CONTENTS

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Corrigendum

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ORIGINAL ARTICLE

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Prevalence of Coronary Risk Factors in Patients with Type 2 Diabetes Mellitus

Prashant Kumar Swarnkar, Abhilash Kumar**, Ajai Kumar Garg***, AK Agarwal****, Esha Singhal******

Abstract

***Introduction:** Diabetes mellitus (DM) remains as one of the impertinent global epidemics of the twenty-first century. Coronary artery disease (CAD) is more common in diabetics and is more extensive. Identification and estimating the prevalence of various coronary risk factors in type 2 DM is essential in preventing/delaying the coronary heart disease.*

***Aims and objectives:** This study aims to assess the prevalence of coronary risk factors in patients with type 2 DM and also to compare and co-relate assessed risk factors in these patients with or without electrocardiographic and/or symptomatic evidence of coronary heart disease.*

***Methods:** This was a cross-sectional study conducted for a period of eighteen months in a tertiary care teaching hospital in North India. 104 patients diagnosed as a case of type 2 DM were included. Detailed history, clinical findings and relevant laboratory investigations were recorded. Non-modifiable risk factors like age, sex, family history and modifiable ones like smoking, obesity, hypertension, hypercholesterolaemia, hypertriglyceridaemia and microalbuminuria were analysed in detail.*

***Results:** The mean age of patients was 53.7 years in male group and 52.6 years in the female group with mean duration of diabetes as 8.8 years. 21.2% had family history of CHD. 14.4% of the patients had BMI greater than 25 and hypertension was prevalent in approximately 1/3 rd. of the cases. Mean HbA1c in the study group was 7.4 %. Prevalence of CHD among type 2 DM patients was 15.4% and the prevalence of CHD increased with age and duration of diabetes. The mean BMI and WHR of the patients with CHD (24.8 and 0.98 respectively) were observed to be higher than the patients without CHD (21.1 and 0.84 respectively). Hypercholesterolaemia was seen in 42.3%, hypertriglyceridaemia in 51.9%, low HDL-cholesterol levels in 40.3% and microalbuminuria was seen in 33.7% of the cases.*

***Conclusion:** This study revealed significant prevalence of both CHD and coronary risk factors in type 2 DM subjects. Serum cholesterol ($p = 0.000004$), LDL ($p = 0.00003$), HbA1c ($p = 0.002$), microalbuminuria ($p = 0.000006$) and hypertension ($p = 0.00006$) were all significant predictors of CHD in both the sexes. Among the female type 2 DM cases, in addition BMI ($p = 0.01$), Waist-hip ratio (WHR) ($p = 0.003$) and low HDL level ($p = 0.008$) are important correlates of CHD. However, if confounding between variables was taken into consideration then microalbuminuria alone appeared to be the best model for CHD prediction.*

Introduction

Diabetes mellitus has become a global pandemic. It is also called 'the disease of complications' highlighting the higher mortality, morbidity and economic burden. As per the International Diabetes Federation(IDF), approximately 463 million adults (20 - 79 years) were living with DM worldwide in 2019 which will rise to 700 million in 2045. 79% of adults with DM are living in low- and middle-income countries.

The rise of type 2 DM in South Asia is estimated to be more than 150% between 2000 and 2035. Although ageing, urbanisation, and associated lifestyle changes are the major determinants for the rapid increase, an adverse intrauterine environment and the resulting epigenetic changes could also contribute in many developing countries[1].

India is the country with the second highest number of DM cases after China, with 72.96 million diabetes cases estimated in 2019. This is expected to increase up to 109 million in 2035[2]. There are large dissimilarities in diabetes prevalence between states in India. DM is found to be maximum in the southern part of the country[3]. The prevalence in urban areas ranges between 10.9% and 14.2% and prevalence in rural India was 3.0 - 7.8% among population aged 20 years and above with a much higher prevalence among individuals aged over 50 years (INDIAB Study)[4].

Silent ischaemia and infarction are more common among diabetics. Hence, the diagnosis is often missed. Sudden death is 50% higher in diabetic men and 300% higher in diabetic women indicating higher prevalence and mortality due to CAD among diabetic females[5]. It is estimated that, number of diabetics is going to be doubled by 2020 and

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CAD among them is going to be tripled. It is going to manifest as "epidemic of diabetes and CAD" in developing countries, especially in India. As type 2 DM shares several risk factors in common with coronary artery disease (CAD), such as age, physical inactivity, obesity, stress, hypertension and dyslipidaemia, an increase in the prevalence of diabetes indirectly implicates an escalating risk of CAD as well[6,7]. Diabetic patients have two to four times increased CAD risk, and CAD has been reported to occur two to three decades earlier in diabetic patients as opposed to non-diabetics[6].

The present study was aimed to identify and establish the prevalence of various coronary risk factors in type 2 DM with or without any evidence of coronary artery disease.

Material and methods

This was a cross-sectional prevalence, analytical study conducted for a period of 18 months in a tertiary care teaching hospital in North India. Informed consent was taken from each patient. 104 known patients of type 2 DM treated with dietary restriction and/or oral hypoglycaemics agents and/or insulin, without the history of ketosis and congestive heart failure, attending the diabetic clinic in the department of General Medicine were included.

Patients presented with history of diabetes were evaluated and thorough history was taken including modified Rose questionnaire, to determine the presence of 'angina' or 'pain of possible infarction[8]. A thorough physical examination was conducted. Blood pressure of all the patients was measured twice with dial sphygmomanometers. Standing height, weight, and waist (the smallest girth between the costal margin and iliac crest) and hip circumference (at the inter-trochanteric level) was also measured.

Resting 12-lead electrocardiograms (ECG) was analysed according to the Minnesota codes. The quantitative determination of glycated haemoglobin (HbA1c) was done using standard glycated haemoglobin kit. Glucose, urea, serum creatinine, uric acid, cholesterol, HDL-cholesterol, triglycerides, VLDL and LDL-cholesterol was assayed by the standard laboratory methods. Gross albuminuria and ketonuria was tested using the Ames multiple reagent strips. Patients whose urine specimen was negative for gross albuminuria (≥ 300 mg/l) were evaluated further for microalbuminuria (MAU). All laboratory investigations were carried out in laboratory of the institution or authorised by the institution.

The data obtained was analysed using SPSS Software version 23. Descriptive results were expressed as Mean and SD of various parameters in the different groups. The mean difference between the continuous variables was assessed using student t-test and categorical variables using chi-square test. P-values less than 0.05 considered as significant and P-values less than 0.001 considered highly significant.

Results

A total of 104 patients (48 males and 56 females) of type 2 DM who fulfilled the inclusion criteria were analysed. The clinical, anthropometric and biochemical features of the study group are shown in Table I. Among females, clustering of risk factors was seen in the age group > 60 years. Whereas among males the age group 51 - 60 years seemed to harbour the maximum risk factors.

Table I: Characteristics of the study group.

	Male N = 48	Female N = 56
Age in yrs. (Mean ± SD)	53.7 (± 8.17)	52.6 (± 7.05)
Duration of DM in yrs. (Mean ± SD)	8.6 (± 6.09)	9.1 (± 5.28)
Smokers	14 (29.2%)	1 (1.8%)
Alcohol consumers	14 (29.2%)	Nil
Sedentary workers	37 (77.1%)	49 (87.5%)
Family history		
DM	24 (50%)	26 (46.4%)
CHD	9 (18.7%)	13 (23.2%)
HT	4 (8.3%)	5 (8.9%)
CVA	3 (6.2%)	1 (1.8%)
BMI (Mean ± SD)	21.3 (± 3.64)	22.2 (± 4.80)
BMI > 25 (N (%)]	5 (10.4%)	10 (17.8%)
Overweight [N (%)]	4 (8.3%)	8 (14.3%)
WHR (Mean ± SD)	0.94 (± 0.09)	0.87 (± 0.07)
Apple-shaped [N (%)]	20 (41.6%)	29 (51.7%)
Systolic pressure (Mean ± SD)	134.36 (± 19.67)	132.28 (18.92)
Diastolic pressure (Mean ± SD)	82.99(± 9.09)	81.76 (± 8.51)
Prevalence of HT (History and/or exam^n)	16 (33.3%)	19 (33.9%)
Blood sugar fasting	155.7 (± 53.92)	173.6 (± 71.70)
Post-Prandial Mean (± SD)	243.4 (± 71.05)	250.9 (± 82.04)
HbA1c (mean ± SD)	7.43 (± 2.88)	7.42 (± 2.53)
HbA1c < 8.5	32 (66.6%)	41 (73.2%)
8.5 - 9.4	8(16.6%)	7 (12.5%)
>= 9.5	8 (16.6%)	8 (14.3%)
Total cholesterol* > =200 mg/dl	18 (37.5%)	26 (46.4%)
HDL Chol. < = 40 mg/dl	18 (37.5%)	24 (42.8%)
LDL Chol. > = 140 mg/dl	14 (29.2%)	16 (28.6%)
S. Triglycerides > = 150 mg/dl	23 (47.9%)	31 (55.3%)
Gross albuminuria	3 (6.2%)	2 (3.6%)
Microalbuminuria	16 (33.3%)	19 (33.9%)
Total albuminuria	19 (39.6%)	21 (37.5%)

Compared to females, significantly more male diabetic subjects were current smokers and alcohol consumers. 29.2% of the diabetic men were found to be currently smoking and/or consuming alcohol, 82% were involved in sedentary physical activity and 21.1% had family history of CHD. The mean triglyceride levels, nephropathy and hypertension were significantly higher among the male smokers compared to those who did not. Neither the anthropometric measurements nor the mean levels of total cholesterol, HDL, LDL and HbA1c varied significantly among the male smokers and non-smokers.

Central obesity was found to be much more prevalent than overall obesity, especially among females.

Approximately one-third of the patients in this study were hypertensive. Among these, 21 patients were diagnosed cases of hypertension at the beginning of study, with 9 patients inadequately controlled on treatment. 14 patients were detected to be hypertensive during the study period. Among hypertensive females, the mean values of BMI, WHR, total cholesterol, LDL and triglycerides was significantly higher. Also, nephropathy was significantly higher in hypertensive compared to the non-hypertensive females (69.2% vs 23.4%).

The hypertensive males had higher mean values of WHR, total cholesterol, LDL, triglycerides and HbA1c, with a significant p-value in all. The mean BMI values were also higher in hypertensive males, but p-values failed to achieve significance. 77.8% of hypertensive males had evidence of nephropathy compared to 28.0% of non-hypertensives.

15.4% of diabetic patients were found to have coronary heart disease. In these patients, the values of mean age, diabetes duration, weight, BMI, waist circumference, WHR, both systolic and diastolic blood pressure, blood glucose, total cholesterol, LDL, VLDL, triglycerides and HbA1c were significantly higher than in those without CHD.

Table II shows the prevalence of CHD in the study group.

Table II: Prevalence of CHD.

	Male, N = 48	Female, N = 56
RQ positive	8 (16.7%)	5 (8.9%)
Past history positive	2 (4.2%)	4 (7.1%)
ECG evidence of CHD	9 (18.7%)	5 (8.9%)
Total CHD	11 (22.9%)	5 (8.9%)

Table III shows the comparison of the biochemical features of the patients with and without CHD in the study group.

Table III: Comparison of the risk factors (Biochemical factors).

	Without CHD [N (%)]		With CHD [N (%)]	
	Female	Male	Female	Male
Chol. > = 200	20 (39.2%)	9 (24.3%)	4 (80%)	10 (90.9%)
HDL < = 40	18 (35.3%)	16 (43.2%)	4 (80%)	3 (27.2%)
LDL > = 140	12 (23.5%)	7 (18.9%)	3 (60%)	6 (54.5%)
TGs > = 150	27 (52.9%)	12 (32.4%)	3 (60%)	9 (81.8%)
HbA1c < 8.5	38 (74.5%)	27 (72.9%)	2 (40%)	6 (54.5%)
8.5 - 9.4	7 (13.7%)	4 (10.8%)	1 (20%)	3 (27.3%)
> = 9.5	6 (11.8%)	6 (16.2%)	2 (40%)	2 (18.1%)
Gross albuminuria	1(1.9%)	1 (2.7%)	1 (20%)	2 (18.1%)
Microalbuminuria	16 (31.4%)	11 (39.7%)	2 (40%)	7 (63.6%)
Total albuminuria	17 (33.3%)	12 (32.4%)	3 (60%)	9 (81.8%)

In patients with nephropathy, both males and females had higher mean values of WHR, BMI, total cholesterol, LDL, triglycerides and HbA1c, compared with those without nephropathy. Also, the prevalence of hypertension was much more common in patients with nephropathy than in those without. Table IV shows the regression analysis for the various parameters. Using logistic regression analysis microalbuminuria was found to be the best model and hence, the most significant predictor of CHD in either sex.

Table IV: Multiple logistic regression analysis dependent variable CHD.

Variable	Deviance	Model P-value	Variables Significance P-value
Age	219.7	0.0029	0.1992
Sex	219.7	0.0028	0.2052
Duration of DM	221.0	0.0024	0.5779
Smoker	208.6	0.0121	0.0010
Alcohol	219.8	0.0028	0.2054
WHR	200.2	0.0322	0.0001
BMI	219.6	0.0029	0.1817
HTN	213.5	0.0066	0.0078
CHOL >= 200	205.7	0.0172	0.0002
HDL <= 40	218.3	0.0034	0.0813
LDL >= 140	203.7	0.0217	0.0001
TGs >= 150	203.9	0.0214	0.0001
HBA1C	195.5	0.0039	0.0278
Microalbuminuria	148.1	0.8238	0.0000

Discussion

Cardiovascular disease is a common comorbidity in type 2 DM and its prevalence has been rising over time. Present study assessed risk factors in 104 type 2 DM patients, followed by comparison and correlation in patients with and/or without electrocardiographic and/or symptomatic evidence of coronary heart disease.

Various studies report widely variable prevalence of CHD among diabetics in India between 6.6% to 33%. This study reported prevalence as 15.4%. Among 104 patients, 56 were females and 48 were male patients. The mean age of all the participants was 53.16 ±7.61 years. The mean age in the CHD group was 56.9 ± 4.8 years and 52.6 ±8.32 years in non-CHD group. Males were commonly affected in the group with and without CHD. Mean age of females in the group without CHD was statistically significant in comparison to with CHD. The Rancho Bernardo study also proved that diabetic females had more classical cardiovascular risk factors than males and also how diabetes eradicates female cardio-protection[9].

Present study also showed significantly higher incidence of the CHD in cases with sedentary work style. Compare to female, significantly more male diabetic subjects were current smokers and alcohol consumers. The family history of DM, hypertension, cerebrovascular accident, and CAD was found to be significantly higher in group with CHD. Similar results have been reported by various studies conducted across India[10,11].

Mean duration of diabetes was around 8 years, slightly higher in females than males. Mean duration of DM of males in the group without CHD was statistically significant in comparison to the CHD group.

55% cases of stable angina, 28.3% cases of unstable angina and 16.7% cases of cerebrovascular accident were identified. Only 15% patients presented with diabetic retinopathy. This observation strengthens the view that, macrovascular complications are duration independent, whereas microvascular complications are duration dependent.

Mean BMI in this study was 21.8 (±4.32) [among males, 21.3 (±3.64) and among females 22.2 (±4.20)]. 14.4% of the patients had BMI greater than 25. The relationship between obesity and diabetes is widely known. DM epidemic can be attributed to the increasing incidence of obesity. It is estimated that about 60 - 90% of all type 2 DM patients are obese (BMI > =30 kg/m2) or overweight (BMI > = 25 kg/m2).

The significance of BMI as an index of obesity has been downgraded with the advent of waist-hip ratio (WHR) for the measurement of regional (central) obesity. It is known by various Indian migrant studies[12,13] that, increased W:H ratio and thus central obesity was very common among diabetic people of Indian origin. It acts as a risk factor for CAD, even in the absence of other risk factors. The mean BMI and WHR of the patients with CHD were observed to be higher than the patients without CHD in this study.

In the study conducted by McKeigue[1] involving South Asian migrants in UK, it was found that these population had higher mean WHR confirming the existence of an insulin resistance syndrome as compare to the European group. Such higher incidence of central obesity leading to diabetes and coronary artery disease resulted in high mortality in South Asians. In UKPDS[14], the WHR for men and women was respectively 0.95 ±0.06 and 0.87 ± 0.08. Hence, presence of central obesity is an important risk factor for people of Indian origin than Western people.

The present study showed prevalence of hypertension in diabetics as 33.6%. Also, the prevalence of hypertension was much more common in patients with nephropathy (77.8%). In the patients with coronary heart disease, the values of mean systolic and diastolic blood pressure were significantly higher than in those without CHD. Venugopal *et al*[15] reported prevalence of hypertension as 25.6% in type 2 DM patients. Hypertension is generally attributed to hyperinsulinemia in diabetics, with resulting increase in renal sodium retention and sympathetic nervous system activity. It is well known that presence of hypertension along with diabetes increases the complications and two fold rises in cardiovascular related mortality.

Lipid abnormalities were widely prevalent in this study, especially hypertriglyceridaemia (51.9%) was found to be the major type of dyslipidaemia. Studies in China and other Asian countries have shown similar results in type 2 DM.[16,17] High cholesterol (>200 mg%), high LDL (>140 mg%), low HDL (< 40 mg%) and high triglycerides (>150 mg%) had a prevalence of 87.5%, 56.2%, 43.7% and 75% in CAD group, respectively as compared to non-CAD group, who had prevalence of 32.9%, 21.6%, 38.6% and 44.3%, respectively. The Strong Heart Study by Lee *et al*[18] reported adult diabetics with high TG and low HDL levels had 1.54-fold greater HR (95% CI 1.15 - 2.06) for CHD (P value 0.003) than non-diabetic adults. Milan study[19] reported statistically significant correlation of serum triglyceride ($p = 0.002$) and serum cholesterol ($p < 0.014$) levels with silent CAD17 while, Gazzaruso *et al* found a correlation of mean serum HDL and silent CAD ($p < 0.05$)[20].

Increased prevalence of microalbuminuria has been consistently reported to occur in diabetic individuals. Microalbuminuria was found in 33.6% of patients in this study. The appearance of microalbuminuria in diabetic patients predict development of coronary artery disease

and macroalbuminuria. Patel *et al*[21], Taneja *et al*[22], Jadhav *et al*[23] observed prevalence of microalbuminuria ranges from 25% to 35%. Various researchers have reported higher prevalence of microalbuminuria in Indians compared to other ethnic groups.

This study has also brought out a significant association of microalbuminuria with body mass index, in the 15 patients with BMI of more than 25, 8 had microalbuminuria (53.33%). Similar findings have been brought forth by other studies[22,23].

The incidence of microalbuminuria was significantly associated with the presence of ischemic heart disease (p = 0.011), hypertension (p = 0.001) and body mass index (p = 0.027) more than 25 kg/m^2. It was also well known that retinopathy and microalbuminuria have a high concordance rate. Several studies have highlighted the occurrence of microalbuminuria as a marker of ischemic heart disease. This study also underscored this point. 56.3% of the patients with CHD had microalbuminuria in this study.

Summary

This study revealed significant prevalence of both CHD (15.4%) and coronary risk factors in type 2 DM subjects. Also, the prevalence of CHD increased with age and duration of diabetes in this study.

Mean duration of DM was 8.3 years in the group without CHD and 10.8 years in the group with CHD. Mean duration of DM of males in the group with CHD was statistically significant in comparison to the non-CHD group.44.4% of male were smoker in the group with CHD; was statistically insignificant in comparison to the non-CHD group.

The relationship between obesity and diabetes is widely known. 14.4% of the patients had BMI greater than twenty-five. The mean WHR in this study was 0.9 while employing the standard method. The mean BMI and WHR of the patients with CHD (24.8 and 0.98 respectively) were observed to be higher than the patients without CHD (21.1 and 0.84 respectively). There was a significant higher mean HbA1c among the CHD group (8.37) compared to non-CHD (7.74) which is statistically significant.

In this study, hypertension was prevalent in approximately 1/3rd of the diabetics. Diabetic dyslipidaemia is a recognised entity. Present study revealed hypertriglyceridaemia (51.9%) and low HDL-C levels (40.3%) as major types of dyslipidaemia in type 2 DM subjects.

Microalbuminuria tended to be 2.54 times more common in the age group of above 50 years as compared to the age group of less than 50 years. This study has also brought out a significant association of microalbuminuria with body mass index of more than 25 kg/m^2 of the 15 patients with BMI of more than 25, 8 of them had microalbuminuria (53.3%). Out of the total 35 patients with microalbuminuria, 15 of them had ischemic heart disease. Using logistic regression analysis microalbuminuria was found to be the best model and hence the most significant predictor of CHD in either sex.

Conclusion

There was a high prevalence of both CHD and coronary risk factors in the type 2 DM subjects. Even modifiable standard risk factors such as smoking (14.4%) and sedentary working (82.7%) habits were prevalent in a significant proportion of the case. Although overall obesity (30.5%) was not so common among Indian type 2DM patients, the prevalence of central obesity (78.8%) was found to be considerably high.

Diabetic dyslipidaemia was commonly present with hypertriglyceridaemia constituting the most common abnormality present in about half the cases (51.9%). Microalbuminuria was prevalent in a significant number of these cases (33.6%). Serum cholesterol (p = 0.000004) LDL (p = 0.00003), HbA1c (p = 0.002), microalbuminuria (p = 0.000006) and hypertension (p = 0.00006) were all significant predictors of CHD in both the sexes. Among the female T2DM cases, Waist-hip ratio (WHR) (p = 0.003) and low HDL level (p = 0.008) are important correlates of CHD. However, if confounding between variables was taken into consideration then microalbuminuria alone appeared to be the best model for CHD prediction.

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ORIGINAL ARTICLE

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The Clinico-Radiological and Pathological Profile of Lung Cancer Patients Exposed to Indoor Pollution by Cooking Fumes

Ramesh Singh Pal, Ram Babu Sah**, Mahismita Patro**

Abstract

Background: Incidence of lung cancer is increasing in the developing world. Combustion byproducts from heating and cooking are major sources of indoor air pollution causing lung cancer in non-smokers. Predominance of adenocarcinoma due to cooking fumes exposure, shown in Chinese and western literature, but lacking in India.

Methods: This is an observational cross-sectional study conducted on lung cancer patients, caused by cooking fumes exposure. Detailed information was taken about duration of cooking, frequency of frying, fuel used for cooking and cooking oil used. Type and size of kitchen with use of exhaust fan/fume extractor were also recorded.

Results: Total seventy lung cancer patients, 37 (52.8%) male and 33(47.2%) female, histologically proven, exposed to cooking fumes were enrolled. Their mean age was 56.88 years.bbbbAdenocarcinoma was seen in 34 (48.57%), followed by squamous cell carcinoma (SCC) 8 (11.42%) and small cell carcinoma in 6 (8.57%). Cumulative effects of cooking fumes exposure and its relationship with histopathology of lung cancer was evaluated. On comparing cooking time years, less than 40 years with more than 40 years, significant predominance of adenocarcinoma (20/14) noted over non-adenocarcinoma group (9/3, p < 0.043).

Significant predominance of adenocarcinoma was seen in kitchen smokiness group on comparison with non-smokiness group (p < 0.053).

Conclusions: Exposure of fumes, generated by burning of cooking fuel and heating of cooking oil are linked with adenocarcinoma lung. Awareness for use of clean fuel, cooking at lower temperatures and installing a suitable kitchen fume extractor is useful.

Key words: Cooking fumes, cooking oil-fumes, adenocarcinoma, smokiness.

Introduction

According to GLOBOCON 2020 report, lung cancer is responsible for 18% of all cancer related death[1]. It is well known that cigarette smoking is the major cause of lung cancer, but previous studies have demonstrated that worldwide 15% of male patients and 53% of female patients with lung cancer were not due to smoking[2]. Asian women have a relatively high lung cancer rate compared to women of other ethnicities, despite low prevalence of smoking[3]. Cigarette smoking alone cannot fully explain the high incidence rates of lung cancer among women[4].

Indoor air pollution is a public health problem in both developed and developing countries[5], and it played a critical role in the development of lung cancer among non-smoking females[6]. In recent years, indoor particulate matter (PM 2.5), housing characteristics, home passive smoking exposure, indoor air pollution, cooking oil fume exposures, and previous respiratory diseases have been demonstrated as the causes of lung cancer[7]. Combustion by products from heating and cooking is one of the major sources of indoor air pollution[8]. Studies in the past have shown that long-term exposure to cooking oil fumes (COFs) may be linked to lung cancer[9-14] and may increase the risk of lung cancer[15,16]. A previous meta-analysis also supports an association between cooking oil fumes and a high-risk of lung cancer among Chinese non-smoking women[17].

In the present study, we investigated the association between lung cancer and fumes emitted from Indian style cooking among adults using a composite index for lifetime cumulative exposure and taking into account the influence of various potential confounding factors. We evaluated possible associations between heating and cooking oil fumes sources, and the lung cancer with its histological typing.

Material and Methods

This is a observational cross-sectional study conducted over a period of six years (from 2014 to 2020) on patients who attended outdoor patient department of Pulmonary

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Medicine at ESI-PGIMSR Hospital, Basaidarapur, New Delhi. Histologically confirmed cases of lung cancer were included in the study.

All subjects had verbally agreed individually to participate in the study. Having assured the confidentiality of all information about the subjects, patients were interviewed face to face in the presence of their close relatives. Details were recorded in a structured questionnaire at the time of the interview. The questions were asked in Hindi and answers given by the patients in Hindi were recorded in English in the proforma (Proforma attached). Information about their education, occupation, income, family history of cancer, present and past medical history, diet pattern, smoking habit, history of alcohol intake, present and past heating and cooking system at home, exposure to any environmental pesticides/carcinogens, were obtained. Detailed history of cooking was taken as number of cooking years, frequency of frying, fuel of cooking used for heating like coal, gas, kerosene and wood. Information about type of cooking oil used like peanut, mustard, coconut, and refined was collected. Type and size of kitchen as closed or open, small or medium and use of exhaust fan/fume extractor were also recorded. Eye irritation during frying as rare or frequent were noted. Smog formation or smokiness during frying was also recorded. For each participant who had cooked at least six months continuously were included. We evaluated the cumulative exposure to COFs through an index of cooking time-years, defined as follows: cooking time-years = Órdr× yr, where dr = average daily times of cooking, and yr = years of cooking. A smoker was defined as someone who smoked at least 100 cigarettes in his or her lifetime; a former smoker was defined as someone who stopped smoking at least one year before the interview.

Results

Total 70 cases of histologically proven lung cancer were enrolled in our study, including 37 (52.8%) male and 33 (47.2%) female. Majority of patients were from lower socio-economic class. They all were having exposure to indoor air pollution by cooking at home or at workplace. The baseline characteristics of these 70 patients are shown in Table I. Their mean age was 56.88 years. About 65.71% of our patients (31 male and 15 female) had smoking history with 31.42% current smokers and 34.2% ex-smokers. The mean pack years of smoking was 25 including 18 for females and 28 for male. Average age of starting smoking was 19.97 years. Passive smoking exposure was found in 37 patients (52%).

The most common presenting symptoms were cough (72.85%) and chest pain (65.71%). The other symptoms were anorexia 50.29%, weight loss 47.95%, breathlessness 38.01% and haemoptysis in 31.57% patients. Average duration of symptoms were cough since 5.04 months, chest pain since 4.22 months, anorexia since 3.34 months, weight loss since 3.5 months, breathlessness since 4.3 months and haemoptysis since 4.45 months. Ten (14%) patients had history of other chronic respiratory diseases. The common associated respiratory diseases were COPD and tuberculosis. The other systemic medical diseases were seen in 20 (28%) cases. The family history of cancer was present in 7 (10%) cases.

On histopathology, adenocarcinoma was seen in 34 (48.57%) of our patients followed by squamous cell carcinoma (SCC) 8 (11.42%) and small cell carcinoma in 6 (8.57%). Cancer histological sub-typing was not established in 22 cases (31.42%). Regarding location of tumours, 41.42% cases had central location of tumour whereas 44.42% had peripheral location.

Table I: Baseline characteristics of patients with cooking fume exposure (CFO).

Characteristic (N = 70)	Number (%)
Age in years (mean ±SD)	56.88 ± 13.06
Gender	
Male	37 (52.8%)
Female	33 (47.2%)
Smoking status	
Non smoker	24 (34.28%)
Current smoker	22 (31.42%)
Former smoker	24 (34.28%)
Mean years of cooking	22.81 ± 12.74
Mean cooking-time years	59.07 ± 7.18
Fuel used for cooking	
Coal	5 (7.14%)
Gas	36 (51.42%)
Kerosene	15 (21.42%)
Wood	14 (20.00%)
Type of kitchen	
Closed	41 (58.57%)
Open	29 (41.42%)
Cooking oil used	
Peanut oil	03 (4.28%)
Mustard oil	42 (60%)
Coconut oil	01 (1.4%)
Refined oil	24 (34.28%)
Presence of family history of cancer	7 (10%)
Presence of industrial occupational exposure	31(44.28%)
Histopathological type	
Squamous cell carcinoma	8 (11.42%)
Adenocarcinoma	34 (48.57%)
Small cell carcinoma	6 (8.57%)
Others/sub-typing not available	22 (31.42%)
Location of lesion	
Peripheral	31 (44.28%)
Central	29 (41.42%)
Others	10 (14.28%)

Table II: Various COFs exposure parameters in relation to lung cancer histopathology.

Characteristic	Adenocarcinoma	Non-adenocarcinoma	P value
Cooking time years (N = 46)			
≥ 40	14	9	
> 40	20	3	0.043
Mean cooking time years	64.79 ± 6.81	51 ± 7.25	0.372
Smokiness while cooking (smog) (N = 48)			
Frequently	30	9	
Never	4	5	< 0.053
Location of lesion (N = 40)			
Peripheral	18	3	
Central	11	8	< 0.049

Table III: Relationship of histological type among females with exposure to only cooking fumes and total cases.

	Female cases (N = 12)	Total (available histopathology) cases (N = 48)	P value
Adenocarcinoma	12	34	
Non-adenocarcinoma	0	14	0.051

Discussion

Majority of patients in our study were exposed to traditional heating and cooking sources when they were much younger, especially those who grew up in rural areas. Till early 2016, around 43% of the Indian population were dependent on solid fuels for cooking, heating, and other household energy services[18]. Residential cooking contributes 20 - 50% of all household PM 2.5 emission across all districts in India. Largest (> 100 μg m^{-3}) exposure of PM 2.5 observed over the Delhi/National Capital Region (Delhi/NCR)[19]. A European cohort study indicated that PM 2.5 exposure increased the risk of lung cancer, particularly lung adenocarcinoma[20].

In cooking activities, both combustion of fuel and heating of cooking oil produce carbonyl compounds. Cooking oil fumes (COFs) are mainly composed of two types of chemical compounds, including polycyclic aromatic hydrocarbons and aldehydes[21].

In this study, we used a composite index, "cooking time-years," to measure the magnitude of exposure to COFs, combining both cooking frequency (cooking times per day) and duration (years). This is a composite measurement to combine both cooking intensity and length. Similar measurement has been used in previous study[22].

The cumulative effects of cooking fumes exposure and its relationship with histological typing of lung cancer had been documented in the past. On comparison of cooking time years less than 40 years with more than 40 years (Table II), significant predominance of adenocarcinoma (20/14) noted over non-adenocarcinoma group (9/3, p < 0.043) in our study which is consistent with the previous studies[23].

In our study, the role of COFs in lung carcinogenesis has been significantly proven on comparison of COF exposed, non-smokers, with COFs exposed smokers. After excluding the occupationally exposed cases of lung cancer, we compare the COF exposed 17 non-smokers with remaining 17 COF exposed smokers. We found that cooking time years was more (66.22) in non-smokers than (45.23) in smokers (p < 0.0301). After excluding the smoking and occupation as confounders in COFs exposed non-smokers group, more cooking time years indicates the possible role of only COFs in development of lung cancer.

Studies in the past have shown that women who waited to cook (stir fry, fry, and deep fry) food until the cooking oil has reached the high temperature had an independently higher risk of adenocarcinoma, but not of squamous/small cell carcinoma[24]. Methanolic extract of heated COFs can apparently lead to cytotoxicity and oxidative DNA damage in human lung carcinoma pulmonary type II-like epithelium cells causing adenocarcinoma[15]. Recently a large number of in vivo studies have revealed the mechanism by which COFs improve lung adenocarcinoma cell survival[7]. A study done in Hongkong among non-smoking women had found strong evidence that cumulative exposure to cooking by means of any form of frying could increase the risk of lung cancer[25].

Smokiness (smog formation) during frying occurs on cooking with heavy temperature. Experimental studies have shown that temperature is the most important factor for mutagen formation[25,26]. Over 50 volatile organic compounds have been identified from heated oil as well as cooked foods, and some of these agents in emissions of cooking oils are mutagens and human carcinogens, such as 1,3-butadiene, benzene, benzo(a)pyrene, dibenzo (a, h) anthracene, acrolein, and formaldehyde[27-32].

We have investigated the relationship between cooking habits and histological typing. Out of 70 cases, 51 reported frequent smokiness during their daily cooking while 19 denied. In 51 cases with frequent exposure to smokiness (smog) while cooking, 39 were proved histologically as lung cancer, out of which 30 were adenocarcinoma and 9 were non-adenocarcinoma. In other group (non-smokiness) of 19 patients, only 9 cases were proven histologically (4 adenocarcinoma and 5 non-adenocarcinoma). On comparison with non-smokiness group, significant (p < 0.053) predominance of adenocarcinoma was seen in smokiness group.

In a study comparison to smokeless cooking, both normal exposure and above-average exposure to COFs were significantly associated with lung cancer[33]. Prolonged cumulative exposure of COFs causes predominant development of adenocarcinoma lung cancer documented in previous studies, has been proved in our study also.

After excluding the occupation and smoking as confounder in our study cases, we have evaluated the relationship between cooking fumes exposure and histological typing of lung cancer in females. We found only 12 female lung adenocarcinomas cases, without any non-adenocarcinoma case. (Table III). On comparison of these 12 adenocarcinomas with total histologically proven 34 adenocarcinoma cases and 14 non adenocarcinoma, statistically significant evidence shows that non-smoker females develop more adenocarcinoma on cooking fumes exposure. (p value < 0.032), as noticed in previous Indian study also[34].

Kitchen size was small in 50 (71.42%) and medium in 20 (28.51%) cases. Kitchen was closed in 41 (58.57%) and open in 29 (41.4%). Most of our cases cooked in small and closed kitchens. Effect of COFs with or without smokiness is more in small and closed kitchens. In an Indian study, cooks cooking in the open outdoors, experience lower exposures compared to those in enclosed kitchens[35]. Proximity to the stove during cooking times is thus a good indicator of exposures for both men and women non-cooks, who stayed at home during cooking. The results of that study had shown that living area concentrations in households with kitchens without partitions are often greater than kitchen concentrations. This would put young children and the elderly, in addition to the cooks, at high-risk of suffering adverse consequences, as they are most likely to be indoors during cooking times.

In our study more than half the patients cooked food on gas stoves and one-fifth on kerosine and one-fifth on wood. A study was also shown that cooking with wood for prolonged periods is a risk for development of adenocarcinoma[24]. Potential carcinogen formaldehyde and benzo(a) pyrene has been found in wood charcoal[36]. Prolonged past exposure to coal fumes due to poor kitchen ventilation increases the risk of lung cancer[37].

On radiological investigations, location of lesion was ascertained in 40 cases with the help of chest radiograph and computerised tomography of thorax (Table II). Peripheral located lesion was seen in 18 adenocarcinoma group and 3 in non-adenocarcinoma group. While 11 adenocarcinoma cases were centrally located and 8 non adenocarcinoma group, statistically significant (p > 0.049) predominance of lung cancer lesion in peripheral location seen in adenocarcinoma group in our study is similar to the previous studies.

Limitations of the study

One of the major limitations of our study is the small sample size and enrolled patients were from a confined region, i.e., Delhi/NCR. Another limitation of our study was smoking as confounding factor. Some diagnosed lung cancer cases were migrants from rural areas from surrounding states of Delhi/NCR and they livea alone in a single room. They also used this single room for cooking food and had a prolonged exposure of indoor air pollution due to cooking fumes exposure. Many subjects were initially exposed to wood, coke at open kitchen in rural areas and then kerosine, LPG in closed small kitchens during their stay at Delhi/NCR.

Conclusion

Indoor air pollution due to heating and cooking at home is a global problem, causing various diseases including lung cancer. Cooking oil fumes are linked to adenocarcinoma, a commonly occurring lung cancer. Awareness for use of clean fuel, changing cooking habits, or cooking at lower temperatures and installing a suitable well designed fume extractor in the home kitchen should be encouraged. Provision of large kitchen should be focussed to prevent the lung cancer.

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ORIGINAL ARTICLE

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Spectrum of Post-Covid-19 Syndrome – Post-Hospitalisation Covid-19 Study

Manoj Saluja, Deelip Meena**, Gaurav Bhargava**, Saurabh Chittora***, Hemant Vimalani***, Chetan P Suman**, Prakarsh Sharma****, Sidharth Sharma*****

Abstract

Backgrounds: Covid-19 pandemic has affected large population across the globe. As the cases around the world rise, Covid-19 related complications are also reported from various areas of the world. Pulmonary complications are mostly reported all over the world. In this review, we emphasized the pulmonary functions in Covid-19 survivors.

Objectives: To determine the impact of Covid-19 on pulmonary functions and analysis of possible lung damage in long-term after covid recovery.

Methods: Study includes lab-confirmed RT-PCR positive, both discharged and home-isolated from Tertiary Care Centre New Medical College and attached Hospitals, Kota. All subjects were to undergo 6-min. walk test (6MWT) and included only those patients for Pulmonary Function Test who could perform 6MWT.

Results: 109 men and 57 women with age range, 21 to 77 years from the 166 subjects. Among these, 71 (42.77%) were discharged from hospitals and 95 (57.23%) were home-isolated. The predicted FVC% was 92.83 ± 12.42, predicted FEV1% 89.94 ± 12.71 and FEV1/FVC% predicted was 98.30 ± 14.13. 6MWT walked distance was 540.50 ± 2.40. 69 subjects (41.57%) faced fatigue during 6MWT. FEV value was significantly($p < 0.05$) higher for hospitalised patients compared to home-isolated patients. The mean FVC value was higher for home-isolated patients compared to hospitalised patients ($p < 0.05$). 23% of study subjects showed restrictive and 7.2% had obstructive pattern while 70.5% had normal PFT.

Conclusion: Covid-19 patients showed compromised respiratory functions, mainly restriction in close to 23% and obstruction in 7% of patients. PFTs explain the possible lung damage by Covid-19.

Keywords: Covid-19, pulmonary function test, 6-minute walk test (6MWT).

Introduction

People across the globe are facing the second wave of the pandemic declared by the World Health Organisation on 11 March 2020, as coronavirus disease 2019 (Covid-19)[1]. Approximately 105.4 million cases have been reported with around 2 million deaths worldwide[2]. India has faced 20.4 million cases overall with 2.62 lac deaths till now[3]. The rate of admission in hospitals due to COVID infection is around 20% which includes 6% in critical care units[4].

Cough, fever, fatigue are the most common presenting symptoms, but body aches, dyspnoea, nausea, vomiting, diarrhoea, headache were also observed in certain subsets – especially in the second wave of the pandemic. Involvement of lungs is in the form of bilateral diffuse lung lesions identified as Covid-19 pneumonia with consequent respiratory failure or acute respiratory distress syndrome (ARDS)[5].

Early studies of Covid-19 suggest that lungs are the organs that are most damaged by Covid-19 in the form of pulmonary consolidation, hyaline membrane formation, alveolar septal fibrous proliferation, and capillary damage. These changes in the lungs result in alveolar remodelling which leads to lung fibrosis and pulmonary hypertension[6].

These findings suggest that direct colonisation, as well as indirect involvement of lungs by Covid-19, may have long-term or permanent effects and this makes it necessary to objectively assess the magnitude and severity of long-term lung injury and its impact on the quality of life of recovered covid cases including those discharged after hospitalisation and those treated in home-isolation.

Methods

We conducted a cross-sectional observational study to assess the long-term impact of Covid on lung functions and capacity in patients. This study was approved by the institutional ethics committee of New Medical College and

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Our case series includes a total of 166 patients, both discharged and home-isolated from a tertiary care center – New Medical College and attached Hospitals, Kota, between September 1st, 2020, to February 10th, 2021. Contact information of subjects was obtained from the central registry. Subjects were contacted telephonically and those who showed willingness and consented to participate were invited to post-covid OPD. They were screened and those who fulfilled the inclusion criteria were included in the study. Written informed consent from the subjects was obtained.

Inclusion criteria were a lab-confirmed RT-PCR positive report from nasopharyngeal swab according to CDC criteria, age between 18 years to 70 years, history of hospitalisation or treatment in home-isolation 2 months ago or more.

Patients with any gross chest deformity, prior respiratory, cardiac, mental, or neurological illness, BMI > 28 kg/m^2, current or past smoking were excluded from the study.

All participants were subjected to a standard respiratory disease questionnaire administered by a single interviewer. Leading questions were avoided, and the response was recorded objectively.

All study subjects were to undergo 6-minute walk test (6MWT) which was done following the ATS guideline. We included only those patients for PFT who could perform 6MWT with moderate severity according to the modified Borg Dyspnoea Scale.

6-minute walk test

A classic 6-minute walk test (6MWT) as described in the American Thoracic Society statement was used to assess the one-time functional status of the patient. The principle of the 6-minute walk test in Covid-19 is to identify patients who are not hypoxic at rest but become hypoxic (silent hypoxia) on a 6-minute walk test. The 6MWT provides evidence of hypoxia defined as SpO2 less than 94% or an absolute drop in SpO2 by more than 3% from baseline during or at the end of the test. The test was done in all patients who were not hypoxic or short of breath at rest. The test was stopped if the subject became hypoxic at rest SpO2 < 94%, developed shortness of breath at rest, and was not able to walk unassisted. Walk test interpretations were done following ATS guidelines. The patient's performance was evaluated in terms of four parameters, i.e., distance walked in 6 minutes, development of dyspnoea and fatigue, heart rate response, and fall in oxygen saturation.

We took 20 healthy controls of different age and sex groups for 6MWT to serve as a reference population.

Pulmonary function test

Pulmonary function tests were performed using MIR (Medical International Research) 'Portable Spirolab 3' spirometer. The subject's age, sex, and height were recorded and entered into the spirometer to obtain predicted curves and values. Forced expiratory volume in the first second (FEV1), forced vital capacity (FVC) and FEV1/FVC ratio were included in the analysis. For each subject, lower limit of normality (LLN) values for FEV1, FVC, and upper limit of normality (ULN) values for FEV1/FVC were taken after the subject's best effort. The test was administered by single medical personnel who ensured correct performance of forced expiration. If any subject was on bronchodilator therapy, that was withheld for 12 hours before PFT. Subjects were made comfortable and preferably had recently emptied their bladder before the performance as the procedure could cause urinary incontinence. Ideally, they are seated for the procedure to avoid the small risk of syncope.

All possible precautions were observed to minimise any cross-infection via the spirometer. We used low resistance barrier filters and disposable mouthpieces to reduce the risk of infection and to protect the equipment from exhaled secretions. A new filter was used for each patient. To protect laboratory staff and health professionals, lung function tests were performed in a room with a negative pressure setting. Staff wore personal protective equipment, including N95 respirators, protective glasses, gloves, and gowns.

Statistical methodology

Statistical analysis was performed using Statistical Package for Social Science (SPSS) Version 22.0. Quantitative Continuous variables data were expressed as mean ± standard deviation whereas Quantitative discrete variables data were expressed as frequencies are expressed as numbers (%). The qualitative data were expressed in Medians with interquartile ranges. The Student's t-test and x2-test were used to compare the difference for means between two or more than two groups or to compare categorical variables, while continuous variables were compared using the Mann- Whitney U test. All statistical tests were two-tailed. Statistical significance was taken as $p < 0.05$.

Results

Enrolled Covid-19 patients

This study involved a total of 166 patients for the study sample. Patients having respiratory and coronary artery disease were excluded. Twenty normal subjects were taken for 6 MWT as controls. The mean duration was 2 months and more (3.9 ±

1.22 months) after successful treatment of Covid-19 in both groups. There were 109 men and 57 women with a mean age of 41.27 ± 14.08 years (age range, 21 to 77 years). Among the 166 subjects, 71 (42.77%) had a history of hospitalisation and were discharged from various wards or intensive care units of the dedicated Covid-19 centre of Medical College, Kota, and 95 (57.23%) had been treated in home-isolation. 39 (23.49%) patients had pre-existing illnesses. These included hypertension (3 patients), diabetes (15 patients), hypothyroidism (20 patients), CVA (1 patient).

The predicted FVC% was 92.83 ± 12.42, predicted FEV1% 89.94 ± 12.71 and FEV1/FVC% predicted was 98.30 ± 14.13. 6MWT walked distance was 540.50 ± 2.40. 69 subjects (41.57%) faced fatigue during 6MWT.

Table I: Baseline characteristics of Covid-19 patients.

Clinicopathologic factors		total (N=166)
Gender	Male	109 (88%)
	Female	57 (12%)
Age, yr.	Mean ± SD	41.27 ± 14.68
	Range	(21 - 77)
Hospitalised	Yes	71 (42.77%)
Home-isolation	Yes	95 (57.23%)
Duration after disease	Mean in months	3.9 ± 1.22
Co-morbidity	CVA	1 (0.6%)
	Hypothyroidism (HT)	20 (12.04%)
	T2DM	15 (9.04%)
	HTN	3 (1.8%)
	No	127 (76.50%)
FVC% predicted	Mean SD	92.83 ± 12.42
	Range	(66 - 122)
FEV1% predicted	Mean SD	89.94 ± 12.71
	Range	(60 - 139)
FEV1/FVC% predicted	Mean ± SD	98.30 ± 14.13
	Range	(55 - 122)
6MWD	Mean ± SD	540.50 ± 2.40
	Range	(450 - 600)
Fatigue	Yes	69 (41.57%)

Table II: Age wise distribution of Covid-19 patients.

Age	Case crequency (N = 166)	Percentage
< 20	0	0.0%
21 - 30	54	32.5%
31 - 40	42	25.3%
41 - 50	16	9.6%
51 - 60	33	19.9%
61 - 70	15	9%%
71 - 80	6	3.6%
Total	166	100.00%

The table indicates that a maximum (32.5%) of subjects are in the age group 21 - 30 years.

Pulmonary function test

The mean Forced Expiratory Volume (FEV) value is higher for hospitalised patients compared to home-isolated patients. The mean difference in FEV value was found statistically significant as the p-value is less than 0.05. The mean Forced Vital Capacity (FVC) value is higher for home-isolated patients compared to hospitalised patients. The mean difference in FVC value was found statistically significant as the p-value is less than 0.05.

The table shows a comparison between hospitalised and home-isolated patients PFT.

Table IIIA: Comparison between hospitalised and home-isolation patients.

Variable	Hospitalised 71 (42.77%)	Home-isolation 95 (57.23%)	t-Test value	Chi-square test/U test	p value
Age (Years)	46.87 ± 13.80	37.08 ± 13.97	3.545		< 0.0001
Sex, Male	48 (67.60%)	61 (64.21%)		0.2077	0.6485
Co-morbidity	22 (30.98%)	11 (11.57%)		9.6082	0.0019
FVC% predicted	88.46 ± 11.65	96.09 ± 12.02	4.098		0.0000
FEV1% predicted	97.53 ± 9.45	91.75 ± 14.47	2.13		0.0171
FEV1/FVC% predicted	100.4 ± 13.59	96.74 ± 14.39	1.646		0.1015

Table IIIB: Comparison between hospitalised and home-isolation patients.

Hospital duration among hospitalised subjects	Total subjects	Restrictive pattern in PFT	Obstructive pattern in PFT	Total (compro-mised lungs)	Chi-square Test	p value
< 5 days	15	3	1	4 (26.6%)	1.3471	0.245777
5 - 10 days	21	7	3	10 (47.6%)	31.0495	< 0.00001
> 10 days	35	16	5	21 (60%)	26.6338	< 0.00001
Home-isolated	95	11	3	14 (14.7%)		
Total	166	37	12	49 (29.51%)		

Table IV: Distribution of lung pathology in the subjects.

Severity remark	Case frequency (N = 166)			Percentage %
	Male	Female	Total	
Normal	75	42	117	70.5%
Restrictive	25	12	37	22.3%
Obstructive	9	3	12	7.2%

Pulmonary function tests of 23% of study subjects showed restrictive pattern whereas 7.2% of subjects had

obstructive pattern. 70.5% of subjects had normal pulmonary function tests.

Table VA: Sex-wise distribution of compromised lungs.

Gender	Case frequency (N = 166)	Number of patient with restrictive lungs	Chi square value	P value
Male	109	25	0.077	0.781
Female	57	12		
Total	166	37		

Table VB: Sex-wise distribution of compromised lungs.

Gender	Case frequency (N = 166)	Number of patient with obstructive lungs	Chi square value	P value
Male	109	9	0.5	0.479
Female	57	3		
Total	166	12		

Table VC: Sex-wise distribution of compromised lungs.

Gender	Case frequency (N=166)	Number of patient with compromised lungs (Restrictive + Obstructive)	Chi square value	P value
Male	109	34	0.428	0.512
Female	57	15		
Total	166	49		

Out of total 166 subjects, 49 subjects had compromised lung function parameters. 34 males and 15 females had compromised pulmonary function tests. Among affected males, 25 had restrictive and 9 had obstructive pattern whereas among affected females 12 females had restrictive and 3 females had an obstructive pattern in PFT.

Table VIA: Age-wise distribution of lung function tests.

Age	Case frequency (N = 166)	Number of patient with restrictive lungs	T value	P value
21 - 30	54	5	22.756	0.0003
31 - 40	42	5		
41 - 50	16	4		
51 - 60	33	12		
61-70	15	8		
71 - 80	6	3		
Total	166	37		

Table VIB: Age-wise distribution of lung function tests.

Age	Case frequency (N = 166)	Number of patient with obstructive lungs	T value	P value
21 - 30	54	0	32.922	0.000
31 - 40	42	1		
41 - 50	16	0		
51 - 60	33	4		
61 - 70	15	4		
71 - 80	6	3		
Total	166	12		

Table VIC: Age-wise distribution of lung function tests.

Age	Case frequency (N = 166)	Number of patient with compromised lungs (restrictive + obstructive)	T value	P value
21 - 30	54	5	53.9	0.000
31 - 40	42	6		
41 - 50	16	4		
51 - 60	33	16		
61 - 70	15	12		
71 - 80	6	6		
Total	166	49		

Subjects from all age groups had altered pulmonary function tests. However, those in the 51 to 60 years age group were the most affected showing both types of lung compromise. Younger age group subjects had a significant compromise. When further explored across various age categories this pattern of pulmonary compromise achieved statistical significance.

Table VII: Mean FVC% predicted in subjects.

Age	Case frequency (N = 166)	Mean FVC% predicted	F Value	P Value
21 - 30	54	96.16 ± 11.65	2.4710	0.034
31 - 40	42	94.83 ± 12.17		
41 - 50	16	89.12 ± 8.85		
51 - 60	33	98.42 ± 12.27		
61 - 70	15	87.46 ± 14.97		
71 - 80	6	90.83 ± 15.60		
Total	166			

There is a significant difference in the mean FVC% predicted value concerning different age groups.

Similarly, there was a significant decline in the mean FEV1% from predicted value across different age groups.

Table VIII: Mean FEV1% predicted in subjects.

Age	Case frequency (N=166)	Mean FEV1% predicted	F Value	P Value
21 - 30	54	96.51 ± 12.43	15.5883	0.0000
31 - 40	42	94.78 ± 10.90		
41 - 50	16	87.62 ± 4.52		
51 - 60	33	82.18 ± 8.44		
61 - 70	15	77.60 ± 10.32		
71 - 80	6	76.66 ± 12.50		
Total	166			

Table IX: Mean FEV1/FVC% predicted in subjects.

Age	Case frequency (N = 166)	Mean FEV1/FVC% predicted	F value	P value
21 - 30	54	101.350 ± 8.22	2.6684	0.024
31 - 40	42	100.97 ± 10.58		
41 - 50	16	98.68 ± 11.56		
51 - 60	33	94.06 ± 16.52		
61 - 70	15	92.26 ± 23.12		
71 - 80	6	88.00 ± 28.92		
Total	166			

Mean FEV/FVC as % of predicted value followed the same trend irrespective of age group.

6 Minute walk rest

Table X: 6MWT in subjects.

		Case n = 166	Reference n = 20
6MWD	Mean ± SD	540.50 ± 2.40	542.65 ± 42.19
	Range	(450 - 600)	(480 - 600)
SPO2%	Mean ± SD	97.51 ± 1.42	98.2 ± 0.83
	Range	(88 - 99)	(96 - 99)
Pulse rate	Mean ± SD	83.76 ± 9.0	83.2 ± 8.88
	Range	(67 - 100)	(67 - 98)
Fatigue	Yes	69 (41.57%)	2 (10%)

Table XI: Borg scale grading (up to moderate) for dyspnoea.

Grade of dyspnoea	Case frequency (N = 166)			Percentage %
	Male	Female	Total	
0	82	37	119	71.69%
1	12	10	22	13.25%
2	7	7	14	8.43%
3	8	3	11	6.63%

Table XII: Distribution of mean 6-minute walk distance predicted among subjects.

Age	Case frequency (N = 166)	Mean 6MWD predicted	F value	P value
21 - 30	54	543.70 ± 44.31	1.766	0.123
31 - 40	42	552.47 ± 42.85		
41 - 50	16	536.06 ± 36.45		
51 - 60	33	531.36 ± 35.48		
61 - 70	15	523.73 ± 27.91		
71 - 80	6	532 ± 41.26		
Total	166			

There is no significant difference in mean 6MWD value concerning different age group

Table XIII: Fatigue faced by subjects among various age groups.

Age	Case frequency (N = 166)	Number of subjects with fatigue	T value	P value
21 - 30	54	13	5.295	0.003
31 - 40	42	9		
41 - 50	16	8		
51 - 60	33	21		
61 - 70	15	12		
71 - 80	6	6		
Total	166	69		

A significant number of subjects in different age categories faced fatigue.

Further subgroup analysis revealed that the degree of initial clinical insult reflected in terms of length of hospital stay, the requirement of oxygen therapy, and the need for mechanical ventilation showed a positive correlation with findings of pulmonary spirometry. Among this duration of hospital stay could be subjected to statistical analysis as the size of the sample proved small for other subgroup analyses. Duration of hospital stay had a linear correlation with the long-term impact of Covid on lung volume and capacities.

Discussion

This can be very well concluded from the study observations that Covid-19 does have a long-term impact on the lungs, which is reflected by changes in pulmonary function tests in the form of both restrictive and obstructive patterns. Importantly these changes persisted even after 4 months of a hospital or domiciliary treatment in home-isolation. Previous studies suggest that pulmonary functions improved after 6 weeks, but some degree of restrictive

and obstructive alterations persisted even after 4 months. In our study, 37 (22.3%) patients had restrictive and 12 (7.2%) patients had an obstructive pattern in the pulmonary function test.

Even among patients who survived severe influenza A (H1N1) pneumonia, pulmonary function tests were found to improve significantly after 3 months but further significant improvement was not seen from 3 to 6 months after discharge[8] and some of them faced permanently altered pulmonary function[9].

Various degrees of destruction in alveolar structure and pulmonary interstitial fibrosis were observed in autopsies of Covid-19 patients[10]. These findings, confirmed by CT[11] further boost the desire to know the long-term deleterious effect in Covid-19 patients. Because restrictive and obstructive spirometry patterns after lung disease have been found to be associated with an increased risk of life-threatening comorbidities[7].

Starting of lung injury by acute inflammation finally terminates into a cascade process for recovery by the host's immune system[12]. This cascade can result in full recovery or can lead to fibrosis of the affected area of the lung. This recovery is by native stem cells and connective tissue deposition at the damaged site[14]. For this process, Alveolar macrophages play an important role by phagocytising alveolar debris and release of cytokines and growth factors[15]. Angiogenesis, fibroblast activation, and collagen deposition come into role[16]. Alveolar exudates are followed by the fibroblastic invasion of the alveoli and its transformation into myofibroblasts results in the deposition of fibroblastic extracellular matrix (ECM)[16]. Epidermal growth factor (EGF) and transforming growth factor-alpha (TGF-α) enhances stem cells for the replacement of damaged alveolar epithelium[17]. Vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) boost pulmonary capillary angiogenesis[18]. If the basement membranes are intact, this process results in full recovery[13,19]. If there is continuous damage or greater impact of the pathogen on the lungs, it can lead to damage to the basement membranes, in such case fibroblastic activity will persist, and this will convert into a fixed and/or progressive fibroblastic tissue[13,20]. The resulting scar tissue distorts alveolar architecture[21]. Deposition of the extracellular matrix is a part of the pathway leading to lung fibrosis. This leads to interlobular septal thickening and traction bronchiectasis[22].

The linear correlation observed between the severity of initial Covid infection and subsequent long-term sequelae of compromised lung functions can be very well explained by the magnitude of the initial inflammatory response. Clinical severity usually parallels the inflammatory response generated. The inflammatory response can be roughly gauged in terms of cytokine levels. However, the observation that subgroups requiring hospitalisation, having a longer duration of hospital stay, and requiring oxygen and assisted ventilation demonstrated deranged late pulmonary function test results.

In Covid-19 infection, chemokines as IL-8 bring more leukocytes to damaged areas of lungs[23] which damage alveolar-capillary with chemical mediators such as histamine, bradykinin, and leukotrienes, and increase endothelial permeability. This results in leakage of fluid into the interstitium and alveolar spaces[12]. Fluid, fibrin, and cellular debris-filled alveolar spaces all lead to respiratory distress. These exudates in the airway, alveolar collapse, and interstitial oedema show as ground-glass opacity, consolidation, and septal thickening in chest imaging[21].

Inflammatory marker CRP, cytokine factor IL-6, and generated series of immune responses by these markers in Covid-19 are found similar to the immunopathogenesis observed in SARS[24]. This is responsible for fibrosis of lung parenchyma during recovery. High inflammatory indicators, interstitial thickening, irregular interface, coarse reticular pattern, and parenchymal bands, are contributory factors in the process of developing lung pathology[25].

In hospitalised patients, ventilator-induced lung injury and oxygen toxicity both are important causes for the generation of fibrosis in severe Covid-19 pneumonia. Because patients with extensive lung involvement due to pneumonia need more oxygen for a prolonged time. Due to this prolonged delivery of oxygen, there is excessive production of oxygen-derived free radicals. These radicals damage the epithelium of the lungs[26]. Patients who are very sick due to acute respiratory distress syndrome (ARDS) due to Covid-19 pneumonia need prolonged mechanical ventilation. High plateau pressures by these ventilators, are also a contributory factor for the generation of lung fibrosis[27].

Thus Covid-19 infection has shown a significant long-term impact on lung volumes and capacities. This very fact highlights the importance of understanding the gravity of Covid-19 infection both for an individual and for the community at large, and emphasizes the importance of following all possible precautionary measures to cut down transmission of the virus. This fact also compels the treating physicians to adopt a more cautious and aggressive approach in handling Covid cases as timing and appropriateness of the therapeutic intervention would not only decide the immediate outcome but also has the potential to limit the long-term morbidity.

Limitations in this study were a small sample size which was stratified and analysed. That was reduced due to the inability of some subjects to perform 6MWT because of the Covid-19 sequelae. Only subjects with up to moderate

severity on the Borg scale were included. Further, a reservation on part of some patients about visiting the hospital and sharing the equipment set also restricted the number of participants. Secondly, we did not perform a follow-up study on subjects. One more limitation was that pre-Covid-19 PFT was not available for these patients, although we had already excluded those patients whose previous illness might confound results.

Conclusion

Post-infection Covid-19 patients showed compromised respiratory function. The most important of the PFT changes was the restriction in close to 23% and obstruction in 7% of patients. The conclusion of PFTs must be analysed carefully and considering the possible damage by Covid-19, further studies in post-Covid-19 infection patients, quantitatively assessing the relation of infection severity and pulmonary function are needed.

Study in the future should be focused on the short and long-term lung damage and sequelae of Covid-19 for the decision-making in the management of this pandemic and better clinical practices. Early aggressive therapy for the acute phase should be started to halt the disease process with suitable antivirals, immunomodulators, immunosuppressants, and plasma therapy so that the process of fibrosis can be prevented or minimised right from the beginning of the disease. After the acute phase is over, management strategies should focus on sequential spirometry. This sequential spirometry should be done every 4 weekly so that early intervention can be initiated in the form of antifibrotic, antioxidant, anti-inflammatory, and tyrosine kinase inhibitor agents, to overcome the symptoms and to attain long-term survival benefits.

Patients should be educated before discharge about the consequences of Covid-19 and the adverse effects of environmental factors such as air pollution and smoking, as these can reduce the efficacy of pulmonary functions. The data collected in this analysis could be useful for further studies.

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ORIGINAL ARTICLE

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Study of Non-Genetic Risk Profile for Mild Cognitive Impairment in Elderly

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Abstract

Background: Identifying risk factors for mild cognitive impairment (MCI) in the elderly aids in early diagnosis and treatment of treatable risk factors, delaying progression to dementia. Relatively less studies have been conducted to predict cognitive disruption in late life. The objective of this study was to assess the non-genetic risk factors for MCI in the elderly population.

Methods: Subjects (N = 500) aged > 60 years were allocated into two groups, i.e., subjects with normal cognition (n = 340) or with MCI (n = 160), based on mini-mental status examination (MMSE score 23 - 26) were diagnosed to have MCI. Laboratory investigations were done to determine the risk factors for developing MCI.

Results: The prevalence of MCI was 32% in the elderly with male predominance. Mean glycated haemoglobin, random blood glucose, systolic blood pressure, thyroid-stimulating hormone, serum cholesterol, triglyceride, creatinine, and sodium levels were significantly higher in subjects with MCI as compared to subjects with normal cognition (P < 0.001). Logistic regression found that odds ratio for progressing to MCI was higher by 5.28 times in diabetics, 4.31 in hypertensives, 4.64 in subjects with ischaemic heart disease, 5.26 in subjects with renal disease, 4.46 in subjects with hypothyroidism, 4.31 in subjects with past history of cerebrovascular accident and 2.67 in subjects with vitamin B12 deficiency.

Conclusion: Non-genetic risk factors can be regarded as the potential markers of MCI. Hence, it is pertinent to evaluate the elderly for MCI, as risk factors that are reversible can be treated with proper intervention.

Keywords: Ageing, co-morbidity, dementia, diabetes mellitus, risk factors, blood pressure.

Introduction

Mild cognitive impairment (MCI), an intermediate state between cognition of normal aging and mild dementia, is a common clinical manifestation among elderly subjects[1]. MCI to dementia progression rates range from 5.4% to 11.7% each year[2]. MCI is a measurable cognitive problem that involves difficulties with memory, thought, language and judgment that is more than any age-related change that does not interfere with daily activities[3]. While dementia is an acquired deterioration that impairs the cognitive abilities and impacts the effective performance of daily activities[4].

The cause of MCI remains unknown; however, it is postulated that structural and functional alterations in the brain that occur due to cerebral hypoperfusion cause cognitive impairment[5]. It has also been reported that cardiovascular risk factors such as ischaemic heart disease (IHD), hypertension, diabetes mellitus (DM) and stroke (including cerebral infarction and cerebral haemorrhage) affect the cerebral perfusion, causing MCI and progression to dementia in the elderly[1]. Various screening tests, including Montreal Cognitive Assessment (MoCA), Mini-Mental State Examination (MMSE) or mini-cog are useful to measure the overall cognitive dysfunction, with varying specificities and sensitivities[6].

Although ample studies have reported the risk factors contributing to the shift from normal cognition to MCI[1], relatively lesser studies have been conducted to predict cognitive disruption particularly in late life, i.e., in the elderly. Identification of MCI, particularly in high-risk subjects is important as adequate preventable measures can be taken against the development of dementia to avoid functional deterioration[3]. Early intervention during the status of early pre-dementia also helps improve the quality of life of the patient[7]. This study thus intended to assess the non-genetic risk factors for MCI in the elderly.

Material and methods

This two-year (2013 - 2015) observational cross-sectional study was conducted on elderly subjects aged > 60 years (who had completed graduation), attending the outpatient department of medicine and neurology. Clinical diagnosis of MCI was based on Petersen's definition of MCI, which included the following – 1. Memory complaint, preferably

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corroborated by an informant. 2. Objective memory impairment (for age and education). 3. Preserved general cognitive function. 4. Intact activities of daily living. 5. Not demented[8].

Subjects who were diagnosed with dementia, hospitalised for acute illness or with neurological infections were excluded from the study. As depression was a common cause for pseudodementia/cognitive impairment, subjects with depression were excluded using the Geriatric Depression Scale (shorter version). Subjects aged > 60 years were regarded as elderly as per the Indian Council of Medical Research survey of the Indian geriatric population. Informed consent from the subjects and ethical approval from the Institutional Ethical Committee [STD-1/EC/13-14] was obtained before their participation in the study.

All subjects were allocated into two groups, i.e., subjects with normal cognition and subjects with MCI based on MMSE. Elderly subjects with MMSE score 23 - 26 were identified to have MCI. An experienced clinical psychologist performed the neuropsychological investigations.

Demographic data, general physical examination, complete clinical history of existing comorbidities with special emphasis on risk factors of the subjects, were recorded. Laboratory investigations including renal function, liver function, thyroid profile, serum vitamin B12, complete blood count, random blood sugar, HbA1c, lipid profile, serum electrolytes, HIV status, neuroimaging and electrocardiography were also performed. Collected data was analysed.

Statistical analysis

SPSS v17 was used to analyse the data. All the quantitative parameters such as age and MMSE were expressed as mean ± SD and tested with the Mann-Whitney U test. Qualitative variables were expressed as proportions and tested with a chi-square test of significance. Independent factors involved in the development of MCI were assessed using logistic regression analysis. Multinomial logistic regression analysis determined the variables that influence the conversion of MCI to dementia.

Results

Of the total 500 elderly subjects, 340 (68%) had normal cognition and 160 (32%) were diagnosed with MCI. The prevalence of MCI was 32% in the elderly with male predominance in either group. Mean age and body mass index significantly differed in both groups (P < 0.001). Most subjects identified with MCI also had anaemia (93.1%), followed by DM (40.6%) and hypertension (33.1%) while most subjects with normal cognition were anaemic (68.8%; Table I).

Table I: Demographic, comorbidity, and neuropsychological profile in the study subjects.

Variables	Normal cognition, n = 340	MCI, n = 160	P value
Age	68 ± 5.61	67.46 ± 4.76	< 0.001**
Male/Female	222/118	122/38	
BMI (kg/m^2)	22.54 ± 1.06	23.28 ± 1.55	< 0.001**
Co-morbidities			
Diabetes mellitus	39 (11.5%)	65 (40.6%)	< 0.001**
Hypertension	36 (10.6%)	53 (33.1%)	< 0.001**
Ischaemic heart disease	18 (5.3%)	33 (20.6%)	< 0.001**
Cerebrovascular accident	20 (5.9%)	34 (20.3%)	< 0.001**
Hypothyroidism	29 (8.5%)	47 (29.4%)	< 0.001**
Renal disease	10 (2.9%)	22 (13.8%)	< 0.001**
Anaemia	234 (68.8%)	149 (93.1%)	< 0.001**
Vitamin B12 Deficiency	22 (6.4%)	25 (15.6%)	0.0018
Hypercholesterolaemia	7 (2%)	23 (14.3%)	< 0.001**
Hypertriglyceridaemia	14 (4.1%)	46 (28.7%)	< 0.001**
Renal dysfunction	9 (2.6%)	22 (13.7%)	< 0.001**
Hyponatremia	44 (12.9%)	39 (24.3%)	0.002*
Smoking	68	25	0.29
Alcohol consumption	77	31	0.48
Neuropsychological assessment			
MMSE	27.64 ± 0.60	24.70 ± 0.82	< 0.001**

***Highly significant; *Significant; MCI, Mild cognitive impairment.*

Mean systolic blood pressure (SBP), cholesterol, HbA1c in diabetics, random blood glucose, thyroid-stimulating hormone, serum creatinine levels were higher in subjects with MCI as compared to subjects with normal cognition. (P < 0.001; Table II).

Table II: Laboratory investigations in the study subjects.

Variables	Normal cognition#	MCI#	P value
Haemoglobin	12 ± 0.8	11.3 ± 0.9	< 0.001**
Random blood glucose	140 ± 29	180 ± 44	< 0.001**
HbA1c (glycated haemoglobin)	6.0 ± 0.3	6.5 ± 0.7	< 0.001**
Systolic blood pressure	136 ± 6.68	141 ± 6.99	< 0.001**
Diastolic blood pressure	80 ± 7.98	81 ± 10.72	0.29
Thyroid stimulating hormone	2.72 ± 1.07	3.42 ± 1.67	< 0.001**
Serum creatinine	0.90 ± 0.20	1.11 ± 0.46	< 0.001**
Cholesterol	140 ± 18	164 ± 28	< 0.001**
Triglycerides	112 ± 25	144 ± 48	< 0.001**
Serum sodium	136.8 ± 1.5	135.8 ± 2.3	< 0.001**
Serum albumin	3.5 ± 0.4	3.3 ± 0.2	0.64

*#Data presented in mean ± SD; **Highly significant; MCI: Mild cognitive impairment.*

Multinomial logistic regression analysis found that DM, hypertension, IHD, hypothyroidism, cerebrovascular accident, vitamin B12 deficiency and renal disease were significant predictors in the conversion to MCI among elderly patients. The odds of conversion to MCI was higher by 5.28 times in diabetics, 4.31 in hypertensives, 4.64 in subjects with IHD, 5.26 renal disease subjects, 4.46 hypothyroid subjects, 4.31 in subjects with history of CVA and 2.67 in vitamin B12 deficiency subjects (Table III).

Table III: Risk factors that influence the development of mild cognitive impairment in the elderly patients.

Variables	Odds ratio, 95% confidence interval
Diabetes mellitus**	5.28 (3.33 - 8.35)
Hypertension**	4.31 (2.67 - 6.97)
Ischaemic heart disease**	4.64 (2.52 - 8.55)
Cerebrovascular accident**	4.31 (2.39 - 7.78)
Hypothyroidism**	4.46 (2.67 - 7.43)
Renal disease**	5.26 (2.42 - 11.40)
Vitamin B12 deficiency**	2.67 (1.45 - 4.91)

***Highly significant.*

Discussion

Several modifiable risk factors for MCI and dementia have been reported, and a proper search for these risk profiles in the elderly is the need of the hour. Although not all MCIs progress to frank dementia; identification of risk profiles aid in early prognosis and in the formulation and modulation of prevention strategies in the elderly population.

The overall prevalence (32%) of MCI among the elderly in our study was quite similar to the prevalence reported in the community-based study by Mohan *et al*[9] (26.6%). We found advancing age to be an independent risk factor for developing MCI. Hussin *et al*[10], also revealed in their study that the MCI group was significantly older (69.2 ± 5.9 years vs. 68.1 ± 5.8 years; $P < 0.05$) than the group without MCI. Most subjects identified with MCI in this study also had history of DM, hypertension, cerebrovascular accident, ischaemic heart disease, renal disease and hypothyroidism. This is in agreement with previous studies[11,12] that identified DM and stroke to be the significant risk factors in the development of MCI. Another study revealed cerebrovascular and cardiovascular risk factors were involved in developing MCI[13]. A retrospective study reported that low vitamin B12 levels did not affect the cognitive functions[14]. Similarly, in this study, vitamin B12 deficiency was only seen in 15.6% of the subjects with MCI, which might be due to coincidence.

It has been reported that cardiovascular risk factors such as mean SBP, cholesterol, triglycerides, HbA1c, serum creatinine, random blood glucose, thyroid-stimulating hormone are the mediating progressors of cognitive impairment in the elderly population[15]. Although the pathogenesis involved is unclear, it is hypothesized that the haemodynamic phenomenon that is disrupted in the presence of cardiovascular risk factors via diverse pathways causes cerebral hypoperfusion and affects the cognitive status in the elderly population[16]. Similarly, in this study, the MCI group reported more comorbid conditions compared to the normal cognition group. The observations in this study were corroborated well with other studies[17-22].

A community-based cohort study conducted among elderly subjects, including Blacks and Whites, reported that change in body mass index significantly declined the cognition, especially episodic and semantic memory, irrespective of the race[17]. A study conducted among non-insulin dependent type 2 diabetic subjects showed that the reduction in HbA1c levels was associated with better cognitive functions in elderly subjects[18]. Contrarily, other studies[19,20] showed no significant correlation between HbA1c and cognitive impairment among diabetics. Similar to our study, a population-based study reported that elevated SBP significantly influences progression to MCI[21]. In contrast, a population-based longitudinal study revealed that elevated diastolic blood pressure independently influences the cognitive function.

A population-based study from Chicago (USA) showed that impaired kidney function rapidly declined the cognitive function in the elderly[22]. A population-based cohort study conducted among women in Denmark reported that cognitive impairment was higher in elderly women who were physically inactive, with high cholesterol levels and with history of depression[23]. A population-based cohort study from Minnesota (USA) reported that neither clinical nor subclinical hypothyroidism was associated with MCI[24]. A large prospective community-based cohort study showed that among elderly subjects, anaemia could accelerate the risk of developing dementia[25]. A community-dwelling study in the older population revealed that lowered extracellular sodium levels contribute to cognitive decline via brain senescence, caused due to the release of oxidative stress markers[26].

This study suggests that the probability of developing MCI in elderly patients is significantly higher among subjects with DM, hypertension, IHD, hypothyroidism, renal disease, vitamin B12 deficiency and with history of CVA. A study by Mohan *et al*[9] in Kerala (India) found that history of lack of balance while walking (adjusted OR: 2.75; CI: 1.46 - 5.17), depression (adjusted OR: 2.17; CI: 1.21 - 3.89), anxiety (adjusted OR: 2.22; CI: 1.21 - 4.05) and alcohol consumption

(adjusted OR: 1.99; CI: 1.02 - 3.86) were significant factors that lead to development of MCI. A community-based study by Su *et al*[27] revealed advancing age, education status, absence of religious attendance and history of stroke to be significant predictors of MCI in older individuals.

In this study, non-genetic risk profiles among elderly subjects revealed that risk factors were similar for both MCI and dementia. It is desirable to ascertain the risk factors in the elderly to possibly prevent high-risk progression of MCI to dementia. Since this is a cross-sectional study limited to risk profile, follow-up of subjects for rectification of correctable risk factors was not performed, therefore prognostication was not possible. All subjects in our study were graduates and may not represent the worldwide population, hence the findings cannot be generalised. Therefore, the study should be replicated in diverse cohorts to validate our findings.

Conclusion

Overall, the study emphasizes that 32% of the elders had MCI. Since MCI is known to convert into full-fledged dementia, it is pertinent to evaluate the elderly for MCI, even though they may be asymptomatic, since risk factors that are reversible can be halted by treatment with appropriate strategies. This constitutes an important preventive strategy against the advancement to dementia, which creates both a physical and an economic burden.

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ORIGINAL ARTICLE

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Clinical and Pulmonary Function Evaluation in Post-Pulmonary Tuberculosis Patients

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Abstract

Introduction: Globally, the best estimate is that 10.0 million people (range, 9.0 - 11.1 million) developed TB disease in 2017. TB is an infectious disease caused by the bacillus Mycobacterium tuberculosis which typically affects the lungs. But many of the fully treated post-tubercular patients are left with permanent changes in lung anatomy (bronchial and parenchymal structural) and are at higher-risk of pulmonary sequelae and premature mortality. They affect the calibre of airways, increase their resistance and decrease airflow. Aim of our study was to determine overall clinical status and pulmonary function through spirometry of the cured post-pulmonary TB patients.

Material and methods: Study was conducted on patients above 18 years of age, coming to the OPD of Pulmonary Neducue department at Santosh Medical College, Ghaziabad, and taken complete treatment under RNTCP in past and declared cured. At the time of study, 200 patients with sputum smear negative for AFB were enrolled in the study. The study was conducted for 9 months after seeking clearance from the Institutional Ethical Committee. Written informed consent was taken from all the patients included in the study. Detailed socio-demographic history, clinical history especially regarding pulmonary symptomatology, details of past anti-tubercular treatment were recorded as per proforma. General physical and detailed chest examination was carried-out. All these patients were subjected to chest X-ray examination, sputum microscopy, and pulmonary function study. Result: Mean age was 51.72 ± 11.89 years (mean ± SD). Mean BMI was 19.23 ± 2.95 Kg/m2 (mean ± SD). Males were 77% and females were 23%. Illiteracy was seen in 34% while only 6.5% were graduate. In present study 84% of participants had dyspnoea and 63.5% had cough. Haemoptysis was seen in 11.5%.Post-tuberculosis 94% patients had fibrosis on their chest X-ray followed by pleural thickening and pleural calcification 28.5%, healed lesions in 24%, destroyed lung 22%, fibro-cavitary lesions in 17.5% , bronchiectasis in 13.5% and only 2% showed normal chest radiograph. In present study we observed that 47.5% patients had mixed blockage in their spirometry post-tuberculosis followed by restrictive finding in 30% of the patients and obstructive in 13.5% of the patients, and only 9% patients had normal spirometric results. Our study also classified both restrictive and obstructive pattern. It showed 2% mild, 11% moderate and 17% severe type of restrictive pattern. It was also found that mild and moderate obstruction was 2% each whereas 5% had severe and 4.5% had very severe obstruction.

Conclusion: In the absence of proper guidelines, most of the post-tubercular lung function impairment patients either suffer in silence or continue to receive irrelevant treatment. Therefore proper guidelines must be made regarding follow-up of patients post-tuberculosis treatment, to assess their lung functions and provide correct management so as to improve their quality of life.

Key words: Tuberculosis; pulmonary function; post-tubercular symptoms; pulmonary sequelae; pulmonary function impairment; spirometry; variable patterns and severity of lung impairment.

Introduction

Tuberculosis, caused by *Mycobacterium tuberculosis*, is a major cause of death worldwide, being the most communicable disease in the world, affecting one-third population. It is estimated that 2 out of every 5 people are infected with TB in India. In 2017, TB caused an estimated 1.3 million deaths (range, 1.2 - 1.4 million) among HIV-negative people and there were an additional 3,00,000 deaths from TB (range, 2,66,000 - 3,35,000) among HIV-positive people[1]. Globally, the best estimate is that 10.0 million people (range, 9.0 - 11.1 million) developed TB disease in 2017.

Considering the enormous burden of disease and limited resources, presently the focus is on early detection and full treatment of affected patients. But many of the fully treated post-tubercular patients are left with permanent changes in lung anatomy and are at higher-risk of pulmonary sequelae and premature mortality[2-5]. These result in pulmonary sequelae that are characterised by bronchial and parenchymal structural changes, including bronchovascular distortion, bronchiectasis, emphysematous changes, and fibrotic bands. Moreover, these changes remain permanently in the lungs after a microbiological cure[6]. They affect the calibre of airways,

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increase their resistance, and decrease airflow. The mechanism of fibrotic scarring can also result in reduced total lung capacity[7]. Therefore delay in diagnosing TB has been shown to relate directly to the severity of pulmonary damage and the frequency of residual morbidities negatively affecting the quality of life and leading to pulmonary disability[8]. Inadequate treatment of bronchial obstruction in patients with active TB can ultimately lead to chronic airway obstruction syndrome, with clinical manifestations very similar to chronic obstructive pulmonary disease. The major burden of both chronic obstructive pulmonary disease (COPD) and pulmonary tuberculosis (PTB) occurs in low and middle income countries. Ninety per cent of the estimated of 3 million death from COPD, and a large majority of the 9 million cases of active PTB occur in these countries[9]. In these populations, factors other than cigarette smoking, (e.g., biomass fuel, and occupational exposure) contribute to the pathogenesis of COPD[10]. In a number of large population-based cross-sectional studies, PTB has also been shown to be strongly associated with the presence of chronic airflow limitation (CAL)[11-14]. In some studies, this association is almost as strong as that for cigarette smoking[13-15].

A total of seven TB guidelines have addressed patient follow-up after TB treatment, but only three have mentioned the problem regarding TB sequelae, while four others have stated about the risk of relapse or recurrence of tuberculosis[16-18]. In an international guideline, it was indicated that early diagnosis of TB may lead to fewer post-tuberculosis sequelae[19]. Two other guidelines explained about the problem of long-term TB sequalae, but both were written for low-burden TB countries. One of the guidelines emphasized on the need of post-TB management and support to address TB sequelae and the other indicated no need for clinical monitoring after TB cure[20,21]. None of these guidelines mentioned about how potential TB sequalae should be identified or managed. Hence, we focussed to determine overall clinical status and pulmonary function through spirometry of the cured post-pulmonary TB patients.

Aims and objectives

1. To determine the pulmonary and overall clinical status of the cured pulmonary TB patients.
2. To determine pulmonary function of these patients through spirometry.

Material and methods

Type of study: Cross-sectional study.

Place of study: Department of Pulmonary Medicine, Santosh Medical College and Hospital, Ghaziabad, Uttar Pradesh. Institutional Ethics Committee clearance was taken before commencing the study. Written informed consent was taken from all the patients included in the study.

Duration of study: 9 months

Study sample: Study population comprised of following patients.

1. Those who completed treatment and declared cured under RNTCP guidelines in Santosh Medical College, Ghaziabad in last five years.
2. Patients coming to the OPD of Pulmonary Medicine department, Santosh Medical College, Ghaziabad and taken complete treatment under RNTCP in the past five years. 200 patients were enrolled in the study.

***Inclusion criteria*:** 1) Age 18 to 65 years; 2) sputum smear for AFB negative at the time of study.

Exclusion criteria: Smear positive for AFB. 2) Any other respiratory disease other than a sequelae of TB. 3) Cardiac co-morbidities of any type. 4) Not willing to participate and give informed written consent. 5) Patients who are unable to perform spirometry. 6) H/o DM, HTN, Hypothyroid, chest wall abnormalities, seizures, etc.

Detailed socio-demographic history, clinical history (especially regarding pulmonary symptomatology), details of past anti-tubercular treatment were recorded as per the proforma. General physical and detailed chest examination was carried-out. All these patients were subjected to chest X-ray examination, sputum microscopy, and pulmonary function study.

Pulmonary Function Test: The pulmonary function tests were conducted according to ATS/ERS guidelines using Portable spirometer of RMS. The entire FVC procedure was demonstrated satisfactorily to the subjects. Nose clips were attached before the test. The subjects were asked to take maximal inspiration and blow into the mouthpiece as rapidly, forcefully, and completely as possible for about 6 seconds. The subjects were verbally encouraged to continue to exhale the air at the end of manoeuvre to obtain optimal effort. A minimum of 3 acceptable Forced vital capacity (FVC) manoeuvres were performed in the standing position with nose pinched and the best manoeuvre were selected and accepted. The parameters measured were Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 second (FEV1), FEV1/FVC ratio, Peak Expiratory Flow rate (PEFR) and Forced Expiratory Flow rate (FEF 25-75).

Statistical analysis

The data were entered on a Microsoft Excel spreadsheet

and imported into Statistical Package for Social Sciences (SPSS) version 22 for statistical analysis. Frequency distribution tables were produced, and the Fishers exact test was used to assess associations of variables. A P value less than 0.05 was considered statistically significant.

Results

Mean age was 51.72 ± 11.89 years (mean ± SD). Mean BMI was 19.23 ± 2.95 Kg/m^2 (mean ± SD). Males were 77% and females were 23%. Illiteracy was seen in 34% while only 6.5% were graduate (Table I). Mean duration since completion of ATT at the time of follow-up study was 19.21 ± 1.34 months (mean ± SD).

Table I: Socio-demographic profile of the participants.

Mean age in years (mean ± SD)	51.72 ± 11.89
Mean BMI in Kg/m^2 (mean ± SD)	19.23 ± 2.95
Gender	No. (%)
Male	154 (77)
Female	46 (23)
Education level	No. (%)
Illiterate	68 (34)
Upto 5th std	38 (19)
6th - 8th	36 (18)
High school	31 (15.5)
Intermediate	14 (7)
Graduate	13 (6.5)
Marital status	No. (%)
Married	182 (91)
Unmarried	14 (7)
Widower	4 (2)

In the present study, 84% of participants had dyspnoea and 63.5% had cough. Haemoptysis was seen in 11.5% (Table II).

Table II: Symptoms of participants.

Symptoms	Present No. N-200 (%)	Absent No. (%)
Cough	127 (63.5)	73 (36.5)
Dyspnoea	168 (84)	32 (16)
Chest Pain	114 (57)	86 (43)
Fever	59 (29.5)	141 (70.5)
Haemoptysis	23 (11.5)	177 (88.5)

Post-tuberculosis, 94% patients had fibrosis on their chest X-ray followed by pleural thickening and pleural calcification each 28.5%, healed lesions in 24%, destroyed lung 22%, fibro-cavitary lesions in 17.5%, and bronchiectasis in 13.5%. Only 2% showed a normal chest radiograph (Table III).

Table III: Chest X-ray findings.

Chest X-ray findings	(n 200)	%
Destroyed lung	44	22
Fibro-cavitary lesions	35	17.5
Bronchiectasis	27	13.5
Fibrosis	188	94
Healed lesions	48	24
Pleural calcification	57	28.5
Pleural thickening	57	28.5
Normal	4	2

Pulmonary function study showed that 47.5% patients had mixed blockage followed by restrictive finding in 30% of the patients and obstructive pattern in 13.5% of the patients. Only 9% patients had normal spirometric results (Table IV).

Table IV: Post-tubercular treatment spirometric findings.

Findings (patterns)	No.	%
Normal	18	9
Obstructive	27	13.5
Restrictive	60	30
Mixed Blockage	95	47.5
Total	200	100

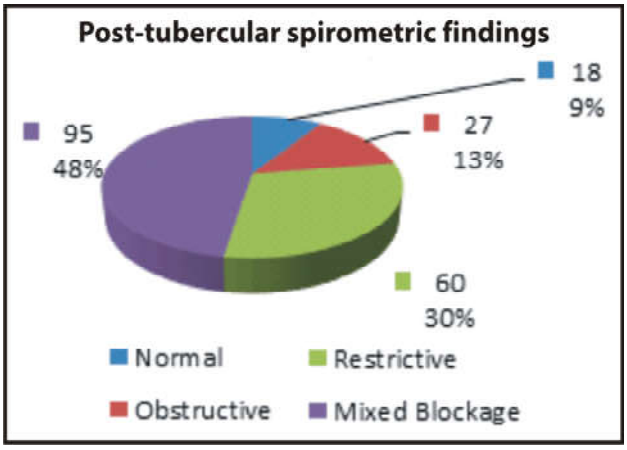

Fig. 1:

We also further classified both restrictive and obstructive pattern on the basis of severity. It showed 2% mild, 11% moderate, and 17% severe type of restrictive pattern. It was also found that mild and moderate obstruction was 2% each, whereas 5% had severe, and 4.5% had very severe obstruction (Table V).

Table 2- Symptoms of participants

Table V: Patterns of spirometry (severity).

Pattern	No.	%
Normal	18	9
Mild Restriction	4	2
Moderate Restriction	22	11
Severe Restriction	34	17
Mild Obstruction	4	2
Moderate Obstruction	4	2
Severe Obstruction	10	5
Very Severe Obstruction	9	4.5
Mixed Blockage	95	47.5
Total	200	100

Table VI: Comparative analysis on the basis of number of times of ATT intake.

		Past H/o ATT once (N - 129)	Past H/o ATT twice (N-71)	Fishers exact test value	P value significant (<.05)
Cough	yes	102	66	.0144	Yes
	no	27	5		
Dyspnoea	yes	105	63	.2273	No
	no	24	8		
Chest X-ray Findings	yes	125	71	.2992	No
	no	4	0		
Abnormal PFT	yes	111	71	.0004	Yes
	no	18	0		

Discussion

Demographic profile

In our study, maximum number of patients were in the age group of 41 - 60 yrs (57%) followed by 22.5% in age group 21 - 40 yrs. Only 20.5% of patients were above 60 yrs of age. Mean age of patients was 51.72 ± 11.89 years (mean ± SD) as compared to Pandey *et al*[22] where mean age was 42.84 ± 16.5 years (mean ± SD). The mean BMI was found to be 19.23 ± 2.95. The finding of the present study correlates with a study conducted by Pandey *et al*[22] with BMI of 20.24 ± 4.44. Illiteracy was seen in 34% while only 6.5% were graduate. Literacy is one of the important factors which can help the patients to understand the disease process and its outcome. It can also help them to recognise their symptoms and seek consultation for their symptoms as early as possible.

Post-tubercular treatment symptoms

In the present study, 84% of participants had dyspnoea and 63.5% had cough. Haemoptysis was seen in 11.5%. A study conducted by Patil *et al*[23] showed that among 500 symptomatic subjects who were included in the study, the most common post-tubercular symptom was of breathlessness in 79% cases, followed by cough in 48%. In a study conducted by Pandey *et al*[22], post-tubercular symptom was of breathlessness in 96% of the patients followed by cough in 58%, sputum production in 18%, and haemoptysis in 9% of the patients.

Radiological changes after tuberculosis

Post-tuberculosis, 94% patients had fibrosis on their chest X-ray followed by pleural thickening and pleural calcification in 28.5%, healed lesions in 24%, destroyed lung 22%, fibro-cavitary lesions in 17.5% , bronchiectasis in 13.5% and only 2% showed normal chest radiograph. One systematic review assessed pulmonary abnormalities with radiological imaging among people with a history of TB and found proportions of between 8.3% - 83.7% for cavitation, 4.3% - 11.2% for bronchiectasis and 25.0% - 70.4% for fibrosis[24].

Post-tuberculosis respiratory function impairment

Normal pulmonary function test: as post-bronchodilator FEV1/FVC >=95%, FVC > 80% of normal predicted value.

Defining restrictive pattern: Patient with restrictive stage COPD as post-bronchodilator FEV1/FVC >=70% , FEV1 < 80% of normal predicted value, FVC< 80% of normal predicted value.

Severity

Mild restriction: FEV1/FVC > 95%, FVC< 80% of normal predicted value.

Moderate restriction: FEV1/FVC > 95%, FVC< 64% of normal predicted value.

Severe restriction: FEV1/FVC > 95%, FVC < 44% of normal predicted value.

Defining obstructive pattern: Patient with obstructive stage COPD as post-bronchodilator (FEV1/FVC) < 70% and FEV1 < 80%, FVC > 80% of normal predicted value.

Severity

Mild stage COPD: (FEV1/FVC) pred% < 70 or < 95% and FEV1 >= 80% of normal predicted value.

Moderate stage COPD: (FEV1/FVC) pred% < 70 or < 84% and FEV1 >=50 and < 80 of normal predicted value.

Severe stage COPD: (FEV1/FVC) < 70% and FEV1 >=30% and < 50% of normal predicted value.

Very severe stage COPD: (FEV1/FVC) pred% < 70 and FEV1 >=0 and < 30 of normal predicted value.

Defining mixed pattern: Patient with mixed blockage as post-bronchodilator (FEV1/FVC) Pred < 95 % and FVC % Pred < 80.

The above data signifies that pulmonary tuberculosis can lead to significant damage of the lung parenchyma thereby leading to various functional abnormalities.

In the present study, we observed that 91% (182/200) patients had pulmonary function abnormality on spirometry. Other studies have described lung function abnormality ranging from 46% to 82%[22,26,28]. Mixed blockage was the most prevalent functional abnormality on spirometry in our study, seen in 47.5% (95/200) of patients, followed by restrictive findings in 30% (60/200)of the patients and obstructive in 13.5% (27/200) of the patients.

Many studies have described pulmonary restriction as the predominant pattern with various proportions[25,26,27]. This restrictive pattern has been explained by the destruction of lung parenchyma volume loss, lung scarring with a reduction of pulmonary compliance and an increase in elastic retraction pressure[29]. On the contrary, some other studies showed that airflow obstruction was the most common defect[12]. The pathophysiology of airflow obstruction following pulmonary tuberculosis treatment is not clear. Bronchial stenosis has been speculated as the result of extrinsic pressure of enlarged peribronchial lymph nodes as well as the consequence of endobronchial involvement of TB with extensive granulation tissue destruction and subsequent fibrosis[30]. Moreover, similar to exposure to smoke, TB increases the activity of metalloproteinases enzymes, contributing to pulmonary damage[31]. Gothi *et al* also demonstrated that post-tuberculous airflow obstruction could be the consequence of obliterative bronchiolitis[32]. Our study also classified severity of both restrictive and obstructive pattern. It showed 2% mild, 11% moderate, and 17% severe type of restrictive pattern. It was also found that mild and moderate obstruction was 2% each, whereas 5% had severe and 4.5% had very severe obstruction. Only few studies have classified such detail. In a study conducted by Manji *et al*[28], the overall prevalence of lung function abnormalities was 74% (371/501) where majority was due to obstruction (42%) (210/501) followed by mixed (19%) (96/501) and restrictive (13%) (65/501) abnormalities. In their study, approximately 79% (166/210) of patients with obstructive dysfunction had mild-to-moderate severity while 73% (47/65) of patients with restrictive abnormalities had mild-to-moderate severity. In our study, only 30% of obstructive patients had mild-to-moderate severity, and 70% of them had severe obstruction. Also, 43% of restrictive patients had mild-to-moderate severity and 57% had severe form of restrictive pulmonary impairement. In other words, severe form of both obstructive and restrictive pattern were more prevalent as compared to other studies. Another study by Pasipanodya *et al* (2007) in the USA, the prevalence of abnormal lung function of any type was 59%, and the prevalence of individual subtypes of impairment for restrictive, obstructive and mixed were 31, 15 and 13% respectively[33], where majority was with restrictive pattern. While the prevalence of pulmonary impairment was as high as 91% (182/200) in our study, it suffices to note that pulmonary functions are abnormal in the majority of patients upon completion of chemotherapy. Mixed blockage 47.5% (95/200) was most prevalent in our study.

In our study, analysis on the basis of number of times of ATT intake revealed that patients who took ATT twice were significantly more likely to have cough (p = .0144) and abnormal PFT findings (p = .0004) as compared to those who took ATT only once. In the Manji *et al*[28] study, patients with recurrent TB were also more likely to have abnormal lung functions compared to those with a first episode of TB (89.3% vs 71.4%) (p = 0.001). As there were only 4 patients in our study (all with history of ATT intake once only) who did not have any radiological findings, understandably there was no statistically significant difference between two groups based on number of times of ATT intake (Table VI). Further, it can be said that despite almost all the patients having abnormal chest X-ray findings, many of these were asymptomatic[32] and had a normal pulmonary function study[18].

These non-communicable post-tuberculous sequelae bring to light the often overlooked processes by which TB impacts the quality of life. Tuberculosis therefore imposes an infectious and non-infectious burden on the healthcare infrastructure. While the infectious and microbiologic domain has received much attention in TB treatment, a lot is still left to be desired in the non-infectious sequelae. International TB guidelines do not address the importance of lung function impairment after tuberculosis, particularly omitting guidance on identification and management. This is concerning because of global rise in mortality and morbidity from non-communicable diseases, including post-tubercular sequelae[34,35]. Consequently, the national TB control programmes are not designed to adequately deal with the problem of post-tubercular lung function impairment.

In view of high TB burden and comparatively limited resources, the national programme in our country is focused on early diagnosis and treatment of active disease only. Due to this, bacteriological confirmation of cure at the end of the treatment is usually the end-point in TB patient care. Therefore there is a need for creating awareness regarding post-tuberculosis sequelae and lung function impairment among policy makers, practitioners, and patients. At least the healthcare staff should be made aware of the increased risk of symptoms due to post-tubercular lung function

impairment, so that they can educate about and discuss the health implications of residual lung damage with patients and their relatives. Unfortunately, post-TB lung function assessment services are often not yet established.

Conclusion

The magnitude of residual lung function abnormalities among patients with tuberculosis is high despite successful administration of anti TB medications. Studies that look at the quality of life and socio-economic impact of residual lung function abnormalities, screening strategies and treatment need to be conducted to supplement the findings of this study. As there are no proper guidelines regarding follow-up of patients with post-tubercular lung function impairment, most of the patients either suffer in silence or continue to receive irrelevant treatment. Therefore proper guidelines must be made regarding follow-up of patients post-tuberculosis treatment, to assess their lung functions and provide correct management so as to improve their quality of life.

Limitations

1. Smokers were not excluded from our study. 46 patients were smokers but never had other respiratory diseases in past, hence were enrolled in our study.
2. We could not follow-up asymptomatic patients as they did not turn up in our OPD. Only few studies have compared post-tubercular symptomatic and asymptomatic patients.

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ORIGINAL ARTICLE

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Is Obesity a Risk Factor for Depression? A Multi-institutional Study Done at an Urban Setting in South India

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Abstract

Objective: To study the association between obesity and depression after controlling the effects of other confounders prevalent in an urban setting.

Methodology: This cross-sectional study was conducted among patients and their attenders visiting two tertiary care hospitals in Mangalore city. Data were collected using a self-administered questionnaire. The Center for Epidemiologic Studies Depression (CES-D-20) scale was used to screen participants for depression. Weight and height of participants were recorded using standard procedures.

Results: Mean age of the 298 participants was 40.7 ± 14.9 years. Overweight or obesity was observed among 168 (56.4%) participants. As many as 147 (49.3%) participants were at risk of depression.

In univariate analysis, female participants aged ≤ 40 years with overweight or obesity (p = 0.008), widow/widowers (p = 0.0.046), those with a current history of alcohol consumption (p = 0.0472), presence of hypertension (p = 0.0426), presence of any co-morbidities (p = 0.002) and those with a family history of mental health problems (p = 0.0097) were associated with risk of depression. In multivariable analysis, family history of mental health problems among participants was associated with the risk of depression.

Conclusion: Obesity and depression were quite prevalent among participants in this study but were not associated. However, family history of mental health problems was independently associated with risk of depression among participants. Thus, familial and genetic factors need to be further analysed to control depression at this setting.

Key words: Obesity, risk of depression, association, multi-institutional study, urban setting.

Introduction

Obesity is one of the most prevalent morbidity. It affects more than 609 million adults worldwide[1]. In India, there are more than 135 million people with obesity. Even then it is a neglected health problem in India[2]. Its prevalence is particularly high in the Southern states of India[2]. In urban areas of Karnataka, the prevalence rate of obesity (BMI ≥ 25) is 39.4% and 37.1% among males and females, respectively[3].

The proportion of Indians who suffer from various depressive disorders is estimated to be 45·7 million[4]. The prevalence is on the rise, particularly in the southern states of India[5]. Based on the above observations, it was essential to find out whether there was any relationship between obesity and depression. This would help to frame suitable preventive strategies to address both morbidities in a clinical setting.

Prior studies have given contradictory findings of an association between these parameters. Some studies reported that an association exists[6,7] while others reported no association[8,9]. Therefore, the present study was done to assess the association between obesity and depression after controlling the effects of various confounders prevalent in an urban setting in South India.

Materials and methods

This cross-sectional study was done at a government and a private tertiary care hospital affiliated to a private medical college in Mangalore city. The study was conducted in January 2021 after obtaining ethics clearance from the Institutional Ethics Committee. The medical superintendents at these hospitals gave permission to conduct this study. People visiting these hospitals either as out-patients or accompanying them were enrolled in this study using the convenience sampling method. The investigators approached them in the waiting area at the out-patient department. Written informed consent was taken from the participants after informing them of the nature and purpose of this study. All consenting participants aged 18 years and above were included in this study. Pregnant and lactating mothers, illiterates, and patients

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diagnosed with pre-existing mental disorders were excluded from this study. Participants were screened for pre-existing mental disorders based on history and the diagnosis stated in the treatment records.

The sample size was calculated using the formula $Z_{\alpha}^{2}PQ/d^{2}$. An Asian study reported that 15.4% of participants with obesity had depression after being screened with the CES-D-20 scale[10]. Based on this proportion, at 95% confidence intervals and 5% absolute precision, the minimum sample size was calculated as 200. Adding a non-response rate of 10%, the final sample size was rounded off to 220 participants.

Data was collected using a self-administered questionnaire. It was a semi-structured anonymous questionnaire. Section A of the questionnaire recorded the demographic details (gender, age, marital status, occupational status, educational status, number of family members, type of family, total monthly family income, and place of residence), history of current usage of substances of abuse (tobacco, alcohol, and drugs), presence of co-morbidities and family history of co-morbidities (including a family history of mental health problems) among the participants.

Section B of the questionnaire was the Center for Epidemiologic Studies Depression (CES-D-20) screening scale[11]. This is a 20 item scale to assess various symptoms suggestive of depression over the past one week. The participant was considered to be at risk of depression if he/she scored $\geq$ 16 points. Sensitivity and specificity of this scale were observed to be 95.1% and 85% respectively[12].

The questionnaire was prepared in the local language Kannada. It was both language and content validated with the help of experts before its use in this study. The investigator was present close by to clarify any doubts among participants while filling the questionnaire.

The Cronbach's alpha value of internal consistency for the Kannada version of the CES-D-20 scale used in this study was 0.875.

In this study, current users of substances of abuse were defined as those using tobacco (in smoked or smokeless form) or alcohol within the recent one month[13].

Socio-economic status (SES) of the participants was assessed using Modified B G Prasad Classification of 2020[14].

The weight and height of the participants were measured using standard procedures. Weight was recorded to the nearest 0.1 kilograms using a digital weighing machine, and height was recorded to the nearest 0.1 cm using a stadiometer. Body mass index (BMI) was calculated as kilograms per square meter. Overweight and obesity were defined as those with BMI $\geq$ 23 and $\geq$ 25, respectively based on Asia-Pacific guidelines[15].

Considering the ongoing COVID-19 pandemic, precautionary steps like hand sanitation, both before handing out the form and after receiving the filled-in form was, practiced by the investigator.

Participants identified as at risk of depression were advised consultation at the Psychiatry department at the respective hospitals.

Data entry and analysis were done using IBM SPSS for Windows version 25.0, Armonk, New York. Unpaired t-test, Chi-square test, and Fisher's Exact test were used to test association. All mutually exclusive variables identified among participants associated with the risk of depression at p value 0.3 or less in the univariate analysis were introduced into the binary logistic regression model. Then backward stepwise logistic regression process was applied. All p values were two-tailed, and a value less than 0.05 was taken as the cut-off to decide significant association.

Results

The mean age of the 298 participants was 40.7 $\pm$ 14.9 years. Majority were males [158 (53%)], were married [192 (64.4%)], were graduates [104 (34.9%)], were professionals [73 (24.5%)] and were from urban areas [224 (75.2%)]. All of them belonged to nuclear families.

SES could be assessed among 40 participants. Thirty seven (92.5%) of them belonged to class I, and the rest belonged to class II status (Table I).

Out of the total participants, underweight, normal weight, overweight and obesity were observed among 12 (4.0%), 118 (39.6%), 83 (27.9%), and 85 (28.5%) participants respectively. Substance abuse in the form of smoking, tobacco chewing, and alcohol consumption were reported respectively by 49 (16.4%), 20 (6.7%), and 61 (20.5%) participants each, out of the total participants. 193 (64.8%) participants had no history of substance abuse.

Co-morbidities were present among 100 (33.6%) participants. These morbidities were identified from the treatment records. The various co-morbidities reported among participants were: Hypertension among 57, diabetes mellitus among 48, asthma among 10, hyperthyroidism among 2, cataract among 2, disc prolapse in 1, osteoporosis in 1, and gastro-oesophageal reflux disease in 1.

Family history of co-morbidities was present among 146 (49.0%) of participants. Family history of mental illness was present among 16 (5.4%) participants.

The responses of participants to the CES-D-20 screening scale have been presented in Table II.

Table I: Socio-demographic distribution of the participants.

Socio-demographic variables	Number	Percentages
Age group (years)		
≤ 20	11	3.7
21 - 30	82	27.5
31 - 40	63	21.1
41 - 50	66	22.1
51 - 60	48	16.1
61 - 70	17	5.7
71 - 80	7	2.3
81 - 90	4	1.3
Gender		
Males	158	53.0
Females	140	47.0
Marital status		
Unmarried	89	29.9
Married	192	64.4
Widow/Widower	17	5.7
Educational status		
Post-graduate	40	13.4
Graduate	104	34.9
Intermediate/ Post-high school diploma	75	25.2
High school	61	20.5
Primary school	18	6.0
Occupational status		
Professional	73	24.5
Semi-professional	31	10.4
Clerk/Shop owner/Farm owner	13	4.4
Skilled worker	39	13.1
Semi-skilled worker	21	7.0
Unskilled worker	18	6.0
Housewives	38	12.8
Students	32	10.7
Unemployed	8	2.7
Retired	25	8.4
Socio-economic status (n = 40)		
Class I	37	92.5
Class II	3	7.5
Type of family		
Nuclear family	298	100.0
Place of residence		
Urban	224	75.2
Semi-urban	65	21.8
Rural	9	3.0
Total	298	100.0

Table II: Distribution of CES-D-20 depression scale parameters among participants (n = 298).

Items	Rarely or none of the time (< 1 day) No. (%)	Some or a little of the time (1 - 2 days) No. (%)	Occasionally or a moderate amount of time (3 - 4 days) No. (%)	Most or all of the time (5 - 7 days) No. (%)
I was bothered by things that usually don't bother me	144 (48.3)	81 (27.2)	54 (18.1)	19 (6.4)
I did not feel like eating; my appetite was poor	149 (50.0)	72 (24.2)	52 (17.4)	25 (8.4)
I felt that I could not shake off the blues even with help from my family or friends	156 (52.4)	77 (25.8)	50 (16.8)	15 (5.0)
I felt I was just as good as other people	56 (18.8)	61 (20.5)	69 (23.1)	112 (37.6)
I had trouble keeping my mind on what I was doing	122 (40.9)	73 (24.5)	71 (23.8)	32 (10.8)
I felt depressed	168 (56.4)	65 (21.8)	51 (17.1)	14 (4.7)
I felt that everything I did was an effort	109 (36.6)	78 (26.2)	68 (22.8)	43 (14.4)
I felt hopeful about the future	60 (20.1)	100 (33.6)	74 (24.8)	64 (21.5)
I thought my life had been a failure	187 (62.7)	58 (19.5)	36 (12.1)	17 (5.7)
I felt fearful	133 (44.6)	71 (23.8)	67 (22.5)	27 (9.1)
My sleep was restless	102 (34.2)	72 (24.2)	71 (23.8)	53 (17.8)
I was happy	57 (19.1)	110 (36.9)	91 (30.6)	40 (13.4)
I talked less than usual	151 (50.7)	77 (25.8)	45 (15.1)	25 (8.4)
I felt lonely	174 (58.4)	55 (18.5)	55 (18.5)	14 (4.6)
People were unfriendly	147 (49.3)	88 (29.5)	41 (13.8)	22 (7.4)
I enjoyed life	68 (22.8)	89 (29.9)	93 (31.2)	48 (16.1)
I had crying spells	171 (57.4)	66 (22.1)	49 (16.5)	12 (4.0)
I felt sad	120 (40.3)	95 (31.9)	62 (20.8)	21 (7.0)
I felt that people dislike me	171 (57.4)	78 (26.2)	39 (13.1)	10 (3.3)
I could not get going	147 (49.3)	80 (26.9)	48 (16.1)	23 (7.7)

Out of the total participants, 147 (49.3%) were found to be at risk of depression.

There was no association between overweight or obese status with risk of depression among participants. However, out of the 49 participants, aged ≤ 40 years with overweight or obese status, 29 (59.2%) were at risk of depression. In comparison, out of the 44 participants, aged ≤ 40 years with underweight or normal status, 13 (29.5%) were at risk

of depression. These differences in proportion were found to be significant ($X^2 = 8.223$, $p = 0.004$).

Out of the 21 female participants, aged ≤ 40 years with overweight or obesity, 15 (71.4%) were at risk of depression. Out of 32 female participants, aged ≤ 40 years with underweight or normal weight status, 11 (34.4%) were at risk of depression. These differences in proportion were found to be significant ($X^2 = 6.966$, $p = 0.008$).

Variables associated with the risk of depression among participants in univariate analysis at p value ≤ 0.3 are shown in Table III.

	Depression status		Total
	At risk mean ± SD	Not at risk mean ± SD	
Age (years)	42.4 ± 16.2	39.1 ± 13.4	
			t = 1.915, p = 0.056
	At risk No. (%)	Not at risk No. (%)	
Gender			
Males	73 (46.2)	85 (53.8)	158
Females	74 (52.9)	66 (47.1)	140
			X^2 = 1.315, p = 0.251
Body mass index			
Underweight	7 (58.3)	5 (41.7)	12
Normal weight	51 (43.2)	67 (56.8)	118
Overweight or obese	89 (53.0)	79 (47.0)	168
			X^2 = 3.045, p = 0.218
Educational status			
Professional/ Post-graduate	21 (52.5)	19 (47.5)	40
Graduate	42 (40.4)	62 (59.6)	104
Intermediate/ Post-high school diploma	43 (57.3)	32 (42.7)	75
High school	30 (49.2)	31 (50.8)	61
Primary school	11 (61.1)	7 (38.9)	18
			X^2 = 6.412 , p = 0.17
Marital status			
Unmarried	46 (51.7)	43 (48.3)	89
Married	88 (45.8)	104 (54.2)	192
Widow/ widower	13 (76.5)	4 (23.5)	17
			X^2 = 6.147, p = 0.046
History of current alcohol usage			
Yes	37 (60.7)	24 (39.3)	61
No	110 (46.4)	127 (53.6)	237
			X^2 = 3.937, p = 0.0472
History of current usage of any substance abuse			
Yes	57 (54.3)	48 (45.7)	105
No	90 (46.6)	103 (53.4)	193
			X^2 = 1.594, p = 0.2068
Diabetes mellitus			
Present	27 (56.3)	21 (43.7)	48
			X^2 = 1.097, p = 0.295
Hypertension			
Present	35 (61.4)	22 (38.6)	57
			X^2 = 4.111, p = 0.0426
Asthma			
Present	7 (70)	3 (30)	10
			p = 0.2134
Any co-morbidities			
Present	62 (62.0)	38 (38.0)	100
			X^2 = 9.668, p = 0.002
Family history of mental health problems			
Present	13 (81.3)	3 (18.7)	16
Absent	134 (47.5)	148 (52.5)	282
			p=0.0097
Total	147	151	298

These variables therefore qualified entry into the multivariable model. Hosmer and Lemeshow test p value was found to 0.579, indicating that this model was a good fit. The independent variables in the model could explain 72.5% of the variability of the dependent variable.

In multivariable analysis, family history of mental health problems among participants was associated with the risk of depression among the participants (Table IV).

Table IV: Multivariable analysis of determinants associated with increased risk of depression among participants (n=298).

Characteristics	Unadjusted OR 95% CI	p value	Adjusted OR95% CI	p value
Marital status				
Married	1		1	
Unmarried	0.7916 (0.4769 - 1.312)	0.3648	2.897 (0.862 - 9.74)	0.086
Widow/widower	0.2619 (0.07133 - 0.8009)	0.01716	1.932 (0.523 - 7.129)	0.323
Educational status				
Professional/Post-graduate	1		1	
Graduate	1.626 (0.7764 - 3.425)	0.1975	1.662 (0.334 - 8.27)	0.535
Intermediate/ Post-high school diploma	0.8239 (0.3779 - 1.797)	0.6251	2.77 (0.607 - 12.645)	0.188
High school	1.141 (0.5097 - 2.561)	0.7495	1.27 (0.269 - 6.005)	0.763
Primary school	0.8864 (0.1865 - 4.005)	0.8805	1.492 (0.315 - 7.069)	0.614
History of current alcohol usage				
Yes	1.78 (1.003 - 3.159)	0.0472	1.726 (0.943 - 3.162)	0.077
No	1		1	
Family history of mental health problems				
Present	4.786 (1.335 - 17.161)	0.0097	4.991 (1.333 - 18.683)	0.017
Absent	1		1	

Discussion

In this study, overweight or obesity status among the participants was not associated with risk of depression among them. However, presence of high BMI among participants aged ≤ 40 years and among them, female participants in particular were at risk of depression. The World Mental Health surveys have identified that the period ranging from middle to late adolescence till early 40 years was the peak risk period for the onset of major depressive episodes worldwide[16]. Moreover, as much as two-third of risk factors of depression are found to be environmental and the rest being inherited[17]. Hence, people aged 40 years and below with extrinsic risk factors like overweight or obesity form a risk group of developing depression. These high-risk groups therefore need to be periodically screened for depression.

The other socio-demographic variable associated with the risk of depression in this study was widow/widower status. Therefore, the social welfare agencies and the local government need to offer appropriate services for their welfare.

No other socio-demographic variables were associated with the risk of depression among the participants in the present study.

In the present study, the current history of alcohol consumption was associated with the risk of depression among participants, which was similar to the observations of Kuria *et al*[18]. Depression is identified as the most common psychiatric disorder among those with alcohol use disorders[19]. A period of 3 to 4 weeks of abstinence was significantly found to relieve depression among patients[20]. The association between alcohol use disorders and depression appears to be due to common genetic, behavioural, and environmental factors[18,21-23].

However, there was no association between current usage of other substances of abuse like tobacco smoking or chewing with risk of depression among participants in this study.

The presence of any co-morbidities was associated with the risk of depression among participants in this study. The social and economic implications of diseases apart from the known medical reasons could be the reason behind this observation.

Hypertensive patients in this study were associated with the risk of depression. In previous studies, hypertension was independently associated with depression[24,25]. Hypertension is known to cause microvascular changes in the brain, leading to structural and cognitive deficits resulting in vascular depression[26].

There was no association of the presence of diabetes mellitus or asthma with risk of depression among participants in the present study, which was contrary to the findings of other studies[27-30].

Family history of mental health problems was independently associated with the risk of depression among participants in this study. This could probably be due to the familial and genetic factors involved in mental disorders like depression.

Hence treatment of depression among participants in the current setting requires a multidisciplinary approach to address familial and genetic factors involved in its occurrence. The role of these factors needs to be further explored to control depression.

The association between SES and depression among the majority of the participants could not be analysed due to the non-disclosure of this information. The association between care-giver burden with depression among persons accompanying patients and of central obesity with depression among all the participants could not be done as the data collection tool did not capture these information.

Conclusion

Obesity and depression are quite prevalent among participants in this study but were not associated. However, family history of mental health problems was independently associated with risk of depression among participants. Thus, familial and genetic factors need to be further analysed to control depression at this setting.

Limitations

The Self-administered questionnaire process was used for data collection. Hence, there is a possibility that the participants filling out the questionnaire may not have completely understood the questionnaire.

Patients and their caregivers were both included in this study. However, the data collection tool did not specify the question whether the respondent filling the form was a patient or a caregiver. Hence, sub-analysis of depression in outpatients versus depression in caregivers could not be performed. There is a possibility that caregivers of even stable patients might also experience substantial caregiver burden, which may present as depressive symptoms. Therefore the confounding effect of the inclusion criteria of enrolling out-patients and their caregivers could be a major limitation in this study.

The non-disclosure of information required to assess socio-economic condition, namely total monthly family income and the number of family members by the majority of the participants (258 out of 298), is another major limitation in

this study, considering the role of SES in the occurrence of depression among the participants.

Anthropometric measurements like waist and hip circumference (to assess central obesity), although non-invasive and measurable on minimal clothing in OPD setting, were not done as it was not included in the questionnaire considering the prevailing conditions.

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REVIEW ARTICLE

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Some Important Points in Oxygen Therapy: An Update for the Clinicians in the Covid Era

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Abstract

The use of oxygen has gained much prominence in the Covid era. However, there are still lacunae in the practical knowledge of health workers regarding proper use of this medical gas. Daily clinical experience still reveals instances of over- and under-use of oxygen. There are various aspects of oxygen use, including choosing the proper source, the proper delivery device, and the proper duration, which must be decided appropriately for maximum benefit of the patient. This article aims to present certain practical aspects of oxygen use for the clinician. While this is an essential knowledge for the Covid era, the learning will be useful for the future too.

Key words: Venturi mask; hyperbaric oxygen therapy; minute volume; HFNC; wound healing.

Introduction

In the Covid era, the use of oxygen has become very common in all patient care settings, whether indoors or outdoors. This has given rise to a lot of confusion and controversy in the initial days. Practically, very few clinicians or nurses have a complete knowledge of the proper use of oxygen and this lack of knowledge leads to the risk of both over- and under-utilisation[1]. Hence, a comprehensive review of the various aspects of oxygen use is an essential tool for every physician.

First of all, it must be reiterated that oxygen is a drug. It is a life-saving drug not only for Covid, but also various other indications. Therefore, like all other drugs, its use must be guided by evidence and protocols. With the mass-scale availability of cheap finger pulse oximeters in the market, the oxygen saturation of any patient may be assessed anywhere, even at home. While this is a great way to monitor oxygen therapy anywhere, on the flip side it also raises the possibility of unnecessary treatment. As the last section of this article will show, oxygen excess is also as harmful as oxygen deficiency. Thus, a goal directed oxygen therapy is the ideal way to benefit the patients with minimum harm.

In this article, the authors have endeavoured to discuss some aspects of oxygen use, which are needed in day-to-day clinical practice.

The oxygen source

For healthcare facilities, we need medical grade oxygen. This is defined as at least 90% V/V of oxygen in the supplied gas. Carbon monoxide must be less than 5 ppm. In hospitals, oxygen is delivered either from a wall socket or a cylinder. The wall socket is usually connected to the oxygen plant or reservoir tank of the hospital by a pipeline. For connecting to a ventilator, the wall socket type source is ideal as it ensures uninterrupted flow.

For reservoir tank of a hospital, the best option is LMO (Liquid medical oxygen). As the name implies, the reservoir tanks hold liquefied oxygen at -183° C. This is a great source of large volume oxygen supply as 1 litre of LMO is equal to 870 L of gaseous oxygen. Also, LMO can provide the purest form of oxygen (> 98%). For installation of LMO tank, medical gas pipeline system throughout the hospital is a must. Usual capacity of LMO tank varies from 2 to 20 Kilo litres. LMO is always generated off-site and delivered to the hospital.

Another type of oxygen plant in hospitals is the PSA plant (Pressure Swing Adsorption). In this plant, the ambient air passes through a filtration system where the nitrogen is separated. The resultant oxygen has varying purity. However, PSA plants are ideal for remote hospitals where daily supply of LMO is impossible.

Even if a hospital has oxygen tank, it is mandatory to keep 2 - 3 days' supply of oxygen in cylinder form. The cylinders come in various sizes (Table I). Oxygen cylinders should have a black body with white shoulder. The various sized cylinders are given alphabetical codes like B, D, E, etc[2]. These cylinders hold pressurised oxygen and the exact volume of oxygen in a cylinder depends on the filling pressure[2]. Each cylinder should have a label indicating the volume of oxygen and the pressure. Cylinders are good for

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bedside oxygen therapy and patient transport.

Table I: The various types of Oxygen cylinders for medical use.

Type	Gas Capacity (maximum gas volume when full: litres)	Pressure (psi)
B	200	1,900
D (commonest for home delivery)	400	1,900
E (commonest in anaesthesia)	660	1,900
F (commonest in hospital wards)	1,360	1,900
H	6,900	2,200

Recently, oxygen concentrators have become very popular, especially for home use[3]. As the discussions below will show, these are not good for hospital use. A concentrator (or generator) extracts the oxygen from atmospheric air. These are basically portable forms of PSA plants described earlier. Maximum oxygen flow rate obtainable from this device is 5 LPM (litres per minute). The expected purity of oxygen is 87 - 96%. If the purity falls below 85%, it is not acceptable. Thus, for patients with high oxygen demand, this is not useful.

There are high flow concentrators that can generate flow rates of up to 10 LPM[3]. But these are extremely costly. For example, a 5 LPM concentrator now costs around 30,000 - 50, 000 INR. An 8 LPM concentrator costs around 60,000 - 70,000 INR. But for 10 LPM machines, the cost crosses 100,000 INR. The device has two other disadvantages: it must be switched off after 3 - 4 hours of continuous use. Thus, it cannot ensure uninterrupted oxygen delivery. Also, it is run on electricity. Thus, it is not suitable for use during transport unless the car has electrical socket. Also, at higher flow rates, the purity of delivered oxygen falls considerably.

Does oxygen need humidification?

It is a standard practise to humidify oxygen (by bubbling it through water). This prevents drying of nasal mucosa and discomfort. But it has been seen that for low flow oxygen (~ 4 LPM), dry or humidified oxygen does not make much difference. Oxygen coming out of a concentrator is partly humidified.

But for high flow cases, esp. HFNC, humidification is a must. The water used for the process must be medically distilled water or normal saline. Tap water should not be used as it contains microorganisms like fungus which can be aerosolised and inhaled by the patient. The water must be changed daily.

Types of oxygen delivery devices

There are various types of oxygen delivery devices in use. Also, it must be remembered that oxygen delivery is required in various settings: during an emergency, in hospital, during transport and currently (post-Covid) at home. Thus, while efficiency of gas delivery is definitely of prime importance, other factors like ease of use and safety must also be considered while choosing a delivery device. The paragraphs below give a brief account of the common delivery methods. There are two types of delivery devices: High flow and low-flow[3]. Low flow systems deliver oxygen up to 15 LPM. In low-flow settings, the oxygen gets diluted by inspired air. Thus, the FiO_2 cannot be calculated accurately. But in high flow devices, the FiO_2 can be fixed quite accurately.

Nasal cannula

Nasal cannula is the ubiquitous low-flow oxygen delivery device. It is a plastic cannula with two terminal prongs for oxygen delivery directly to the nostrils. The advantage of this device is that the patient is able to eat or talk while on oxygen. The cannula is easy to use and even non-medical care givers can be taught to attach it to the patient. Studies have also shown that patients prefer this mode of delivery. But the prongs can get dislodged from the nostrils during any movement and in patients with nasal obstruction, obviously this is futile. Also, another disadvantage is that the FiO_2 varies with the breathing pattern of the patient and the minute volume. The following table (Table II) shows the approximate FiO_2 according to the flow rate of oxygen.

Table II: Table showing FiO_2 in nasal cannula according to oxygen flow rate.

Oxygen flow rate (LPM)	FiO_2 (%)
1	24
2	28
3	32
4	36
5	40
6	44

For flows greater than 6 LPM, often the patient experiences considerable discomfort and nasal drying and it is better to switch to other delivery devices. Also, for higher rates of oxygen flow through the cannula, the FiO_2 becomes more variable.

But nasal cannula is the cheapest delivery device and especially suited for home oxygen, (e.g., post-Covid). Since home oxygen source is mostly the oxygen concentrator (highest flow rate 5 LPM), the nasal cannula is aptly suited for the role.

Face mask

Face mask is the next level of delivery device. There are many varieties. One common problem with all varieties is claustrophobia[4]. For some patients this may be a limiting factor.

Simple oxygen mask

This one is a plastic mask with exhalation holes on the sides. This prevents CO_2 rebreathing. The mask is held in place by elastic straps going round the back of the head. It must be remembered that an oxygen mask operates properly only at flow rates of 6 - 10 LPM. Very low flow oxygen (1 - 2 LPM) is not suitable through a mask. At the proper oxygen flow rate, the FiO_2 achieved is 35 - 60%. Thus, oxygen concentrators can not be used with a face mask (as their flow rates is below 6).

An oxygen mask is suitable for short (typically < 12 hours) periods of oxygen delivery. However, disadvantage of the device is that unless the mask is sealed properly around the nose and mouth, the oxygen gets diluted. Also, a patient cannot eat or drink while on mask. During meal times, the patient must be shifted to nasal cannula.

Partial rebreather mask

The above two devices are low-flow systems. But a re-breather mask is a high flow oxygen delivery device. A re-breather mask has a reservoir bag attached to the oxygen pipe just before it joins the mask port. There are separate exhalation ports on the sides of the mask. The bag and the ports have one-way valves. Thus, the exhaled air goes out only through the exhalation ports. After that, when the patient inhales, he/she takes the pure oxygen from the bag through the valve (for a partial re-breather mask, some air is mixed with the oxygen). For this reservoir bag to work efficiently, the oxygen flow must be maintained at a minimum of 6 LPM and the bag should be partially inflated during inspiration. For optimum functioning, the oxygen flow rate should be 10 - 15 LPM.

This mask provides FiO_2 of up to 80%. This mask is ideal for patient transport or quickly oxygenating the patient before intubation, etc.

Non-rebreathing mask

This mask is similar to the previous one. But the valves of the reservoir bag are more efficient to ensure that none of the exhaled air enters the oxygen reservoir. Hence, the FiO_2 is higher and may reach 100% at flow rates of 15 LPM. However, the precise FiO_2 is difficult to calculate.

Venturi mask

Venture mask is a high flow oxygen delivery device. The main difference of this device with the others mentioned here is that it allows a precise FiO_2 to be delivered[5]. This mask comes with color coded jet adaptors. Each adaptor corresponds to a particular FiO_2 at a particular oxygen flow rate. Thus, for venturi masks to be used, a precise oxygen flow rate has to be ensured. The following table 3 describes the colour coding of these masks

Table III: Table showing oxygen parameters of venturi mask.

Colour	Oxygen flow rate (LPM): minimum	FiO_2
Blue	2	24
White	4	28
Orange	6	31
Yellow	8	35
Red	10	40
Green	15	60

The oxygen flow rate given in this table is the minimum rate required for achieving that FiO_2. If the oxygen flow rate is higher, the same FiO_2 is achieved but total air delivered to the patient is higher. For example, in the red adaptor, min flow rate required is 10. If the flow rate is 12 or 14 LPM, the FiO_2 is still 40. But total minute volume delivered to the patient is higher for higher flow rates. If the COPD patient is dyspnoeic with high minute ventilation, then it is advisable to use the higher rates of oxygen flow for that coloured adaptor so that the total delivered air matches the minute ventilation[5].

Venturi mask is especially suitable for patients with COPD where excess oxygen use can precipitate a carbon dioxide narcosis[5]. Thus, in such cases, precise oxygen delivery is needed. But since oxygen flow rate needs constant monitoring, this mask is not suitable to be used at home. Also, for the FiO_2 to be achieved, a good seal around the mask is needed.

Oxygen hood

An oxygen hood is a plastic dome or box that is used for infants. This is placed over the baby's head so that he/she can breathe in the oxygenated air without getting stimulated by a skin-touching facial contraption like a mask. A similar device is an oxygen tent.

Face tent

This is a wide plastic mask that covers the mouth and nose but does not form a seal around them. This is thus, essentially a low flow system.

This is ideal for patients with facial trauma or burns or for those who are too claustrophobic. The oxygen flow rate

must be kept high (around 15 LPM) as there is no seal and the oxygen gets diluted. The FiO_2 naturally is variable.

Transtracheal oxygen catheter

As the name implies, this device is inserted percutaneously into the trachea[6]. Oxygen is delivered directly to the trachea, bypassing the dead space. But this method is not very popular due to the invasive nature of the procedure[6].

HFNC

High flow nasal cannula (HFNC) device has become very popular in the Covid era. As the name implies, this is a cannula where gas flow rate is increased massively[7]. But that is not the only function of this device. It also humidifies the oxygen and in this machine, the FiO_2 can also be fixed. While in conventional nasal cannula the maximum FiO_2 achieved is around 40%, in HFNC the maximum can be 100%[7]. The flow rate can be increased up to 60 LPM, although in some modern devices it can be even higher at 90 LPM. These two parameters can be adjusted independently.

In the usual oxygen delivery devices discussed till now, humidified oxygen comes from the cylinder and the cannula or the mask just acts as a conduit. But in HFNC, the machine itself has the means to humidify the gas. This is essential, as flow of dry gas at 50 or 60 LPM through the respiratory tract would cause immediate mucosal injury.

When a dyspnoeic patient is having high minute ventilation, the oxygen delivered through the nasal cannula is not enough as the patient is also breathing through the mouth. Thus, the oxygen gets massively diluted. But an HFNC, by increasing nasal flow, reduces the mouth breathing, and thus reduces dilution of the oxygen delivered.

Also, the HFNC reduces the dead space in the pharynx and increases efficiency of breathing. HFNC can never be used at home and is only suitable for hospitals which have assured constant high flow oxygen.

For type 1 respiratory failure, NIV was the preferred therapy earlier. But now, the American College of Physicians have recommended the use of HFNC as first-line in suitable cases[8].

Some other modes of oxygen therapy

The preceding section discussed the various devices that are used to deliver oxygen to the patient. The next section will briefly discuss two other methods of oxygen treatment which are used for limited indications.

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBOT) is a completely different treatment method. This is only used to treat conditions like gas gangrene, decompression sickness, carbon monoxide poisoning, or cyanide poisoning[9].

In this therapy, the patient is put inside a hyperbaric chamber where 100% oxygen is delivered at 1.5 - 3 times the atmospheric pressure. Each session lasts 2 - 3 hours. This delivers more oxygen to the tissues compared to oro-nasal delivery and also can inhibit the growth of certain bacteria[9]. This also promotes vasculogenesis. Multiple sessions may be needed, and in the USA, this is covered by insurance. Since the therapy takes place inside a high pressure chamber, it is not suitable for persons with middle ear surgery or tympanic perforation.

Topical oxygen therapy

In hyperbaric oxygen therapy, the patient is put inside a chamber and oxygen at supra-atmospheric pressure is delivered to the chamber. But this involves subjecting the entire body to high pressure oxygen, which may have untoward consequences. Thus, local delivery of oxygen only to the body part needed is an attractive idea.

As the name implies, Topical Oxygen Therapy (TOT) involves delivering oxygen directly to the body area of interest[10]. This is an experimental therapy which is becoming popular now. In diabetic non-healing foot ulcers, local oxygen therapy can sometimes help in wound healing[10]. The oxygen source is connected to a large plastic cover which is wrapped around the infected foot in an air-tight manner (like a plastic boot). The oxygen may be delivered either at normal or supranormal pressures.

There are three main types of devices for local oxygen delivery:

I. Continuous low flow oxygen diffusion device

II. Constant pressure delivery device

III. Cyclical high pressure delivery

However, the use of TOT is still controversial. A lot of physicians are still sceptical of its utility. Earlier data regarding the efficacy had been controversial, but recently some small trials have shown marked favourable results. This therapy must be used for a prolonged time for perceptible benefit[11].

Side-effects of oxygen therapy

As discussed previously, excess oxygen is quite harmful. In the critical care setting, it is often found that patients are given oxygen till the SpO_2 reaches 100%. Not only is this unnecessary, *but some recent studies have found this to be positively harmful*[12]. Thus, patients should not be maintained on SpO_2 of 100% for prolonged periods. For normal patients,

the target saturation is anything above 94%[12]. But 98% is the upper limit. For COPD cases, the target saturation is 88 - 92%. Excess oxygen therapy leads to some problems:

Absorption atelectasis

Continuous high flow oxygen therapy leads to replacement of alveolar nitrogen with oxygen. Nitrogen is not absorbed from the alveoli. Thus, it maintains the patency of the alveoli. If oxygen replaces that nitrogen, then the oxygen will be quickly absorbed in the blood. Thus, gas volume inside the alveoli falls and this can cause collapse of the lung units[13].

Retrolental fibroplasia

This is a disease of premature infants (< 31 weeks) who are given excess oxygen. There is fibrovascular proliferation in the retina[14].

Conclusion

In conclusion, oxygen is a life-saving drug. But it must be used judiciously. Like all other drugs, oxygen must be used only for the minimum duration needed and in proper concentration. Proper delivery devices must be chosen considering the target SpO_2, comfort of the patient, and condition of the lungs. The need for oxygen in a patient must be reviewed daily during the clinical rounds.

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CASE REPORT

JIACM 2022; 23 (1-2): 47-49

Neuromyelitis Optica – Sometimes a Misnomer

Paromita Das, Nitasha Pasricha**, Pratap Singh***, MPS Chawla*****

Abstract

Neuromyelitis optica spectrum disorder is an autoimmune, demyelinating disease of the central nervous system. Characteristic clinical features include longitudinally extensive transverse myelitis and optic neuritis. Around 70 - 80 per cent cases are associated with aquaporin-4 antibodies. Treatment involves high-dose corticosteroids and immunosuppressants to prevent relapse. Here we present a case of seropositive NMO without optic neuritis.

Key words: Neuromyelitis optica, longitudinally extensive transverse myelitis, aquaporin-4, optic neuritis.

Introduction

Neuromyelitis optica is an autoimmune disorder of the central nervous system. It's prevalence in India is 2.6/ 1,00,000[1] and shows a high female preponderance. It is classified under the entity – NMOSD (neuromyelitis optica spectrum disorder). Earlier it was considered to be the optico-spinal variant of the more commonly encountered disease – Multiple sclerosis (MS). After the identification of aquaporin-4 antibodies in 2004, the two diseases were identified as separate entities[2]. However, aquaporin-4 antibodies are not universal to the disease, and are not found in 30 per cent cases of NMO, which are diagnosed based on the more stringent MRI criteria as elucidated by the 2015 International Diagnostic Criteria for NMO-SD. The core clinical characteristics include acute myelitis, optic neuritis, area postrema syndrome, brainstem syndrome, acute diencephalic syndrome and symptomatic cerebral syndrome[3]. On magnetic resonance imaging, longitudinally extensive transverse myelitis (LETM) which is defined as contiguous involvement of three or more spinal segments is specific for NMO compared to multiple sclerosis which presents as acute transverse myelitis. Similarly, optic neuritis in NMO is also longitudinally extensive and has a predilection for the posterior segment of the optic nerve and can be bilateral at presentation, whereas multiple sclerosis usually affects the anterior segment and is usually unilateral. Area postrema syndrome is the presenting feature in 12% of cases[4]. Neuromyelitis optica is rarely seen without the simultaneous or successive involvement of the optic nerve and the spinal cord. However, since the discovery of aquaporin-4 antibodies, presence of optic neuritis is not mandatory for diagnosis of NMO. Presence of any one of the core clinical characteristics along with aquaporin antibodies, clinch the diagnosis of NMO, after exclusion of other possible aetiologies. Our case highlights one such rare instance where neuromyelitis optica was seen without the presence of optic neuritis. We present a case of seropositive NMO without optic neuritis, from a tertiary care hospital in North India.

Case summary

Our case is a 38 years, right-handed female, who presented with gradually progressive, asymmetrical weakness of both lower limbs (right more than left), proximal weakness followed by distal weakness, and a sensation of gradual stiffening of both lower limbs. This was associated with sensory loss in the form of decreased touch, pain and temperature in both lower limbs compared to the upper limbs. There was no bladder or bowel involvement, no involvement of the muscles of eyelid, deglutition, speech or respiration and no diurnal variation. She had no band-like sensation over trunk, no visible wasting of any limb or any abnormal limb movement. There was no history of cranial nerve involvement. However, prior to the onset of weakness, she did not have any fever or respiratory or gastrointestinal infection or recent vaccination. She was recently diagnosed to have hypothyroidism and was on replacement therapy for the same. She had a past history of tuberculous meningitis for which she had taken a full course of ATT. She had no other co-morbidities. She followed a vegetarian diet. She had four normal vaginal deliveries with no bad obstetric history.

Clinical examination revealed normal higher mental function, no spinal deformity, normal visual acuity of 6/6 in both eyes, both pupils normal is size and reaction, no relative afferent pupillary defect, normal colour vision, normal visual fields in both eyes and normal fundus examination. There was clasp-knife rigidity in both lower limbs. Tone was also increased in both upper limbs with presence of Hoffman's

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and Wartenberg's sign. Power was 4/5 across joints of upper limb and 1/5 across hip, knee and ankle joints of right lower limb, and 3/5 in left lower limb. Deep tendon reflexes were brisk throughout with presence of sustained ankle clonus. Abdominal reflex was absent bilaterally, and bilateral planters were extensor. There was loss of pain and temperature sensations along with impaired vibration and position sense up to the level of the anterior-superior iliac spine on both sides. However, there was no sensory involvement of the upper limb. Lhermitte's sign was present on examination. Cerebellar, autonomic functions were normal. Gait could not be evaluated in our patient as she was unable to bear weight in lower limbs.

Based on history and examination, a provisional diagnosis of spastic quadriparesis due to cervical myelopathy was made, and baseline laboratory investigations were done. Blood investigations revealed normocytic, normochromic anaemia (haemoglobin: 7.4 gram/deciliter), total leucocyte count of 9,700 per microliter, platelet count of 250,000 lac per deciliter, normal ESR, normal kidney function test, normal liver enzymes, normal vitamin B12 and folate levels. Lipid profile showed hypertriglyceridaemia (triglyceride: 260 milligram/deciltre). HIV, hepatitis B, hepatitis C, VDRL serology were non-reactive. Thyroid function test revealed primary hypothyroidism: TSH: >100 IU/l (high), free T3: 0.46 nanogram/deciliter (low) and free T4: 3.31 microgram/deciliter (low). Anti-TPO antibody was within normal limits. Chest X-ray and non-contrast CT scan of head were within normal limit. Cervical spine X-ray revealed straightening of cervical lordosis. X-ray of thoracic spine was within normal limits.

Contrast-enhanced MRI (CE-MRI) of whole spine with focus on cervical spine was done. It revealed long segment T2-hyperintense intramedullary signal extending from C6-D8 vertebral levels causing its mild expansion with patchy enhancement at D5-D6 level (Fig. 1). This was suggestive of longitudinally extensive transverse myelitis (LETM) in our patient. CE-MRI brain was within normal limits.

Differential diagnosis of LETM includes NMOSD, idiopathic, systemic lupus erythematosus (SLE), Sjogren's syndrome, spinal tumours, dural arterio-venous fistulas, acute disseminated encephalomyelitis (ADEM), and multiple sclerosis[5]. Accordingly, further work-up was done. Cerebro-spinal fluid analysis showed cell count of 5 cells, all mononuclear; protein: 122 mg/dl; sugar: 66 mg/dl; ADA: 0.84 IU/l (normal < 5 IU/l); IgG index – normal. Serum aquaporin 4 IgG was positive. Serum MOG antibody was negative. Serum ANA, anti-Ro antibody, anti-La antibody, APLA profile were negative. So, a final diagnosis of LETM due to neuromyelitis optica was made. She was started on injection methylprednisolone 1 gram intravenous daily for five days, followed by tablet prednisolone 40 mg once daily

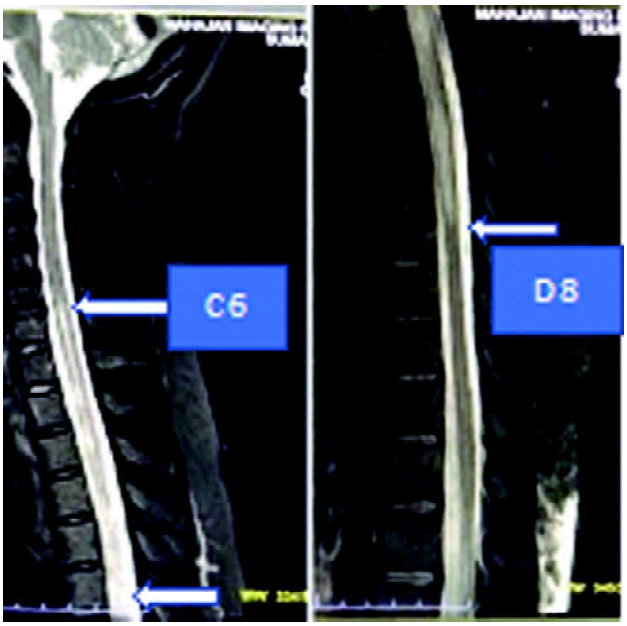

Fig 1: *CEMRI spine showing longitudinally extensive transverse myelitis from C6-D8 level.*

and tablet azathioprine 50 mg twice daily. Physiotherapy of both lower limbs was also initiated during hospital stay. Rehabilitation measures during the recovery period like use of crutches while walking, and avoiding physical exertion, were explained to the patient and her family members. She had no optic involvement during her course of stay in hospital and Visual-evoked potential study was normal in both eyes (Fig. 2). She improved symptomatically, gradually regained motor power in both her lower limbs and was able to walk with support. She was discharged after three weeks of oral steroids with plan to follow-up closely for relapse of myelitis and/or new onset optic neuritis while simultaneously optimizing the dose of immunosuppressant.

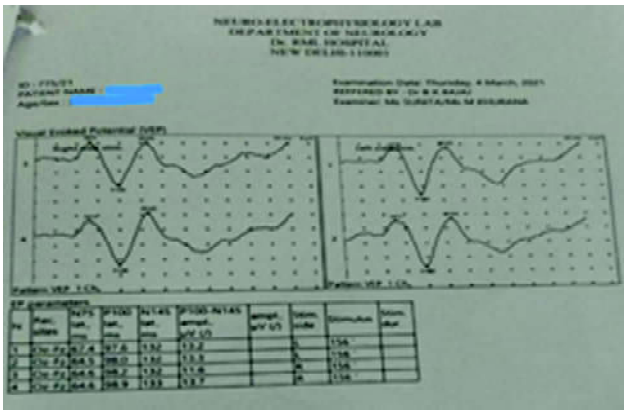

Fig 2: *Visual-evoked potential study showing normal P_{100} latency in both eyes.*

Discussion

Neuromyelitis optica is a demyelinating disease of the central nervous system. According to 2015 Internatinal diagnostic criteria for NMO-SD[3], seropositive NMO requires the presence of at least one core clinical characteristic among the following – optic neuritis, acute myelitis, area postrema syndrome, brainstem syndrome, acute diencephalic syndrome, symptomatic cerebral syndrome, along with presence of aquaporin-4 IgG antibody and exclusion of alternative diagnosis. Seronegative cases account for upto 30 per cent of NMO and they require more stringent criteria – presence of at least two core clinical criteria which must include acute myelitis with LETM or optic neuritis or area postrema syndrome with evidence of dissemination in time and space. Aquaporin-4 is widely distributed in the body with highest concentrations in the foot process of the astrocytes of the brain and spinal cord[6] which accounts for the classical clinical presentation of myelitis and optic neuritis. Antibody directed against this antigenic target causes compliment mediated lysis of the astrocytes which then leads to the widespread demyelination. NMO can be primary or secondarily associated with other autoimmune conditions like SLE, Sjogren's syndrome, etc., presence of aquaporin-4 antibody with LETM confers a risk of relapse of fifty per cent within 12 months[7]. The disease follows a relapsing course and seropositive cases are associated with higher degrees of relapse. NMO without optic neuritis is rarely encountered, as previously reported Flores-Alfaro *et al* in BMJ Case Reports CP 2019.

In our case, the presence of longitudinally extensive transverse myelitis along with the presence of aquaporin-4 antibodies clinched the diagnosis of NMO. However, it is worthwhile to note that around 30 - 40% cases will be seronegative NMO.

Standard treatment in the acute phase involves pulse methylprednisolone one gram for five days followed oral prednisolone at the rate of 1 mg/kg which is gradually tapered off. If no improvement is seen within days of administration of steroids, plasma exchange should be initiated. Some data support plasma exchange as first line therapy for relapse.

In the absence of treatment, fifty per cent patients are wheelchair bound or blind within the first five years of diagnosis, and there is a thirty per cent mortality rate[8]. This makes it imperative to promptly diagnose and initiate long-term immunosuppression for these patients to reduce both mortality and morbidity associated with NMO. Long-term immunosuppression is initiated at the first attack of seropositive NMO. Most commomly used agents are mycophenolate mofetil and azathioprine. The choice of agent depends on the age of the patient with azathioprine being selected in younger females. B-cell depleting therapy rituximab is given a second line therapy.

Learning points

1. Neuromyelitis optica is a distinct disease entity from multiple sclerosis and can have involvement of parts of central nervous system other than spine and optic nerve.
2. Rare instances of sparing of optic nerve in NMO have been reported, thus questioning the nomenclature of the disease.
3. NMO antibody (aquaporin-4) has a proven role in diagnosis of this disease, and criteria of diagnosis differ based on presence or absence of these antibodies.
4. Spinal cord involvement in the form of longitudinally extensive transverse myelitis is specific for NMO, and useful differentiating point from multiple sclerosis where it is more classically single segment involvement.

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CASE REPORT

JIACM 2022; 23 (1-2): 50-51

Chlorantraniliprole Poisoning

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Abstract

Insecticide poisoning has become a common modality for deliberate self-harm in India. The past three to four decades have seen a remarkable change in the incidence and type of poisoning. A number of new compounds are being added every year, making management of poisonings a challenge. Early recognition of toxic substance and its prompt management is the key for saving a patient's life. Here, we present a case of alleged suicidal chlorantraniliprole poisoning with an overview of symptoms and its management.

Case report

A 33-year-old male presented to our emergency department with alleged history of ingestion of unknown amount of insecticide – chlorantraniliprole – at his own residence, which was followed by abnormal body movements associated with frothing from the mouth. Patient was a farmer by profession and he had no history of known psychiatric illness or addictions. Patient's family denied any such similar episodes of suicide attempts in the past by the patient. Patient presented in a gasping state with frothing from his mouth and altered mental status within 3 hours of ingestion of the substance. Gastric lavage was done in a local hospital with normal saline and then patient was referred to our hospital.

On examination, the patient was afebrile with pulse rate of 38 beats/min, blood pressure not recordable, respiratory rate 28/min, SpO2 27% on room air. He was unconscious, pupils were pinpoint bilaterally, tongue bite was present with no active seizures. Patient had frothing from mouth, on auscultation heart sounds were normal with no murmurs, chest had no crepitations, and bilateral plantar reflex was mute. Patient was intubated immediately and put on mechanical ventilator (PRVC mode with PEEP 5 mmHg) in view of respiratory distress and GCS of 3/15, and started on noradrenaline infusion in order to maintain blood pressure.

National Poison Information Centre of AIIMS, New Delhi was called to enquire about available antidote of this compound. Upon knowing that no specific antidote is available and no case was reported in past in our area, symptomatic treatment was started. Patient developed bradycardia and went into cardiac arrest within 2 hours of hospital admission. CPR was initiated following ACLS protocol and atropine 1 mg IV was given. Patient was then started on atropine infusion 1 ml/hr. Patient was shifted to Intensive Care Unit for further care.

On admission, his haemoglobin was 14.1 g/dl and total leucocyte count was 26.3 cells/mm3 with differential leucocyte count showing 77% neutrophils and 12% lymphocytes. Renal function test showed urea of 38 mg/dl and creatinine 1.0 mg/dl with sodium and potassium 148 mEq/l and 3.00 mEq/l respectively. Prothrombin time was 19.7 sec, INR 1.53 sec. Urine routine and microscopy showed no albumin, few white blood cells and no RBCs. Patients ABG showed severe respiratory acidosis (pH 6.8, pCo2 92, lactate 6.59, bicarbonate 14.8). Chest X-ray showed no abnormality. Blood culture showed growth of *Klebsiella pneumoniae* on 3rd day. ECG showed QT prolongation, although 2D echo revealed no abnormality. Contrast enhanced MRI of brain showed mild diffuse cerebral oedema.

Routine investigations were repeated every day and antibiotics were upgraded depending on blood, urine, endo-tracheal tube and bronchoalveolar lavage culture and their sensitivity reports. His serum pseudo cholinesterase levels were low (1830 U/L) which was suggesting that this substance produces anti-cholinesterase-like effect. Subsequent serum pseudocholinesterase levels were repeated (3995 U/L) and dose of atropine was titrated accordingly.

Due to need for prolonged ventilation, patient was tracheostomisd on 7th day post-admission. Later, the patient's parameters improved and he became better symptomatically and clinically. Patient was then shifted to the general ward and tracheostomy tube was removed on 20th day of admission. Patient was discharged subsequently after a counselling session by psychiatrist after a long stay of approximately 25 days. Patient is being followed-up in

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the OPD and currently is asymptomatic.

Discussion

Chlorantraniliprole[1] is a newer generation insecticide gradually gaining in popularity in pest control. Chlorantraniliprole is chemically 3-Bromo-*N*- [4-chloro-2-methyl-6-(methyl carbamoyl) phenyl]-1-(3-chloro-2-pyridine-2-yl)-1H-pyrazole-5-carboxamide. Chlorantraniliprole is a novel anthranilic diamide insecticide that functions via activation of the insect ryanodine receptors within the sarcoplasmic reticulum causing impaired regulation of muscle contraction. Sustained release of calcium levels within the cytosol leads to muscle contraction, paralysis and eventual death of the organism. While insects possess a single form of the ryanodine receptor distributed in muscle and neuronal tissue, mammals possess three forms which are widely distributed in muscle and non-muscle tissues. Insects showed rapid cessation of feeding, lethargy, muscle paralysis, and death after ingestion of this compound[2].

No data is yet available regarding its toxic effect in humans. However, we can only hypothesize from this case that chlorantraniliprole acts like an organophosphorus compound since this patient had pin point pupils, excessive secretions (frothing), bradycardia, low pseudocholinesterase levels and improvement upon atropine infusion.

Studies showed no specific antidote is available, but timely intubation and ventilatory support for respiratory muscle paralysis, atropine infusions for bradycardia and treating of concomitant infections can go a long way in treating patients with chlorantraniliprole poisoning. Mishra *et al*[2] reported conduction defects by this compound in their case report. Bhattacharya *et al*[3] reported a case of suicidal attempt with this compound presenting with fever and altered sensorium. However, previous studies on chlorantraniliprole poisoning have not reported such adverse effects of this substance and this prolonged stay. Hence, we are reporting this case to create awareness about the dangerous effects of this compound which can aid in saving the life of a patient presenting with its ingestion.

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CASE REPORT

JIACM 2022; 23 (1-2): 52-56

Anti-ds DNA Negative Lupus Nephritis with Secondary Sjogren's Syndrome

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Abstract

Systemic lupus erythematosus and Sjogren's syndrome co-exist with presence of multiple circulating autoantibodies and variable prognosis. A middle-aged female presented with polyarthralgia, photosensitivity rash on the face and ear lobules, dyspnoea, swelling of both lower limbs with reduced urine output since few months. General physical examination showed pallor, poedal oedema, skin hyperpigmentation in malar prominence and both ears, BP - 160/90 mmHg. Eye examination showed grade 3 hypertensive retinopathy and positive Schirmer's test. Investigations revealed anaemia with leucopenia, creatinine - 1.48 mg/dl, low C3 levels, urine routine examination showed proteinuria and hematuria. USG abdomen showed bilateral grade 2 renal parenchymal disease. Echocardiography showed moderate conc LVH, minimal pericardial effusion. RA factor was positive. ANA showed RO 52 positive, SSA RO 60 positive and anti-ds DNA negative which was confirmed by ELISA. Renal biopsy confirmed diffuse proliferative glomerulonephritis lupus nephritis class IV. Labial biopsy revealed Sjogren's syndrome. She was treated with intravenous methylprednisolone, cyclophosphamide and hydroxychloroquine, leading to remission.

Key words: Systemic lupus erythematosus, secondary Sjogren's syndrome.

Introduction

The association of Sjogren's syndrome (SS) and systemic lupus erythematosus (SLE) was first highlighted in a case series published by Heaton in 1959[1]. The link between these 2 diseases was strengthened by positive anti-Ro and anti La antibodies in common to both diseases. The relationship between the 2 disease processes is debated. SS may be a secondary manifestation of SLE with autoimmune exocrinopathy. The anti-double stranded DNA antibodies (anti-ds DNA) are a specific marker for SLE associated with renal involvement by their deposition in glomeruli, subendothelial an subepithelial spaces, mesangium, basement membrane and tubules. The interaction with toll like receptor 9 (TLR 9), anti-ds DNA complexed with DNA could determine the activation of dendritic cells with consequent B and T-cells activation and the release of proinflammatory cytokines[2]. Despite the central role of these antibodies in the disease pathogenesis, a percentage of SLE patients ranging from 2 to 30% result negative for anti-ds DNA[3]. Association of Anti-Ro antibody alone with lupus nephritis is less known in literature. The prevalence of secondary Sjogren's syndrome (sSS) in SLE is 14 % - 17.8%[4]. We report a rare case of Anti-ds DNA negative lupus nephritis with sSS.

Case report

A 42-year-old female with no past medical history presented with pain in bilateral interphalangeal joints, dryness of mouth and eyes for 6 months, photosensitivity rash on the face (Fig. 1) and ear lobules (Fig. 2) for 3 months, facial puffiness, dyspnoea on exertion, swelling of both lower limbs and reduced urine output for 2 months. There was no significant family history or drug history. She was married with 3 children and had regular menstrual cycles. General physical examination showed pallor, bilateral pitting pedal oedema, facial puffiness, skin hyperpigmentation in malar prominence and both ears. P - 86/min, regular, BP - 160/90 mmHg, JVP not raised. Joint tenderness was present in bilateral proximal and distal interphalangeal joint of index finger and 3rd finger without redness or swelling. Fundus showed grade 3 hypertensive retinopathy. Respiratory, cardiovascular, abdomen and neurological system were within normal limits. Investigations revealed Hb - 7.9 g/dl, WBC - 3,500/cumm, platelets - 1,50,000, DLC - N 67, L20 M8 E3, ESR - 56 mm/hr. Peripheral smear showed microcytic hypochromic anaemia with leucopenia, creatinine - 1.48 mg/dl, urea - 49.2 mg/dl, uric acid - 7.4 mg/dl. LFT, electrolytes, lipids, thyroid profile, ECG, CXR were normal. RA factor was positive. ANA by ELISA showed 2+ (Titres > 1: 160), ANA 15 screen by Line Immuno assay method (LIA) showed RO 52 positive, SSA RO 60 positive, anti-ds DNA and anti-U1 RNP were negative. HIV, HbsAg, Anti-HCV and Anti-CCP were negative. Anti-ds DNA confirmed by ELISA was negative and positive for RO 52 and SSA RO 60 antibodies. Urine routine microscopy

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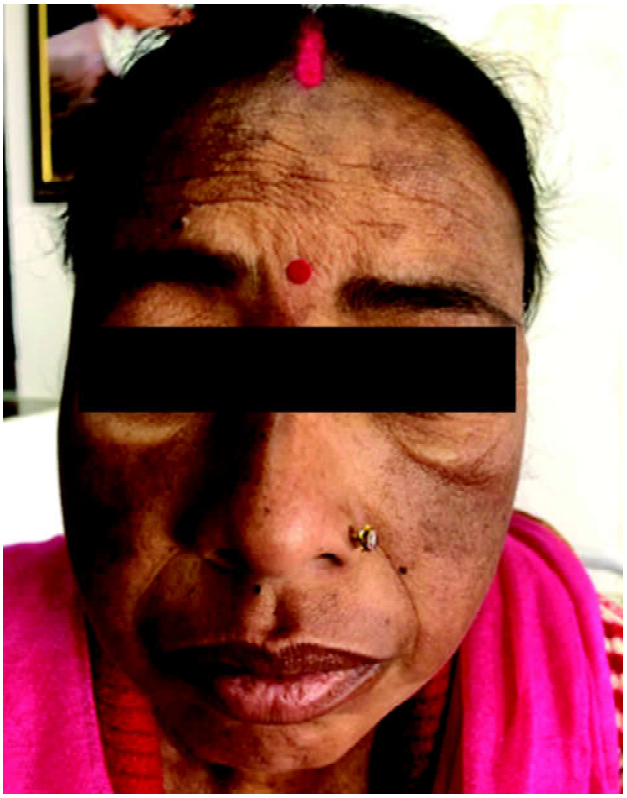

Fig. 1: *Hyperpigmented skin lesion with photosensitivity on malar prominence.*

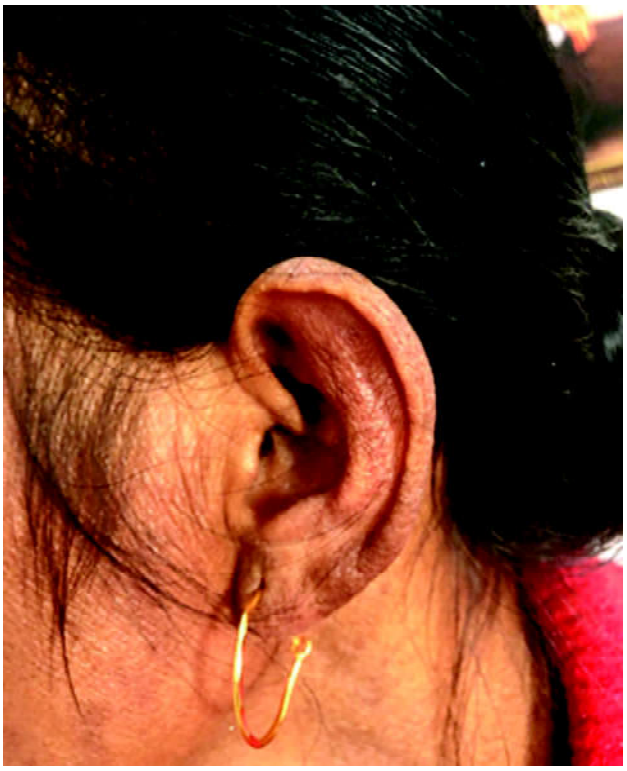

Fig. 2: *Hyperpigmented skin lesion with photosensitivity on ear lobules.*

showed protein - 500 mg/dl, RBC - 33 - 34/hpf. There were no dysmorphic RBCs or casts. Urine micro total protein - 783 mg/dl, urine protein: creatinine ratio of 7.04, complement levels of C3 were 14.7 mg/dl (Low) and C4 - 2.38 mg/dl (Low). Urine culture showed no growth. USG abdomen showed both kidneys normal in size, shape and maintained cortico-medullary differentiation with bilateral grade 2 renal parenchymal disease. Echocardiography showed moderate conc LVH, minimal pericardial effusion, grade 2 diastolic dysfunction, EF - 58%. Eye examination revealed severe dry eyes, tear film breakup time of 4 seconds in both eyes, tear meniscus height of 0.5 mcm in both eyes, Schirmer's test was 4 mm in right and left eye. There was no evidence of parotid gland enlargement or salivary gland swelling. Renal biopsy revealed diffuse

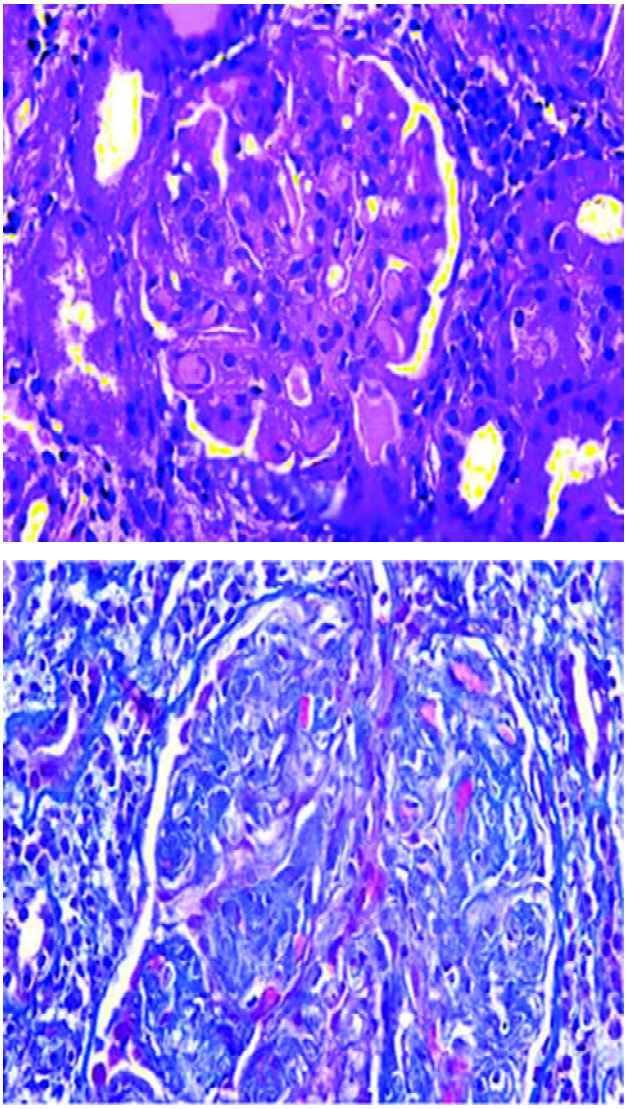

Fig. 3 and 4: *Renal biopsy showing diffusely thickened glomerular basement membrane and 13/18 glomeruli showing wire loop lesions and hyaline thrombi in majority of the glomeruli.*

endocapillary hypercellularity with lobular accentuation. 1/18 glomerulus showed partial cellular crescent, diffusely thickened glomerular basement membrane and 13/18 glomeruli showed wire loop lesions and hyaline thrombi in majority of the glomeruli (Fig. 3 and 4). Tubulointerstitial findings in renal biopsy revealed no chronic damage within the cortex, tubules containing uromodulin casts, no RBC casts seen, interstitium with moderate mixed inflammatory infiltrate consisting of few polymorphs, lymphocytes, and abundant plasma cells. Active tubulitis was present. Morphological and immunofluorescence features of diffuse proliferative glomerulonephritis, lupus nephritis class IV with activity index of 13/24 (Fig. 5). SLEDAI score was 16 (Presence of arthritis, haematuria > 5 RBCs/HPF excluded infection, stone, presence of proteinuria, new rash, low complement). Labial biopsy measuring 1.2 x 1 x 0.5 cm in dimensions with hematoxylin (Fig. 6) and eosin stain (Fig. 7) showed non keratinised squamous epithelium with connective tissue of salivary gland consisting of mucous acini. At least 2 foci (> 50 mononuclear infiltrate) of periductal lymphocytic infiltrate seen adjacent to normal acini. Calculated focal score of 3 suggestive of Sjogren's syndrome. Systemic lupus erythematosus Disease Activity Index (SLEDAI) score was 16. Score of 6 and above are considered to be consistent with active disease requiring therapy. Based on the above findings of renal biopsy, labial biopsy, positive anti-RO 52 and SSA RO 60 antibodies, SLEDAI score of 16, diagnosis of anti-ds DNA negative lupus nephritis with secondary Sjogren's syndrome was made. She was treated with intravenous pulse therapy with methylprednisolone 500 mg for 3 days followed by injectable cyclophosphamide 500 mg i.v., once a month for 6 months, T. hydroxychloroquine 200 mg BD, T. cilnidipine 10 mg OD, T. Prednisolone 40 mg OD, and subsequently started on Telmisartan 20 mg OD. Follow-up after 6 months showed s. creatinine of 1.2 mg/dl and urine micro total protein was 360 mg/dl.

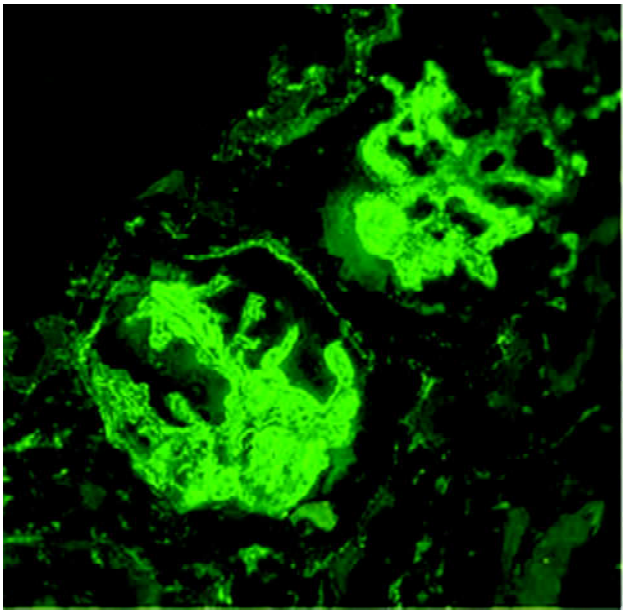

Fig. 5: *Immunofluorescence features of diffuse proliferative glomerulonephritis – lupus nephritis class IV.*

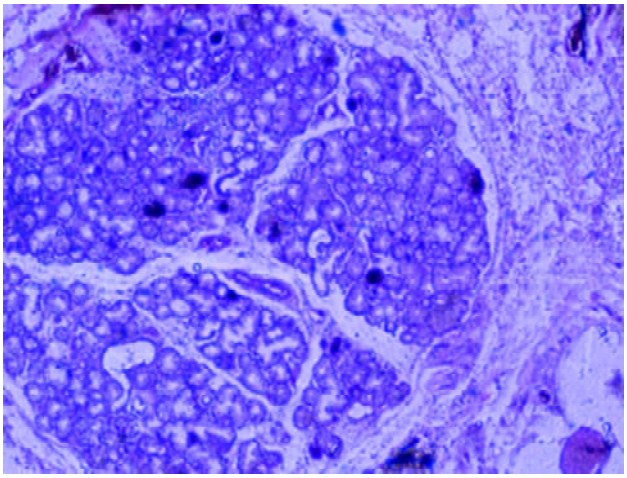

Fig. 6: *Labial biopsy haematoxylin stain showing > 50 mononuclear infiltrates of periductal lymphocytic infiltrate suggestive of Sjogren's syndrome.*

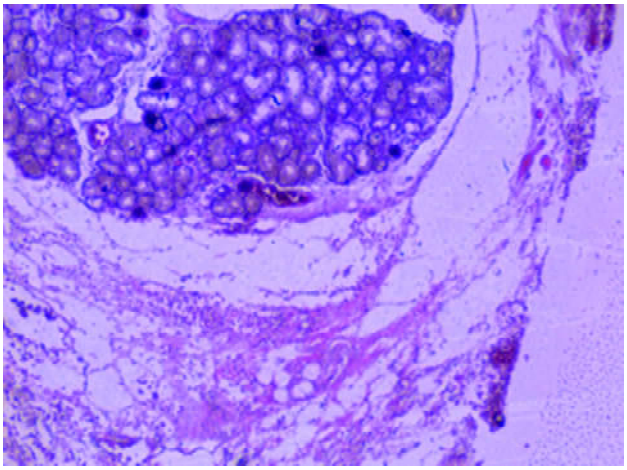

Fig. 7: *Labial biopsy eosin stain showing > 50 mononuclear infiltrates of periductal lymphocytic infiltrate suggestive of Sjogren's syndrome.*

Discussion

SLE, a serologically diverse, chronic autoimmune disease involving multisystem is diagnosed after consideration of clinical, laboratory, pathological findings, and validated classification systems which include the revised American College of Rheumatology (ACR) criteria and the Systemic Lupus International Collaborating Clinics (SLICC) criteria[5].

The 2 main types of renal injury identified on renal pathology are immune complex deposition disease as characterised by the known classifications of lupus nephritis (LN) and non-immune complex disease including thrombotic microangiopathy, podocytopathy and tubulointerstitial disease. Immunofluorescence (IF) is characteristic for the presence of the 3 classes of immunoglobulins (IgG, IgM, IgA) and classic and alternative complement pathway deposits (C3, C4, C1q). This patient presented with simultaneous renal and extrarenal manifestations of SLE. Very few patients were identified in the literature with renal and extra-renal manifestations and absent serologies for SLE. Among the autoantibodies which have been detected in the sera of patients with autoimmune disease are anti-Ro60 (anti-SSA) and anti-Ro52 (TRIM21)[6]. It is reported that anti-Ro60 is detected in SLE and Sjogren's syndrome with a much higher percentage in cutaneous lupus erythematosus while anti-Ro52 is associated with more diseases as interstitial lung disease, congenital heart block, neoplastic diseases and infections. Elsayed *et al*[7] reported that patients with LN class-III and class-IV (focal and diffuse) had the highest frequency of positivity for the five autoantibodies, where 66.6% for anti-dsDNA, 61% for anti-nucleosome, 67.38% for anti-histone, 52.37% for anti-Ro60, and 44.72% for anti-Ro52. Fabrizio *et al*[8] reported that renal involvement was more frequent in anti-ds DNA positive and serositis was more frequent in anti-ds DNA negative SLE. Our patient had negative anti-ds DNA negative lupus nephritis proved in renal biopsy. Jain *et al*[9] reported a case of negative anti-ds DNA and positive anti-Ro antibodies LN with its possible role in the pathogenesis of LN. SS may be classified as primary Sjogren's syndrome (pSS), or secondary Sjogren's syndrome (sSS) (also called polyautoimmunity), due to its association with other autoimmune disorders, especially SLE, rheumatoid arthritis (RA) and Systemic sclerosis. The classification criteria of the American-European Consensus Group (2002)[10] for sSS are based on association with other autoimmune diseases and combination of the following items: 1) dry eye symptoms; 2) dry mouth symptoms; 3) abnormalities in objective ocular tests; 4) alterations in objective oral tests; 5) positive circulating anti-Ro (SSA) and/or anti-La (SSB) antibodies; and 6) histological analysis of the minor salivary glands revealing a focal lymphocytic sialadenitis (focus score $\geq$ 1/4 mm^2 of glandular tissue). The prevalence of secondary Sjogren's syndrome ranges between 6% and 19% in SLE[11]. To be classified with secondary Sjogren's syndrome, patients must have symptoms of keratoconjunctivitis sicca or xerostomia and objective evidence of decreased tear or salivary flow which is present in this patient. Symptoms of dry eye and dry mouth for > 3 months, and/or feeling the presence of foreign bodies in the eyes, and/or use of artificial tears more than three times a day and/or recurrent or persistent parotid gland enlargement, and/or difficulty swallowing solid foods, requiring fluid intake for relief of this symptom. Prevalence of autoantibodies of Anti-ds DNA in SLE is 60% and Anti-Ro/SSA in SLE is 30% which is associated with Sjogren's syndrome, photosensitivity, subacute cutaneous lupus erythematosus, neonatal lupus, congenital heart block[12]. ACR/European League Against Rheumatism (EULAR) 2016[13] have proposed new classification criteria for pSS validated specifically. The Johns Hopkins Lupus cohort study conducted by Baer *et al*[14] showed that 14.5% patients had sSS with SLE and had a higher frequency of photosensitivity, oral ulcers, ocular involvement, Raynaud's phenomenon, and anti-Ro antibodies, and a lower frequency of renal disease, anti-dsDNA antibodies, and RNP antibodies. In SLE patients, anti-Ro antibody associates to haematological manifestations (anaemia, leucopoenia, lymphopenia, and thrombocytopenia), palpable purpura and sSS. Careful analyses of the clinical features and investigations are important for the differential diagnosis between both syndromes.

Conclusion

The possible development of sSS in SLE patients should be considered in patients with positive anti-Ro (SSA) antibody. sSS-SLE patients have a peculiar profile of clinical and serological manifestations, such as higher prevalence in females, older age of disease onset, and longer disease duration.

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CASE REPORT

JIACM 2022; 23 (1-2): 57-59

Hungry and Heavy, Hidden Tumour and High Insulin: A Saga of Insulinoma

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Abstract

Hypoglycaemia in non-diabetics can be due to Renal failure, Addison's disease, Liver failure and due to drug effects. Excessive endogenous insulin secretion from pancreas is a rare cause of hypoglycaemia. We hereby report the case of a young male who presented primarily for evaluation and treatment of recent excessive weight gain. History revealed episodes of sweating and general weakness over several months. The patient was resorting to excessive feeds to counter these episodes. Investigations revealed the cause to be an insulinoma. Surgical removal of the tumour corrected the symptoms and he lost significant weight after surgery.

Key words: Whipple's Triad, neuroglycopenia, islet cell tumours, obesity.

Introduction

Hypoglycaemia is commonly encountered in patients on therapy for diabetes, but also occurs in patients with renal insufficiency, liver disease, malnutrition, or sepsis. Other but less common causes are insulin secreting pancreatic and some non-pancreatic tumours. Insulinomas are the most common functioning endocrine neoplasm of the pancreas having inappropriately high secretion of insulin[1]. Patients have hypoglycaemic episodes, more characteristically fasting hypoglycaemia. However, the presenting symptoms of insulinoma vary a great deal and most of the time the condition goes unrecognised and undetected for many years. We hereby report the case of a young male who came to hospital primarily seeking medications for weight loss but after evaluation was found to have an insulinoma.

Case report

A 24-year-old male shopkeeper presented to the Medicine Out Patient Department of our hospital for consultation regarding obesity. He and his parents had noted significant increase in body weight over last few months. On questioning it was revealed that he was having episodes of light headedness associated with diaphoresis, palpitations, tremulousness, feeling of weakness, for the last one-and-a-half years, which were relieved after eating something – especially sugary foods. Over-exertion brought out such episodes more frequently. The parents had noted that the patient was consuming more frequent feeds to overcome the repeated episodes of weakness. He had ignored the symptoms and had not consulted any doctor prior to the present consultation. The patient was admitted at his request for further evaluation and investigations.

He had no history of diabetes or thyroid disease. He was not on any medications for other ailments. He was not taking complementary food or medical supplements. His diet was omnivorous. There was no history of disturbed sleep or snoring. He denied smoking and alcohol habits.

On examination he was obese with weight 90 kg, height 168 cms, BMI 31.9 kg/mt^2. Blood pressure 150/90 mmHg, and respiratory rate 20 per minute. The abdomen showed no palpable masses. Cardiovascular and respiratory systems were normal, and on nervous system examination there were no deficits.

Haemogram was normal. Urea, creatinine, electrolytes, chest X-ray, ECG were within normal limits. RBS was 60 mg/dl. A fasting Blood sugar done next day was 57 mg/dl, HbA1c was 5.2%. Ultrasound abdomen was reported as normal. However, in view of the clinical picture, highly suggestive of an insulinoma, a computed tomography of the abdomen with contrast was done which demonstrated a well-defined hyper-vascular lesion involving pancreas. There were no intraabdominal lymph nodes seen.

Other investigations were as follows: Fasting Insulin level was elevated at 44.8 micU/l (normal range 2 to 25 micU/ml). There was elevated fasting C-peptide level of 11.4 ng/ml (normal range 0.81 to 3.85 ng/ml). Serum cortisol level was 6.2 µgm/dl (normal 4.82 to 19.5 µgm/dl). Thyroid function tests were within normal range.

The patient underwent surgical removal of the pancreatic mass (Fig. 1). Post-operative glucose levels were never in

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the hypoglycaemic range and were always more than 100 mg/dl. Histopathological evaluation (Fig. 2, 3) revealed nests of cells separated by well vascularised thin fibrous stroma. The neoplastic cells had round, moderately anisomorphic nuclei with small nucleoli and eosinophilic granular cytoplasm. This was consistent with an endocrine neoplasm – insulinoma of pancreas.

The patient was discharged in good health with proper normal levels. Insulin and C-peptide levels were not repeated because of symptomatic improvement. Subsequent follow-up showed significant weight loss to reach 68 kgs and normalisation of BMI to 24.1 kgm/mt^2.

Discussion

The incidence of insulinoma is around 1 to 4 per million per year[2,3]. More commonly, insulinoma is a single benign tumour, and only in 5.8% of cases, it can be malignant[2]. In patients with insulinoma, there is continued production of insulin in spite of a lower glucose level. Fasting hypoglycaemia is the most characteristic finding of insulinoma, reported in 73% of the population and around 20% of patients have both fasting and post-prandial hypoglycaemic symptoms[4].

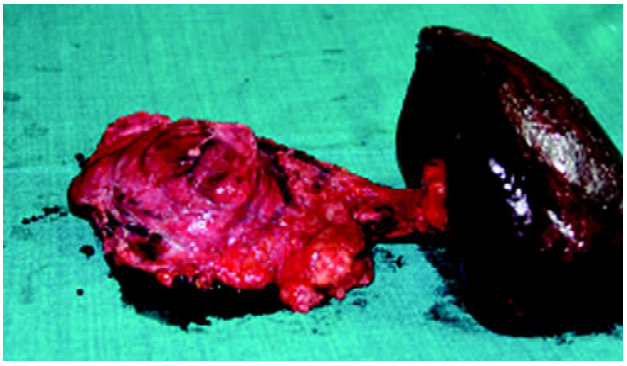

Fig. 1: *Post-operative specimen showing the tumour. The spleen is also seen.*

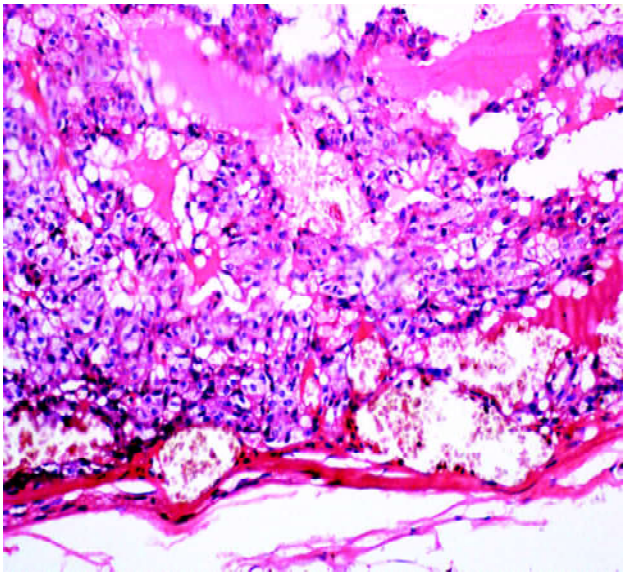

Fig. 2: *Histopathology of biopsy material. Nests of cells separated by thin fibrous stroma. Neoplastic cells are round, have moderately anisomorphic nuclei and eosinophilic granular cytoplasm.*

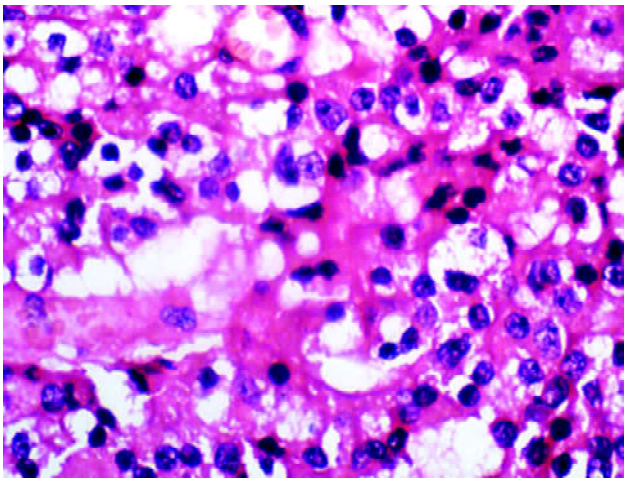

Fig. 3: *Histopathology of biopsy material. The characteristic "Salt and Pepper" chromatin is seen. Suggestive of solid pseudopapillary tumour.*

Hypoglycaemia can present with sympathoadrenal activation symptoms, including palpitations, tremulousness, and diaphoresis. Severe hypoglycaemia can cause neuroglycopenic symptoms, including blurry vision, confusion, seizures, or a change in behaviour. Amnesia of the hypoglycaemic event is common.

A 72-hour fast is the gold-standard test for diagnosing insulinoma[5]. It is useful when the Whipple triad is not observable[6]. The combination of plasma glucose concentration below 55 mg/dl, insulin level greater than or equal to 3 microUnits/ml, C-peptide level greater than or equal to 0.6 ng/ml, and a simultaneous negative sulfonylurea level indicates that the hypoglycaemia induction is by hyperinsulinaemia.

CT detects 70 to 80% of the tumours where the insulinoma usually presents as a small solid mass, which enhances after contrast[7]. Magnetic resonance image (MRI) detects about 85% of the insulinomas that seem to enhance homogeneously after gadolinium administration[8]. 90% of insulinomas are benign, and it is essential to surgically remove this tumour in view of potentiality to cause hypoglycaemia-related deaths. Surgical resection is recommended for local disease[9]. If the tumour is unresectable or already metastasized, or if the patient is a poor surgical candidate, diazoxide is an option[10].

Insulinoma is known to have varied presentations in different age and gender groups. Suresh *et al*[11] reported the case of a young female patient presenting with unwitnessed cardiac arrest later diagnosed as insulinoma. In another case report Eichelberger *et al*[12] describe the case of a pancreatic insulinoma in an 86-year-old female, a rare presentation at that age. There was absence of clinical symptoms for up to one year prior to hospitalisation. In most other settings also the diagnosis of an insulinoma is done late inspite of the availability of improved diagnostic techniques.The median duration of symptoms before diagnosis remains variable and can be 12 - 18 months on an average[13].

Our patient was diagnosed after two years of onset of symptoms. He was having episodes of hypoglycaemia manifesting as hunger, but he was "managing" the same by overeating, and this gradually led him to obesity. Notably, he did not have other symptoms such as palpitations, sweating, etc. The unique feature of this case is that the patient actually sought medical care and therapy for obesity and not for any of the hypoglycaemic symptoms. This case once again reveals the varied presentation of an insulinoma.

Conclusion

A high index of suspicion towards insulinomas in all young adults presenting with suggestive symptoms can provide early diagnosis leading to better care – and even cure – in this potentially lethal condition. It is essential for physicians to keep in mind insulinomas as a rare cause of weight gain in patients with hypoglycaemic episodes.

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CASE REPORT

JIACM 2022; 23 (1-2): 60-62

Cerebral Fat Embolism Syndrome – Pathogenesis and Treatment

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Abstract

We describe a case of cerebral fat embolism – which developed 3 days after roadside accident, in a young boy who suffered limb fracture of femur and tibia. In cerebral fat embolism that manifests chiefly as disturbances of cerebral circulation and ischaemia, chest dyspnoea and pulmonary manifestations are strikingly lacking leading to misdiagnosis or delay in its diagnosis. The present case chiefly developed cerebral fat embolism syndrome. Early recognition and comprehensive management is warranted for a better outcome. Aetiopathogenesis, presentation, diagnosis and treatment of cerebral fat embolism is briefly described and discussed.

Key words: Cerebrum, fat embolism, limb fracture.

Introduction

Fat embolism is defined by the presence of lipid droplets in the blood circulation blocking the small vessels. The term fat embolism syndrome refers to the clinical scenario following an insult that releases fat droplets in the circulation with resultant pulmonary and systemic involvement. The severity of fat embolism depends on the size and quality of the lipid droplets, and the level of systemic involvement – lung, brain. or both. The diagnosis of pulmonary or mixed type (pulmonary and brain) is often easier as pulmonic features like dyspnoea, haemoptysis, wet rales in the lungs, patchy shadows on imaging studies, hypoxaemia, etc., are recognised easily; while central fat embolism manifests as disturbances of cerebral circulation that typically manifests in isolation from development of acute confusional state/ altered level of consciousness to seizures and focal defects[1,2]. In cerebral fat embolism, that manifests chiefly as disturbances of cerebral circulation and ischaemia, chest distress, dyspnoea and pulmonary manifestations are strikingly lacking, leading to misdiagnosis or delay in its diagnosis.

Case report

A 24-year-old male was hospitalised at the department of orthopaedics following a traffic accident. History of concussion, seizures, vomiting were denied. Physical examination revealed normal mental status with normal pupillary and corneal reflexes. He was found to have comminuted fractures of the right limb – femur neck and tibial shaft. His vitals were maintained. Lungs, CVS and per abdomen examinations were unrevealing. SpO_2 was normal. The detailed neurologic examination was within normal limits. The right lower limb was fixed by external fixation with restrained movements. After 24 hrs, the patient's consciousness deteriorated, X-ray chest done was normal, SpO_2 was 88%. Patient was transferred to medical ICU, brought in a semi-comatose condition, and was responding to questions with delay. Pupillary and corneal reflexes were normal. Systemic examination, including neurologic, were normal. X-ray chest and HRCT done were within normal limits. Blood gas analysis reports were within normal limits. MRI brain showed long T1 T2 signals with diffuse punctuates and high signal intensity as diffusion weighted imaging DW1, throughout bilateral cerebral cortex, white matter, basal ganglion and thalamus (Fig. 1). Patient was provided with symptomatic and supportive treatment with nasal oxygen, fluids and methylprednisolone 500 mg 8 hrly x 5 days, LMWH in dose of 0.6 cc BD x 5 days. Repeat counts and blood gas analysis were normal on day 5 of hospitalisation and subsequently within normal limits. Repeat MRI after 2 weeks revealed significant regressions of diffuse punctuate and high signaled intensities on DW1. Patient was discharged after 2 weeks of hospitalisation with a diagnosis of cerebral fat embolism and long bone fractures with normal vitals and systemic examination with advice to seek an orthopaedic consultation.

Discussion

Almost all cases of fat embolism syndrome (FES) are due to fractures of long bones and/or pelvic bones. However, certain cases are non-orthopaedic and/or non-trauma

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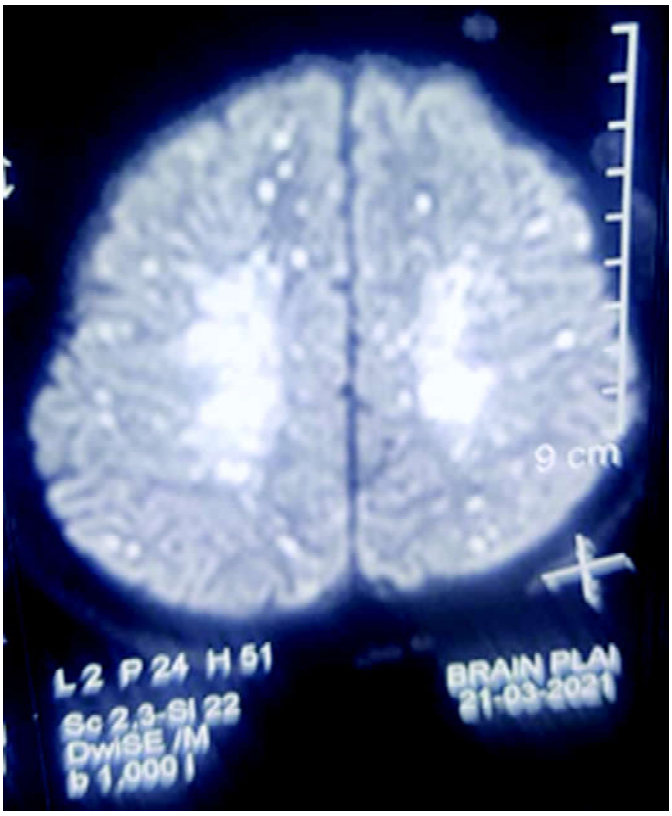

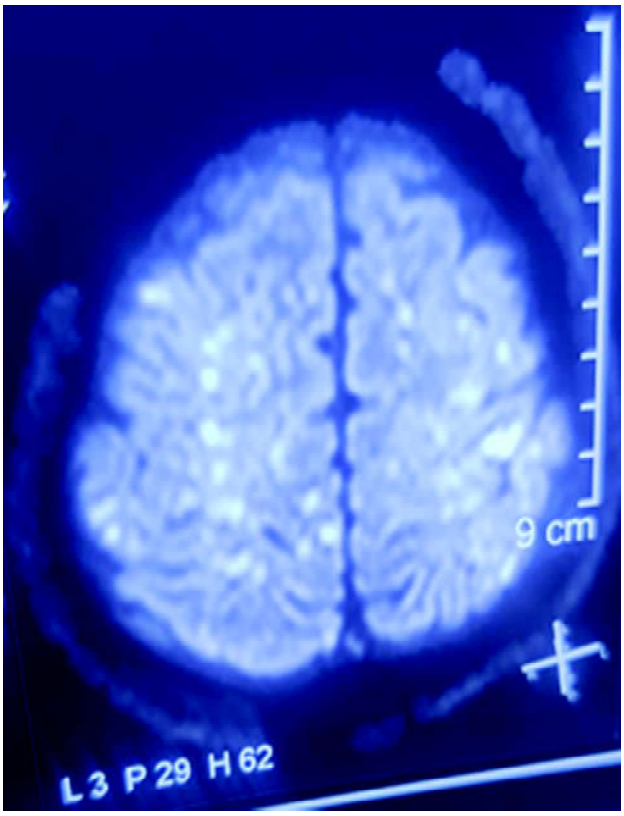

Fig. 1: *Shows T1 and T2 signals with diffuse punctuates and high signal intensities on DW1 throughout bilateral cerebral cortex, white matter, basal ganglion and thalamus.*

related. Rib fractures also have been responsible for FES. Surgical trauma occurring during surgical procedures such as hip/knee arthoplasty where excess bone marrow needs to be handled, interosseous access, infusion of lipid-based material, contrast agents, intramuscular injections of oil for cosmetic purposes, fatty liver disease are relatively uncommon causes of this syndrome[3]. In one autopsy data, in non-traumatic population, 63% cases had FES, representing the entity to be subclinical[4].

The exact pathogenesis is unknown. The present case had inflicted roadside trauma with long bone fractures of right lower extremity. He was conscious for 24 hrs post-injury and developed consciousness disturbances 30 hrs post-injury. Patient respiration was stable without obvious dyspnoea and pulmonary manifestations. SpO_2 was normal initially on admission but dropped to 88% after 24 hrs. Patient's X-ray chest and HRCT were normal. This patient's history was denied for any lucid interval, focal lesions. The MRI showed diffuse abnormal signals in the bilateral cerebral hemispheres, long T1 T2 signals with diffuse punctuates and high signal intensity on DW1 throughout bilateral cerebral cortex, white matter, basal ganglion, and thalamus. A possibility of cerebral fat embolism was strongly entertained. Though fat embolism often occurs in the lungs, an isolated brain fat embolism is however rare and its pathogenesis is not fully understood. Though SpO_2 done was 88% for a short period, subsequent X-ray chest and HRCT were within normal limits. Biochemical-induced hypoxaemia or shunt development was postulated as a probable mechanism for cerebral manifestations in the case. Echo was also done. It did not reveal evidence of patent foramina ovale or any cardiac shunt. Though in normal, PFO is open in 35% healthy individuals.

In cerebral fat embolism, normally the embolus from the venous system migrates to intracranial vessels only through pulmonary circulation. The ischaemia and hypoxaemia of pulmonary circulation manifests with spectrum of clinical features, but without the development of vital pulmonary features. Cerebral changes are noted in 86% of patients with FES. The present patient developed cerebral fat embolism bypassing the pulmonary manifestations and paradoxical embolisation. Two theories have been postulated under such circumstances:–

I. Microembolisation: which may occur when emboli are very small. Perhaps because of a few fat droplets with a small diameter < 7 - 20 µm which pass through the pulmonary capillaries into the systemic circulation

and lodge in the cerebral vessels[5]. This mechanism is supported by the findings of embolised material to systemic side in absence of cardiac shunts or PFO. The theory does not explain why the patient remains normal for a 24 - 48 hrs interval following acute insult of injury.

II. The other postulation is based on biochemical theory. The hypothesis is that the embolised fat degrades in two toxic intermediaries with pro-inflammatory effects and is supported by enhanced level of free fatty acids and cytokines including TNFα, IL-1, IL-6 and CRP. CRP is elevated in the present case suggestive of increased inflammation. The elevated level in the present case appears to be responsible for lipid agglutination obstructing blood flow in microcirculation.

The production of proinflammatory lipid mediators may explain the 24 - 48 hrs delay from the injury event to clinically apparent FES. This latent period explains the onset of symptoms that coincides with degradation and agglutination of fat and development of intermediaries. The clinical classic triad of hypoxaemia, neurologic abnormalities, and petechial rash are sometimes considered specific for FES. Rashes are red-brown, seen in 20 - 50% of cases, seen on non-dependent regions including head, neck, anterior chest, axilla and conjunctiva. Hypoxia sometimes may be part of ARDS syndrome, often noted in 96% of cases. ARDS develops in 50% of such individuals. Such cases may require assisted ventilation for severe hypoxaemia. None of these classic triad features, however, are specific for FES. Less commonly, patients of FES present with anaemia, thrombocytopenia, DIC, hypotension, shock[6].

The diagnostic evaluation requires assessment for severity of the disease of FES especially in the absence of pulmonary manifestations and bid for the need of supportive care in the case. Early intervention for the management of fracture may prevent development of FES. Though here, prompt supportive care remains the mainstay of therapy in clinically symptomatic brain FES. Management requires oxygen therapy, fluid resuscitation, steroids, low molecular weight heparin and NIV or invasive mechanical ventilation whenever applicable.

Use of corticosteroids, though controversial, but rationale for the use is based upon its anti-inflammatory effect targeting stabilisation of cell microsomal membranes, reduction of inflammatory response caused by FFA, capillary permeability and reducing tissue oedema. Methylprednisolone provided as 500 - 1,000 mg/day x 3 - 5 days or dexamethasone 20 - 30 mg/day or even 60 mg/day until brain oedema subsides.

5% alcohol glucose solution can inhibit formation of fat droplets. Low molecular weight heparin can reduce blood viscosity and reduce stress-induced chemical bio-metabolites and improve microcirculation. Low molecular weight dextran also is used in clinical practice[7].

Effectiveness of early hyperbaric oxygen therapy for cerebral fat embolism has been found useful as it enhances oxygen content, pressure as well diffusion in capillaries of brain micro-circulation[5]. In isolated cerebral fat embolism, chest distress, dyspnoea and pulmonary manifestations are strikingly lacking leading to misdiagnosis or delay in its diagnosis. Early recognition of features are warranted.

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CASE REPORT

JIACM 2022; 23 (1-2): 63-69

The Spectrum of Imaging Findings of Hypoxic-Ischemic Encephalopathy: A Must Know for the Critical Care Specialist

Vikash Kumar, Rajaram Sharma**, Tapendra Nath Tiwari**, Saurah Goyal**, Kritika Sharma*, Sunil Chugh***, Girish Mathur*****

Abstract

Hypoxic-ischemic injury (HII) is a worldwide cause of mortality and critical neurological disability. Patients may present with acute onset neurological deficit or acute, chronic neurological events. Imaging investigations are essential to make the diagnosis and proper treatment. There are many factors influencing findings on imaging, such as the patient's age that defines brain maturity, duration and severity of injury/insult, type of injury, and timing of imaging investigation. In HII, term and preterm preferentially affects the deep grey matter, with perirolandic involvement seen in later age group. There are less profound injury characteristics such as periventricular white matter injury in preterm neonates, intraventricular haemorrhage and parasagittal watershed territory infarct in term neonates. In the postnatal period, severe HII results in diffuse grey matter insult with associate the sparing of the perirolandic cortex and posterior circulation supplied structures. Profound hypoxic ischaemia insult is characterised in children and adults, injury seen in the deep grey-white matter nuclei, cortices, hippocampi and cerebellum. Imaging modality provides valuable information about the disease and helps in management in acute onset. In critical care settings, it is of utmost importance to have a basic idea about the imaging features of HII to start the appropriate treatment. In most cases, there is a long time gap between the imaging and its reporting by a radiologist, and the time is what a critical care physician often does not have.

Introduction

Hypoxic-ischemic injury (HII) is an encompassing mechanism, which starts during the insult/injury and extends into the recovery stage after resuscitation. Hypoxic-ischemic encephalopathy (HIE) in infants, children, and adults, also known as global HIE, is seen in many instances and often has a death or grievous neurological sequelae. Neuro-imaging with magnetic resonance imaging (MRI) plays an essential role in diagnosis, early interventions workup, evaluation of the severity of the disease, injury extension and follow-ups[1,2,3]. Treatment of HII includes long-term supportive care to prevent the current injury that occurs immediately after the causative insult/injury. Making early diagnosis and mapping out the extension of injury is essential for a better disease prognosis. Many treatments options are available, including administration of excitatory amino acid antagonists and hypothermia. These treatments have a limited time of effectiveness (in a few cases, six hours), so early imaging investigation is critically important for better prognosis and proper treatment[4]. Imaging findings in HII are fluctuating, which depends on brain maturity, duration of insult, the severity of the disease, timing of the investigation, and type of imaging modality used for investigation. On imaging, acute or early insult findings can be subtle and are often ignored. So, for detecting the subtle findings, it is of utmost necessity to know about the pattern of injury in the suspected case of the HII.

Most commonly, HII is caused by low cerebral blood flow (known as ischaemia) and reduced blood oxygenation (known as hypoxaemia). Infants and children commonly have asphyxial events, (i.e., drowning, chocking, or nonaccidental trauma) that causes hypoxic brain ischemic injury, while adults have secondary hypoxia during a cerebrovascular disease or cardiac arrest[5].

Severe asphyxial injury in postnatal infants and young children between 1 - 2 years of age results in injuries to hippocampi, lateral geniculate nuclei, the corpora striata and cerebral cortex (particularly the anterior frontal and parietooccipital cortex), with relative sparing of the thalami and perirolandic cortex[6].

Mild-to-moderate asphyxia in postnatal infants and young children result in watershed zone injury involving the subcortical white matter and cortex.

In adults, mild-to-moderate injury lead to watershed zone infarcts, while the severe insult primarily affects the grey matter structures; cerebellum, hippocampi, cerebral cortex (in particular the sensorimotor and visual cortices, although involvement is often diffuse), the basal ganglia and thalami[7].

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Case series

Case 1

A 13-month-old boy with a history of birth asphyxia and delayed milestones underwent an MRI scan. Diffusion-weighted image (Fig. 1A) demonstrated abnormal high signal intensities with loss of grey-white matter differentiation in bilateral parietal and occipital lobes; FLAIR (Fig. 1B) and T2WI (Fig. 1C) showed subtle hyperintense signal in periventricular white matter in peritrigonal area and hypointense signal in corresponding areas on T1WI (Fig. 1D). The diagnosis was made as mild-to-moderate HII.

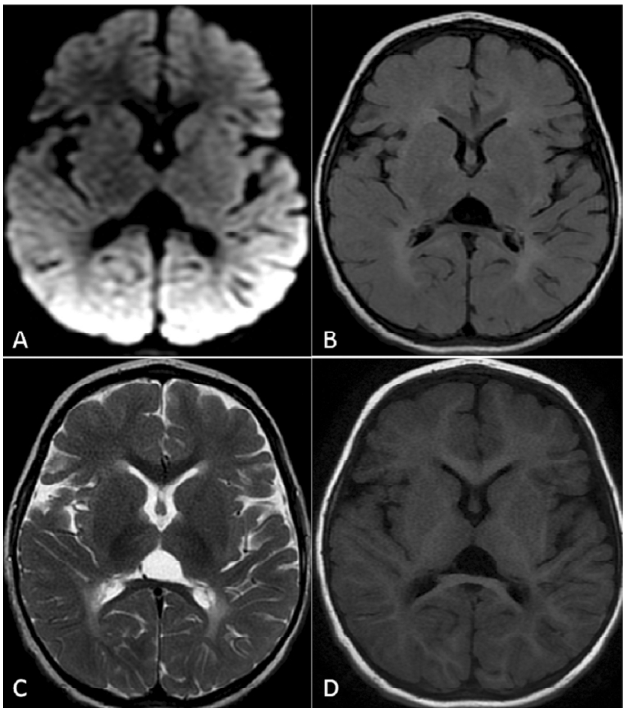


Fig. 1: *A 13-month old boy with a history of birth asphyxia and delayed milestones underwent a magnetic resonance imaging (MRI) scan. (A) Diffusion-weighted image (WI) demonstrates abnormal high signal intensities with loss of grey-white matter differentiation bilaterally in parietal and occipital lobes, (B) Fluid-attenuated inversion recovery and (C) T2WI are showing subtle hyperintense signal in periventricular white matter in peritrigonal area and hypointense signal in corresponding areas on T1WI (D).*

Case 2

Non-contrast computed tomography head in a two-year-old boy who presented with status epilepticus revealed features of chronic mild-to-moderate hypoxic-ischemic injury in the form of areas of cystic encephalomalacia/gliosis, focal loss of white matter and colpocephaly (dilated occipital horns) (Fig. 2).

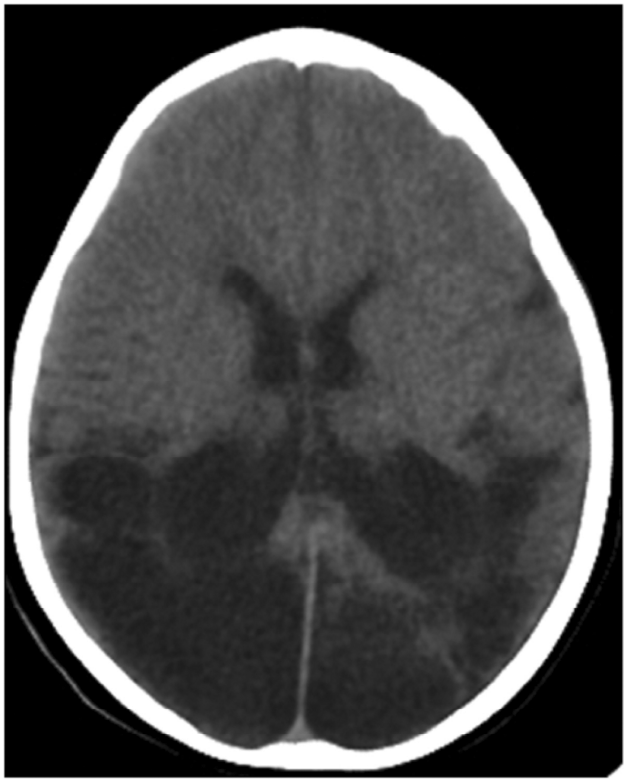
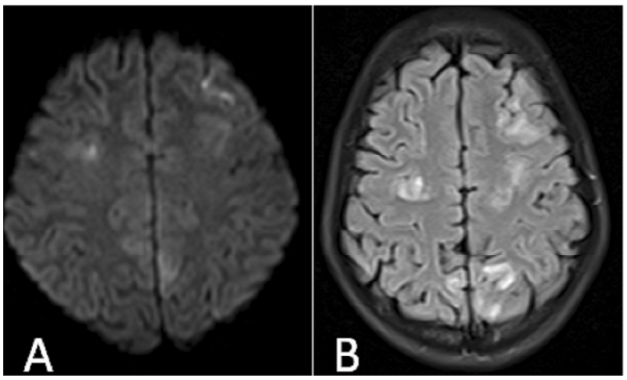


Fig. 2: *Non-contrast computed tomography head (axial) in A 2-year-old term boy showing features of chronic mild moderate hypoxic ischemic injury in the form of areas of cystic encephalomalacia/gliosis, focal loss of white matter and colpocephaly (dilated occipital horns).*

Case 3

A 15-year-old female came to the hospital with complaints of generalised tonic-clonic seizure for the last five hours. The patient underwent an MRI scan in which diffusion-weighted images showed diffuse restriction in subcortical regions of bilateral parietal lobes (watershed territory infarcts) (Fig. 3A). FLAIR (Fig. 3B) and T2 (Fig. 3C) weighted images demonstrated high signal intensities in the corresponding areas suggestive of cytotoxic oedema. A diagnosis of mild-to-moderate global HII was made based on these MRI findings.



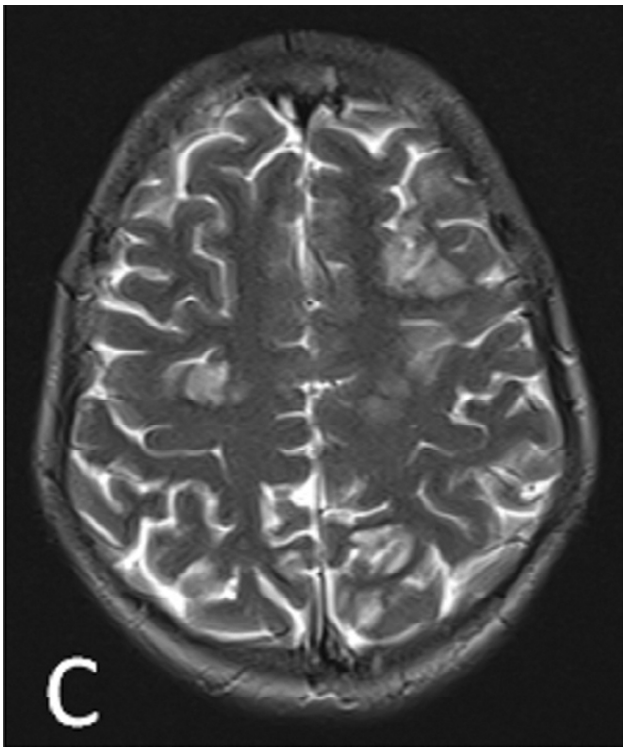
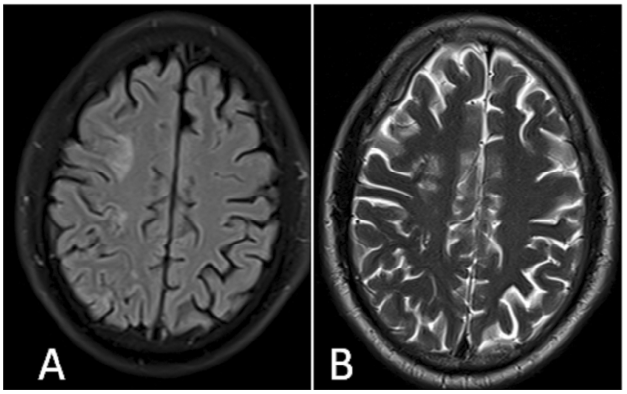


Fig. 3: *A 15-year-old female came to the hospital with complaints of generalised tonic–clonic seizure since five hours. The patient underwent MRI scan (A) Diffusion-weighted image showing diffuse restriction in subcortical regions of bilateral parietal lobes (watershed territory infracts). (B) Axial FLAIR and (C) axial T2 weighted images demonstrate high signal intensities in the corresponding areas suggestive of cytotoxic oedema.*

Case 4

A 32-year-old male presented with seizures and unconsciousness one day and underwent an MRI scan. FLAIR (Fig. 4A) and T2 (Fig. 4B) weighted images demonstrated a high signal area in the right high frontal lobe with restriction on the diffusion-weighted image in the corresponding areas (Fig. 4C). The diagnosis was made as mild-to-moderate HII. In mild-to-moderate global HII in adults result in watershed infarcts which are better evaluated on the diffusion-weighted images.



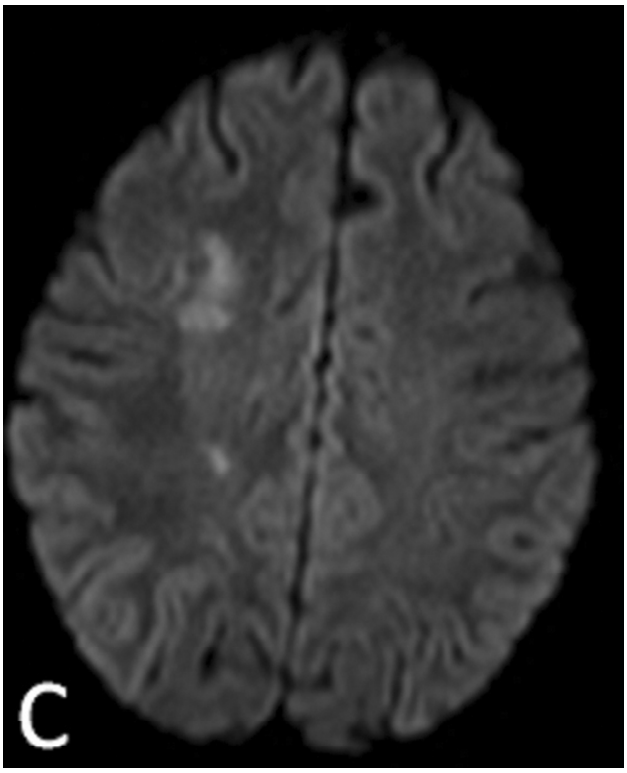


Fig. 4: *A 32-year-old male presented with seizures and unconsciousness since one day and underwent MRI scan (A) axial FLAIR and (B) axial T2 weighted images demonstrate high signal area in the right high frontal lobe with restriction on the diffusion-weighted image in the corresponding areas (C).*

Case 5

A 5-month-old preterm male infant underwent an MRI scan for the complaints of seizures. The FLAIR weighted images (Fig. 5 A and B) revealed extensive bilateral areas of cystic encephalomalacia with moderate dilatation of ventricles. Findings were in favour of typical prolonged and severe grade of HII.

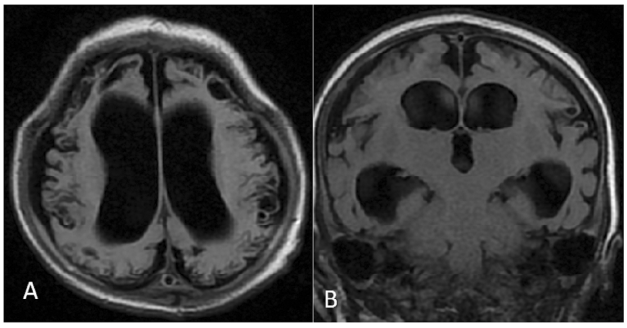


Fig. 5: *A 5-month-old preterm male infant underwent MRI scan for the complaints of seizures (A) axial and (B) coronal FLAIR images reveals extensive bilateral areas of cystic encephalomalacia with moderate dilatation of ventricles.*

Case 6

A seven-month-old boy with a preterm low birth weight birth history presented to the hospital with a cardiac arrest. The patient was admitted under the cardiac department for the treatment of cardiac arrest, and for further workup of his neurological symptoms, the patient underwent a CT scan. Axial unenhanced CT brain showed diffuse cerebral swelling. There was a reversal of the typical grey-white matter attenuation pattern within the cerebral hemispheres (reversal sign) with relative sparing of the cerebellum (white cerebellum sign) (Fig. 6). The diagnosis of severe grade HII was made.

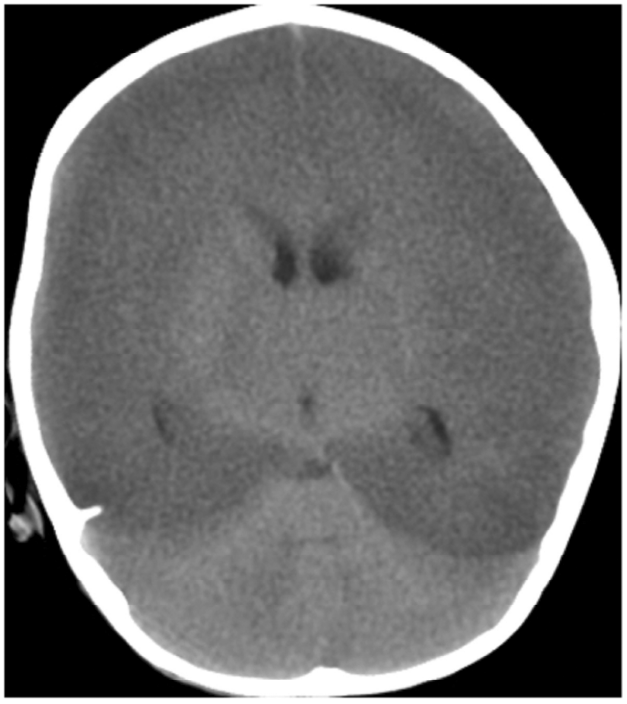


Fig. 6: *A 13-month-old boy with a history of birth asphyxia and delayed milestones underwent a magnetic resonance imaging (MRI) scan. (A) Diffusion-weighted image (WI) demonstrates abnormal high signal intensities with loss of grey-white matter differentiation bilaterally in parietal and occipital lobes, (B) Fluid-attenuated inversion recovery and (C) T2WI are showing subtle hyperintense signal in periventricular white matter in peritrigonal area and hypointense signal in corresponding areas on T1WI (D).*

Case 7

A two-year-old female child bought to the hospital with a history of foreign body inhalation that caused asphyxia, followed by an episode of seizure. In the emergency ward, the foreign body was removed. For further work-up, the patient underwent an MRI scan. Diffusion-weighted image (Fig. 7A) showed symmetrical areas of restricted diffusion in bilateral globus pallid; FLAIR and (Fig. 7B) T2 (Fig. 7C) weighted images demonstrated markedly increased signal intensities in bilateral globus pallidi with low signal intensities on the corresponding T1 (Fig. 7D) Weighted image. These findings suggested the diagnosis of a severe grade HII. MR imaging is the first choice of imaging modality for evaluating children with HII. Diffusion-weighted images demonstrate high signal intensities in the ventrolateral thalamic and basal ganglia (particularly the posterior putamina).

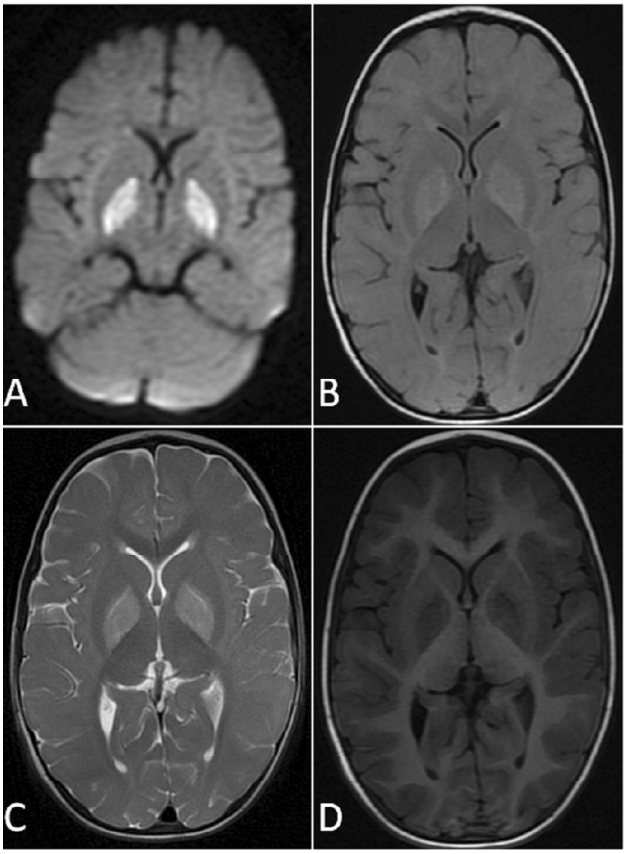


Fig. 7: *A Two-year-old term female child bought to the hospital with seizures and a history of foreign body inhalation that caused asphyxia. The patient underwent MRI scan (A) Diffusion-weighted image shows symmetrical areas of restricted diffusion in bilateral globus pallidi (B) Axial FLAIR and (C) Axial T2-weighted images demonstrating markedly increased signal intensities in bilateral globus pallidi with low signal intensities on corresponding T1-Weighted image.*

Case 8

A 12-year-old female patient who presented with cerebral palsy, presented with seizures. For further work-up for her condition, the patient underwent an MRI scan, where T2W (Fig. 8A), FLAIR (Fig. 8B), and coronal FLAIR (Fig. 8C) images revealed bilateral symmetrical areas of cystic encephalomalacia predominantly involving the occipital lobes, which showed high signal on T2 and suppression on FLAIR weighted images. Bilateral symmetrical areas of gliosis were also observed in the occipital and temporal lobes. DWI (Fig. 8D) images showed no diffusion restriction. There was generalised cortical atrophy with ex-vacuo dilatation

of the ventricular system. The diagnosis was made as sequel to severe grade HII.

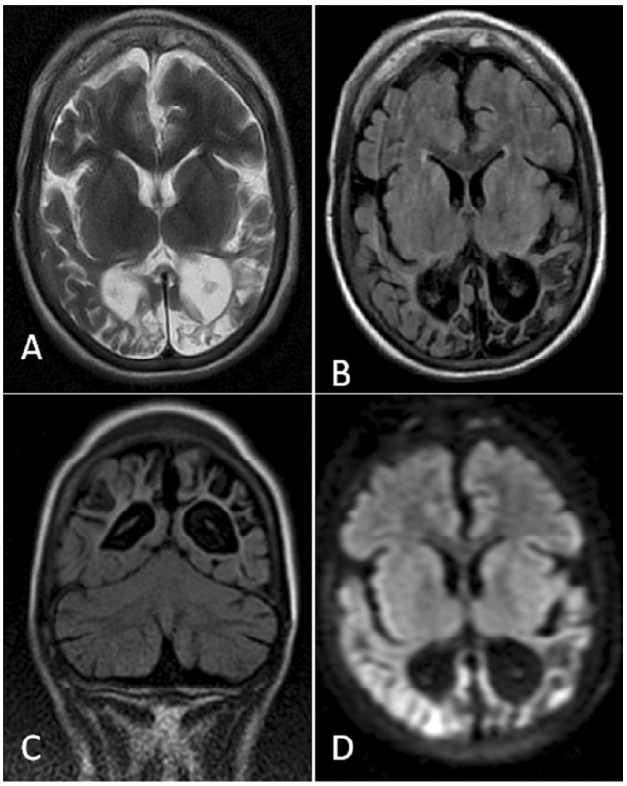


Fig. 8: *MR images of the 12-year-old female patient with cerebral palsy. Axial T2W (A), axial FLAIR (B), and coronal FLAIR (C) images show bilateral symmetrical areas of cystic encephalomalacia predominantly involving the occipital lobes, which show high signal on T2 and suppression on FLAIR weighted images. Bilateral symmetrical areas of gliosis are also seen in occipital and temporal. DWI (C) image shows no diffusion restriction. There is generalized cortical atrophy with ex-vacuo dilatation of the ventricular system.*

Case 9

A 15-year-old male experienced sudden cardiac arrest in which his blood pressure decreased to a non-palpable pulse level for 10 minutes. The patient was admitted to the cardiac department for further work-up, and after stabilisation, he underwent an MRI scan for further evaluation. A diffusion-weighted image (Fig. 9A) revealed restricted diffusion along the cortical and subcortical regions of bilateral cerebral hemispheres. FLAIR (Fig. 9B) and T2W (Fig. 9C) images showed no obvious signal abnormality in the corresponding areas. The diagnosis of acute severe grade HII was made. Acute HII findings are more conspicuous on the diffusion-weighted images than on the FLAIR and T2W images.

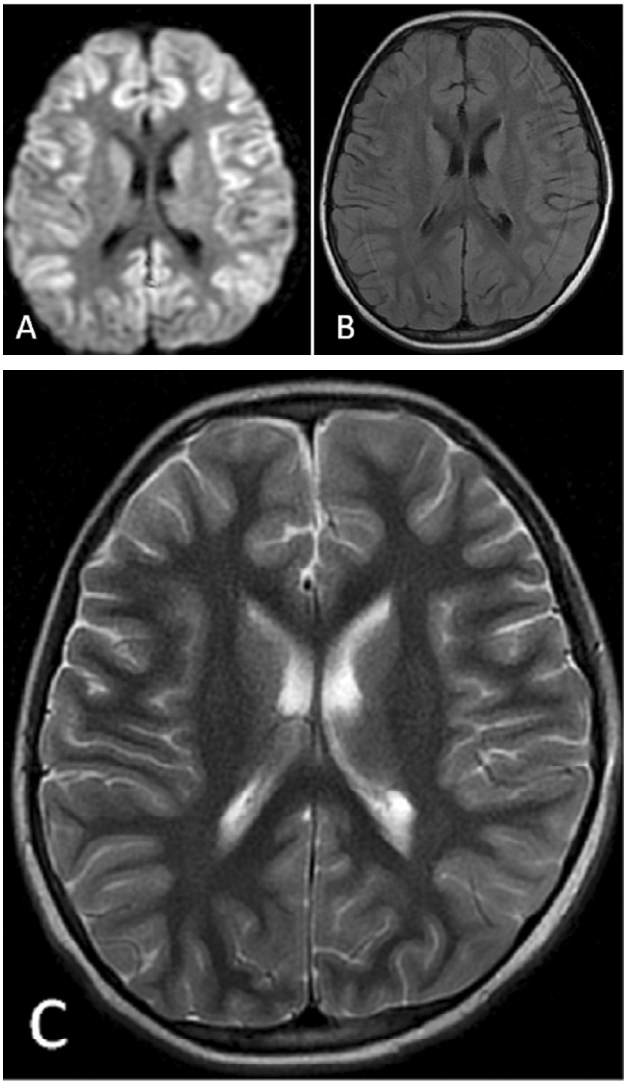


Fig. 9: *A 15-year-old male experienced sudden cardiac arrest in which her blood pressure decreased to non-palpable for 10 min. Diffusion-weighted image (A) shows restricted diffusion along the cortical and sub cortical regions of bilateral cerebral hemispheres. Axial FLAIR (B) and axial T2W (C) images show no obvious signal abnormality in the corresponding areas. Acute HIE findings are more conspicuous on the diffusion-weighted images than on the FLAIR and T2W images.*

Case 10

An 18-year-old female presented with a status epilepticus. The MRI scan demonstrated mild diffusion restriction along the cortical and subcortical regions of bilateral cerebral hemispheres on the diffusion-weighted image (Fig. 10A) and subtle hyperintense signal in periventricular white matter in peritrigonal areas corresponding to FLAIR image (Fig. 10B). Patient admitted in female intensive care unit under neurology department, treated with anticonvulsants and therapeutic hypothermia. A follow-up scan was performed after ten days to assess progression in disease

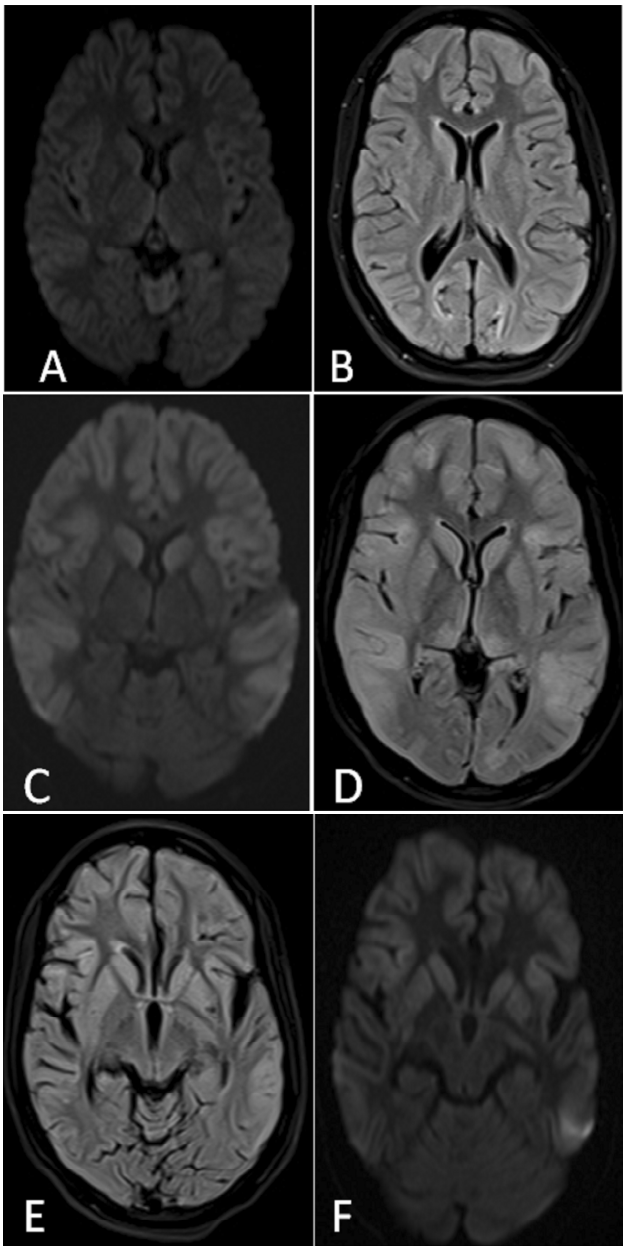


Fig. 10: *An 18-year-old female presented with a status epilepticus. The MRI scan demonstrates mild diffusion restriction along the cortical and sub cortical regions of bilateral cerebral hemispheres on diffusion weighted image (A) and subtle hyperintense signal in periventricular white matter in peritrigonal areas in corresponding FLAIR image (B). Follow-up scan after ten days for assessment of progression in disease and treatment effect. The MRI reveal bilateral symmetrical areas of altered signal intensities seen involving bilateral basal ganglia, inferomedial aspects of bilateral thalami, bilateral frontal, temporal and parietal lobes. There is mild swelling of underlying cortical grey and subcortical white matter that appear hyperintense on axial FLAIR image (C) and show restriction on the diffusion-weighted image (D). Follow-up scan after twenty days for progression of disease and treatment effect where MRI demonstrates bilateral symmetrical abnormal high signals on axial FLAIR image (E) involving caudate nucleus, putamina and cortical gyri showing restriction on the diffusion-weighted image (F). These MRI findings are showings further deterioration in the patient condition.*

and treatment effect. The repeat MRI revealed bilateral symmetrical areas of altered signal intensities involving bilateral basal ganglia, inferomedial aspects of bilateral thalami, bilateral frontal, temporal and parietal lobes. There was mild swelling of underlying cortical grey and subcortical white matter that appeared hyperintense on axial FLAIR image (Fig. 10C) and showed restriction on the diffusion-weighted image (Fig. 10D). The patient continued with the same treatment. The following follow-up scan was done after twenty days to evaluate the disease status, where MRI demonstrated bilateral symmetrical abnormal high signals on FLAIR image (Fig. 10E) involving caudate nucleus, putamina and cortical gyri showed restriction on the diffusion-weighted image (Fig. 10F). These MRI findings corroborate the clinical deterioration in the patient's condition. This case of severe grade HII highlighted the importance of MRI in diagnosis and follow-up for such patients.

Case 11

A 35-year-old male bought to the hospital with the complaints of seizures, cerebrovascular accident, and unconsciousness for one day. The MRI scan demonstrated acute ischemic changes. FLAIR image revealed high signal intensities in both hippocampi (Fig. 11A) and bilateral subcortical white matter showed restricted diffusion (Fig. 11B). This was an another case of severe grade HII.

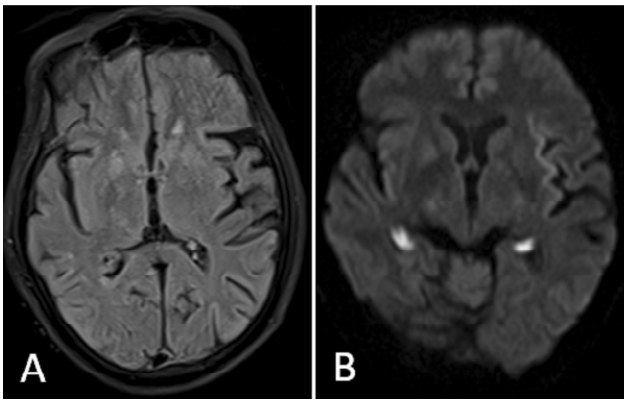


Fig. 11: *A 35-year-old male bought to the hospital with complaints of seizure, cerebrovascular accident, and unconsciousness for one day. The MRI scan demonstrates acute ischemic changes, which are (A) Axial FLAIR image reveals high signal intensities bilateral hippocampi, bilateral subcortical white matter show restricted diffusion on the diffusion-weighted image (B).*

Case 12

In older patients, diffusion-weighted MRI is the earliest modality to detect or evaluate the injury within a few hours after the insult. Here we discuss a case of a 44-year-old

male who had respiratory failure following oesophageal perforation. The patient was treated with emergent medical stabilisation and sent for an MRI scan for further evaluation. MRI scan showed restriction diffusion along the frontal, temporal-parietal and occipital cortices and the hippocampi bilaterally. Extensive bilateral hemispheric cortical oedema more in the occipital lobes was seen on the – attenuated inversion – recovery (FLAIR) image (Fig. 12A and B). The diagnosis was made as severe grade HII.

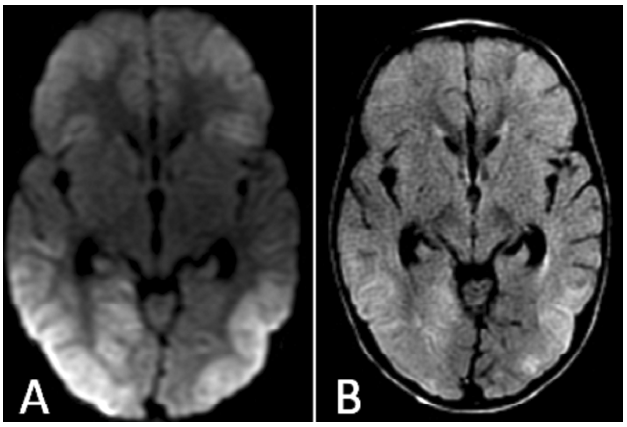


Fig. 12: *A 44-year-old male had respiratory failure following oesophageal perforation. He underwent an MRI scan: (A) diffusion-weighted image shows high signal intensity areas along the frontal, temporal-parietal and occipital cortices, and the hippocampi bilaterally. Extensive bilateral hemispheric cortical oedema more in the occipital lobes is seen on the axial fluid-attenuated inversion – recovery (FLAIR) image (B).*

Treatment

The prognosis of HIE is very challenging because of the decisions to withdraw life-supporting therapies which define its prognosis. Therapeutic hypothermia stands to be very effective in limiting the neurological damage. After the asphyxial event or brain injury, the outcome of resuscitated patients is improved by providing mild-to-moderate hypothermia (temperature 32° to 34° C) in staring hours. Treatment has to start as soon as possible after stabilising the patient and maintaining a low temperature for 48 hours. The suggested protocol is to maintain a goal temperature of 32° to 34° C for 12 or 24 hours, followed by gradual rewarming (0.25° C/hour). The most common advantage of therapeutic hypothermia is reduced intracranial pressure which also reduces the seizure frequency. Therapeutic hypothermia causes shivering, so sedation (and potentially neuromuscular blockade) may be required to facilitate cooling. All our patients were managed using therapeutic hypothermia and anti-epileptics as and when required. Some of the adverse effects of therapeutic hypothermia were also noted in some of the cases like impaired coagulation, arrhythmia, hyperglycaemia, hypovolaemia, hypomagnesaemia, hypophosphataemia, hypokalaemia and increased risk of infection. Supportive and symptomatic treatment was administered as per the patient status and underlying disease profile. In our case series the mortality was zero; however, morbidity in the form of permanent residual neurological deficit and requirement of lifelong drug support remained high.

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CASE REPORT

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Covid-19 Associated Fungal Pneumonia: A Case Series

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Abstract

Fungal pneumonias are difficult to diagnose and are likely underestimated. Aspergillus and Candida infections in COVID-19 patients will require early detection by a comprehensive diagnostic intervention {histopathology, direct microscopic examination, culture, (1,3)-β D-glucan, galactomannan, and PCR-based assays} to ensure effective treatments. Particularly in the setting of COVID-19, where the clinical picture, and radiological findings of fungal pneumonia resemble those of severe COVID-19; blood tests lack sensitivity and, most importantly, sampling of the primary site of infection is rarely performed, due to the risk of COVID-19 transmission through bronchoscopy with bronchoalveolar lavage. We performed Fiber-optic bronchoscopy and collected samples in all 5 cases of this series, and confirmed the diagnosis of CAPA which made it possible to start treatment timely.

Key words: Covid-19, fungal pneumonia, aspergillosis, BAL galactomanan, corticosteroids.

Introduction

Invasive fungal infections have been increasingly reported in patients with coronavirus disease-2019 (COVID-19), primarily invasive candidiasis and pulmonary aspergillosis[1,2].

Aspergillosis, like mucormycosis, has classically been seen primarily in immunocompromised patients; however, it has been increasingly observed in patients admitted to intensive care units, patients with severe influenza, and now COVID-19, termed COVID associated pulmonary aspergillosis (CAPA)[3].

These infections may reflect impaired mucosal barrier and a dysfunctional immune response in severe viral infections and the use of immunosuppressive medications like corticosteroids and interleukin (IL-6) inhibitors like tocilizumab[4,5].

Of note, CAPA incidence rates reported to date have varied widely, ranging from 4%[6] to 35%[7] in mechanically ventilated critically ill patients. Factors that may contribute to the differing incidence rates are 3-fold. First, fungal diseases and specifically CAPA are difficult to diagnose and are likely underestimated, particularly in the setting of COVID-19 associated ARDS, where the clinical picture and radiological findings of CAPA resemble those of severe COVID-19[8,9]; blood tests lack sensitivity due to the primarily airway invasive growth of aspergillus in nonneutropenic patients[10]; and, most importantly, sampling of the primary site of infection is rarely performed, due to the risk of COVID-19 transmission through bronchoscopies with bronchoalveolar lavage (BAL) or autopsies (due to the overlap of imaging findings between CAPA and COVID-19, post-mortem fine needle biopsies alone may not be sufficient to detect focal CAPA[11], which are both aerosol-creating procedures[12]. Random diagnosis of CAPA, without specifically and creatively searching for it, is therefore virtually impossible in this setting, and diagnosis requires specific expertise and awareness, which is rare given that fungi are neglected pathogens[13,14].

We found 5 cases of post-covid associated pulmonary aspergillosis.

Case 1

A 67-year-old male, a coal mine worker and chronic smoker with no other associated comorbid condition, tested positive for COVID-19 by RT-PCR on 10/5/21 and tested negative on 27/5/21. During hospital stay he was given symptomatic treatment for COVID-19 alongwith oral steroids. Patient was requiring oxygen support at 5 l/min. CT scan of the patient was done on 27/5/21 which showed interstitial, peripheral pleural and interlobular septal thickening. Patchy areas of ground glass opacification were noted. Para-septal and centriacinar emphysematous changes were seen in both lungs.

Fiber-optic bronchoscopy (FOB) was done on 27/5/21 and it came out to be positive for fungal stain with occasional budding yeast cells in broncho-alveolar lavage (BAL) fluid. Fungal culture was positive for *Aspergillus flavus*, *Candida tropicalis* and mucor species in BAL fluid. Repeat CT scan was done which showed area of consolidation with internal cavity communicating with bronchi in B/L lower lobes. CT severity index was 14/25. Repeat FOB was done on 7/6/21

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and samples were sent for KOH stain, fungal culture and sensitivity, pyogenic culture and sensitivity, galactomannan antigen, AFB stain, and CBNAAT. Results were as follows: BAL KOH: negative; BAL galactomannan: negative; BAL AFB stain: negative; BAL CBNAAT: negative; BAL fungal culture: *Candida tropicalis*. Results of his blood investigations were: Total leucocyte count: 15,860/microlitre with 89.1% neutrophils, 7.20% lymphocytes and 3% monocytes; haemoglobin: 11 gm/dl; blood urea: 42 mg/dl; serum creatinine: 0.60 mg/dl; total bilirubin: 0.30 mg/dl; aspartate transaminase: 30 U/L; alanine transaminase: 44 U/L; serum sodium: 137 meq/l; serum potassium: 4.20 meq/l; prothrombin time: 19.5 sec; INR: 1.46; APTT: 33.6; D-dimer: 2012; C-reactive protein: 2.4 ng/ml; procalcitonin: 0.11 ng/ml; serum galactomannan antigen: positive; serum β- d-glucan: positive (574 pg/ml); HbA_1c: 6.6; interleukin 6: 29.46 pg/ml; HIV, HBs antigen, HCV: negative; serum ferritin: 593.6ng/ml. Based on clinical, radiological and microbiological investigations, diagnosis of covid-associated pulmonary mucormycosis with covid-associated pulmonary aspergillosis with pneumoconiosis with chronic obstructive pulmonary disease was made and patient was started on broad spectrum antibiotics alongwith injection amphotericin B and symptomatic treatment. He was discharged on 21/6/21 on oral posaconazole for 14 days. Patient was reviewed on follow-up where he showed clinical and radiological improvement. He was advised to continue with inhaled medications.

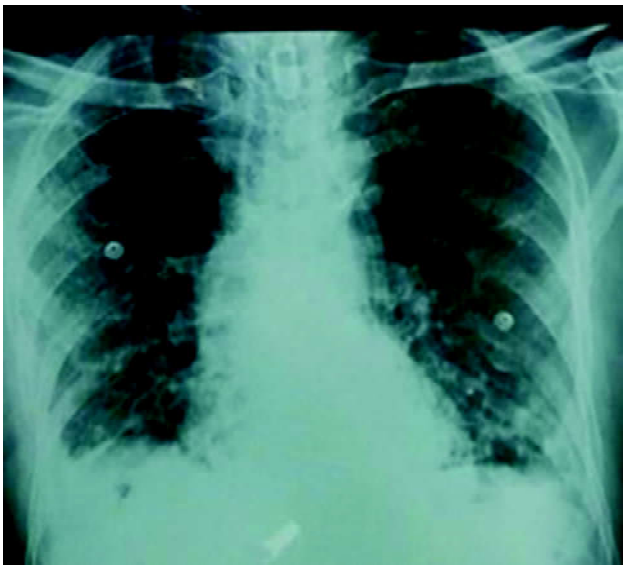

Fig. 1: *Chest X-ray.*

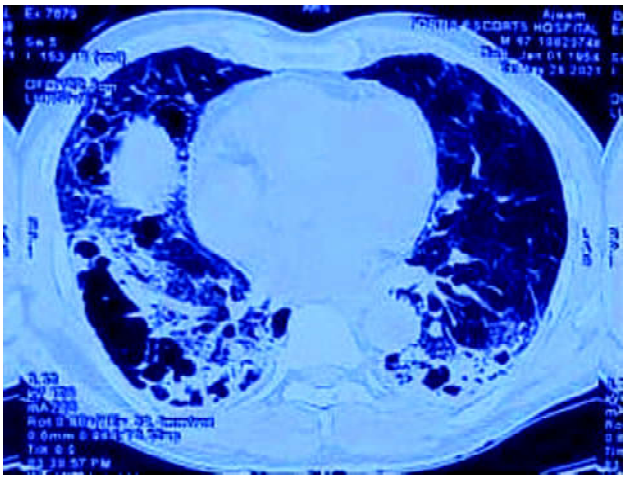

Fig. 2: *CT chest.*

Case 2

A 45-year-old male, sweet maker, nonsmoker, with no history of any chronic illness, tested positive for COVID-19 by RT-PCR on 29/4/21 and tested negative on 27/5/21. Patient was initially requiring high flow oxygen support. He was given symptomatic treatment for COVID-19 along with steroids and injection remdesivir. CT scan was done on 29/05/21 which showed multifocal areas of ground glass attenuation with interstitial thickening, cavitatory nodules, and fibroatelectatic lesions in both lung fields with subcentrimetric mediastinal lymphadenopathy. There was improvement in his oxygen requirement to 2 l/min. Fiberoptic bronchoscopy was done on 4/06/21. BAL for fungal stain showed septate hyphae, acute angle with branching. No yeast cells/psedo-hyphae seen. BAL AFB was negative. A repeat CT scan was done on 4/06/21 which showed resolution of interstitial thickening and fibroatelectatic lesions, but there was formation of a cavity with air crescent sign in the right upper lobe, and another small cavity in the left lower lobe. Repeat fiber-optic bronchoscopy was done on 9/06/21 and BAL fluid was collected from the right upper lobe and posterior basal segment of the left lower lobe.

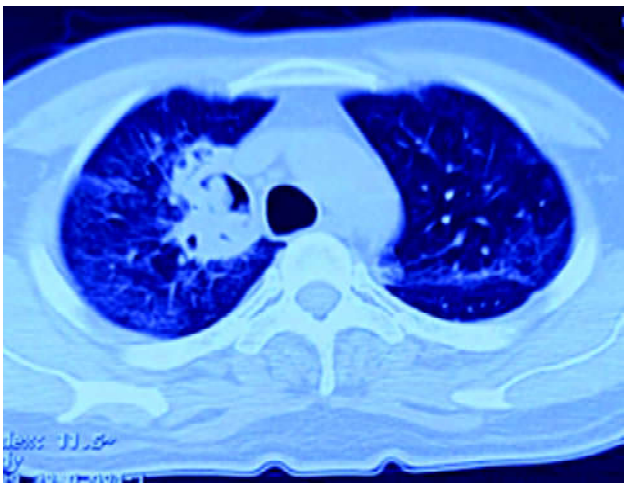

Fig. 3: *CT chest.*

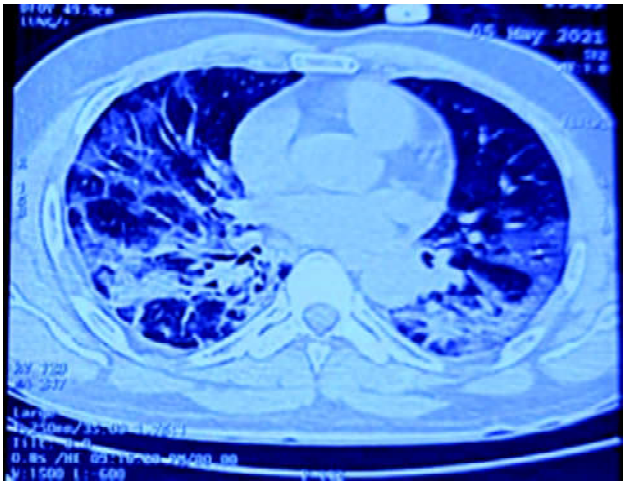

Fig. 4: *CT chest.*

BAL CBNAAT was also positive with very low *Mycobacterium tuberculosis* load and rifampicin resistance was absent. BAL KOH stain: negative; BAL galactomannan: positive; BAL AFB stain: negative; BAL fungal culture: no growth after 3 weeks of incubation. Results of his blood investigations were: total leucocyte count: 6,100 /micro l; haemoglobin: 10.6 gm/dl; blood urea: 16 mg/dl; serum creatinine: 0.60 mg/dl; total bilirubin: 1.04 mg/dl; aspartate transaminase: 42 U/L; alanine transaminase: 44 U/L; serum sodium: 131 meq/l; serum potassium: 4.20 meq/l; prothrombin time: 13.1 sec; INR: 0.97; APTT: 28.5; D-dimer: 1,374 ng/ml; C-reactive protein: 2.4 ng/ml; procalcitonin: 0.09 ng/ml; serum galactomannan antigen: positive; HbA_1c: 8.4; lactate dehydrogenase: 790 U/L; interleukin-6: 55.5 pg/ml; HIV, HBs antigen, HCV: negative; serum ferritin: 508 ng/ml. Based on clinical, radiological, and microbiological features, a diagnosis of covid-associated pulmonary aspergillosis with new onset diabetes mellitus with pulmonary tuberculosis was made and the patient was started on tablet Voriconazole 200 mg BD, oral hypoglycaemic drugs, and antitubercular treatment under DOTS category 1. Patient was discharged on the same treatment; and when reviewed on follow-up after 10 days showed radiological resolution.

Case 3

A 68-year-old male who was apparently well 3 months back when he started having episodes of fever for which he took medication elsewhere for 20 - 25 days. RTPCR for Covid-19 was done at that time which was negative. However, his son and daughter-in-law tested positive for Covid-19 around the same time. After around 1.5 months, patient started having cough with copious amount of expectoration, yellow in colour, mucoid in consistency and sometimes blood tinged. He started having episodes of shortness of breath on climbing upstairs, and generalised weakness. For these complaints he was hospitalised, and his routine blood investigation were done along with CT Thorax. CT scan showed a regular area of consolidation with central breakdown/cavity formation in the anterior basal segment of the left lower lobe. A similar smaller area of peribronchovascular sub pleural consolidation with a central area of breakdown are noted in bilateral upper lobes. Associated parenchymal bands changes were also seen. Few defined small nodular opacities were seen in bilateral upper lobes. Multiple variable sized discrete mediastinal and hilar lymph nodes were also seen.

Following CT scan, fiber-optic bronchoscopy was done and broncho-alveolar lavage fluid was sent for investigation and results showed fungal KOH stain: negative; fungal culture: *Aspergillus*; gene expert for *Mycobacterium tuberculosis*: negative; AFB stain: negative; pyogenic culture showed no growth. Patient was given injection amoxycillin/clavulanate

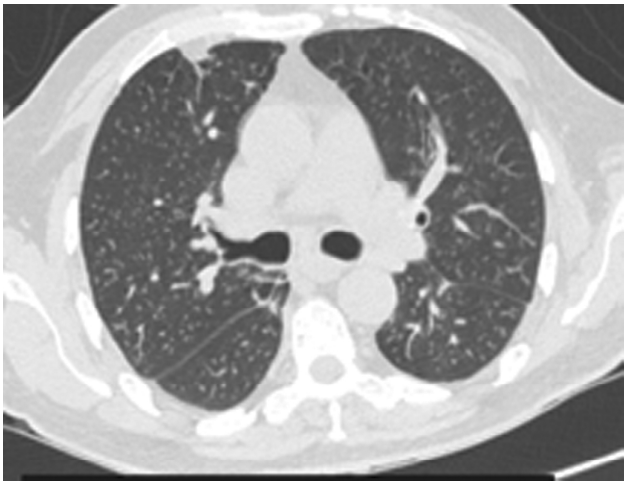

Fig. 5: *CT chest.*

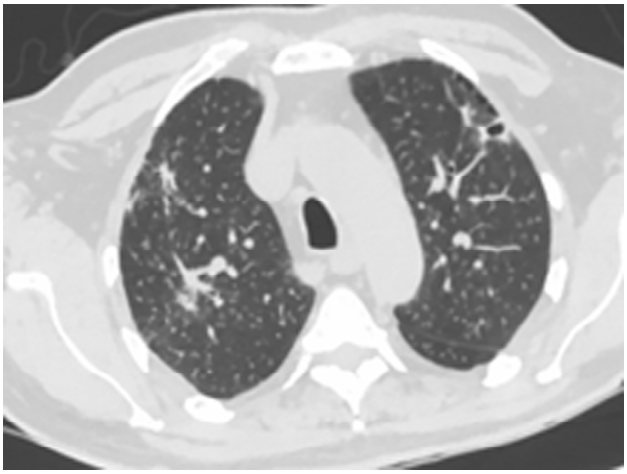

Fig. 6: *CT Chest.*

for 5 days along with other symptomatic treatment. He was a chronic Bidi smoker and used to smoke 24 BD per day for around last 40 years. He was a known case of type 2 diabetes mellitus for last 4 years on and was on oral hypoglycaemic drugs for the same. He was a water supplier by occupation for around 40 years and was vaccinated with covid vaccine single dose in March 2021. Upon admission, his routine blood investigations were done and results were – haemoglobin: 10.20; TLC: 5,500; platelets 1,64,000; blood urea: 34; serum creatinine: 8.70; total bilirubin: 1.35; SGPT: 31; HbA_1c: 8.4; prothrombin time: 17.10 seconds; INR: 1.28; aPTT: 30.90s; procal: 0.05 mg per ml; covid antibodies were positive; total 643; IgG: 16. Repeat CT scan done on 2nd July 2021 showed interstitial pneumonia with CT score of 7/25. A repeat fiber-optic bronchoscopy was done and broncho-alveolar lavage was sent for investigation and results were BAL KOH stain: negative; BAL CBNAAT for *Mycobacterium tuberculosis:* MTB detected in traces; rifampicin resistance: indeterminate; pyogenic culture sensitivity: *Klebsiella pneumonia* which was sensitive to amoxicillin-clavulanate and supportive drugs. Diagnosis of covid-19 pulmonary mucormycosis with type 2 diabetes mellitus with pulmonary tuberculosis was made and patient was started on injection meropenem 500 mg TDS, tablet ciprofloxacin 500 mg BD, injection amphotericin B 5 mg per kg body weight, insulin regular and basal along with other symptomatic treatment. Patient was followed-up in OPD after discharge where he showed improvement.

Case 4

A 31-year-old female started having episodes of fever since 3 months for which she took some medication elsewhere and the fever subsided after 6 days. There was no history of cough, expectoration or shortness of breath associated with fever. After around one week of no fever, she started having complaint of bilateral chest pain more on left then right, non radiating to other sites, relieved for some time by taking some injectable medication from a local practitioner in the village. She also started having shortness of breath which was gradual in onset and progressive in nature. Her oxygen saturation on room air was between 80 to 85% during that period and she was put on home oxygen cylinder therapy of 2 - 3 litre per minute around 15 to 16 hours per day for around 10 days. After 10 days, her saturation improved and she was maintaining saturation of 95% on room air. CT scan of the patient was done at that time which showed multifocal variable-sized ground glass opacities with interlobular septal thickening and fibrosis involving both lungs consistent with atypical viral pneumonia with CORADS score of 6 and CT severity index of 19/25.

However, the RTPCR for covid-19 was negative at the same time. She also started having cough with expectoration aggravated on lying down and while talking. She was diagnosed as a case of type 2 diabetes mellitus 6 month back but was not on any regular medication for the same. She was also a known case of hypothyroidism for the last 6 years for which she was on tablet thyroxine. Patient presented with increased frequency of stools, pain abdomen, weakness and cough on 23rd June 2021 in a private hospital, where her random blood sugar was found to be 36 mg/dl and she was therefore admitted for further management. Routine blood investigation were done along with chest X-ray and CT thorax on 24th June 2021 which showed diffuse fibrointerstitial thickening with patchy ground glass attenuation and sub-pleural atelectatic bands, multiple random ground glass nodules in the right lung field with few of them showing tree-in-bud appearance, two thick-walled cavitatory lesions along anterior aspect of left upper lobe, basal segment of left lower lobe with thick enhancing pleura. Fiber-optic bronchoscopy was done on 25th June 2021 and results were – Gene expert for *Mycobacterium tuberculosis* was negative; ZN staining: negative; GMS stain: positive for fungal hyphae; BAL pyogenic culture: no growth; BAL galactomannan: positive; BAL AFB culture: negative;

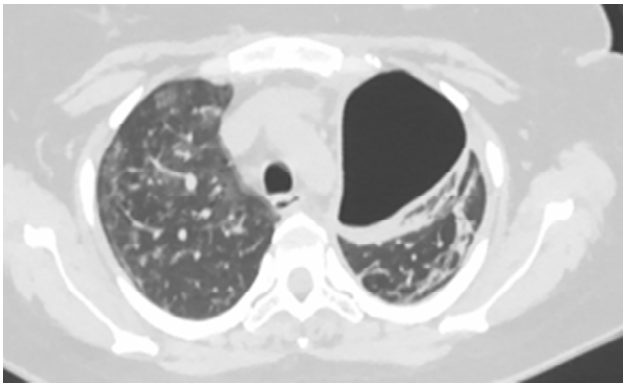

Fig. 7: *CT chest.*

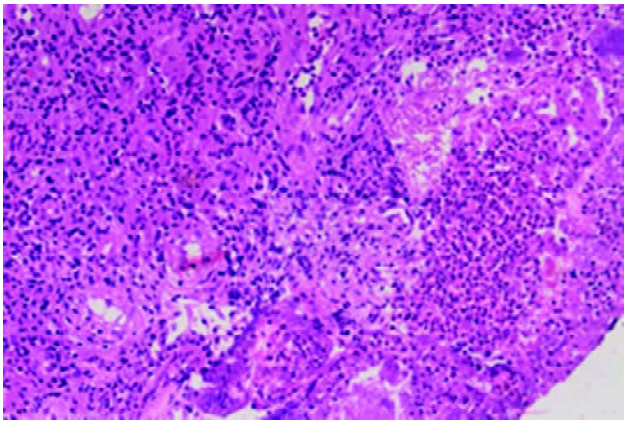

Fig. 8: *Endobronchial biopsy: HPE showing broad septate fungal hyphae in necrotic tissue bits.*

endobronchial biopsy: positive for septate branching hyphae showing acute angle branching with presence of you non-septate broad hyphae, suggestive of pulmonary aspergillosis with mucormycosis. CTPA was done on 26 June 2021 which showed saddle-shaped pulmonary thrombus involving right and left branches of main pulmonary artery, 80 to 90% occlusion of left main pulmonary artery and 20 - 30% occlusion of right main pulmonary artery. Thrombus is seen extending into the right descending lower arteries and segmental branches. Few small filling defects also extending into right descending lower arteries and segmental branches. Few linear filling defects extending into right upper lobe pulmonary artery. On the left side there was eccentric filling defect in the pulmonary artery branches supplying the anterior basal segment of the left lower lobe. MPA: 2.1 cm, RPA: 1.5 cm; LPA 1.3 cm. Colour Doppler of bilateral lower limbs and upper limbs was normal. Echocardiography showed tachycardia, PA prominent, LVEF: 55 to 60%, diastolic relaxation abnormality grade 1; and NT-Pro BNP was raised: 157 pg/ ml. Result of coagulation profile was normal factor 8 functional: 25%; cardiolipin antibody IgG: 8.07 GPL; cardiolipin antibody IgM: 13.2 MPL; homocysteine quantitative: 6.25 micro mol per litre; antithrombin functional: 82.00%; protein C functional: 118%; proteins free antigen: 96%; CRP: 50.4 mg/dl; procalcitonin: 0.77 mg/ ml; TSH: 0.321; sputum for AFB: negative; pyogenic culture: no growth; fungal sputum stain: budding yeast cells with pseudohyphae. Patient was not vaccinated for covid-19. Upon admission routine blood investigations were done and results were – TLC: 23,150; haemoglobin: 10.1; platelet count: 389000; blood urea: 16; serum creatinine: 2.8; total bilirubin: 1.43; SGOT: 20; SGPT: 20; sodium: 136; potassium: 3.9; D-dimer: 1,226 mg/dl; PT: 19.9; INR: 1.49; APTT: 33.0; Covid antibodies were positive: 8.16. Repeat chest X-ray and CT scan were done which showed bilateral interstitial pneumonia with CT severity score of 17/25, but RT PCR for Covid-19 was still negative. Repeat fiberoptic bronchoscopy was done and BAL fluid was sent for investigation. Results of BAL – fungal KOH stain: negative; pyogenic culture showed *Klebsiella pneumoniae*; CBNAAT was negative; Endobronchial biopsy was positive. On the basis of clinical, radiological, and micro biological reports, the diagnosis of Covid-19 associated pulmonary mucormycosis with acute pulmonary embolism with type 2 diabetes mellitus with hypothyroidism was made. Treatment was started with broad-spectrum antibiotics, injection enoxaparin, oral hypoglycaemic drugs, injection amphotericin B along with symptomatic treatment.

Case 5

A 60-year-old female, a known case of diabetes for the last 3 years, presented to us on 28/06/21 for swelling of face (Rt > Lt), right eye ptosis, and deviation of mouth (left) were present. She was evaluated for mucomycosis and nasal endoscopy and biopsy was done on 30/06/21. KOH: Broad aseptate hyphae and septate hyphae seen; fungal culture: *Aspergillus fumigatus* isolated in culture. Impresssion: k/c/o mucormycosis. 30/06/21 (CECT chest) Impression: F/S/O Nectrotising consolidation with cavitation and centrilobar nodules surrounding it and mediastinal lyphadenopathy as described – likely infective aetiology – ? Tubercular. The CEMRI study reveals mucosal thickening, heterogenous enhancement of B/L maxillary, B/L ethmoid, Rt frontal and B/L sphenoid sinuses with extra and intracranial involvement of right optic nerve infarct and intracranial involvement (dorsal enhancement, cavernous sinus involvement, left ICA partial thrombosis and an acute lacunar right frontal infarct) as described. 20/07/21 – HBsAg: NR; Anti-HCV Ab: NR; HIV I and II: NR.

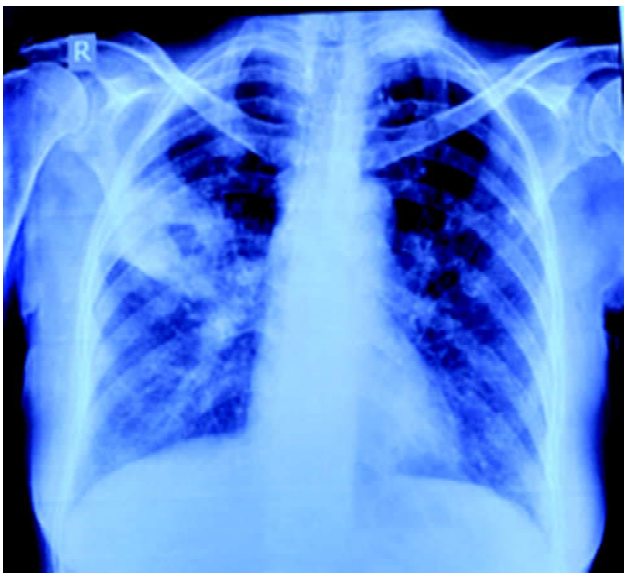

Fig. 9: *Chest X-ray.*

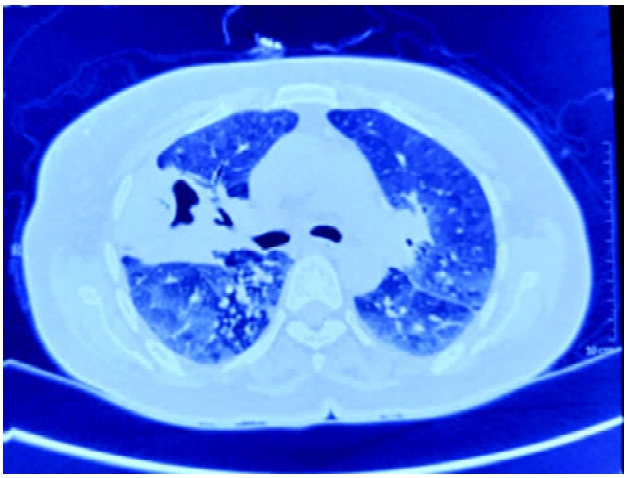

Fig. 10: *CT chest.*

CBNAAT (25/07/2021) – Mtb detected (low); no Rif resistance detected. 28/07/2021 – Fungal Culture (KOH): No fungal elements seen. 02/08/2021 – Blood urea: 21.0 mg/dl; S. creatinine: 0.50 mg/dl; Magnesium: 1.2 mg/dl; Na: 137 mg/dl; K: 2.7 mg/dl; Hb: 9.7 gm/dl; TLC: 3,200/UL; 28/07/21- D-Dimer: 1,384 mg/ml; 28/07/21 – Bronchoscopy Impression: Infective?? On the basis of clinical, radiological and micro-biological reports, the diagnosis of Covid-19 associated Rhino-orbital mucormycosis with pulmonary aspergillosis with diabetes type 2 was made.

Inj. Amphotericin B was started and total Amphotericin B given: 4,800 mg. Patient was discharged and followed up in OPD.

Discussion

Clinicians are alert to the possibility of bacterial co-infection as a complication of lower respiratory tract viral infection; for example, a recent review found that 72% of patients with COVID-19 received antimicrobial therapy. However, the risk of fungal co-infection, in particular COVID-19 associated pulmonary aspergillosis (CAPA), remains underappreciated. For secondary invasive pulmonary aspergillosis in influenza patients, the median time to diagnosis is between 5 and 10 days after ICU admission[23].

Fungal co-infections associated with global COVID-19 might be missed or misdiagnosed. Further, as a life-threatening infectious disease, COVID-19 patients showed overexpression of inflammatory cytokines, and impaired cell-mediated immune response with decreased CD4 and CD8 T-cell counts, indicating its susceptibility to fungal co-infection. The main fungal pathogens for fungal co-infections in severe COVID-19 patients are *Aspergillus* and *Candida*. Other infrequent opportunistic pathogenic fungi caused lung infections also need to be considered, such as *Mucor* and *Cryptococcus*[22].

The radiological differentiation between IPA and COVID-19 is often complex. For instance, ground-glass opacities and dense consolidation are often found in COVID-19 and IPA. CT may help distinguish between "typical" COVID pneumonia (bilateral peripheral ground glass opacity which may be rounded or associated with intralobular septal thickening giving a crazy paving pattern) and "typical" invasive pulmonary aspergillosis (nodular consolidation with a ground glass halo)[21].

The consensus case definition of IAPA/CAPA from Verweij and colleagues were adapted for clinical decision making before the 2020 ECMM/ISHAM consensus criteria[14]. In patients with no underlying immunosuppression, severe SARS-CoV-2-related pneumonia seems at low risk of invasive fungal secondary infection, especially aspergillosis[15]. Among our patients, 4 out of 5 were diabetic. One of them was a new onset diabetic. Prolonged use of corticosteroids is known to be a risk factor for invasive fungal disease[16]. 2 out of 5 were on steroids during covid treatment, while 3 patients had not produced any documents in support of steroid therapy. However, the numbers are too small to determine whether it could be attributed to STEROID SARS-CoV-2 therapy. In diagnosing CAPA, little was known on the performance of serum GM and the 'panfungal' marker BDG. Serum GM testing in neutropenic non-CAPA patients with proven invasive aspergillosis has been shown to have a sensitivity of around 70%, and 25% in the non-neutropenic host[17]. 4 patients out of 5 were s. galactomannan positive. 3 patients out of 5 were BAL galactomannan positive, 1 was negative. CAPA patients are generally non-neutropenic and sensitivity of serum GM reported in these patients are similarly low (15.6% - 21%)[18,19]. Whilst BDG testing is nonspecific, its sensitivity in the ICU population for invasive fungal disease has been shown to be high (88%)[20]. 2 patients out of 5 were s. beta d glucan positive. BAL CBNAAT was positive for 3 patients and negative for 2 patients. BAL for KOH mount was negative for all the patients while fungal culture

Table I: Comparision of Investigation reports of all cases.

Lab investigations	Case 1	Case 2	Case 3	Case 4	Case 5
Presentation after covid test positive	54	30	*	*	*
S. Galactomanan	+	+	+	+	*
BAL Galactomanan	-	+	+	+	*
S. Beta D glucan	+	+	*	*	*
BAL CBNAAT	-	+	+	-	+
BAL Fungal culture	*Candida tropicalis*	-	*	*	*Aspergillus fumigatus*
BAL KOH mount	-	-	-	-	-
Endobronchial biopsy	*	*	*	+	*
Pyogenic culture	*Klebsiella pneumonia*	*	*Klebsiella pneumonia*	*Klebsiella pneumonia*	
Diabetes mellitus	-	New onset	Type 2 DM	Type 2 DM	Type 2 DM

was positive for 2 patients, one for candida and other for aspergillus. Endobronchial biopsy was positive for only 1 patient.

IPA can complicate severe COVID-19 pneumonia. The diagnosis of CAPA is often challenging and requires a high index ofsuspicion. A constellation of clinical and biochemical tests are required to establish the diagnosis. Timely diagnosis and management are required for better outcomes. If left untreated, the complications of fungal pneumonia can be fungal sepsis, dissemination to brain, skin, liver, spleen, kidneys, etc., blood vessel invasion leading to haemoptysis, myocardial infarction, septic emboli. The mortality of untreated infection can be up to 80% in mucormycosis, while in treated cases it comes up to 25%[24].

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Lariat Loop

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Abstract

Insertion of nasogastric tube is one of the commonest clinical procedures. However, very rarely, the tube can coil on itself to form something called a Lariat loop. This is a knot that can cause the tube to get stuck inside the pharynx and can precipitate emergencies like laryngeal obstruction or esophageal rupture. A brief discussion of a case along with the causes and prevention of this complication has been done.

Key words: Ryle's tube; nasogastric; Magill forceps.

Introduction

Insertion of Ryle's tube for nasogastric feeding is one of the commonest procedures performed in clinical practice. This is done both for admitted patients and in clinic settings or even at home. Usually, this is an extremely safe procedure with minimal complications, if done by trained personnel. However, rarely, serious complications may arise during regular use of this feeding tube. This article describes one such extremely rare complication. There are only a handful of similar reported incidents.

The report and discussion

A 72-year-old woman in coma was seen by her family physician at home. In view of the Covid-19 epidemic, the family members refused hospitalisation and opted for domiciliary care. Since she was unconscious and her swallowing was deemed unsafe, a nasogastric tube (no. 12) was inserted for enteral feeding. After three days of feeding, it was found that the tube was blocked and nothing could be aspirated through it. Thus, decision was taken to replace the tube. However, as the old tube was being pulled out, it got stuck after some time and could not be moved further. Any manipulation of the tube led to bleeding in the mouth and fall in SpO_2. At this point, inspection of the oral cavity using a tongue depressor revealed that the tube was massively coiled around itself in the posterior pharynx. The patient had to be taken to an emergency room and the tube was extracted, using special forceps, through the oral cavity. The extracted tube showed (Fig. 1) a perfectly formed lariat loop.

The nasogastric tube is a common medical equipment used for gastric decompression, feeding of unconscious patients, or the management of poisoning[1]. Common complications include local ulceration in the nose, misplacement of the tube in the respiratory tract or blockage of the tube[1]. Very rarely, the tube can coil on itself and form a tight knot. This is called a Lariat loop. Predisposing conditions for formation of this loop include narrow bore tube, deep insertion into the stomach and/or frequent manipulations of the tube[1]. In our patient, a no. 12 tube was used, which is quite narrow; also, the technician inserting it had put almost the entire tube inside with only about 15 cm remaining outside the nostrils. These two factors were probably responsible for this loop formation.

While in our case the main problem was blocking of the tube and inability to extract it through the usual route, there may be other serious complications of Lariat Loop[1,2]. These include blocking of the larynx with laryngeal injury and respiratory distress and sometimes, oesophageal puncture. Also, forceful attempts to take out a Ryle's tube with Lariat loop by an amateur care giver may lead to severe nasopharyngeal injury. Excessive traction on the tube will only lead to further tightening of the knot. Thus, when a Ryle's tube gets stuck, the dictum is to stop applying further traction immediately. Then, a lateral skull X-ray may be done, which will show the knot[3]. The tube can be taken out either through the nose or the mouth (as done in our patient) using special techniques. A Magill forceps is generally used for oral extraction of a knotted Ryle's tube under direct visualisation[1].

Some techniques to prevent Lariat loop formation are: using a wide-bore tube, measuring the exact length of tube to be inserted and avoiding too hot liquids through the tube. Hot liquids can cause softening of the tube and predispose to coiling. Since infants are eligible for only the narrowest of tubes, such loops are more likely in the paediatric

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population. Also, if there is resistance while inserting the tube, it should never be forced inside, but rather, expert help should be sought. Although in our case the knot was probably formed during extraction of the tube, similar knots can also form during insertion[4].

Our case reminds one of the fact that any "simple" medical procedure may cause life-threatening complications if basic guidelines are not followed.

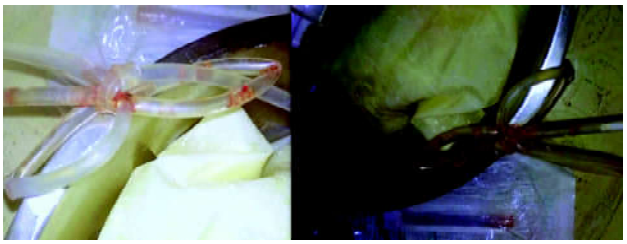

Fig. 1: *Figure showing Lariat loop in Ryle's tube taken out from the pharynx.*

Conclusion

We present this case to sensitize clinicians to this unique and extremely rare complication of nasogastric tube insertion. In the post-Covid era, home care is established as an attractive option for many debilitated patients. Such patients often need interventions like tube feeding at home. But procedures like insertion and extraction of tubes and catheters must always be done by trained professionals to avoid untoward incidents.

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