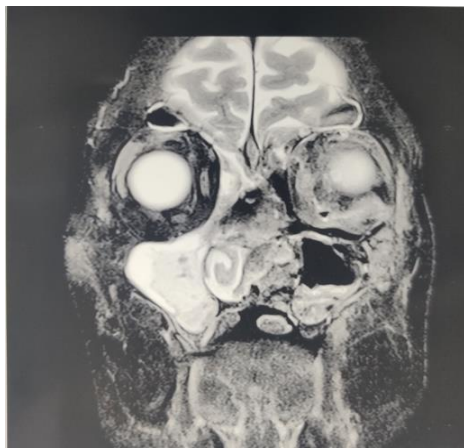


Figure 3: CT Scan of Paranasal sinuses showing extent of involvement in CAM



Figure 4: Morbidity as palatal perforation in CAM



DISCUSSION

The 90 patients in our study ranged from the age of 18-73 years, with mean age being 49.6 ± 12.6 years. Which ranged 20-75 years in a study by Gupta et al and 58.28 ± 8.57 in similar study on CAM by Mishra et al.⁵ The sex ratio in our study was 69:21 which varied amongst the studies with 17:15 in a study by Mishra et al, while 8:2 in Arjun et al.^{2,5}

The interval between Covid positive test and positive test for mucormycosis ranged widely in our study from 0 to 97 days. With median of 24.5 days. This interval was 17.28 ± 11.36 in the study by Mishra et al.⁵ Median incubation period of mucor is not known & considered as 7-10 days as stated in their study by Smith RM et al.²⁰

Risk factors for CAM

Incidence of mucormycosis in DM is 1.6 cases/1000.⁵ India has highest global burden of mucormycosis. Currently, 14,872 cases of CAM have been notified in India as of May 28, 2021.⁴

Diabetes Mellitus is most frequent comorbidity in mucormycosis.⁹ Other risk factor associated with CAM was steroids but not all patients had received it as seen in a study by Arjun et al.² Diabetics with Covid infection triggers increased release of glucocorticoids and catecholamines

causing hyperglycaemia and abnormal glucose variability.²¹

In a study by Patel et al on mucormycosis patients 73.5% were diabetics with 14.6% as DKA, 81.6% as uncontrolled diabetes while 12.9% were diagnosed during evaluation for mucor.⁹ Also recent study on CAM by Mishra et al had 87.5% diagnosed as diabetes.⁵ While Gupta et al had 67% uncontrolled diabetes patients with 47.2% having HbA1c levels >7.5%.²² Average BSL in a study by Mishra et al was found to be 242.63± 84mg/dl.⁵

Pathogenesis & spread of Mucormycosis in Covid 19 & in DM

Diabetes is a proinflammatory state which leads to deficient control of SARS COV2 replication and severe infection.^{23,24} Also leads to increase in insulin, increased lymphocyte.^{7,25} Covid19 & DM affect immune system. SARS COV 2 causes endothelial dysfunction.²⁶ It causes endothelial adhesion and angioinvasion.²⁷

Pathogenesis of spread

Originates in the paranasal sinuses but spreads to orbit.^{7,28} Most common presentation in a wide ranged study by Patel et al, Rhinoorbital mucormycosis was the most common type seen in 315/465 (67.7%) patients.⁹

Diagnosis of DM- HbA1c and random plasma glucose level comparison

In a large multicentre study with 465 patients on mucormycosis by Patel et al, the mean HbA1c levels were 10.2, while a study on CAM by Mishra et al got it as 9.06± 2.19.⁵

Use of oxygen & steroids- stats and need for detailed study

Steroids also cause immunosuppression and hyperglycaemia.⁵ In a study by Arjun et al, 8 out of 10 patients received both oxygen supplementation and steroids while 30 out of 32 patients received steroids as either dexamethasone or methyl prednisolone in a study by Mishra et al.^{2,5}

HOSPITAL STAY AND AMPHOTERICIN B

Amphotericin B was first line of treatment immediately after diagnosis. Liposomal was preferred over Deoxycholate, except in case of non availability of the drug depending on the renal function of the patient. Posaconazole was the preferred alternative or adjuvant drug as also seen in the study by Gupta et al.²²

In the study by Patel et al, 81.9% patients were treated with Amphotericin B as primary therapy and 11.4% received with Posaconazole.⁹

Surgical debridement allows better penetration of antifungal agents. Combined surgical and medical treatment is associated with better outcomes (Fig 1). Despite appropriate antifungal therapy, mortality was high amongst the inoperable, suggesting a need for early diagnosis and better therapeutic strategies.⁹

OUTCOME

Mortality, morbidity

Mortality in mucor with DM is 40-50%.²⁹ In a study by Patel et al 90 days mortality was 52% in 465 patients with mucormycosis. It was significantly higher in intracranial extension as majority were inoperable.⁹ Morbidity in CAM Eye- 50%, Face- 46%, Palate – 15% (Figure 4).²² This can be reduced by early diagnosis, early medical therapy to halt progression, and early debridement not only to prevent further spread but to facilitate penetration of antifungal agents. Prognosis improves with surgery <10%.³⁰

Mortality was less in our study as compared to other studies possibly due to early detection. But needs long follow up of 12-24 weeks.⁵ Combined medical and surgical treatment is associated with better outcomes and high survival with median time to death being 32 days, as seen in this study in 62.2% patients.^{9,31} Most common combination drug therapy used was Amphotericin B with Posaconazole in 60.9% cases.⁹

Challenges in management of mucormycosis

Financial constraints, cost of liposomal being tremendous, difficult for non-affording patients. Delay in seeking healthcare, lack of knowledge amongst physicians/doctors are some of the

common challenges faced in our study as also seen by Patel et al.⁹

Ours is a one of a kind research that studies screening in covid patients to early detect and treat the fast spreading mucormycosis in order to prevent its ghastly morbidity and mortality. Although it has indicated HbA1c as a valid tool for screening, the disease here is multifactorial not restricting to any age or sex group or any one risk factor. Hence like any other study our study too had some limitations, which can be overcome by further studies on contributing risk factors with a control group to strengthen the association.

CONCLUSION

- Early diagnosis can be done by keeping high level of suspicion. HbA1c should be used to screen covid 19 patients to rule out the most common high risk factor of CAM i.e. diabetes especially in undiagnosed DM.
- These patients can be warned regarding symptoms of mucor and evaluated at regular intervals doing nasal endoscopy, as rhinoorbital mucormycosis being the commonest presenting type.

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