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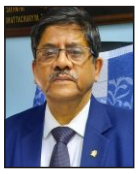

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Editorial

Perspectives of COVID-19 — Epidemiology, Prevention, Surgery and Medical Education

The pandemic of COVID-19 apart from a difficult medical condition regarding clinical care brings out lots of different issues, like comorbid condition care, surgical plan, vaccine strategy and its efficacy. The safety of health care workers and handling of potentially high aerosol generating situations is of utmost importance to restrict spread of disease to care givers. Due to the long lockdown the usual medical education has to take some alternate path. All this factors are being addressed by this issue of JIMA. These articles will definitely generate thinking among the readers if they consider themselves in different role playing mode. As a primary care giver to the community as well as a medical graduate we have faced all of these situations in our professional life in past two years.

The article comparing epidemiological profile of paediatric COVID patients between June 2020 and 2021 actually reflects two different major surges of patients. The diagnosis of COVID was done by naso and oro pharyngeal swab. The testing for paediatric patients in the Jaipur hospital was only 5.4% with respect to total tests. This reflects unwillingness of parents for evaluation of their child due to visual complexity of the procedure. Due to this we actually missed a lot of patients which was similarly remained undiagnosed throughout the world. Fortunately the hospitalization and severe COVID with hypoxia were negligible and no death happened. Less cumbersome procedures like gargle could have picked more patients. The surge of patients during second wave among above 6 year population may be showing the need of vaccination for this population although that has been incorporated by government of India recently.

Vaccination started in India in mid-January 2021 for the health care workers. Within few months vulnerable population and subsequently adult population became beneficiary of that. The study from Thrissur was under taken in the month of August 2021 to understand breakthrough of COVID after vaccination. Moreover the time of study was just after the surge of cases as happened in second wave. So the population may had concurred COVID in past along with that they were vaccinated. There were 56 breakthrough cases where only 3 required admission. This is actually

indicating that in a state where vaccination drive is good the actual risk of hypoxia due to COVID is pretty low and survival is likely. Still in some parts of our country people are reluctant about the second dose of COVID vaccine, this study can be anexample to show them that how vaccine is working to mortality from COVID in India.

Surgery during the COVID time was initially restricted to emergency situations. With prolong restriction and less communication to the hospital lots of cold surgical patients faced significant morbidity. This issue was addressed in an article. It also covered the ethics related to onco-surgery and dilemma of aerosol generation with respected to surgeon &anaesthesiologist risk to acquire the infection. The pros and cons of risk of getting COVID due to hospitalization for surgery is also taken into account. Moreover the intensive care beds meant for surgery needs to be there to provide care for surgical patients. This controversial yet ethical situation has been put forward from a surgeon's point of view.

As a doctor our nurturing place is a Medical College. We cannot halt the education of our medical juniors due to restrictions. A cross sectional study tried to cover many burning difficulties faced by medical educators and their learners. We had to take online teaching and learning unthinkable previously in medical fields based on hands on training and workshops. 87% of the study population was not comfortable to it yet they found it convenient. The study revealed that online training mostly focuses on cognitive domain and skill development was not given priority. In future online programs should be considering that as skill is the best power of a doctor. But online classes actually helped us to become more technologically advanced. Post COVID era when all of us will return to our usual teaching & learning methods adaptation of a well-structured online education will definitely add new horizon in Medical pedagogy.

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Original Article

A Hospital based Observational Study of Clinical spectrum and Outcome of Mucormycosis during the COVID Pandemic

Nandini Chatterjee[1], Jyotirmoy Pal[2], Indranil Khatua[3], Pranabananda Pal[4], Bibhuti Saha[5], Debashish Bhattacharya[6], Ajoy Chakraborty[7]

Background : Mucormycosis is a life threatening fungal disease caused by the filamentous fungi mucormycetes. Though a known entity for decades, it began to manifest in an unprecedented manner in the COVID scenario specially with the second wave in India. The objectives were to describe the demographic characteristics, clinical presentations, risk factors, therapy and in-hospital mortality of patients with Mucormycosis.

Material and Methods : We conducted a retrospective observational study for a period of six months from March 2021 to August 2021. The data was collected for cases of mucormycosis from multiple centres all over West Bengal and analysed. All consecutive individuals with confirmed mucormycosis were enrolled in this study. The data documenting demographic particulars, presentation, predisposing factors and comorbiditieswere recorded in a pre validated case report form Details of investigation recording site and extent of disease, therapeutic intervention and outcome was mentioned . Statistical analysis was done using SPSS 21.0 for MS-Windows.

Results : The total number of cases from March to August 2021 was 263 . There were 171 males and 92 females and the mean age of occurrence was 50.8±0.4 years .In West Bengal clusters of cases were being reported most commonly from the districts of North 24 Parganas, Kolkata, Jalpaiguri, Darjeeling and Hooghly. Some cases admitted here hailed from outside states like Bihar, Jharkhand, Odisha and Assam.

The majority of the cases 74.22% (196)were COVID Associated Mucormycosis (CAM) while only 25.78% were non COVID associated. Diabetes mellitus was associated in 78.7 % and history of prolonged steroid therapy in 57.4% of cases. We encountered rhino orbital mucormycosis in 99.24 % of cases and cerebral involvement in 47.3%. They were treated with Amphotericin B deoxycholate along with endoscopic debridement. The most common side effects of Amphotericin B Deoxycholate were hypokalemia (93%), hypomagnesemia (32%) and AKI (74%) of the cases .The number of patients discharged was 16.7% and 10 left against medical advice (LAMA) . In hospital deaths were recorded to be 26.7%. Cause of death was commonly -AKI, septic shock and multiorgan failure .

Conclusion : Prevention is better than cure of this devastating disease which is difficult todiagnose and treat .Awareness about mucormycosis and careful clinical evaluation of post-COVID patients is mandatory in this era in order to rapidly diagnose and treat mucormycosis.

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Key words **: COVID associated Mucormycosis, Diabetes mellitus, Rhino orbital.**

COVID associated mucormycosis (CAM) is Mucormycosis in COVID-19 patients, often with co morbidities, in the later part of its clinical course. In India, prevalence of mucormycosis has been estimated as 140 per million population, which exceeds that in western countries by almost 70 times. There was a surge of mucormycosis cases during September–December 2020 which continued to enhance in the second wave of COVID-19 next year. CAM prevalence was found to be 0.27% among patients in hospital wards and 1.6% in ICU[1] and eleven states in India had declared it an epidemic.

Mucormycosis is a challenge to the medical fraternity as it is difficult to suspect,diagnose and treat. Awareness about this entity is of prime importance.

We undertook a retrospective observational study to characterize mucormycosis patients admitted in

Editor's Comment :

- Awareness about mucormycosis is important in the COVID era.
- Prevention is better than cure. Early diagnosis and prompt institution of therapy improves outcome markedly.

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various centresof West Bengal for a period of six months.

Aims and Objectives

The study objectives were to describe the demographic characteristics, clinical presentations, risk factors, therapy and in-hospital mortality of patients with Mucormycosis.

Material and Methods

We conducted the study from March 2021 to August 2021. The data was collected for cases of mucormycosis from multiple centres all over West Bengal and analyzed. Ethics committee approval was taken.

Inclusion criteria : All consecutive individuals with confirmed mucormycosis who gave informed consent, were enrolled in this study.

We defined a case of mucormycosis as those individuals with clinical and radiological features indicating disease with the demonstration of fungi in the tissue by direct microscopy (broad ribbon like aseptate hyphae) and histopathology with or without positive culture.

Patients underwent all routine investigations followed by contrast enhanced MRI of sinuses, orbit and brain and CT Scan of thorax. Tissue biopsies were taken from debrided material and sent for smear/ stain, culture, and histopathology.

Microscopy was performed using the KOH mount method. Culture was done in Sabouraud Dextrose Chloramphenicol Agar (SDCA).

The tissue samples submitted for histopathological examination were examined using Gomori's methenamine silver stain.

All participants had received treatment at the discretion of the treating physician.

The data were recorded in a pre validated case report form documenting demographic particulars, presentation, predisposing factors and comorbidities.

Details of investigation, recording site and extent of disease, therapeutic intervention and outcome were mentioned.

The data were analysed using SPSS 21.0 for MS-Windows with the help of descriptive statistics . The chi-square test (or Fischer's exact test) and Mann–Whitney test were used as appropriate for categorical as well as continuos variables as appropriate. A p-value <0.05 was considered as significant.

Result

The total number of cases from March to August 2021 was 263. There were 171 males and 92 females and the mean age of occurrence was 50.8±0.4 years. In West Bengal clusters of cases were being reported most commonly from the districts of North 24 Parganas, Kolkata, Jalpaiguri, Darjeeling and Hooghly. Some cases admitted here hailed from outside states like Bihar, Jharkhand, Odisha and Assam (Table 1).

The majority of the cases (196) 74.22% were COVID Associated Mucormycosis of which (125) 47.52% were post COVID and (71)26.7% were suffering from COVID-19 at the time of mucor infection. The mean duration of development of COVID -19 and mucormycosis was 21.7 days (5-35 days). Of these patients 59%had required oxygen support. Non COVID Mucormycosis was seen in 25. 78% of the cases.

Table 1 — District wise distribution

Sl No	District	Case
1	North 24-Parganas	38
2	Kolkata	30
3	Jalpaiguri	19
4	Darjeeling	19
5	Hooghly	14
6	Purulia	12
7	Bihar	12
8	Paschim Medinipur	12
9	Bankura	12
10	South 24 Parganas	10
11	East Midnapore	11
12	Nadia	7
13	Howrah	8
14	Jhargram	6
15	Alipurduar	6
16	Murshidabad	6
17	Paschim Barddhaman	6
18	Dakshin dinajpur	6
19	Purbo Barddhaman	4
20	Malda	4
21	Birbhum	4
22	Others	17

Diabetes mellitus was the single most important accompanying disease for mucormycosis patients, being present in 78.7 %(207) of the patients. More than half of the patients had history of steroid intake 57.4% (151). There were 3 post renal transplant patients in our series, while 4 patients had cancer. Other co morbiditiesfound were ischemic heart disease (97) , Hypertension (89) , COPD (20) Chronic Kidney Disease (28) and Chronic liver Disease(9)(Table 2).

We encountered Rhino Orbital Mucormycosis (ROCM) in 99.24 % of cases, cerebral involvement in 47.3% and pulmonary involvement in 0.76% cases (2 Cases). One case of penile cutaneous mucormycosis was diagnosed.

Common symptoms were headache /orbital pain (90%), nasal blockade and discharge, blurring or dimness of vision and loosening of teeth. Unilateral Swelling of eye was the commonest sign seen in 62%

Table 2 — *Co- morbidities*

Comorbidities	N = 263 (%)
Diabetes mellitus	207 (78.7)
Ischemic Heart Disease	97 (46.8)
Hypertension	89 (33.8)
Chronic Kidney Disease	28(10.6)
COPD	20(7.6%)
CLD	9 (0.03%)
Renal Transplant	3(0.01%)
Malignancy	2(0.007%)

followed by facial swelling, palatal ulcer,l oss of ocular motility and loss of vision.

Of the investigations, the markers of inflammation like CRP, Ferritin and D Dimer were universally raised. The commonest radiological findings were diffuse mucosal involvement in nasal, maxillary and ethmoid sinuses in nearly 64%, orbital involvement in 42%. Orbital apex was involved in 18%. In the CNS, cavernous sinus was most commonly involved in 45% of cases. Cerebral infarction was found in 15 patients. Cerebral involvement was predominantly found in CAM patients.

Therapy was given with Amphotericin B Deoxycholate at a dose of 1mg/kg/day in our Government set upsfor 4-6 weeks followed by Posaconazol tablet orally. Debridement was done in addition to medical management in 67% of casesand orbital exenteration was performed in 8 patients while maxillectomy was done 5 patients. One patient underwent penile resection. The outcome of open surgery was dismal with mortality in 60% of the cases.

The most common side effects of Amphotericin deoxycholate were hypokalemia in 93% hypomagnesemia in 32% and Acute Kidney Injury in 74% of the cases (Table 3).

Table 3 — *Complications of therapy*

Complications of therapy	(%)
Hypokalemia	93
Acute Kidney Injury	74
Hypomagnesemia	32
Agranulocytosis	10
Allergic reaction	4
Hypotension	2

The number of patients discharged was 16.7%, 10 left against medical advice (LAMA). In-hospital deaths in CAM were recorded to be 26.7%. Cause of death was -Acute Kidney Injury, septic shock and multiorgan failure.

Discussion

According to a Government of India advisory, many states in India had made mucormycosis a notifiable disease in May 2021. A study by Patel et al reported that 6% of hospitalized COVID patients incurred systemic fungal infection. Therewas a doubling of mucormycosis cases during September–December 2020 in comparison to 2019.CAM prevalence was found to be 0.27% among patients in hospital wards and 1.6% in ICU[2]. Gujarat Maharashtra, Andhra Pradesh, Madhya Pradesh and Telengana were topping the list of states with mucormycosis though eleven states had declared it an epidemic .

This fungus belongs to the genus Mucorales order of the class of Zygomycetes. The fungi have broad, aseptate, ribbon like hyphae with branching at wide angles. *Rhizopus arrhizus* is the most common subtype worldwide, *Apophysomyces variabilis*is common in Asia and *Lichtheimia* species is more frequent in Europe.In our country , Rhizopus and Apophysomyces are the common isolates[3,4].

Demonstration of fungal hyphae with characteristic morphology on direct microscopic examination enables rapid diagnosis, enabling clinicians to start antifungal treatment right away. Fungal culture is positive in approximately one third to half of the cases, hence histopathology helps to confirm in most cases .Species identification however requires a positive culture .Angioinvasion is the histopathological hallmark of diagnosis . Giant cell invasion, thrombosis, infarction and eosinophilic necrosis of the underlying tissue are characteristic findings[5].

In our series the total number of cases from May toAugust 2021 was 263. There was male preponderance. Diabetes mellitus was identified as an important risk factor, 99% cases being Rhino-orbito-cerebral-mucormycosis (ROCM). Very low number of pulmonary cases were found. Several pulmonary mucormycosis cases also might have remained undiagnosed because of challenges in obtaining diagnostic respiratory samples among critically ill COVID-19 patients.

This pattern has also been seen in a series by Patel et al and others .Post-pulmonary tuberculosis and chronic kidney disease have been found to be emerging risk factors based on studies in the Indian population[2]. The disease can affect the Nose, Sinus, Orbit, CNS, Lung, Gastrointestinal Tract, Skin, Jaw Bones, Heart, Kidney, and Mediastinum.

Reported literature states that the Asian continent shows abundance of Rhino-orbito-cerebral-mucormycosis (ROCM) and high frequency of diabetes as the predisposing factor , whereas haematological malignancies and transplantation are the major risk factors in the United States and European countries with pulmonary mucormycosis being the commonest site[6].

It is important to note that mucormycosis prevalence had increased greatly in COVID times and more so in India (70 times the the world figures) as the hot and humid weather is conducive to fungal growth. Widespread use of cowdung manure may also be a factor . The predisposing factors are different in Europe USA than Asia where diabetes is predominating .and mortality pattern is also different as indicated by different studies[7-9](Table 4).

Apparently healthy individuals can get skin-soft

TABLE 4 — *The predisposing factors*

	Pre -COVID	Pre-COVID	Pre-COVID	CAM	CAM
Study	Prakash *et al* 2019 India	WEBB *et al* 2018 USA	Skiada A *et al* 2011 Europe	Patel *et al* 2021 India	Chatterjee *et al* 2021 India, West Bengal
Prevalence	14 Cases/Million	0.3 Case /Million	O.12 Cases/Million	O.27% in Admitted COVID PTS	–
Commonest Predisposing Factors	Diabetes Mellitus 57% Post Pulmonary TB CKD	Stem Cell /Solid Organ Transplant 2-15% Hematological Cancer	Hematological Cancer 38-62% Transplant HSCT/SOT	Diabetes Mellitus Steroid Therapy	Diabetes Mellitus 78.7% Steroid Therapy 57.4%
Commonest Presentation	ROCM Pulmonary	Pulmonary ROCM	Pulmonary ROCM	ROM/ ROCM	Rom/ Rocm
Mortality	46%	57%	52-76%	45.7%	26.7%

tissue mucormycosis following traumatic injuries in natural disasters like tornado, tsunami, and roadside accident.Healthcare-associated mucormycosis fromcontaminated ventilation systems, air conditioners, and ongoing construction in hospitals have been postulated as a risk factor of mucormycosis in the past .However, we could not estimate the burden of Mucormycetes spores in the hospital environment[10].

In Indian patients with COVID-19, DM was seen in 11-23% of the hospitalized patients. New onset DM was seen in 20.6% of patients with mild to moderate COVID-19. The virus is said to damage the pancreatic islet cells producing new onset DM, worsening of pre-existing DM or DKA. The cytokine storm indirectly fuels this by resulting in insulin resistance. Corticosteroids also precipitate hyperglycemia and DKA. Hyperglycemia leads to glycosylation of transferrin and ferrtin.which affects the capability of transferrin to chelate iron. There is increase in free iron levels helped by an acidic environment allowing mucor to multiply.There is a dysfunction of cellular immunity with impaired chemotaxis , phagocytosis and oxidative /nonoxidative damage performed by neutrophils and mononuclear cells[11,12].

In our series 78.7% of patients had DM and steroid therapy was documented in 57.4% cases.

The most common symptoms were fever, nasal discharge, and headache but the loosening of maxillary teeth and jaw involvement were very peculiar feature in our patients and its presence should be considered a point of suspicion in post COVID patients. Diagnosis was confirmed by histopathology in our patients as culture identified the etiologic agent in only 44.1% cases. In our series, the peak was seen between days twelveto twenty one days with 56% patients developing ROCM symptoms within 14 days from the diagnosis of COVID-19.

Liposomal Amphotericin B had been used in most series with a survival rate of 67 % in comparison to deoxycholate that was 60%[13]. Survival was increased to 70% when surgery was combined with deoxycholate[14]. In our study Amphotericin B Deoxycholate was used for 4-6 weeks followed by posaconazole oral therapy and the percentage of hypokalemia (93%) hypomagnesemia (32%) and AKI (74%) of the cases was higher than the series by Patel *et al* where liposomal variety was used.

Surgical debridement/de-bulking of necrotic lesion is a very important component of mucormycosis therapy. Surgical debridement improves drug penetration to the infected site and improves the outcome. In our series open surgery had poorer outcome (mortality 60%) than endoscopic debride ment in conformation to other studies[15].

Mortality of mucormycosis infection varies between 20 to 50% depending on site of infection and nature of comorbidity. It is nearly 70-90% for cases of disseminated Mucormycosis. Our figure of 26.7% was much less probably because of reporting bias , patients being lost to follow up or the fact that most patients had rhino orbital involvement with better prognosis. Also hospitalized patients are better monitored which leads to better outcome[16].

The overall mortality rate of mucormycosis is high (overall 47%) with the highest mortality in HSCT (76%) recipients. Observed mortalityis in patients with hematological malignancy (52%), pulmonary mucormycosis (56%), patients with disseminated

mucormycosis (58%), and diabetic patients (44%)[17,18].

A recent multicenter study published from India also reported high mortality of 52% at 90 days follow up, mainly as some patients had left the hospital before initiation of therapy and 14% left against medical advice after initiation of therapy[19].

Limitations of our study were many. Patients were lost to follow up. Confirmation by culture or species identification was not possible and sensitivity patterns could not be studied . Patients received amphotericin B deoxycholate which was an alternative choice due to cost factors. Comparison of CAM and Non CAM was not done

We also do not have data on the duration of amphotericin B use, timing of surgery, or duration of sequential antifungal therapy, which are critical factors that have a bearing on mucormycosis outcomes.

Conclusion

There was a surge of cases during the second wave of COVID-19 that was much higher than the first wave and research is ongoing as to what was the critical factor determining this steep rise . The combination of the delta variant of COVID (that causes more severe disease) along with sudden overwhelming use of steroids after the RECOVERY Trial and COVID Induced hyperglycemia could have been the deciding factors. It is of prime importance to be aware of this entity as prompt clinical suspicion , early diagnosis and treatment improves outcomes. However prevention by proper glycemic control, logical use of immuno-suppressants optimal management of COVID-19 and mass vaccination, is vital.

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Original Article

Comparative Study of Serum LDL And HDL In Alcoholics & Non-Alcoholics

Arniban Borah[1], Bhaskar Kanti Nath[2], P Bhattacharjee[3]

Background : Alcohol abuse is one of the major form of addiction and a major threat to public health in developed as well as developing countries. Alcohol intake is increased in quantity and frequency over last few decades. Alcohol consumption pre-disposes subjects to changes in serum Low Density Lipoprotein (LDL) and High Density Lipoprotein (HDL) which are associated with cardiovascular risk.

Methods : 100 alcoholics were compared with 100 non-alcoholics. Alcohol drinking history was assessed by interview and questionnaire and we measured serum LDL and HDL level.

Results : There were significant rise in HDL and LDL in chronic alcoholics when compared with non alcoholics with p value <0.00001, 0.019567 respectively. When serum LDL and HDL were compared among moderate and heavy drinkers, we found increased level of LDL with p value <0.00001 in heavy drinkers. There is decrease in HDL cholesterol level among heavy drinkers when compared to moderate drinkers with p value 0.000016, which is significant. But remains elevated compared to non alcoholics.

Conclusion : This study shows that alcohol intake increases the levels of LDL and HDL. Moderate alcohol intake increases HDL cholesterol whereas heavy alcohol consumption increases LDL and decreases HDL.

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Key words **: Alcohol abuse, addiction, cardiovascular risk, heavy drinkers**

Alcohol abuse is one of the major form of addiction seen in developed as well as developing countries. India too carries a significant burden of this. Multiple reasons like financial burden of being low socio economic status, heavy field work leading to physical stress and mental stress. According to World Health Organization (WHO) reports of 2014, globally alcoholism alone causes 5.9% deaths every year and the burden of the disease accounting to 5.1%[7]. In an alarming revelation, the Global Status report on alcohol and health 2014, released by WHO states that the amount of alcohol consumption has raised in India between the periods of 2008 to 2012. In addition to the average volume of alcohol consumption, the patterns of drinking markedly contribute to the associated burden of disease and injury[1,2]. There are different ways by which alcohol alter lipid metabolism. The enhancement of postalimentary lipemia by ethanol has been thought to be due to delay in the rates of gastric emptying and/or fat absorption[3,4]. Alcohol may increase hepatic fatty acid uptake by increasing hepatic blood flow[3]. In alcoholics, the metabolism of alcohol produces increased amounts of reduced hepatic Nicotinamide Adenine Nucleotide (NADH+). Increased NADH2/NAD ratio inhibits the oxidation of fatty acids[3]. Chronic ethanol intake has been shown to reduce the activity of carnitine palmitoyltransferase-1 (CPT-1), which may impair the transport of fatty acids into mitochondria that in turn may result in reduced fatty acid oxidation[3]. Recently researchers have demonstrated that chronic ethanol administration can significantly increase the production of hepatic sterol regulatory element-binding protein (SREBP-1), which is associated with increased expression of lipogenic genes as well as accumulation of triglycerides in the liver[3]. Several animal studies suggest that alcohol intake can increase esterification of free fatty acids into triglycerides. This is primarily due to ethanol-induced up-regulation of Phosphatidate Phosphohydrolase (PAP), the rate limiting enzyme in triglyceride synthesis[3].

So we have come to know that consumption of alcohol in large amounts for a long duration impairs lipid metabolism, thus alters serum LDL and HDL, hence pre-disposes to cardiovascular disease. The aim of the study is to compare the serum LDL and HDL

Editor's Comment :

- Cessation of alcohol intake may significantly reduce the risk of development of cardiovascular disease.

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among Alcoholics (cases) and Non-alcoholics (controls).

Aims and Objectives

Estimation ofserum LDL, serum HDL in Alcoholics (cases) and Non-alcoholics (controls) and its comparison between cases and controls.

Material and Methods

The present study is a comparative case-control study conducted in the Department of General Medicine, Silchar Medical College and Hospital, Silchar, Assam after getting permission from local ethical committee.The study period was from June 2018 to May 2019 for a period of 1year. A total of 200 patients from the OPD and IPD of the Department of General Medicine were included randomly for the study, after fulfilment of inclusion and exclusion criteria. Among them 100 were male alcoholics (of age 30-50 years consuming alcohol more than 8 years) and 100 males who did not consume alcohol were included in the study. Among alcoholics some were heavy drinkers (≥4 drinks per week) and some were moderate drinkers (2-3 drinks per week). Patients with diabetes mellitus, hypertension, renal disease, liver disease other than Alcoholic liver disease, Pancreatitis, Malnutrition, Family history of Hyperlipidemia were excluded from the study. Subjects who are on drugs affecting lipid metabolism also excluded. Individuals belong to other age groups, females and who did not give the consent were excluded from the study.

Sample : About 5ml of fasting blood samples (overnight fast for 8-12 hours) were drawn from the median cubital vein on the anterior forearm (the side within the fold of the elbow) into clot activator tubes (to aid clotting and separate serum). The clotted blood was centrifuged at 2000 revolutions per minute (rpm) for 5 minutes to separate the serum from the deposit. The serum was used to estimate HDL and LDL.The parameters were measured on Beckman Coulter AU analyzer and estimated by the following methods:

(1) High Density Lipoprotein: The method was direct homogenous test. This method has two steps. In the first step, chylomicrons, Very Low Density Lipoprotein (VLDL) and LDL cholesterol are specifically eliminated and destroyed by enzymatic reactions. In the second step, the HDL fraction is determined by well established specific enzymatic reactions in the presence of surfactants for the HDL.

(2) Low density lipoprotein : Estimation of LDL was done by Friedwald's equation {LDL = Total cholesterol (TC) – HDL – [Triglyceride (TG)/5]} and method was direct homogeneous test.

Statistical analysis : Statistical analysis was performed using Microsoft excel program. Pearson's correlation co-efficient was used to examine the association between various continuous parameters. Independent samples t-test was used to compare means of different variables. Data were presented as Mean±Standard Deviation (SD). The results were considered statistically significant when the two tailed p value was < 0.05.

Results

The results and observations are incorporated in the following tables and diagrams and also discussed below (Tables 1&2 and Figs 1-4).

Discussion

In our study, HDL is raised in cases with mean value 43.12±7.06 mg/dl when compared to controls which is 37.49±7.04 mg/dl. P value is 0.004, which is significant. LDL is raised in cases with mean value of 105.74±35.70 mg/dl when compared to controls which is 97.90±12.29 mg/dl. P value is 0.019567, which is significant.This result is consistent with the study conducted by Wiilliam p *et al*[5], which showed alcohol consumption is positively associated with HDL cholesterol. This study is also consistent with the study done by Vaswani M *et al*,[6] in which HDL, LDL

Table 1 — Comparison of Lipid profile in cases and controls

Lipid profile	Controls	Cases	P value
HDL (mg/dl)	37.49±7.04	43.12±7.06	< .00001
LDL (mg/dl)	97.9±12.29	105.74±35.70	.019567

Table 2 — *Comparison of serum LDL and HDL in cases on the basis of quantity of alcohol intake*

Lipid profile	Type of alcoholic		P value
	Moderate drinker	Heavy drinker	
HDL (mg/dl)	46.5±8.85	40.71±4.21	0.000016
LDL (mg/dl)	86±26.17	118.91±35.56	<0.00001

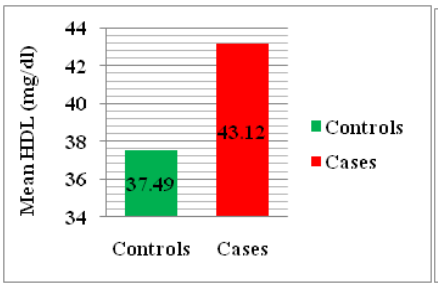

Fig 1

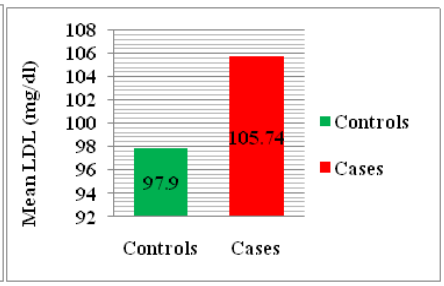

Fig 2

Fig 1 & 2 — Comparison of serum HDL and LDL in cases and controls

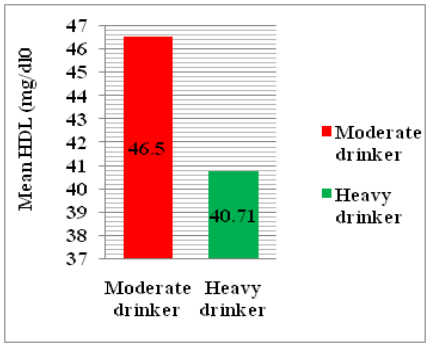

Fig 3

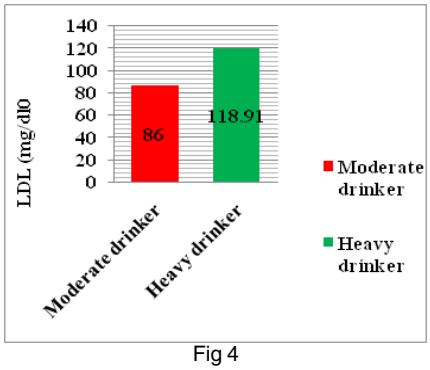

Fig 4

Fig 3 & 4 — Comparison of HDL and LDL in cases on the basis of quantity of alcohol intake

were significantly higher in alcoholics when compared to non alcoholics (p< 0.001). Data showed that HDL cholesterol is low in heavy drinkers with a mean value of 40.71±4.21 mg/dl when compared to moderate drinkers, which is 46.50±8.85 mg/dl. There is a significant change in HDL cholesterol with p value 0.000016. There is raise in LDL cholesterol by mean value 118.91±35.56 mg/dl in heavy drinkers in comparison to moderate drinkers which is 86.26±26.17 mg/dl. Significant change is found with p value <0.00001. This result is similar to the study done by Arun Lakshmipathy *et al*[7] who found that there is an increase in HDL levels when alcohol is consumed in moderation, but there may be a decline in HDL when alcohol is consumed in excessive quantity.There is an another study with similar finding conducted by Sheethal K C *et al*,[8] in which the mean value of HDL, LDLin heavy drinkers were 40.44±4.03, 123.44±38.44 and in moderate drinkers were 47.16±9.32, 80.42±26.31 respectively with p value <0.05.

Conclusion

It is concluded from the present study that there is significant correlation between alcohol intake and serum HDL and LDL levels. Serum HDL has also a significant correlation with drinking pattern whether heavy drinkers or moderate drinkers. It is reasonable to conclude that chronic heavy alcohol intake may be a factor in development and progression of cardiovascular disease by raising LDL and lowering HDL.

Limitation : The study was hospital based study with small sample size of 100 cases and 100 controls, conducted over a limited period of 1 year. So to gather detail information regarding correlation between alcohol intake and serum lipid profile, it needs broader study covering large no population over a longer period of time.

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Original Article

Multi Slice Spiral CT Pulmonary Angiography in Dynamic Pitch Mode using Volume Helical Shuttle Technology for the Diagnosis of Pulmonary Embolism

Jijo Joseph[1], Rajeev Anand[2], Reshma Francis[3]

Introduction : Multi slice Computed Tomography Pulmonary Angiography (CTPA) in dynamic pitch (Volume Helical Shuttle-VHS) mode is an evolving method to visualize pulmonary arteries including the peripheral pulmonary vasculature. The purpose of this study is to evaluate CT Pulmonary Angiography in dynamic pitch mode (Volume Helical Shuttle) for pulmonary embolism in comparison with standard pitch mode.

Methods : We have done a multicentric analytical comparison study with study group involving patients undergone CTPA in dynamic pitch mode-Volume Helical Shuttle (VHS) and comparison group involving patients undergone CTPA in standard pitch mode.

Results : Optimal contrast enhancement phase of the pulmonary artery in the study group in Phase I to III were 22.6%, 43.4% and 34%. The best phases were the last two phases in our study. Study Group main pulmonary artery mean signal intensity is 423.83±75.94 HU and comparison groups mean signal intensity is 361.74±98.28HU (P value = 0.039). The percentages of analyzable segmental arteries were 91.6% in study group and 87.3% in comparison group (P value-0.008). The percentages of analyzable sub segmental arteries were 89.5% in study group and 84% in comparison group (P value-0.004). The study group shows less percentage of motion artefacts and higher image quality than the comparison group, however it was not statistically significant (P value >0.05).

Conclusions : Multislice CTPA in dynamic pitch mode using Volume Helical Shuttle (VHS) technology increase the ability to obtain the Optimal contrast enhancement in pulmonary arteries, improves the overall image quality, obviate the need for breath holding.

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***Key words* : Multi slice Computed Tomography Pulmonary Angiography, Pulmonary embolism, Dynamic pitch mode, Volume Helical Shuttle-VHS, Standard Pitch Mode.**

Pulmonary embolism is the third most common Acute Cardiovascular Disease after Myocardial Infarction and Stroke and results in thousands of deaths each year because it often goes undetected. Computed Tomographic Pulmonary Angiography (CTPA) has been evaluated with meta-analysis and has demonstrated sensitivities of 53%-100% and specificities of 83%–100%, wide ranges that are explained in part by technologic improvements over time[1].

Today multi slice helical CT technology has made it possible to image the thorax in a short period of time. This technique can cover the entire chest in 1-mm slice thickness or less, in one short breath-hold and allows a better analysis of peripheral pulmonary arteries with a better depiction of sub-segmental and peripheral clots[2].

Editor's Comment :

- Multi slice CTPA in dynamic pitch mode [Volume Helical Shuttle-(VHS)] is a safe, non-invasive and patient-friendly method for CT pulmonary angiography.
- Fast scanning using dynamic pitch (VHS) technology obviates the need of breath holding and is useful in patients with acute pulmonary thromboembolism.
- Dynamic mode CTPA allows to take three or more angiographic phases using fast scanning technology which is useful for attaining optimal contrast enhancement in the pulmonary arteries and improves overall image quality.

The main limitations of Multi-slice spiral CT are :

(A) Lack of optimal Pulmonary Artery contrast enhancement :

Pulmonary CT Angiography is often performed with fixed scan delays. In patients with normal right ventricular outflow, a 12-15 second scanning delay usually provides sufficient latitude so that the pulmonary arteries almost always well opacified. For patients with right ventricular failure and patients with pulmonary hypertension, a longer scanning delay is required, varying from 15-18 seconds[3,4-6].

With MDCT, a bolus-tracking method has been

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increasingly used to determine timing and reported to be particularly beneficial for patients with Right Heart Failure or Pulmonary Hypertension. However, no analytic study has been conducted on the appropriate implementation of a bolus-tracking method[4,7].

(B) Motion artefacts in patients with poor breath holding:

In some instances, results in suboptimal diagnostic quality of pulmonary CT angiographic images are motion artifact due to patient respiration or transmitted cardiac pulsation. The shorter breath-hold times that are possible with multi–detector row CT should facilitate investigation in dyspnoeic patients and reduce the occurrence of respiratory motion artifacts[8,9].

Pulmonary Angiography with Multi-slice spiral CT in Dynamic Pitch mode using Volume Helical Shuttle (VHS) Technology.

CTPA is widely used in clinical diagnosis of pulmonary embolism as a non-invasive method. Imaging in the optimal pulmonary artery enhancement phase is one of the key factors in the success of CTPA. According to conventional CTPA, after contrast injection 13~16s scan, most of which can obtain satisfactory image; but because there are individual differences in optimal pulmonary artery enhancement phase, in some cases catch less than optimal pulmonary enhancing phase. VHS technology has a wide range of fast roundtrip shuttle scan imaging advantages may facilitate capture optimal pulmonary artery enhancement phase[2].

With helical (also called spiral) scanning, the table moves at a constant speed while the gantry rotates around the patient. This geometry results in the X-ray source forming a helix around the patient. The pitch of the helical scan is defined as, Pitch = F table /nT, where F_{table} is the table feed distance per 360-degree rotation of the gantry and nT is the nominal collimated beam width. With the latest generation of multi detector CT scanners, it is possible to cover large volumes of anatomy in a very short time. However, when width of coverage increases, it might increase phenomena's such as cone beam artifact (wide cone angle for wide-area detector), heel effect (non-uniform illumination of X-ray of the tube anode for wide-area detector) and scatter of X-ray photons. These inconveniences are reduced by VHS method.

Shuttle mode allows a CT scanner to repeatedly image a volume of tissue that is wider than the detector array (nT). The table rocks back and forth a prescribed distance, during the temporal acquisition procedure. Due to the change in direction of the table, shuttle mode results in image data being acquired during table acceleration and deceleration, which implies that the reconstruction algorithm needs to accommodate for the changing pitch. The result is more than 300mm of high-resolution volume coverage for 4D CTA studies can perform a 4D CTA study to characterize the inflow and outflow of contrast in the arterial and venous system over a length of 312.5mm, equivalent to a 500-slice image[2] (Fig 1).

Using VHS technology, continuous scanning bed regularly move back and forth, to achieve a wide range of the z-axis direction of the reciprocal scanning in a short time, improving the time resolution in CT acquisition. An entire lung scan path about 3s, continuous scanning is possible to capture the best phase[2].

When imaged using VHS CTPA performed, in order to reduce radiation, which adopt a higher noise figure. Automatic dose adjustment technology CT scan, as noise increases exponentially lower radiation dose scan. CTPA using VHS technology for imaging can evaluate the average rate of pulmonary artery segment level to 88.39 percent, with the literature reported similar to bolus tracking technology. Compared with bolus tracking technology CTPA imaging, the process of operation is relatively simple, high success rate, more suitable for patients with severe Acute Pulmonary Embolism[2].

Volume Helical shuttle allows you to characterize arterial and venous inflow and outflow, measure volume coverage for a length of 312.5mm, perform perfusion studies for the body and organs, improve temporal sampling and use acquired scan data during acceleration and deceleration[2].

The advantages of Multi slice CT Pulmonary

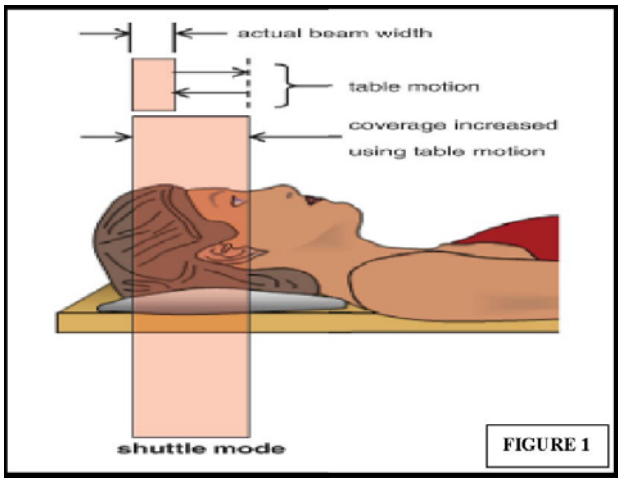

Fig 1 — Shuttle mode: Table rocks back and forth a prescribed distance, during the temporal acquisition procedure and increase the volume of coverage.

angiography in dynamic pitch mode using Volume Helical Shuttle technology are:

(1) Fixed delay of 10 seconds makes it operator independent.

(2) Good contrast delivery providing superior luminal contrast and obtain optimal contrast opacification.

(3) Shuttle mode with fast scanning obviates the need for breath holding.

(4) Lack of partial voluming[2].

Materials and Methods

The analytical comparison study was conducted in the Department of Radiodiagnosis and imaging, Medical Trust Hospital, Ernakulam and Department of Radiodiagnosis, Malankara Orthodox Syrian Church Medical College, Ernakulam for the time duration of January 2015 to December 2018 after taking consent from patients and approval by the ethics committee.

Reference population :

The patients selected for study were referred from Respiratory Medicine/General Medicine/Cardiology Department at our Hospital, who were clinically suspected to have pulmonary embolism.

Study group : Patients with suspected pulmonary embolism, referred to the Radiology Department, Medical Trust Hospital, Ernakulam from January 2015 to December 2018 for CT Pulmonary Angiography. (Undergone CTPA in Dynamic Pitch mode-Volume Helical Shuttle, VHS using 128 slice CT GE Optima 660)

Comparison group : Data collected from records from the Department of Radiodiagnosis, Malankara Orthodox Syrian Church Medical College, Ernakulam for the time duration of January 2015 to December 2018. (Undergone CTPA in standard pitch mode using PHILIPS BRILLIANCE 64 slice CT).

Total 106 patients (53 patients each in study group and comparison group) were included in the study.

Exclusion criteria included age <18 years, history of severe allergy to contrast media and severe renal dysfunction (eGFR <30 mL/min) not on dialysis.

Scanning technique :

Dynamic pitch (Volume Helical Shuttle-VHS) CTPA Protocol (Study group)

- Dynamic pitch CTPA done using Volume Helical Shuttle (VHS) technology by GE with 128 slice CT GE Optima 660.
- Automatic control technology mA, tube voltage 120kV, noise figure 18, FOV 50cm, pitch 1.375:1,0.4 sec / rev, reconstruction using adaptive statistical iterative algorithm (Adaptive statistical iterative reconstruction, ASIR) reconstruction, ASIR take 50%.
- Scans with fixed 10 sec delay
- Contrast media – Omnipaque 350 mg/ml
- Contrast administration – bolus of 90ml at the rate of 4.5ml/sec.
- Injector used is MEDRAD salient single head S-80465
- 18 gauge cannula through antecubital vein
- Scans were taken without breath holding
- Three passes(arterial phase) taken in dynamic pitch (VHS) mode at 12sec,15sec and 18sec, covering from lung apices to diaphragm
- Venous phase scan taken to include IVC (Helps to plan IVC filter) Standard CTPA protocol (Comparison group)
- Standard CTPA studies done with PHILIPS BRILLIANCE 64 slice CT.
- Automatic control technology mA, tube voltage 120kV, noise figure 9.8, FOV 50cm, pitch 0.984:1,0.8 sec / rev
- Scan done with bolus tracking method, ROI in SVC, 3 sec delay
- Contrast media – Omnipaque 350 mg/ml
- Contrast administration – bolus of 90ml at the rate of 4.5ml/sec.
- Injector used is MEDRAD salient single head S-80465
- 18 /20 gauge cannula through antecubital vein
- Scans were taken with single breath holding

AIMS

- To evaluate CT Pulmonary Angiography in dynamic pitch mode (Volume Helical Shuttle) to obtain optimal contrast enhancement phase.
- To compare dynamic pitch (Volume Helical Shuttle) CTPA with standard pitch CTPA with respect to:

a) Motion artefacts in aortic root, ascending aorta and main pulmonary artery.

b) Optimizing contrast enhancement in Main pulmonary artery

c) Visualisation of peripheral pulmonary vasculature(Segmental and sub segmental arteries)

d) Overall image quality

Image Interpretation :

Image analysis using the GE Advantage Windows 4.4 workstation after processing.

All cases were analyzed by two experienced radiologists.

Observed all scans including study group and comparison group in random order for —

(1) Motion artefacts :-

In the Aortic root, ascending aorta and main pulmonary artery

(2) Optimal main pulmonary artery contrast enhancement :-

Measuring the Main Pulmonary Artery (MPA) mean signal intensity (HU value) using circular or elliptical ROI placed in the corresponding blood vessels, ROI > 1cm2, to avoid artefacts.

Recorded the main pulmonary artery standard deviation. The MPA and branch pulmonary artery optimal enhancement phase is considered as the best phase. If more than one phase came good, then considered an earlier phase as best phase. Mean signal intensity value >250HU is considered as satisfaction level.

(3) Analysis of peripheral pulmonary arteries:

By using a scoring sheet similar to that used by Remy Jardin *et al*[5], 20 segmental, and 40 sub segmental arteries were evaluated in each patient. Each artery was individually coded and was considered analyzable when depicted from the proximal to the distal portions on a single or successive transverse CT scans without partial volume effects. The reason for inadequate arterial depiction including respiratory and/or cardiac motion artifacts, partial volume effects due to the small size of the vessel, and absence of an artery because of anatomic variants.

Each artery was individually coded as analyzable or not, leading the readers to determine the number of arteries analyzable per patient in each lung. These results were presented as rates of recognition of pulmonary arteries, expressed as percentages and calculated by means of the following formula: The rate of recognition equalled the number of arteries coded as analyzable in a given patient multiplied by 100 and divided by the maximum number of arteries anatomically present per patient.

(4) Overall Image Quality :

Two Radiologists asses the overall image quality using five point scoring system.

1-Poor, 2-Suboptimal, 3-Satisfactory, 4-Good, 5-Very Good.

Mean of both scores calculated and classified as, Excellent (> 3 points), Can be diagnosed (3 points), Poor (<3 points).

Statistical Methods :

Tabulation: Data from the proforma were entered into a Microsoft Excel spread sheet and exported into a statistical analysis suite. Analytical statistical analysis has been carried out in the present study. Results on continuous measurements are presented as Mean ± SD (Min-Max) and results on categorical measurements are presented in Number(%). Significance is assessed at 5% level of significance.

Statistical software: All data were expressed as Mean ± SD, and statistical analysis was performed with SPSS version 20.Chi square test and student t test used to compare between study group and comparison group, P value < 0.05 was considered statistically significant.

Statistical comparison and diagrams were carried out using Microsoft Excel and SPSS version 20 software.

Results

In this analytical comparison study, we included 53 patients with suspected pulmonary embolism in the study group who had undergone multislice CTPA in dynamic pitch mode (Volume Helical Shuttle), which we compared with 53 patients who had undergone multislice CTPA in standard pitch mode (comparison group).

The age distribution of study group from 37 to 86years, mean (61.51±12.28) years. The age distribution of comparison group from 33 to 81years, mean (62.92±11.55) years. The maximum numbers of patients were seen in the age group 61-70 years in both study group (35.86%) and comparison group (32.07%).In the present study, there is female predominance in both study group and comparison group.

Optimal Contrast Enhancement Phase in Study Group (Dynamic mode-VHS) :

Optimal contrast enhancement phase in the pulmonary artery can be evaluated in the study group. In our study, three arterial phases are included in the study group (Dynamic pitch mode CTPA-VHS mode).The phases are: Phase I (at 12 second scan delay), Phase II (at 15second scan delay) and Phase III(at 15 second scan delay).

The percentage of cases in Phase I to III was 22.6% (12/53), 43.4% (23/53) and 34% (18/53). The best phases were the last two phases (Phase II & III).

Mean signal intensity (HU value) in Main Pulmonary Artery :

In present study, study Group(multislice dynamic pitch CTPA-VHS) Main Pulmonary Artery mean signal intensity is 423.83± 75.94 HU and the comparison groups(multislice standard CTPA) mean signal intensity is 61.74± 98.28HU.

Study Group MPA mean signal intensity lowest value is 274HU and comparison group MPA mean signal intensity lowest value is 190HU. The comparison group had eight cases of MPA mean signal intensity value

lower than 250HU. Study Group main pulmonary artery mean signal intensity value satisfaction rate (> 250HU) is higher than the comparison group.

Student t test was used to compare mean signal intensity (HU value) in MPA between study group and comparison group. There is statistically significant difference (P value = 0.039) of mean signal intensity value between the study group and comparison group.

Motion artefacts in pulmonary angiography :

The percentage of motion artefacts in the study group was 16.9% at the level of aortic root, 5.7% at the level of ascending aorta and 7.5% at the level of MPA. The percentage of motion artefacts in the comparison group was 58.5% at the level of aortic root, 17% at the level of ascending aorta and 30.2% at the level of MPA.

In the present study, the study group shows less percentage of motion artefacts than the comparison group.

Chi square test was used to compare motion artefacts between study group and comparison group. Table 1 shows that there is no statistically significant difference (P value >0.05) between the study group and comparison group.

Analysis of peripheral pulmonary arteries :

The two readers analyzed 1060 segmental arteries (third order arteries) in study group and comparison group (20 segmental arteries per patient).They analyzed 2120 sub segmental arteries (fourth order arteries) in both study group and comparison group (40 sub segmental arteries per patient). The percentages of analyzable segmental arteries were 91.6% (971 of 1060 segmental arteries) in study group and 87.3% (925 of 1060 segmental arteries) in comparison group. The percentages of analyzable subsegmental arteries were 89.5% (1898 of 2120 sub segmental arteries) in study group and 84%(1781 of 2120 subsegmental arteries) in comparison group.

Student t test was used to compare the total number of analyzable segmental and sub segmental arteries between the study group and the comparison group.

Table 1 — *Percentage of motion artefacts in the aortic root, ascending aorta and MPA*

Motion artefacts		Study group	Comparison Group	P value
Aortic root	Yes	9(16.9%)	31(58.5%)	0.72
	No	44(83%)	22(41.5%)	
Ascending aorta	Yes	3(5.7%)	9(17.0%)	1.000
	No	50(94.3%)	44(83.0%)	
MPA	Yes	4(7.5%)	16(30.2%)	0.077
	No	49(92.5%)	37(69.8%)	

Statistically signiûcant difference (P-value <0.05) was found in the total number of analyzable segmental and sub segmental arteries in between study group and comparison group.

Overall Image Quality :

In the study group showing 86.79% 'excellent'(> 3 points), 11.32% 'can be diagnosed'(3 points) and 1.89% 'poor'(<3 points) scores. In the comparison group showing 60.38% 'excellent', 18.87% 'can be diagnosed' and 20.75% 'poor' scores. In the study group, very less number of patients are included in poor image quality score.

Chi square test was used to compare overall image quality between study group and comparison group. There is no statistically significant difference (P value >0.05) between the study group and comparison group.

Representative Cases :

(1) Comparison of Motion Artefacts (Fig 2) :

(2) Optimal Phase in CTPA Dynamic Pitch Mode (VHS) (Fig 3) :

(3) Optimal Contrast Enhancement in MPA (Fig 4) :

(4) Visualization of Peripheral Arteries (Fig 5):

(5) Overall Image Quality (Fig 6) :

Discussion

CTPA is widely used in clinical diagnosis of pulmonary embolism as a noninvasive method. Optimizing the best imaging phase in the pulmonary artery is one of the key factors in the success of CTPA. According to conventional multislice CTPA experience after contrast injection 13 ~ 16s scan, most of which can obtain satisfactory image; but because of the individual differences in pulmonary artery optimal enhancement, in some cases catch less than optimal

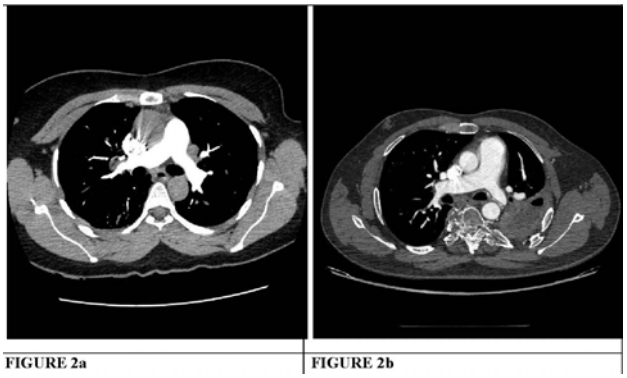

Fig 2 — Transverse MDCT views (WL-40,WW-400) of (a) dynamic pitch mode CTPA scan and (b)standard CTPA scan at the level of MPA shows reduced motion artefacts in dynamic pitch mode CTPA in comparison with standard CTPA scan

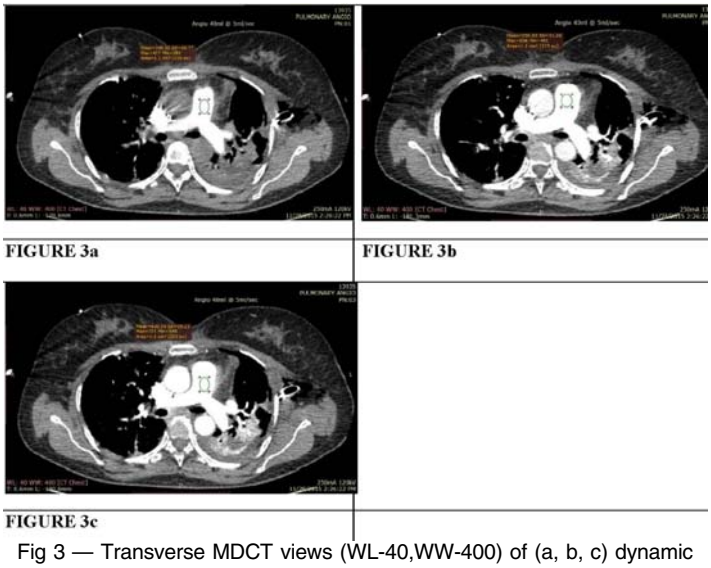

Fig 3 — Transverse MDCT views (WL-40,WW-400) of (a, b, c) dynamic pitch mode CTPA scan (in 56 years old female) showing three arterial phase in dynamic mode. a) Phase- I, Mean HU-348.02±28.77, Only pulmonary vasculature is filled with contrast. b) Phase- II, Mean HU-550.95±31.26. c) Phase- III, Mean HU-626.55±29.23, Mean signal intensity is higher in this phase.

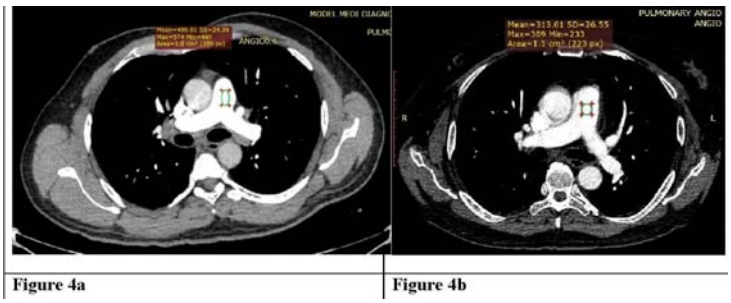

Fig 4 — Transverse MDCT views (WL-40,WW-400) of (a) dynamic pitch mode CTPA scan and (b)standard CTPA scan at the level of MPA shows mean signal intensity (identical region of interest with ROI>1cm^2) is higher in dynamic CTPA scan(Mean HU-499.91±24.38) than standard CTPA scan(Mean HU-313.01.39±16.76)

pulmonary artery enhancement phase. Using VHS technology, continuous scanning bed regularly move back and forth, to achieve a wide range of the z-axis direction of the reciprocal scanning in a short time, improving the time resolution in CT acquisition. An entire lung scan path about 3s, continuous scanning is possible to capture the best phase. When imaged using VHS CTPA performed, in order to reduce radiation, which adopt a higher noise Figure[2].

Multi slice Computed Tomography (CT) Pulmonary Angiography in dynamic pitch (VHS-Volume Helical Shuttle) mode is an evolving method to visualize pulmonary arteries including the peripheral pulmonary vasculature. Dynamic pitch mode (Volume Helical Shuttle) is a new adaptive technology enabling the CT table to travel back and forth using continuous periodic table movement during the acquisition. This allows to take multiple scans during the passage of contrast without inter scan delay within a short period of time. Multislice CTPA in dynamic pitch mode enabled a fast imaging technique and reduce the percentage of motion artefacts in patients due respiratory and cardiac movement in comparison with multislice CTPA in standard mode.

With the introduction of multi slice CT scanners in dynamic pitch mode, allows to perform up to 500-slice (312.5-mm) dynamic studies. Dynamic pitch cone beam reconstruction offers reconstruction for non-constant or dynamic helical pitch and creates images acquired during table acceleration and deceleration and thereby making it possible to scan entire Pulmonary Arterial System with good contrast opacification and less artefacts. Advances in reconstruction algorithms using Adaptive Statistical Iterative Reconstruction (ASIR) technology make it possible to reduce the radiation dose for each examination to acceptable levels[2].

Shuttle mode allows a CT scanner to repeatedly image a volume of tissue that is wider than the detector array. The table rocks back and forth a prescribed distance, during the temporal acquisition procedure. Due to the change in direction of the table, shuttle mode results in image data being acquired during table acceleration and deceleration, which implies that the reconstruction algorithm needs to accommodate for the changing pitch. The result is more than 300mm of high-resolution volume coverage for 4D CTA studies. We can perform a 4D CTA study to characterize the inflow and outflow of contrast in the arterial and venous system over a length of 312.5mm, equivalent to a 500-slice image[2].

Conclusion

From the present study it was noted that multislice CTPA in dynamic pitch mode using VHS Technology is a promising technology for pulmonary Angiography for acute Pulmonary Embolism. The ability to obtain the optimal contrast enhancement in pulmonary arteries using shuttle mode and detection of segmental, sub segmental & more distal pulmonary arteries make it superior to other methods of spiral CTPA. VHS method provides fast imaging with wide range of Z-axis coverage and has reduced the need for breath holding and is more favorable in patients with acute pulmonary embolism. Adaptive Statistical

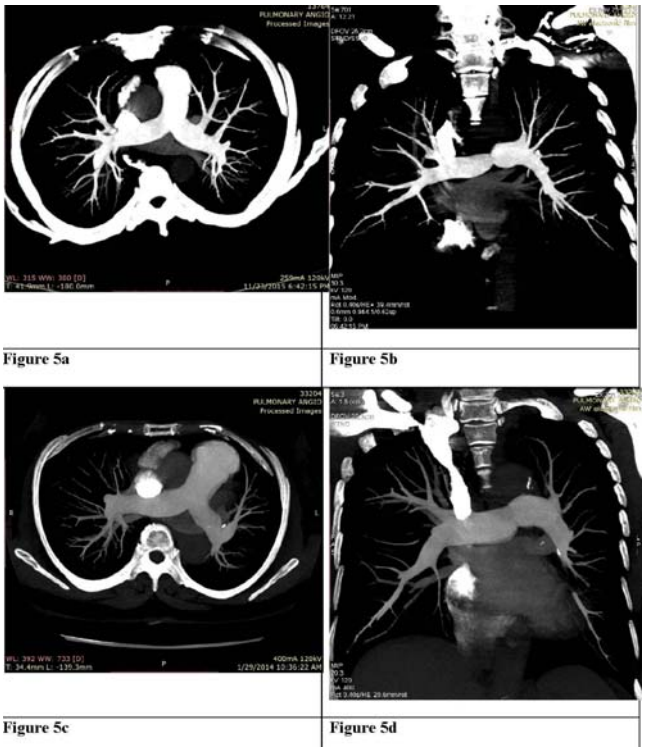

Fig 5 — MDCT Maximum Intensity Projection (MIP), axial and coronal views of dynamic pitch mode CTPA scan (a, b) and standard CTPA scan(c, d) showing better visualization segmental (third order) and sub segmental (fourth order) arteries in dynamic pitch mode CTPA scan.

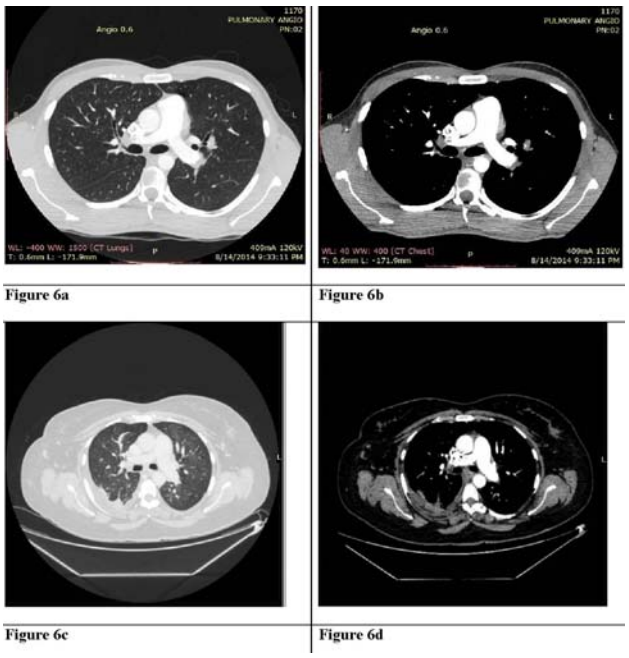

Fig 6 — MDCT Transverse views (Lung window & mediastinal window) of dynamic pitch mode CTPA scan (a, b) and standard CTPA scan(c, d) showing better overall image quality in dynamic mode CTPA scan.

Iterative Reconstruction (ASIR) technology used to maintain the high noise figure, which reduces the radiation dose and improves the overall image quality. Using VHS technology multislice CTPA advantageous to capture the best imaging pulmonary artery enhancement phase. Using a larger noise figure and appropriate ASIR value, the image quality to meet the diagnostic needs.

Acknowledgements

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Original Article

NCD Risk Factors in Different Administrative Divisions of West Bengal: An Insight Analysis from National Family Health Survey-5 Report

Amitava Acharyya[1], Kaushik Ghosh[2]

Introduction : This study was designed to find out the group mean prevalence of NCD risk factors in different administrative divisions of West Bengal (WB) and to explore the probable reasons of these differences in different indigenous habitat wise groups of districts of West Bengal.

Methods : This descriptive study was conducted on available secondary data from National Family Health Survey-5 (NFHS-5) regarding NCD risk factors. For this study, WB's districts were divided into five administrative divisions namely Presidency, Medinipur, Burdwan, Malda and Jalpaiguri. Again WB State divided into three groups namely Jangalmahal (forest region), Pahar (Himalayan Hilly region) and "Rest of West Bengal" (ROW) on the basis of habitat of major indigenous people. Data are analyzed by Microsoft excel software in percentage and group mean.

Results : Presidency (M: 20.6% *versus* F: 21.9%) with Medinipur (M: 20.3% *versus* F: 19%) divisions and Jangalmahal group of districts (M: 22.1% *versus* F: 16.5%) have higher group mean prevalence of high blood sugar in West Bengal. High group mean prevalence of high blood pressure was observed in Pahar (M: 26.6% *versus* F: 25.2%) group of districts and Jalpaiguri (M: 24.7% *versus* F:24%) division. The group mean prevalence of alcohol intake is very high in Jalpaiguri division (M: 25.2% *versus* F: 3%). The group mean prevalence of obesity (women aged 15-49 years) is increased from the last NFHS -4 survey.

Conclusion : The group mean prevalence of alcohol intake and high blood pressure are very high in Pahar. The tobacco use related habit is comparatively high in Jangalmahal and Pahar group of districts. The group mean prevalence of high blood sugar is comparatively high in Jangalmahal and Presidency division areas.

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Key words **: Group mean prevalence, NCD risk factors, Administrative divisions of West Bengal, NFHS-5.**

Non-communicable Diseases (NCDs) contribute to around 38 million (68%) of all the deaths globally and to about 5.87 million (60%) of all deaths in India. Four NCDs (cardiovascular diseases, chronic respiratory disease, cancers and diabetes) are contributing to about 82% of all NCD deaths[1]. Current study recommended, if comprehensive measures (eradicating the common risk factors, mainly tobacco use, unhealthy diets, physical inactivity, and the harmful use of alcohol)are implemented properly then 80% NCDs (Heart diseases, Stroke, Hypertension and Type 2 Diabetes, and over a third of Cancers) related premature deaths can be minimized[2]. To deal with this problem the Government of India has launched the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular diseases and Stroke (NPCDCS) in 2010[3]. This initiative has to be implemented in full swing across Pan-India with proper policy that addresses all components of the programme[4]. It is also noticed that the NCD related health literacy is very low in India[5, 6] as well as in West Bengal[7].

Editor's Comment :

- The burden of alcohol intake and high blood pressure are very high in Pahar group of districts (hilly tribal zone of West Bengal).
- The tobacco use related habit is comparatively high in Jangalmahal and Pahar group of districts (tribal area predominantly).
- The group mean prevalence of high blood sugar is comparatively high in Jangalamahal (rural tribal area) and Presidency (urban predominant) division area.
- The female population has a higher burden of overweight and higher WHR especially in urban areas of West Bengal.

In National Family Health Survey-5 (NFHS-5) (2019-2020) an effort was employed to measure the district level health status of Indian population by the Government of India (GoI)[8]. With this available district level data of NCD risk factors, this study is designed to find out the group mean prevalence (GMP) of NCD risk factors in different administrative division of WB[9] and to explore the difference of GMP of NCD risk factors in different indigenous habitat wise group of districts of West Bengal (WB). This effort has clearly demonstrated the difference of prevalence of NCD risk

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factors in urban vs rural, tribal area vs Non-tribal area, plan land *versus* hilly area and male vs female population.

Materials and Methods

The secondary data available from the NFHS-5 (2019–2020) was analyzed at district level focusing on WB. The required Information of WB was gathered from 18,187 households, 21,408 women, and 3,021 men during 21 June, 2019 to 8 November, 2019 by Indian Institute of Health Management Research (IIHMR)[8].

Operational definition of risk factors[8]

High blood sugar — Random blood sugar >140 mg/dl or taking medicine to control blood sugar level

High Blood Pressure — Elevated blood pressure (Systolic e"140 mm of Hg and/or Diastolic ≥90 mm of Hg) or taking medicine to control blood pressure

Tobacco consumption — Men or Women age 15 years and above who use any kind of tobacco

Alcohol consumption — Men or Women age 15 years and above who consume alcohol

Overweight women: Women who are overweight or obese (BMI ≥25.0 kg/m2)

Women with high waist to hip ratio (WHR): Women who have high risk waist-to-hip ratio (≥0.85)

Group mean prevalence (GMP): The group mean prevalence is the mean prevalence of any variables of a group of districts. The prevalence of different risk factors of different districts were considered as "unit of data".

Selection of districts in West Bengal

NFHS-5 survey conducted in 2019-2020 included 19 districts of WB In the NFHS-5 portal, there is no data available regarding three newly developed districts (Jhargram, Kalimpong and Alipurduar) of WB. The WB state is divided into five administrative divisions namely Presidency, Medinipur, Burdwan, Malda and Jalpaiguri (Table 1-A)[9]. For the purpose of this article the WB State has been further divided into three groups Jangalmahal (forest region), Pahar (Himalayan Hilly region) and "Rest of West Bengal" (ROW) on the basis of habitat of major indigenous people (Table 1-B). The Jangalmahal[10] and Pahar[11] group of districts have a comparatively large number of tribal populations.

Ethical clearance : No ethical clearance is necessary to analyze the secondary data which are publicly available. The required data was retrieved on

Table 1 — *List of districts of West Bengal under Administrative divisions and group of Districts on the basis of habitat of major indigenous people*

(A) Administrative divisions of West Bengal

Presidency	Medinipur	Burdwan	Malda	Jalpaiguri
Majority of population stay in Urban area (flat land)	Majority of population stay in rural area and majority are from tribal (Austro-Asiatic) community (flat land) (Naxalite area)	Majority of population stay in rural area and they are normally non-tribal community (flat land)	Majority of population stay in rural area and they are normally non-tribal community (flat land sharing Bangladesh border)	Majority of population stay inrural area and they are normally tribal (Tibeto-Burman and Austro-Asiatic) and Nepali community (flat land but some areas are high altitude area)
Kolkata Howrah 24 Paragana (N) 24 Paragana (S) Nadia	Medinipur (E) Medinipur (W) Purulia Bankura Jhargram	Burdwan (E) Burdwan (W) Birbhum Hooghly	Malda Murshidabad Dinajpur (N) Dinajpur (S)	Jalpaiguri Darjeeling Coochbihar Alipurdwar Kalimpong

(B) Group of Districts on the basis of habitat of major indigenous people in West Bengal

Jangalmahal	Pahar	Rest of West Bengal (ROW)	
Majority of population stay in rural flat area and majority are from tribal (austro-asiatic) community (partly Naxalite area)	Mainly multicultural community however significant of population stay in rural hilly area and they are normally Nepali and Tibeto-Burman tribal community –Lepcha, Bhutia, Tamang, Limbo, Sherpa etc (partly Gorkhaland movement area)	Majority of population stay in urban and rural area (flat land). Majority populations are non-tribal.	
Medinipur (W) Purulia Bankura Jhargram	Jalpaiguri Darjeeling Kalimpong	Medinapur (E) Kolkata Howrah 24 Paragana (N) 24 Paragana (S) Nadia Burdwan (E) Burdwan (W)	Malda Murshidabad Dinajpur (N) Dinajpur (S) Coochbihar Alipurdwar Birbhum Hooghly

27th December, 2020 form National Family Health Survey website[8].

Statistical Analysis : The descriptive statistics were computed by using Microsoft excel software in percentage and group mean.

Results

Results are divided into five parts:

(A) Distribution of group mean prevalence of high blood sugar of different zones

(B) Distribution of group mean prevalence of high blood pressure of different zones

(C) Distribution of group mean prevalence of tobacco use of different zones

(D) Distribution of group mean prevalence of alcohol use of different zones

(E) Changing group mean prevalence of overweight among women age 15-49 years in NFHS-4 and NFHS-5of different zones

(F) Distribution of high Waist to Hip ratio (WHR) among women age 15-49 years of different zones

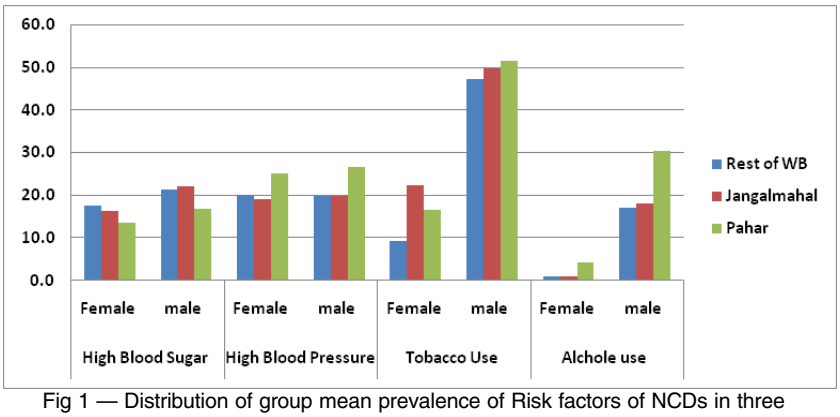

Fig 1 — Distribution of group mean prevalence of Risk factors of NCDs in three demarcated areas of West Bengal (data presented in percentage)

(A) Distribution of high blood sugar :-

Table 2 described the administrative division-wise district level analysis of group mean prevalence of high blood sugar in WB. The table denotes that the high blood sugar patients are more among male population of Medinipur division (22.6%). According to Indigenous habitat -wise district level analysis, it is found that, group mean prevalence of high blood sugar is high amongst the Jangalmahal (male: 22.1% and female: 16.5%) and ROW (Male: 21.5% and Female: 17.6%). (Table 4, Fig 1)

(B) Distribution of high blood pressure :-

The higher group mean prevalence of high blood pressure was notified in the Jalpaiguri division (male: 24.7% and female: 24.0%) in administrative division-wise district level analysis in WB (Table 2). Almost ¼th adult populations are affected with high blood pressure. Jangalmahal and ROW groups of districts have less group mean prevalence of high blood pressure and it is almost 19-20 % among the adult population. In Indigenous habitat -wise district level analysis of WB found, Pahar (Male: 26.6% and Female: 25.2%) area has a very high group mean prevalence of high blood pressure. The group mean prevalence of high blood pressure is more among male population than the female population in all groups.

(C) Distribution of tobacco use :-

Male adult population outnumbered the female population regarding the use of tobacco in any form. Almost ½ of the whole adult male population are using tobacco in WB. The group mean prevalence of tobacco use among adult females is quite higher among Medinipur (20%) and Jalpaiguri (18.6%) divisions' area than other divisions of WB.

(D) Distribution of alcohol use :-

Male adult population outnumbered the female population regarding the prevalence of intake of alcohol. Almost ¼th of the whole adult male population are using alcohol in WB. The group mean prevalence of alcohol intake is very high among Jalpaiguri (Male: 25% and Female: 3%) divisions than other four administrative divisions in WB. However, Table 4 and Fig 1 clearly denoted that prevalence of using alcohol in the Pahar group of districts (Male: 30.6% and Female: 4.3%) is very higher than "ROW" and Jangalmahal group of districts.

Table 2 — *Distribution of group mean prevalence of high blood sugar, high blood pressure, tobacco use and alcohol use in five administrative divisions of West Bengal*

Name of Division	High Blood Sugar (%)		High Blood Pressure (%)		Tobacco Use (%)		Alcohol use (%)	
	Female	Male	Female	Male	Female	Male	Female	Male
Presidency	18.8	22.1	21.9	20.6	6.4	46.9	0.6	17.3
Medinipur	17.7	22.6	19.0	20.3	20.0	47.4	1.3	17.4
Burdwan	17.2	22.1	20.1	20.0	9.5	48.5	1.3	19.5
Malda	16.6	20.1	18.0	18.5	9.1	46.3	1.3	16.1
Jalpaiguri	13.5	17.5	24.0	24.7	18.6	53.1	3.0	25.2

(E) Changing GMP of overweight among women age 15-49 years in NFHS-4 and NFHS-5

Table 3 and Fig 2 denote that the group mean prevalence of overweight among women aged 15-49 years has increased from NFHS-4 to NFHS-5 in all administrative divisions of WB state. In WB, the presidency division and Medinipur division have the highest and lowest group mean

Table 3 — *Distribution of group mean prevalence of Overweight and High WHR women in administrative divisions of West Bengal*

Name of Division	Obesity (%)		High Waist to Hip ratio (%)
	NFHS-5	NFHS -4	NFHS-5
Presidency	25.6	28.6	82.0
Medinipur	17.3	12.7	59.6
Burdwan	23.1	20.1	69.0
Malda	20.5	12.5	75.9
Jalpaiguri	20.5	16.0	77.7

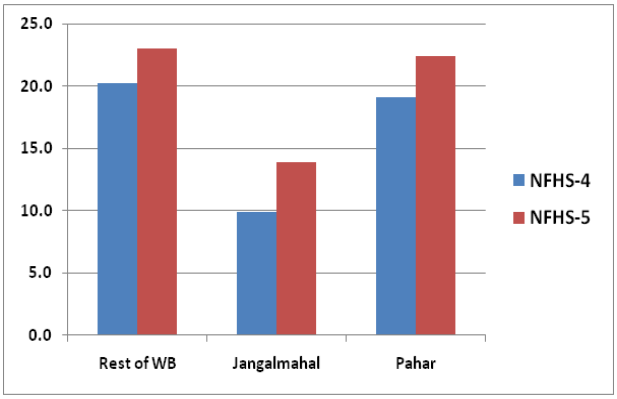

Fig 2 — Distribution of changing group mean prevalence of Overweight among women (age 15-49 years) in three demarcated areas of West Bengal (NFHS-4 and NFHS-5) (data presented in percentage)

prevalence of overweight women aged 15-49 years respectively (Table 3). In Indigenous habitat -wise district level analysis of WB found, Pahar and "ROW" group of districts have almost 20% of group mean prevalence of women (age 15-49 years) with overweight. In the Jangalmahal group of districts, this group mean prevalence is only 10%.

(F) Distribution of high WHR among women age 15-49 years

The group mean prevalence of WHR is very high among women aged 15-49 years in all administrative divisions of WB. Table 5 denotes that the presidency division has the highest group mean prevalence of women with high WHR among all administrative divisions of WB. However the Indigenous habitat -wise district level analysis of WB found, Pahar and the "ROW" group of districts have an almost high

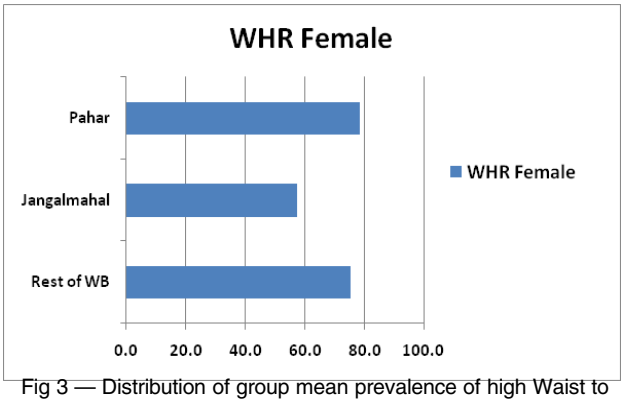

Fig 3 — Distribution of group mean prevalence of high Waist to hip ratio (WHR) among women aged 15-49 years in three demarcated areas of West Bengal (data presented in percentage)

prevalence of women with high WHR and it is more than 77%. But the Jangalmahal group of districts' group mean prevalence of women with high WHR is only 57% (Fig 3).

Discussion

The analysis is attempted to estimate the group mean prevalence of NCD risk factors in different administrative divisions of WB and to explore the difference of group mean prevalence of NCD risk factors in different indigenous habitat wise groups of districts of WB based on the data available from NFHS-5.

The NFHS-5 report documented that WB's prevalence of high blood sugar among adult male and females are 23.1% and 17.5% respectively[12]. In NFHS-4 report, the prevalence of high blood sugar were 17.3% and 10.9% among male and female respectively[13]. It is clearly visible that prevalence of high blood sugar in increasing tread in West Bengal. The male population is more affected with diabetes mellitus than the female population in WB. In comparison between urban and rural adult populations, we observed a slightly different pattern of prevalence[12]. Among adult female population prevalence of high blood sugar is 19.4% and 16.5 % in urban and rural areas respectively. However the prevalence of high blood sugar among the adult male population is 20.4% and 21.3% in urban and rural areas respectively[12]. Urban female population burden for diabetes mellitus is higher in comparison to rural adult female population. But the figure of prevalence of high blood sugar is almost the same in urban and rural adult male populations.

Moreover, the analysis regarding group mean prevalence of high blood sugar revealed that the Presidency

Table 4 — *Distribution of group mean prevalence of NCD risk factors in three demarcated areas of West Bengal*

Name of Area	High Blood Sugar (%)		High Blood Pressure (%)		Tobacco Use (%)		Alcohol use (%)	
	Female	Male	Female	Male	Female	Male	Female	Male
Pahar	13.5	16.9	25.2	26.6	16.7	51.6	4.3	30.
Jangalmahal	16.5	22.1	19.3	19.9	22.3	49.8	1.1	18.2
Rest of WB	17.6	21.5	20.1	19.9	9.4	47.	1.0	17.2

division (Male: 22.1%, Female: 18.8%) has a higher burden for diabetes mellitus than any other administrative division in WB. The Presidency division is a predominantly urban region of the state with high GDP. The same type of picture is also observed when the analysis is performed on the basis of area of Indigenous habitat. The tribal predominant areas like Pahar and Jangalmahal have less burden of prevalence of high blood sugar than "ROW" (Male: 21.5%, Female: 17.6%). Sikkim, a neighbor state of WB with 30% tribal population, has less prevalence (Male: 15.7%, Female: 12.2%) of high blood sugar than the whole WB among adults as per this survey[12]. However in NPCDCS report-2011, Sikkim was reported with the highest percentage of high blood sugar (13.67%) and high blood pressure (18.16%) among all states in India[14]. It is reflected that Sikkim and WB's prevalence of high blood sugar is in increasing trend. A significantly higher group means prevalence of high blood sugar is also observed among male population of Medinipur (22.6%) division which is predominantly a nonurban and partly tribal zone of WB. It reflects a rising burden of high blood sugar in rural as well as tribal areas of WB. It has been documented in West Bengal[15] that, in hospital mortality due to Myocardial Infarction (MI) was higher in IFG (impaired fasting glucose) patients (18%) which is near about same in proportion with diabetes patients (20%) in compression of euglycemic patients (4%). This shows that the earliest attention is required to prevent cardiac mortality by prevention of IFG and diabetes.

Regarding high blood pressure, NFHS-5 survey reported quite a higher burden of high blood pressure in WB (male: 20.1%, female: 20.5%)[12]. The prevalence of high blood pressure on the basis of gender difference is not observed in WB. In WB, urban population (male: 23.3%, female: 21.5%) has more prevalence of high blood pressure than rural population (Male: 19%, Female: 19.9%). In Indigenous habitat -wise district level analysis revealed the people of "Pahar" group of districts have more burden of high group mean prevalence of high blood pressure than Janagalmahal and "ROW". The people of Pahar group of districts have different cultural practices, traditional dietary habits, genetic architecture and language (Tibeto-Burman) than other parts of WB. However, the group mean prevalence of high blood pressure is almost same in Medinipur, Burdwan and Presidency administrative divisions among male adults which are also quite high and almost same with state average. The prevalence of high blood pressure is markedly increased with high altitude in this area as the data present in this survey report. In comparison of NFHS-4 data, West Bengal is in increasing trends of prevalence of high blood pressure[12,13,16].

NFHS-5 survey reported very basic prevalence related information about harmful use of products like tobacco and alcohol which are major behavioral risk factors for NCDs. The prevalence of tobacco use among male adults in WB (Male: 48.1%, Female: 10.8%) is fairly higher in comparison to the female population[12]. Again it is observed that the prevalence of use of tobacco is also high in rural area in WB (rural male: 49.9%, rural female: 12.3% *versus* urban Male: 44.7%, urban Female: 8%) than urban area[12]. The number of adult male tobacco users is almost four times higher than female adult tobacco users. In division wise district level analysis in WB revealed that the group mean prevalence of adult female tobacco users is very high in Medinipur (20%) and Jalpaiguri (18.6%) division like tribal predominant areas. In Indigenous habitat -wise district level analysis, it is clearly observed that the group mean prevalence of adult female tobacco users in Janagalmahal and Pahar are almost double than "ROW". Same type of high prevalence of tobacco use was noticed in tribal population[17] and sub-Himalayan area[18] of WB in other studies. Especially smokeless tobaccos in the form of KHAINI and DOKTA and Bidi like smoking tobacco are widely practiced in rural populations of WB.

Regarding the alcohol intake habit, NFHS-5 survey reported higher prevalence of alcohol intake person among male population in WB (male: 18.1%, female: 1.1%)[12]. The group mean prevalence of alcohol intake habit is almost same in Jangalamahal (male: 18.2%, female: 1%) and "ROW" (Male: 17.2%, Female: 1%) group of districts which are quite similar with the state figures. The studies from Jhargram[19] and West Medinipur[20] documented a very high prevalence of alcohol intake in tribal populations in West Bengal. The Pahar group of districts have a very high group mean prevalence of male alcohol intake habits (Male:30.6%, Female: 4.3%), which is quite similar to neighboring state Sikkim as both areas share common cultural, social and behavioral habits. There is no social stigma of alcohol intake in this high altitude Himalayan society and this habit is very much socially acceptable. This type of high prevalence is also observed in one sub-Himalayan study in WB[17]. However in comparison of NFHS-4 data, both states are in decreasing trends of prevalence of alcohol use[12,13,16].

According to the NFHS-5 and NFHS-4 report, WB's prevalence of overweight is increasing treads". Almost 1/5th adult Bengalis are overweight, which is the leading

risk factor of diabetes, hypertension, dislipidemia, stroke, depression and heart diseases. The burden of prevalence of overweight is higher in the urban population than the rural population in WB. The division wise district level analysis of WB revealed that urban dominated Presidency division (25.6%) has a major burden of overweight in women (aged 15-49 years) which is almost double than Jangalmahal (13.9%) group of districts (Austro-Asiatic prevalent tribal area). Same observation is also noticed in a comparison study in WB[21]. However the presidency division area's group mean prevalence of obesity among women (aged 15-49 years) is improved than NFHS-4 survey report.

WHR is an independent risk factor for Metabolic Syndrome and diabetes. Almost 2/3rd female and more than 50% male adult populations have high WHR[12]. The presidency (82%) and Medinipur (59%) division have the highest and lowest group mean prevalence of WHR among women (aged 15-49 years) than any other administrative divisions respectively. The Jangalamahal (57.4%) has comparatively less group mean prevalence of high WHR among women (aged 15-49 years). This finding may be due to high physical activity level, genetic cause and dietary habit of this area[22].

Conclusion

As a gross, rural population has competitively very high prevalence of tobacco and alcohol intake habits. The female population has a high burden of overweight and WHR related problems especially in urban areas. The male and female have almost the same burden of group mean prevalence of high blood pressure in WB. The urban adult population has a comparatively high burden of overweight and high blood sugar. The group mean prevalence of alcohol intake and high blood pressure are very high in Pahar (hilly tribal zone of WB). The tobacco use related habit is comparatively high in Jangalmahal and Pahar group of districts (tribal area). The group mean prevalence of high blood sugar is comparatively high in Jangalamhal (rural tribal area) and Presidency (urban predominant) division area. Urgent and focused attention towards these risk factors is required for planning and implementation of targeted interventions in view of effective NCD control in the WB.

Limitation of the study : There are two major limitations of this review study. Firstly, "group mean prevalence" has been presented in this study where prevalence of different risk factors of different districts were considered as "unit of data". The "unit of observation" is presented in the "group of districts'' level. The "group mean prevalence" is not directly similar with the terminology "Prevalence" as this analysis has not been computed with the data collected from individual person sample data. Secondly, the Standard Deviation (SD) has not been evaluated as numbers of districts are very small in each group of districts to provide any significant conclusion

Way forward to deal with this crisis :

(1) Community level awareness activity to improve NCD related health literacy in urban and rural areas and special focus should be given on locally prevalent unhealthy modifiable risk factors.

(2) Community level screening on NCDs and early treatment to prevent complications

(3) Free annual health check up for all 30+ aged people.

(4) Special focus should be given on behavioral risk factor modification as primordial prevention approach.

(5) Affordable, available and accessible comprehensive diseases management with assured sustainable medicine supply and required investigations as per NPCDCS guidelines.

(6) Supportive and periodical monitoring of NPCDCS and Ayushman Bharat programme.

(7) Development and improvement of health care infrastructure to deal with the future burden of NCDs and reduce the "out-pocket expenditure".

(8) Periodical training of health care staff on updated guidelines and management

(9) Multi-stakeholders involvement and political willingness

(10) Involvement of AYUSH system of medicine in an integrative approach with updated evidences and mainstreaming the AYUSH manpower in preventive, promotive, curative and rehabilitative NCDs care.

(11) Increase taxation on tobacco and alcohol related products.

(12) Development and implementation of Information technology or HMIS for proper follow up, health awareness and referral (with reverse referral) system.

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Original Article

Seasonal, Regional and Demographic Trends in Patients with Acute Undifferentiated Fever in Northern India

Sanjana Sharma[1], Monica Gupta[2], Nidhi Singla[3], Sarabmeet Singh Lehl[4], Saurabh Gaba[5]

Introduction : Acute Undifferentiated Fever (AUF) has a myriad of etiologies most common of which are Vector Borne Diseases in a country like India. The etiology and diagnosis of AUF is driven by the regional disease burden, seasonality of infectious diseases, spectrum and severity of disease, availability of diagnostics and access to health care facilities.

Methods : A twelve-month prospective study was conducted at our centre to determine the commonly occurring causes of AUF. Monthly incidence of each of the common etiologies was noted and a graph was plotted to understand the seasonal distribution of each disease. Other parameters including age, gender, occupation and regional distribution were also studied.

Results : The mean age (±SD) of the population in the present study was 33.16 (±15.88) years. Our study established that Scrub Typhus, Dengue fever and malaria were the most common reasons for AUF. The maximum incidence of AUF was between the months of June to October, peaking in the month of August. Urban population, younger age and males were more affected by AUF. Haryana followed by Punjab and Chandigarh had the highest regional burden of disease.

Conclusion : It is imperative that we understand the seasonal and regional trends of AUF so that we can plan the resource allocation. Identifying the population at risk and timely intervention at Community level may help to reduce disease transmission.

[*J Indian Med Assoc* 2022; **120(5):** 33-8]

Key words **: Acute undifferentiated fever, demography, seasonal trends.**

Fever disproportionately affects the most vulnerable human communities of the tropical regions. Populations that live in poverty, without adequate hygiene and sanitation become more prone to febrile illnesses due to the abundance and relentless propagation of mosquitoes, ticks, mites and other disease-transmitting vectors. In India, the population is expanding exponentially outpacing the existing infrastructure and overwhelming our sanitation and disposal facilities. Urbanisation, deforestation and human migration has led to encroachment into the habitat of the various organisms leading to a disruption in the ecological balance with consequent increase in the incidence of tropical illnesses.

A vast number of organisms can cause Acute Undifferentiated Fever (AUF) ranging from bacteria to viruses to protozoa to fungi and account for many preventable deaths in developing countries. In the Western World, AUF is mainly due to viral illness, but in underdeveloped countries including India it is mostly due to avertable illnesses such as Malaria, Dengue Fever, Scrub Typhus, Leptospirosis, Chikungunya and Enteric fever[1].

India, being a tropical country, sees a diverse variation in the climatic condition ranging from extreme summers and harsh winters to torrential rains.The monsoon season in particular is responsible for a rise in AUF as it provides fertile grounds for the transmission of Arthropod Borne Diseases like Dengue Fever and Malaria[2]. Dengue fever and malaria epidemics have been reported from various parts of India during the monsoon season. Leptospirosis and Scrub Typhus are zoonotic infections which have slowly engulfed many regions of the country in the last decade. Chikungunya has been on the rise in the Northern and

Editor's Comment :
- Most AUF in India are due to vector borne diseases.
- The monsoon and post-monsoon season sees the largest number of tropical fevers.
- Demographics of AUF is widening and susceptible population is increasing.
- Understanding the seasonal and regional variations of AUF is crucial.

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Eastern parts of India. Enteric fever is endemic throughout India. There is greater focus on Non-malarial AUF with the decline of Malaria in many regions of India.

Being aware of the occurrence of diseases during a particular season can help us to understand these diseases better so that the can be identified at the earliest and thereby effectively controlled. Improving our understanding of how Environmental factors affect Tropical diseases can help us chalk out life-saving management strategies.

Materials and Methods

Study Design and Setting :

This observational study was conducted at Government Medical College and Hospital, Chandigarh from January to December 2019. The study was aimed at observing the common etiologies of AUF in Northern India and the seasonal distribution along with age, gender, occupation and the regional burden of these fevers. The study was approved by the Research and Ethics Committees of the Medical College.

Study Participants and Sampling :

A total of 200 patients with AUF were included in the study. Hospitalised patients older than 12 years of age with fever of ≤14 days were included in the study. Localized infection was ruled out by History, Physical Examination, Complete Blood Counts, Urine Analysis and Chest Radiography at the time of initial presentation. Immunocompromised patients and those who had received prior antibiotics or hospitalisation were not included.

Data collection Tool and Technique :

A written and informed consent of all the participants was taken. A descriptive analysis was done to characterize the participant population by socio-demographic data (eg, Age, Gender, Place of residence and Occupation). All Non-parametric variables were compared using Chi-square and Kruskal Wallis. Mean (SD) or median (range) were calculated for the parametric variables and they were analysed using Student's t-test. All data was expressed as mean ±SD. Empirical therapy was started as per clinical suspicion and preliminary investigations. It was subsequently modified after a diagnosis was established.

Methodology :

Diagnosis was confirmed by suitable laboratory tests after clinical examination. Relevant investigations included Complete Blood Counts, Urinalysis, Renal Function Tests, Liver Function Tests and Chest Radiography. Abdominal Ultrasonography, Electrocardiography, Echocardiography, Arterial Blood Gas, Coagulogram, CT scan and Fluid analysis were done as per the clinical suspicion.

Suspected Malaria was diagnosed based on Rapid Diagnostic Tests for antigen detection and peripheral blood smear for malarial parasite (trophozoite of Plasmodium falciparum, Plasmodium vivax or mixed). Thick smears were used to screen for the presence or absence of parasites while thin smears will be used for species identification. Dengue fever was confirmed by the detection of NS1 antigen or IgM antibody, leptospirosis by IgM ELISA and Scrub typhus by IgM antibody detection by ELISA for *O tsutsugamushi*. Blood cultures were sent for suspected cases of enteric Fever. For Chikungunya, IgM ELISA serology for detection of Anti-Chikungunya virus antibodies was done. The distribution of varied etiologies of AUF was noted for every month over the course of the study.

Results

Out of 340 total cases of acute fever who visited the emergency during the study period, 200 AUF were included in the study after appropriate exclusions. Fig 1 depicts the distribution of fever in our study population. 53 (26%) patients were confirmed cases of Scrub Typhus, 49 (24%) patients were proven to have Dengue fever, 28 (14%) patients established to be Malaria, 22 (11%) patients had mixed infections, 7 (4%) patients had Acute Viral Hepatitis, 5 patient had Leptospirosis, 5 patients diagnosed to be Enteric Fever, 1 patient confirmed Acute Myeloid Leukemia, 2 patients had Infective Endocarditis and one patient had Tubercular Meningitis. 27 (13.5%) patients remained undiagnosed despite a complete analysis for fever. Our study did not find any patients with isolated Chikungunya infection. However, Chikungunya was

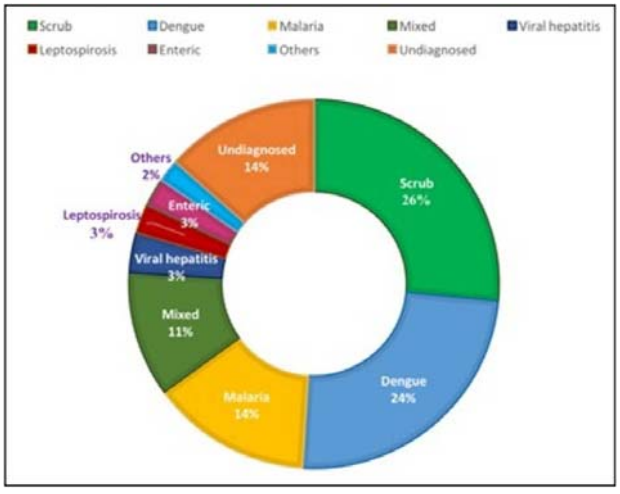

Fig 1 — Graphical representation of distribution of AUF in total study population

found as a co- infection with Dengue fever in 1 patient.

The maximum incidence of AUF was between the months of June to October, peaking in the month of August as shown in Fig 2. Out of the total 200 patients, 48 patients of AUF were admitted in August with 39, 20, 18 and 16 in the months of September, October, June and July, respectively.

Demographics of the Study Population :

The mean age (±SD) of the population in the present study was 33.16 (±15.88) years. The age ranged from 12 to 85 years. The mean age in patients of Scrub Typhus, Dengue Fever, Malaria and Mixed Infections was 34.47 (±13.65), 36.63 (±18.79), 24.78 (±11.34) and 30.13 (± 17.38) years, respectively. The number of males outnumbered the females, 118 (59%) being males and 82 (41%) being females. Out of the total 200 patients, 150 were less than 40 years of age. Similar results were seen in established cases of Scrub Typhus, dengue fever and malaria with 38, 35, 26 patients below 40 years. Only 17 patients of the total 200 study population were above 60 years of age. Gender wise distribution of fever among various febrile illnesses in our study population is shown in Fig 3.

Occupation :

In 67 (33%) patients were students, 56 (28%) were engaged in a private job and only 9 (5%) patients had an agricultural background. This is illustrated in Fig 4.

Residence :

All the participants were residents of Chandigarh and the adjoining states. Fig 5 shows the state wise distribution of fever in our study population. The contribution from Haryana (45%) was maximum followed closely by Punjab (33%). The contribution from

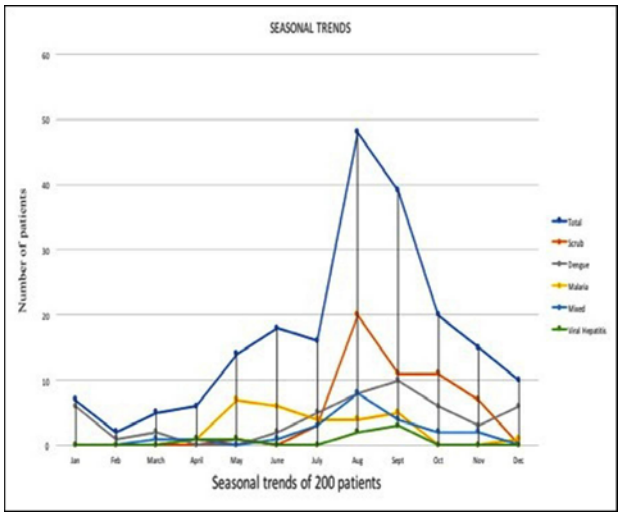

Fig 2 — Monthly distribution of various detected acute febrile illnesses

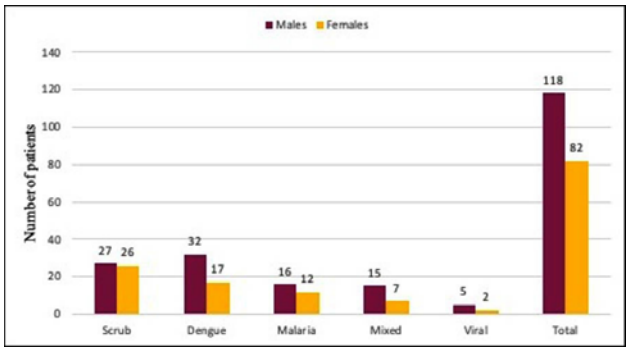

Fig 3 — Gender-wise distribution of fever

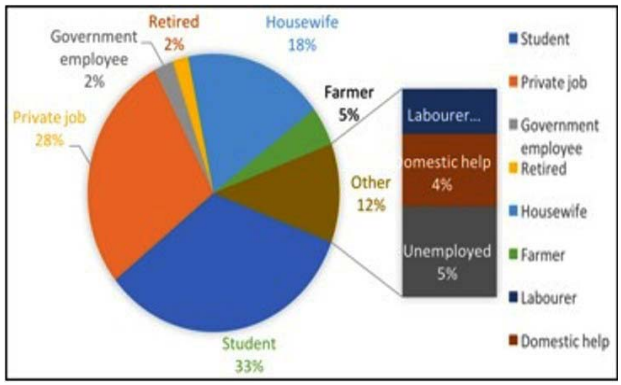

Fig 4 — Graphical representation of various occupations of study population

Chandigarh was on the lower side, however, at 9% with Himachal Pradesh and Uttar Pradesh contributing only 7% and 6%, respectively. In our study more patients belonged to an Urban background, 54.5%, rather than a Rural one, 45.5%. Fig 6 depicts the distribution of various febrile illnesses in our study population based on rural and urban backgrounds. Although with Scrub Typhus, patients with a rural background (50.9%) took a marginal lead than patients dwelling in Urban areas (49%), the other patients with Dengue Fever, Malaria, Mixed Infection or Viral

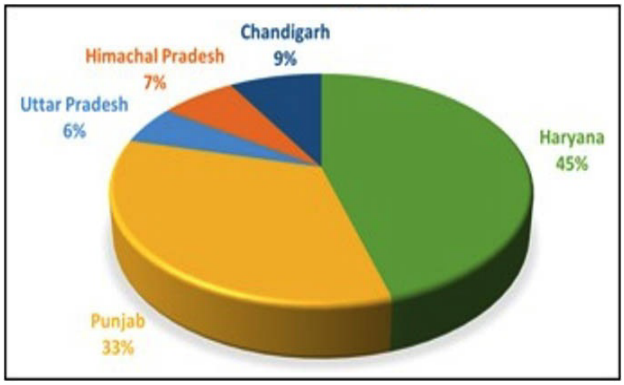

Fig 5 — Geographical distribution of study population

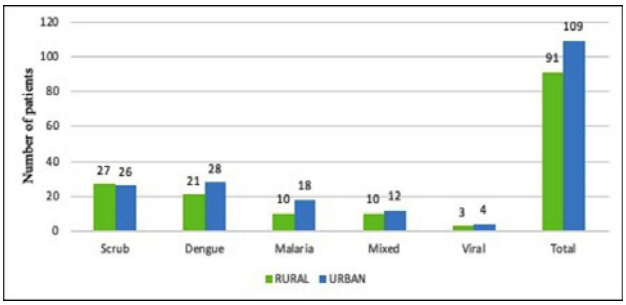

Fig 6 — Distribution of fever in rural and urban areas

Hepatitis had a higher urban to rural ratio.

Discussion

Out of the 200 patients, the maximum participants with AUF turned out to be Scrub Typhus followed by dengue fever. Remarkably, 18% of the AUF still remained undiagnosed despite all relevant investigations. Another element was the presence of 11% of the study population with mixed infections. Scrub typhus has become the leading of AUF not only in India but also in other South Asian countries like Nepal, Bangladesh and Thailand although the relative incidence of the pathogens varies from region to region[3]. A study conducted by Abhilash *et al* in South India also found Scrub, Dengue Fever and Malaria to be the main culprits of AUF[4]. The overall incidence of malaria and its impact on health in India and the neighbouring Countries, however, is declining similar to what was observed in our study[5]. In a recent study conducted in Karnataka, Scrub typhus was identified as the most common causes of Acute fever, followed by dengue fever[6]. Leptospirosis, Malaria, Scrub Typhus, Murine Typhus and Dengue Fever have been identified as major causes of AUF in various studies conducted in Thailand, Malaysia, and Nepal[7-11]. Dengue fever was found to cause one third of all cases of acute undifferentiated non-malarial fever in a similar study conducted in Vietnam[12]. In a study conducted at a Tertiary Hospital in North India, most common causes of AUF consisted of Dengue (37.54%), Enteric Fever (16.5%), Scrub Typhus (14.42%) and Bacterial Sepsis (10.3%)[13].

The peak month recorded for admissions for AUF in our study was August with maximum distribution between the months of June to October. With the onset of monsoon season, the cases with AUF start to rise and this trend continues till the end of the year. This can be ascribed to the humid climate during that season along with immense rainfall. This is in accordance with the reported patterns of disease transmission of Scrub and Dengue Fever[14,15]. However, no significant seasonal variation was found for malaria in our study. Changes in temperature and rainfall are the most critical factors responsible for an increase in the transmission of Vector Borne Diseases. Climate change has had a huge impact on the rate of vector growth and as well as virus amplification rates. Warm humid temperatures help increase the population size of mosquitoes, mosquito life cycle length as well as the rate of reproduction. Increased rainfall and rising sea levels because of global warming provide breeding sites for vectors thereby increasing disease risk[16,17].

Most of the patients in our study were from Haryana (45%) followed by Punjab (33%). Chandigarh only showed a 9% incidence of acute fever. Himachal Pradesh, which was previously the epicentre of Scrub Typhus, showed a lesser incidence of acute fever than previous studies suggesting a shift in the main belt affected with tropical fevers and thereby reflecting the changing demographics. Scrub typhus has been reported in Southern India as well as the Himalayan Region for many years. In the past decade, scrub typhus has started to emerge in the Sub-Himalayan belt as well as parts of Central and Western India. Haryana, Punjab, Himachal Pradesh, Delhi and Chandigarh have emerged as one of the hotspots of Scrub Typhus in recent times[18]. In a South Korean study, squatting in the grass for defecation, working with bare hands and short sleeved clothes are reasons for cases of Scrub Typhus, reasons which are quite applicable to India as well[19]. Our results are consistent with most studies in Northern, Western, and North East India, all of which report cases from July to November[20,21]. This does not apply to studies from the Southern States which report cases from October to February mostly[22].

In our study, Dengue fever cases began to rise in June with a progressive upward slope and finally peaking in September followed by a decline in October and November. This is similar to most studies conducted in India which report peak dengue fever cases in August and September[23]. All 4 Dengue fever virus serotypes are prevalent in various parts of the country. For the past 2 decades, the Dengue fever cases have exponential increased in India with Southern States of Karnataka, Tamil Nadu, Maharashtra and the Northern belt of Delhi, Haryana, Punjab, Chandigarh and Rajasthan showing a meteoric rise.[24] El Nino effect which is a warm climate pattern leading to warming of the Pacific Ocean and causing climate variation has been found to affect the Indian monsoon with a positive Association in terms of Malaria and Dengue fever cases[25].

Our study did not find a discernible trend in the

cases of malaria nor any significant peaks. This may be attributable to a smaller figure of Malaria cases reported. However, the cases were more evidently seen in the monsoon months. According to one study conducted in India, the season with the highest average total Malaria cases occurrence was June to August and the minimum Malaria cases were observed during the winter[26]. Both *P.vivax* and *P.falciparum* cases were observed.In the Northern States of India, with extremes of summer and winters, malaria transmission rate remains subpar for most of the year. It is only with the advent of monsoon that the transmission rates pick up. This is in contrast to the Southern States where a stable Malaria Transmission sustains due to minimal temperature variation throughout the year and considerable rainfall. As we move from the west to the east, the rainfall improves tremendously leading to more stable malarial transmission.

Acute Viral Hepatitis has been reported throughout the year. Though HEV is found all year round, according to one study maximum cases were seen from July to October. HAV was highest in the summer[27]. Hepatitis B and C did not show any seasonal variation. Warmer and wetter climates significantly worsen the transmission of Salmonella. A study conducted in Gujarat established that Enteric Fever cases started to rise from March to May due to increasing warm climate leading to Salmonella replication, peaking in the monsoon due to transmission of Salmonella via unhygienic food and water and then declining at the end of the season with a low incidence in the winter months[28].

It is difficult to ascertain a seasonal trend for Leptospirosis in our study as there were only 5 cases of Leptospirosis in our study. Leptospirosis has usually been reported in the Southern and Western states which receive torrential rainfall associated with a predominant agrarian life[29]. Leptospirosis has previously been considered as Non- endemic in North India. However, over the last 2 decades it has slowly gained prominence. This has usually been seen in the months from July to October which sees a good amount of rain during monsoon clubbed with a farming background in the Gangetic belt. In a 5 year study in North India, Leptospirosis was reported from the states of Punjab, Haryana, Himachal Pradesh and Uttar Pradesh[30].

The predominant age group affected by AUF in our study was the younger population rather than the elderly. The mean age in all the febrile illnesses in our study including Scrub Typhus, Dengue fever and malaria was less than 40 years with an overall mean age of 33.16±15.88 years. This is similar to a study conducted in 200 patients of AUF in Thailand where the mean age was 41 years.[3] Males were more affected than the females. Similar results were seen in a multi centre trial in India where the mean age was 34 years with a range of 5-105 years with a predominant male population (57%)[31]. A possible explanation for a higher male involvement could be related to more outdoor activities and, thus, a higher risk of mosquito bites amongst the males.

Reflecting a shift from the previous studies, our study depicted a higher number of Urban population affected by Acute Febrile Illness than the Rural areas. This might be due to increased urbanization of rural areas. The main limitation of our study was that it was a limited period study and therefore, may not translate into longer duration trends. A recent paper discusses the seasonal prevalence, epidemiology and management of six seasonal acute febrile illnesses with high prevalence and burdens in India[32]. A thorough enquiry into the seasonal and epidemiologically relevant contextual history and meticulous general examination can guide the Clinician to identify the etiological diagnosis and initiate management[33].

Conclusion

Fever remains a crucial cause for which patients are hospitalized in India. Determining the etiologies would help and guide Physicians on formulating the most appropriate treatment especially in places where infrastructure and access to facilities is difficult. Establishing diagnostic test for all the possible disease is impractical. Our study found sCrub Typhus, Dengue Fever and Malaria to be the most common causes of acute fever. The demographics of these acute febrile illnesses are widening and it is no longer restricted only to the Rural areas. Appropriate facilities may not be readily available at all centres and in those scenarios suspected cases of various acute febrile illnesses should not be denied targeted Antimicrobial Therapy. Thankfully, the outcome is expected to improve since the medical fraternity is becoming more aware about these diseases and its associated complication profile.

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Original Article

Study of Neuro-developmental Outcome of Preterm Babies Using Risk Stratification Score at a Tertiary Care Hospital

Sweety Patel[1], Vaidehi Mehta[2], Hardik Parmar[3], Aasheeta Shah[4]

Introduction : Recent advances and improvements in technology in Neonatal Intensive Care Unit (NICU) over the past few decades have increased the survival of preterm infants. India ranks first amongst the number of preterm birth. Though the survival of preterm babies have increased Neuro-developmental morbidity amongst such babies still persist. Through this study we aim to establish a risk stratification tool and predict neurodevelopmental delay at 1 year of age.

Materials and Methods : A total number of 77 babies were enrolled in the study after fulfilment of inclusion and exclusion criteria. Follow up till 1 year of age of corrected gestational age was done. Development assessment was done through Child Development Centre (CDC) grading, Amile-Tison Angle, Developmental Observation Card, Trivandrum Developmental Screening Chart and development quotient. Vision and Hearing Assessment was also done.

Conclusion : Neuro-developmental outcome prediction at 1 year of age is inadequate and proper long term follow up is needed. Overall preterm babies needing extensive resuscitation and 5 minute APGAR <6 had much poor neurological outcome.

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***Key words* : Neuro-development outcome, Neurodevelopment delay, Preterm, Amiel-tison angle, CDC grading, Trivandrum Developmental Screening Chart (TDSC).**

Every year, an estimated 15 million babies are born preterm and this number is rising[1]. India ranks first amongst the number of preterm births with 3.5 million premature birth annually and incidence of 7-9% and constantly rising. Low birth weight is an important cause of morbidity & mortality in the developing countries like India[2].

Understanding the causative etiology of preterm birth is the most integral part for evaluating risks and formulating preventive protocols. WHO has developed new guidelines for reducing preterm births and improving outcomes of premature babies[1]. Out of 10 elements recommended by WHO antenatal corticosteroids, tocolytics, magnesium sulfate and Kangaroo Mother Care are currently included in India's Clinical Standards of Preterm Care at hospital level.

The survival of preterm babies has increased due to improvement in the quality of Perinatal Care Implementation of WHO recommended guidelines and advances made in Obstetric and Neonatal Intensive Care.

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Editor's Comment :

- Every neonate if screened timely can have improved quality of life.
- Simple assessment tool for evaluating risks and establishment of preventive protocols is essential at present to reduce preterm morbidity and mortality.
- Antenatal care is essential for good outcome of the neonate.
- Follow-up of high risk neonates should be done timely to evaluate and intervene in case of developing Neuro-development disability.

Every attempt is made for survival without disability but such babies are at substantial risk for future neurodevelopmental delay. The major adverse Neuro-developmental outcomes which can be associated with preterm birth include Cerebral Palsy, impairment in Motor and Cognitive Function, visual and auditory deficits and behavioral problems. Early prediction of such morbidities and timely appropriate intervention can prevent or modify many of these disabilities. And for this a well-structured follow up program for high risk neonates with good compliance is the need of the hour.

Materials and Methods

The present study is an prospective-observational study which was carried out in Department of Paediatrics at Tertiary Care Hospital. Over a period of 6 months from preterm infants were enrolled and then followed up till 1 year of age. A total 64 preterm

participated in the study in accordance to the inclusion and exclusion criteria. All preterm babies >34 weeks discharged from NICU and both inborn and out born babies referred in first 48 hours were included in the study. Preterm infants with Congenital Malformations, Congenital Heart Disorder, Intrauterine Infections, referred from outside after 48 hours and those transferred to another hospital before completion of care were excluded from the study. A questionnaire was formed to obtain information regarding participants. Demographical data, birth details and risk factors were obtained from case report file. Accordingly the babies were categorised into mild, moderate and severe risk based on the risk score obtained. Monthly follow up was taken of the enrolled preterm infants upto 1 year of age. Amiel-Tison Angle and Scarf sign was assessed every 3 months. Developmental Observational Card was used to check for achievement of major milestone and CDC grading of milestone was done at completion of 2, 4, 8 and 12 months. Trivandrum Developmental Screening Chart was used to screen children for developmental delay up to 1 year of corrected Gestational Age. Visual assessment was done to check for retina of prematurity and hearing assessment was done to check for deafness. Apart from this preterm babies head circumference was monitored and persistence of neonatal reflexes and presence of red flag signs for Cerebral Palsy was checked. Development quotient of each infant was assessed at 1 year of age. At the completion of 1 year outcome was predicted. Outcome was categorised into primary and secondary. Primary outcome was defined as death before 12 months of age post discharge or major Neuro-development delay in form of cerebral palsy, Mental impairment, Blindness and Profound Hearing loss. Secondary outcome was defined as normal baby or minor Neuro-development disability in form of refractive error/squint, impaired hearing not requiring assisted devices, growth delay and delay in achieving milestone in two or less than two domain.

Data Analysis : Data were entered in Microsoft excel 2016 and analysis was carried out using SPSS version 21 (Figs 1 & 2).

Statistical Test : Chi-square test with level of significance <0.05 and Odds ratio was used for as statistical test to test various associations.

Age (months)	Adductor angle	Popliteal angle	Dorsiflexion angle	Scarf sign
0-3	40°-80°	80°-100°	60°-70°	Elbow does not cross midline
4-6	70°-110°	90°-120°	60°-70°	Elbow crosses midline
7-9	110°-140°	110°-160°	60°-70°	Elbow goes beyond axillary line
10-12	140°-160°	150°-170°	60°-70°	

Fig 1 — Amiel – Tison Angle and scarf sign

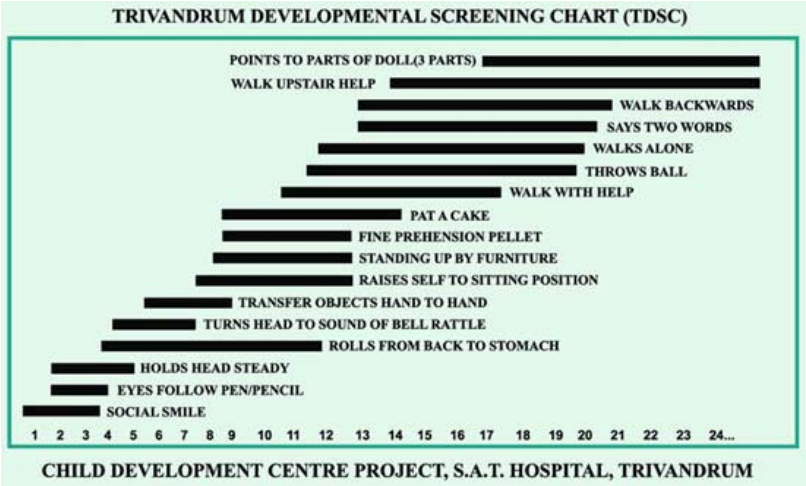

Fig 2 — Trivandrum Developmental Screening Chart

Observation

Odds ratio >1 indicates a significant association with a poor outcome and <1 indicates a significant association towards better or normal outcome. In univariate model, the risk factors associated with poor primary outcome are 5 minutes APGAR < 6, birth weight <1200 g, extensive resuscitation at birth, ventilation for >7 days, maternal hemoglobin <8g/dl, Gestational age <30 week, Sepsis, Encephalopathy, Abnormal Neurological examination at discharge and incomplete or no antenatal steroids received, in order of strength and were found to be statistically significant (Table 1).

Shock, Hypoglycemia, Abnormal Neuro-sonogram and history of previous preterm delivery or primi mother are also inclined towards poor primary outcome but they are statistically insignificant (Table 2).

Babies with low risk had better outcome than those with high risk score. The Chi-square statistic is 6.96 and p-value is <0.008 (<0.05) which is statistically significant (Tables 3 & 4).

Death or major Neuro-developmental Disability (NDD) was seen in 28 (36.3%) babies and minor NDD or normal outcome was seen in 39 (50.6%) babies (Table 5).

Among Major NDD Cerebral Palsy (66.6%) was the most common NDD seen followed by hearing impairment (25%) and in Minor NDD majority of the

Table 1 — *Odds ratio for risk factors associated with poor primary outcome*

Risk Factors	Signifi-cance	Odds ratio	95% CI	
Gestational age ≤30 week	0.0001	9.65	3.088	30.15
Primi/Previous Preterm	0.690	1.26	0.39	4.00
Maternal anemia- Hb <8g%	0.0356	10.36	1.17	91.7
Birth weight <1200g	0.0002	58.7	7.01	491.98
Male	0.659	0.8	0.30	2.13
IUGR	0.605	0.75	0.25	2.2
Multiple gestation	0.054	0.12	0.01	1.03
Resuscitation	0.0001	20.40	5.72	72.64
5 min APGAR <6	0.002	90.7	5.07	1621.00
Ventilation >7 days	0.004	7.76	1.91	31.51
Sepsis	0.039	9.31	1.11	77.67
Hypoglycemia	0.951	1.05	0.21	5.11
Shock	0.059	5.04	0.93	27.20
Incomplete/ No antenatal steroids	0.002	7.00	2.04	23.98
Abnormal Doppler	0.444	0.68	0.25	1.8
Abnormal neuro-sonogram	0.152	2.06	0.76	5.54
Encephalopathy	0.002	9	2.22	36.33
Hyperbilirubinemia	0.659	0.80	0.30	2.13
NEC	0.629	0.45	0.01	11.46
PDA	0.394	0.26	0.01	5.69
Abnormalneurological examination on discharge	0.009	8.76	1.71	44.68

Table 2 — *Risk score of outcome obtained*

Risk Score	Present study		KIMS study	
	Normal Outcome	Abnormal Outcome	Normal Outcome	Abnormal Outcome
Low (1,2)	11 (55%)	9 (45%)	188 (95.5%)	9 (4.5%)
High (3,4,5)	1 (8.3%)	11 (91.6%)	23 (82.2%)	5 (17.8%)
Total	12	20	197	28

Table 3 — *Comparison of different outcome with KIMS study*

Outcome	Present study(n=64)	KIMS study(n=225)
Incidence of Major NDD	17.9%	6.2%
Mean birth weight	1455.9g ± 345.71 gram	1425 ± 376 gram
Mean gestational age	31.7 ± 2.19 week	30.6 ± 2 week
ROP requiring laser	1.5 % δ 30 week	37% - <28 week 9.5% - 29-30 week 5.7% - 31-33 week
Refractive error requiring spectacles	2.9%	3.5%
Squint	7.46%	1.3%

preterm had vision impairment in form of refractive error or squint (41.1%) followed by delayed development (35.29%) (Table 6).

Out of 12 babies having abnormal ATA 8(66.6%) had Major NDD and 4 (33.3%) had Minor NDD. Trivandrum Developmental Screening Chart (TDSC) was delayed in 28 (41.7%) babies of the study population from which 12 (42.8%) had developed Major NDD and 16 (55.1%) had Minor NDD (Table 7).

Table 4 — *Distribution of outcome*

Primary outcome(n = 28) (36.3%)	Major NDD Death	12 (15.5%) 16 (20.7%)
Secondary outcome(n = 39) (50.6%)	Minor NDD Normal	17 (22%) 22 (28.5%)
Lost to follow-up		10 (12.9%)
Total		77

Majority of the babies with abnormal neurological examination had major NDD (81.8%) and none had normal outcome at the end of 1 year follow up.

Discussion

Total 77 babies enrolled in our study over period of 6 months. Out of 77 babies, 13 babies died before discharge (16.8%) and remaining 64 (83.1%) were followed up. Out of 64, 10 babies were lost to follow up. During follow up, 3 babies died out of which 2 died within 3 months because of severe Septicemia which was due to mismanaged feeding. And one baby expired by 8 months of age due to respiratory illness. The remaining 51 were followed up till 1 year of corrected age. In a study by Astbury *et al*[3], it was found that the Neuro-developmental delay also may be under-estimated at 1 year of age. Voss *et al* have concluded that atleast 6 year outcome may be necessary to derive meaningful conclusions[4].

51 babies were followed up from which 12 had major NDD, 17 had minor NDD and 22 had normal outcome. Out of 12 major NDD, 3 babies (25%) had hearing impairment requiring assisted devices and 1 baby (8.3%) had vision impairment (blindness in one eye) and rest 8 babies (66.6%) had Cerebral palsy. 39 babies fell into secondary outcome with 17 of them having minor developmental delay in form of delay in achievement of milestone in 2 or less than 2 domain in development quotient, impairment of hearing not requiring assisted devices and impairment of vision in form of squint or refractory error. 2(11.7%) of the babies had refractory error. 4 babies (23.5%) had impaired hearing but did not require assisted devices and 5 (29.4%) babies had squint.Regular follow up was carried and babies were assessed during each follow

Table 5 — *Distribution of Neurodevelopment Disability*

NDD		Total	Percentage
Major	Cerebral Palsy	8	66.6%
	Hearing Impairment Requiring Assisted Devices	3	25%
	Vision Impairment (Blindness)	1	8.3%
Minor	Delayed Development (2 or<2 Domain Affected)	6	35.29%
	Refractiveerror/Squint	7	41.1%
	Hearing Impairment Not Requiring Assisted Device	4	23.5%

Table 6 — *Abnormal results on Neuro-development parameters*

Parameter	Total	Major NDD	Minor NDD
Abnormal Amiel-Tison Angle(ATA)	12	8 (66.6%)	4 (33.3%)
CDC grading	13	8 (61.5%)	5 (38.4%)
TDSC (delayed)	28	12 (41.3%)	16 (55.1%)
Any delay (vision/hearing)	14	4 (28.5%)	10 (71.4%)

Table 7 — *Neurological examination versus outcome*

Neurological examination at discharge	Survived			Death post discharge	Total
	Major NDD	Minor NDD	Normal		
Normal	3 (6.9%)	15 (34.8%)	22(51.1%)	3(6.9%)	43
Abnormal	9(81.8%)	2(18.1%)	0	0	11
Total	12	17	22	3	54

up for their neuro-development and at 1 year of corrected age on basis of all the parameters used and development quotient deduced the outcome of babies were determined.

5 minute APGAR score <6 has an odds ration 90.7 for predicting death or Major Neuro-developmental delay. In the VON network study[5], the adjusted odds ratio is 2.06 for severe delay.

Abnormal Neuro-sonogram odds ratio was 2.06 and is one of the most consistent poor prognostic indicator in previous similar studies.

In a study by Fazzi *et al*[6], it was found that the sonographic abnormalities correlated more closely with neuromotor delay rather than cognitive delay which was seen in our study also.

Most of the studies from Western World even some decades ago, had a very low incidence of poor neurologic outcome of <20%[7]. But the studies from the developing world are different. In a study from Bangladesh in 2006, the incidence is 68% in <33 weeks of preterm babies.[8]In our study 53.2% babies had some form Neuro-developmental Disability either Major or minor.

Children who present with symptoms of Cerebral Palsy, earliest manifestations is abnormality in muscle tone. The variation in tone can be picked up early by method of evaluation devised by Amiel-Tison and abnormality of tone was measured with Amiel-Tison Angles (ATA). In present study total 12 babies had abnormal ATA out of which 8 went out to develop major NDD in form of Cerebral Palsy.

Though the initial neuromotor status lays the foundation of future cognitive development according to Piagets theory, the correlation may not be accurate.

Infants with mild to moderate abnormalities may improve with time. This is known as transient Neuromotor Dysfunction and in growing brain with plasticity, many infants become normal. The infants with severe early neurologic dysfunction is unlikely to make complete recovery and likely to have worst neurodevelopmental outcome[9].

Conclusion

From this study we concluded that the strongest association with a poor neurological outcome is seen with 5 minute APGAR score <6, birth weight <1200 gram, extensive resuscitation required at birth and Maternal Haemoglobin < 8g/dl. Growth delay was present proving catch up growth is inadequate at 1 year of corrected Gestational age. Long term follow up is needed for much accurate outcome. Parameters like ATA , CDC grading and TDSC chart can help in early recognition of Neuro-developmental disability. Early stratification of neonates with possibility of abnormal outcome can help in early intervention and moving towards an intact survival of high risk neonates. Standardized follow up program should be an integral part of every neonatal unit to improve the outcome of high risk neonates.

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Review Article

Clinical Spectrum of Tuberculosis

Agam Vora[1]

Being the second leading cause of mortality due to infectious diseases, the burden of tuberculosis is huge globally as well as in India. Therefore, timely diagnosis and treatment are essential to improve the clinical outcomes of the disease. It is therefore essential to create awareness and educate all concerned regarding the clinical spectrum of the disease which includes both pulmonary and extrapulmonary manifestations. Apart from typical systemic manifestations, depending on the organ affected infected patients may present with atypical signs and symptoms. The challenge is establishing definitive diagnosis in absence of discrete symptoms. Also, the EPTB generally are insidious in onset and diagnosis usually occurs in advanced stages. Therefore, a high index of suspicion is necessary particularly in absence of fever, weight loss and fatigue to avoid delay in diagnosis and thereby reduce risk of complications. It is worth mentioning that apart from high-risk individuals with HIV, chronic kidney failure, poor glycemic control, patients being treated with immunosuppressants, and both pediatric and geriatric populations who are immunocompromised, TB can be reactivated and EPTB can occur regardless of the individuals' immune status. This review article elucidates different clinical presentations of patients with both pulmonary and extra-pulmonary TB which may facilitate early management even in settings with lack of advanced diagnostic evaluation or additionally offer a right direction to perform appropriate investigations. [*J Indian Med Assoc* 2022; **120(5):** 43-7]

Key words **: Pulmonary, Extrapulmonary, Symptomatology, Tuberculosis.**

Globally, a total of 1.5 million people die from Tuberculosis (TB) making it the second leading cause of death due to infectious disease[1]. In 2020, India was among the eight countries accounting for approximately 66% of the total TB burden, leading the count, followed by other Asian neighborsand South Africa[1]. In India, 40% of the population has a latent infection that has the potential to flareup[2].

TB is a droplet infectionthat occurs due to mycobacterium tuberculae, with the bacilli settling in the airways after inhalation. In approximately 3-8 weeks the infection spreads locally in the lungs and associated lymph nodes causing Pulmonary TB (PTB). Subsequently, it may encompass other organs leading to Extrapulmonary Tuberculosis (EPTB).[3] In a recent Indian study, EPTB was most frequent followed by PTB and disseminated TB. The clinical manifestations of pulmonary and extrapulmonary TB will be reviewed in this article.

Patients with TB infection can experience a range of clinical manifestations, from no symptoms to critical illness.

Primary TB infection :

Asymptomatic PTB :

After primary infection, a large portion of hosts remain asymptomatic with the majority of these clearing the infection. Nevertheless, a fraction-transforms to the latent phase with the probability of possible reactivation in subsequent years, known as latent TB[4]. It is a state in which the bacteria do not multiply with symptoms similar to primary infection on reactivation[4,5]. Reactivation risk is higher in individuals with chronic kidney failure, poor glycemic control, patients being treated with immuno-suppressants, and both pediatric and geriatric populations.

Editor's Comment :

- Tuberculosis can manifest in multifarious organ systems.
- Pulmonary tuberculosis is the commonest involvement while TB lymphadenites is the commonest extrapulmonary TB.
- It is important to recognise early and monitor full treatment.

Symptomatic PTB :

Nearly 10% of the subjects with symptoms develop primary lung infection. Extended hours of fever both low- and high-grade are the most frequent symptom. Other non-respiratory symptoms include pharyngitis, lymphadenopathy, and fatigue[6]. Respiratory symptoms such as chest pain, dyspnoea, and coughare present in only 66% of those with pulmonary involvement[7]. Approximately one-fourth of the patients develop retrosternal pain with half of these revealing pleural effusion on examination. The patient may complain of retrosternal and dull interscapular pain which worsens with swallowing. The physical examination in mild disease is generally normal with non-specific pulmonary findings crackles or tubular breath sounds. These sounds are not noted over consolidation areas. The patient may experience anorexia, weightloss, and loss of muscle mass in advanced stages[8]. Less

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common symptoms may include fatigue, cough, arthralgia, and pharyngitis.

Postprimary TB and Reactivation TB :

Postprimary TB symptoms appear only late in the course of the disease and hence at risk of delayed diagnosis.Fifty to 66% develop a cough, weight loss, and fatigue, while fever, night sweat or night sweats alone were also present in 50% of patients. Chest pain and dyspnea occur in 33% and hemoptysis in 25% of patients. Due to the high incidence of non-specific symptoms, patients are diagnosed incidentally on consultation for distinct symptoms[9]. Low-gradefever which progresses to high gradewith a diurnal pattern associated with night sweats is common in advanced stages.

Cough which is initially mild and non-productive may produce greenish or blood-stained sputum as the disease progresses. In the early stages cough occurs only in the morning or intermittently, however, in advanced stages, it becomes continuous and predominantly nocturnal[10].

In untreated cases,the disease may worsen to a severe form which manifests as painful ulcers of the upper GI tract. In some patients' anorexia, wasting and malaise could be isolated features of advanced disease.

Older adults present more frequently with dyspnoea and fatigue. Physical findings of PTB are usually lacking in mild-moderate disease. Dullness with diminished fremitus, or posttussive crackles, whispered pectoriloquy may be noted. Extrapulmonary signs include clubbing and findings localized to other regions involved.

Complications :

The complications of PTB include pneumothorax, broncholithiasis, bronchiectasis,wide-ranging pulmonary destruction, respiratory failure, septic shock, and chronic pulmonary aspergillosis. Manifestations include cough, hemoptysis, wheezing, or evidence of recurrent pneumonia, progressive dyspnea, and weight loss.

Extrapulmonary TB :

Approximately 15-25% of those with primary lung infection progress to EPTB with numbers snowballing in the last few years. Immunocompromised individuals such as those withhuman Immune Deficiency Virus (HIV) infection are more susceptible to EPTB. However, EPTB can occur regardless of a patient's immune status[11].

Usually, EPTB diagnosis is more challenging than pulmonary TB and requires a high index of suspicion since it mimics several other pathological conditions[12,25]. The individuals with EPTB seldom present with typical pulmonary symptoms.Up to 60% of patients with evidence of extrapulmonary TB may not have been diagnosed with PTB.

Depending on the organ affected, the symptoms and clinicalmanifestations of EPTB vary.They may thus present with a higher frequency of abdominal pain,diarrhoea, infertility, monoarticular joint pain, headache, meningism, orlymphadenopathy depending upon the organ involved.

Lymphatic Tuberculosis or Lymph node Tuberculosis :

Lymph Node Tuberculosis (LNTB) is one of the most common (40%) extrapulmonary manifestations of tuberculosis which comprises nearly 15-20% of all cases of TB in India[12]. It is particularly common in Asians and Africans and comprises any regional lymph nodes[25]. The clinical manifestation of TB lymphadenitis is mostly based on the anatomical location of the infected nodes and the immune status of the host. However, predominantly affected lymph nodes include those of the neck and supraclavicular regions (scrofula). Cervical lymphadenopathy is the most common representing 63-77% of the cases. Febrile illness has been reported in a greater proportion of individuals with than without HIVinfection (60-80% *versus* 20-50%)[13]. Systemic symptoms are not widespread. The most common manifestation in young adults is isolated chronic non-tender lymphadenopathy which may be present for nearly a year before diagnosis[14,15]. Physical examination recognizes a steady, isolated mass of nodes anchored to adjacent structures. The skin spread over the mass may be firm or hardened. Fluctuance, draining sinus, or erythema nodosumis unusual[12].

Cervical lymphadenopathy may be complicated by ulceration, fistula, or abscess formation. Based on the region in which the lymph nodes are affected the patient may present with dysphagia, vocal cord paralysis, or pulmonary artery occlusion similar to pulmonary embolism[16-18]. If it encompasses the hepatic lymph nodes the clinical presentation may include jaundice and portal hypertension[19,20].

Persons living with HIV/AIDS (PLWHA) in addition to the above manifestation may also demonstrate systemic symptoms such as sweats, and weight loss[12].

Tuberculous pleural effusion or pleurisy :

It is the second most common form of EPTB. These patients are generally febrile with the majority (>90%) presenting with non-productive cough and pleuritic chest pain (>75%) along with constitutional symptoms[21]. Apart from these symptoms PLWHA also manifestshepatosplenomegaly and lymphadenopathy.

Ocular Tuberculosis :

The prevalence of ocular TB is approximately 10-18%[22]. Ocular tuberculosis may affect any intraocular

or extraocular tissue[22,23]. Posterior uveitis is the most common presentation of intraocular TB. It may not be associated with clinical evidence of pulmonary TB.

Patients with ocular TB usually have normal chest radiographs andno chest complaints. However, these patients may show signs of tubercular lymphadenitis or scrofula. Ocular TB can manifest as any kind of ocular inflammation either acute or chronic inflammation and unilateral or bilateral. Besides these, patient complaints may also include headaches, photopsia, myodesopsias or muscaevolitantes, or conjunctivitis. Choroid tubercles in proximity to the macula present with weakened visual acuity and photosensitivity. Small tubercles in the peripheral fundus are likely to be asymptomatic, hencethe absence of obvious visual symptoms does not exclude ocular TB[23].

Musculoskeletal TB :

Skeletal TB accounts for 10-35% of cases of EPTB and can virtually affect any bone. Children are more predisposed to have skeletal TB than adults[24]. The most usual form of skeletal TB is Pott disease or spondylitis representing ~50% of the cases followed by tuberculous arthritis[25,26].Tuberculous osteomyelitis is less common than tuberculous arthritis. Primary tuberculous tenosynovitis involving the hand and wrist is very rare. Tuberculous arthritis is typically monoarticular and most often affects the knee or hip. Patients usually have broad clinical symptoms, and imagingfindings are similar to those of other inflammatory arthropathies. The clinical symptoms are a result of synovial membrane inflammation andtypically cause severe, persistent localized pain and swelling[27]. Nevertheless, in Pott's disease of thespine, the disease progresses insidiously with progressive localized pain occasionally with muscle spasm and rigidity for weeks to months beforediagnosis, thus delaying it[25]. The patient is extremely cautious and evadesshaking of the spine and walks with head and chest thrown backward and the legs apart[28]. Systemic symptoms occur in less than 40% of cases[29,30].

Similar to Potts disease, Tuberculous osteomyelitis is usually insidious but infrequently it may have an acute or subacute presentation. It may present as a 'cold abscess' with swelling, slight erythema or pain, and negligible warmth[27]. Unifocal participation is more common.However, multifocal osteomyelitis is more frequent,particularly in children and affects the femur, tibia, carpals and tarsals spontaneously without any pulmonary manifestations. Depending on the bone affected it may present as a breast mass or facial nerve palsy. Further, it may occur in a previously injured bone resulting in a diagnostic dilemma[27].

Abdominal Tuberculosis :

It is the sixth most frequent site of EPTB and accounts for 5% of all TB cases globally[31].

Peritoneal TB :

Clinical manifestations persist for weeks or months before the diagnosis is made which include ascites (>90%), abdominal pain (>70%), and fever (~60%)[32-35]. Nearly 90%of patients at presentation have ascites without cirrhosis[36]. In the remaining cases, the presentation involves adry type with adhesions which is a fibroadhesive form of the disease[37,38]. The absence of signs of chronic hepatic disease should prompt a high clinical suspicion for TB peritonitis[39]. In ESRD patients on peritoneal dialysis, within a year they develop clinical manifestations of tuberculous peritonitis[40].

Intestinal TB :

Clinical manifestations indicating intestinal ulceroconstrictive disease which generally occurs in malnourished patients include intestinal colic, abdominal distension, chronic diarrhea, nausea, vomiting, constipation, and bleeding. Involvement of adjoining structures results in ascites, lymph node enlargement and reproductive system-associated symptoms. Systemic manifestations such as fever, fatigue, weight loss, and night sweats do occur.

Almost one-fourth to half of the patients present a palpable abdominal mass in the right lower quadrant[41,42]. Abdominal pain is the most common manifestation. Diarrhoea occurs in 11-37%, bleeding in 5-15% of patients, and constipation in 50% indicating small or large intestine involvement[41]. Bowel obstruction is also a frequent complication. Apart from these symptoms, patients may complain of early satiety and postprandial fullness. Rectal TB classically presents as hematochezia and constipation followed by systemic symptoms. Anal TB may present as pilonidal sinus, persistent perianal growth, anal ulceration with inguinal lymphadenopathy, anal fissure, fistulae, or stricture[43].

Hepatic TB :

It includes miliary hepatic disease and isolated hepatic disease which manifest as hepatomegaly (80%), fever, respiratory symptoms, abdominal pain, and weight loss occur in 60-66% of patients. Splenomegaly, ascites, and jaundice have been reported in 20-30% of patients[44].

Several other forms such as those involving the pancreas, stomach, and duodenum are rare and may manifest as abdominal pain, jaundice, and constitutional symptoms.

Tuberculous meningitis :

Tuberculous Meningitis (TBM) is a manifestation of extrapulmonary TB, occurring in 1%-5% of the total cases of TB globally. TBM can occur either as a lone manifestation of TB or concomitantly with pulmonary

or other extrapulmonary sites of infection in nearly 50% of cases[45].

Patients with TBM present subacutely and often without characteristic signs of meningitis in the early stages. Some may develop typical symptoms and signs of meningitis including headache, fever, and stiff neck. Individuals may initially present with nonspecific symptoms and signs including apathy, irritability, headache, malaise, fever, anorexia, nausea, and vomiting, without any change in the level of consciousness (Glasgow Coma Scale GCS 15). Some individuals may present with disturbed consciousness in absence of coma or delirium but with slight focal neurological signs. Symptoms and signs of meningism and meningitis may coexist with focal neurological deficits, isolated CN palsies, and atypical involuntary movements (GCS 15 *with* focal deficits, or GCS 11–14 *without* focal deficits). An advanced stage of the patient manifests as stupor or coma besides dense neurological deficits, seizures, posturing, and/or abnormal movements (GCS≤10). Predominantly, TBM individuals from poor-resource settings are in stage 3 at the time of presentation with a GCS of ≤10[46-48]. Hemiparesis, paraparesis, seizures,and cranial nerve palsies, are frequently present and should raise suspicion for TBM[49]. The duration of symptoms preceding presentation lies between days to months[47,48].

Urogenital TB :

Urogenital tuberculosis (TB) is the third most frequent form of EPTB[50]. It occurs in 2-20% of patients with pulmonary TB[51]. Nearly half of these patients have a history of TB and around 10% may have an active infection[51]. It is usually seen in adults due to a long incubation period[19].

In the early stages renal and urologic TB are not associated with explicit symptoms. Pyuria or hematuria may be just secondary findings. However, disease progression to the bladder results in dysuria, urgency, and nocturia in 50% of cases with evident hematuria and low back pain in more than 30% of the cases[51]. Systemic symptoms are fairly rare[52]. Indices of advanced disease include end-stage kidney disease and, infrequently, refractory hypertension[53,54].

PLWHA are more susceptible to tuberculous kidney and prostate abscesses compared to those without HIVinfection[55].

Genital tract tuberculosis :

It is the third most common form of EPTB. It occurs in 2-20% of patients with PTB.

TB can affect the entire male genital tract, with epididymitis being the most common clinical manifestation in 10-55% of cases[52]. Scrotal nodule and fistula may manifest in 50% of cases with bilateral involvement in 34% of cases with hydrocele being less frequent.[56] Prostate involvement is usually subclinical and abscess occurs majorly in PLWHA.[57] The most first common symptom is infertility in 10% of males due to poor sperm parameters[57,58]. External manifestations include ulcerated papules mistaken as genital ulcers or deformed penis[59].

Among women, genital tract TB causes infertility in 0.2 to 21% of infected cases and this is the presenting symptom in the majority of cases. Besides, pelvic or abdominal pain or mass and menstrual disorders may be the manifestations in 25-50% of infected females[51,60,61].

Summary (conclusion) :

The most common manifestation of TB is PTB, followed by EPTB, and lastly disseminated TB. The clinical spectrum of affected individuals ranges from being asymptomatic to developing fatal complications depending on the time of diagnosis, degree of immunity, age, and comorbidities. Most of the symptoms of EPTB are non-specific and insidious in development, thus delaying the diagnosis and resulting in an advanced disease stage at presentation. Therefore, most of the manifestations should raise a high degree of suspicion for prompt identification and management.

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Review Article

Ethical Issues in Surgery during COVID-19 Pandemic

Kaushik Bhattacharya[1], Neela Bhattacharya[2]

Surgeons were facing considerable ethical dilemma during this COVID-19 pandemic-whichpatient to select for surgery and which patient to be deferred for a later date. Surgeons also had a difficult taskof protecting themselves and their team and perform a safe surgery without infecting the patient. There were also ethical issues of using Oxygen or an Intensive Care Unit (ICU) bed during this time for the surgical patient when it was in short supply. A critical factorwas balancing the benefit of surgery for the patient against the risk of contacting the COVID-19 virus and the complications of the disease process.

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Key words **: COVID-19, Pandemic, Ethics, Altruism, PPE.**

"Ethics is knowing the difference between what you have a right to do and what is right to do"
— Potter Stewart

COVID-19 pandemic reduced the ability to perform elective surgical procedures worldwide, giving rise to a multitude of ethical, practical, and medical dilemmas for the surgical fraternity. Surgeons were being forced from patient -centred ethics to public health ethics. It goes without saying that this situation was unprecedented for anyone in their lifetime.

Dilemma of stopping elective surgery :

As soon as the World Health Organisation declared novel Corona virus disease 2019 (COVID-19) as a pandemic, the American College of Surgeons brought out a guideline – "Each hospital, health system, and surgeon should thoughtfully review all scheduled elective procedures with a plan to minimize, postpone, or cancel electively scheduled operations, endoscopies, or other invasive procedures until we have passed the predicted inflection point in the exposure graph and can be confident that our health care infrastructure can support a potentially rapid and overwhelming uptick in critical patient care needs"[1]. This restriction inevitably caused mental distress for surgeons as they were forced to alter elective surgical schedules and shift to other aspects of patient care , to help in "flattening the curve". Two important shifts in ethical framework have been to stop elective surgery to accommodate COVID-19 patients in the hospital and to reduce the use of Personal Protective Equipment (PPE) due to short supply in most of the pandemic zones. As the elective surgeries were stopped, surgeons have been asked toonly perform those surgeries that are both medically necessary, lifesaving and time sensitive to perform. While no surgeon likes cancelling or postponing surgery, the necessary protocol to choose which operation to proceed with and which surgery to postpone or cancel was an unusual circumstance and unfavourable task for most of the surgeons. There were instances where patients' non urgent surgery was cancelled even when the patients had stated that they were willing to accept the risk of having surgery with the probability of getting COVID-19 in the process.

Editor's Comment :

- Covid-19 will always be remembered for the surgical dilemmas and ethical issues a surgeon faced during this pandemic. While on one side, the surgeon had to face the patient during the surgery and had the risk of himself and his family members getting the disease, it was never an ethical choice for the surgeon to stop all the elective surgeries till the curve straightens down. It was a catch- 22 situation for the entire surgical fraternity.

Another unique surgical challenge was the personal risk of contracting infection during surgery while prioritization of who received the limited available surgical care. Ethical issues also arise when surgeon faces scarcity of PPE increasing the risk of getting infected, when called to manage a surgical patient in the COVID-19 unit.

The backlog of postponed surgical procedureswas another major cause of professional headache for the surgeons. An important source of mental distress for many surgeons during the pandemic was to stay home unless specifically called upon to render surgical care during emergency. Surgeons are used to rigorous

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operating schedules and long outpatient clinics and have never been accustomed to waiting at home or work from home[2].

Guidelines for Surgeons in Emergencies :

Surgeon should follow the fundamental principle of Medical Ethics as defined by Beauchamp and Childress which includes Beneficence, Nonmaleficence, Autonomy and Justice[3]. Beneficence is to care for or help others and "do good". Nonmaleficence is to "do no harm". The responsibility of every surgeon is to act in the patient's best interest without being influenced by any personal consideration and patient must trust the surgeon to do the right thing. This trust was often challenged during the pandemic as surgical services were crippled and were not functioning normally. The duty of the surgeon was to protect the most vulnerable, but they were under no obligation to offer treatment they consider futile or risky[4].

At the same time, even though there wasa high mortality rate postop inthe COVID-19 positive patients, a 30% increased mortality rate especially in the elderly population , the surgeon knew that its not feasible or rational to consider all surgery futile in the aged patients. Emergency surgery when life or limb saving had to be undertaken regardless of the COVID status of the patient, after evaluating the blood and lung functions and taking adequate precautions, after obtaining a detailed consent from the patient. The simplest and the fastest surgery that will fix the emergency needs to be carried out, with all refinements later after the patient has fully recovered from COVID. It was recommended that further surgery be postponed at least 4 to 6 weeks after complete recovery[6].

Ethics in Cancer Surgery :

Cancer patientswere a vulnerable group where delay in Oncosurgery may deprive them of the golden opportunity for an early surgical cure with decrease in 5 year survival whereas ironically, contracting COVID-19 during treatment does exposes them to a higher morbidity and mortality due to their immunosuppressed state. The surgeon also faces particular risk due to physical proximity and contact with potentially infected body fluids, saliva, blood, urine and faeces of the patient. Many surgeons died after performing surgery on COVID -19 patients due to the disease process contamination intraoperatively. As a result, in many cases, patients with aggressive disease have been initiated or maintained on a conservative line of oncology with systemic therapy or chemotherapy rather than radical surgery. Though prolonged utilization of chemotherapy in cancer patients do sometimes provide radiographic control but invariably it does not always translate into pathological control. An ethical balance was therefore required between postponing surgical treatment that were currently considered too risky during the pandemic versus continuing to save the lives of cancer patients with urgent surgery irrespective of the COVID-19 pandemic situation.

Ethics of Altruism :

Altruism is defined as the selfless concern for the wellbeing of others. Surgeons will have to place themselves invariably selflessly at risk to help patients and support other colleagues. Surgeons have demonstrated that it is possible to provide safe surgical care even for novel Corona virus 2019 positive patients, while minimizing nosocomial infection to the healthcare workers. So, postponing elective surgery especially in patients with other co-morbid conditions where surgery may alleviate pain and make the patient disease free and aid in functional improvement with normal quality of life will be hard to justify always. This also applies to patients waiting for organ transplant. So again, an informed, altruistic choice had to be made regarding the timing of such surgery when Oxygen and ICU resources can be diverted to these elective procedures. A surgeon -patient relationship should be considered a partnership, in which the surgeons' duty is to honestly educate and empower patients to make appropriate informed choices about surgical care. Informed consent for surgery needs to be drafted especially for the pandemic which should include the risk, benefits, and alternatives[5].

Ethical issues and Constant Mental stress :

Surgeons during the pandemic were under constant stress and depression. Surgery under general anaesthesia and Laparoscopic surgery were considered high risk since it causes aerosol formation during intubation, pneumoperitoneum induction and suction. Cardiopulmonary resuscitation if the need so arises in the acute setting was also under scanner as it also causes aerosolization of the virus. Surgeons daily used to hear about their colleagues either contracting COVID or succumbing to the disease. Considering these risks, many surgeons had closed shop or retired early. And that is not a decision that is easy or morally uplifting. Surgeons forced to do that because of their associated health or family issues live in guilt, low self-worth and worry regarding the financial issues even after the third wave of COVID-19.

The active surgeons must decide to offer those

patients requiring acute surgical treatment, an alternative to the conventional gold standard approach thatcan be inferior butis outweighed by the reduced risk of COVID -19 related morbidity and mortality. Rarely, the patient may have trust deficit and can doubt if the surgeon is wantonly mistreating him and that can add to the stress and physical or mental harassment[7].

Conclusion :

"The Ethical person should do more than he is required to do and less than he is allowed"
Michael Josephson

Surgeons were facing one of the most challenging time and multiple ethical dilemmas during this novel Corona virus 2019. Every surgical decision needs to weigh with risk of contracting the virus. On one side , surgeon must go all out to save the life of the patient during surgical procedure whereas on the other side, the surgeon must save himself and his team from getting infected. It was the tough call for the conscientious surgeon to opt for a conventional, non-conventional or non-operative management during this pandemic and retaining the patient's best interest at the heart of surgical practice as well so that the professional integrity is always preserved.

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Case Report

Retinal Detachment in Primigravida with Antepartum Eclampsia : A Case Report

Saura Kamal Dutta[1], Gautam Paul[2], Ankita Chakraborty[3]

Eclampsia is a new-onset generalized seizure in patients with preeclampsia. Retinal detachment is one of the rare complications of pre-eclampsia. Here we describe a case of a primigravida presenting at term pregnancy with eclampsia and vision loss. She was found to have a serous retinal detachment in one eye and features of Eclampsia-associated Retinopathy in another eye. She underwent cesarean section due to fetal distress, with the delivery of a healthy baby. In the postpartum period, serial examination showed, complete reattachment of the retina.

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Key words **: Retinal Detachment, Hypertension, Preeclampsia, Eclampsia.**

Pre-eclampsia affects 5 % of pregnant ladies and is defined as new-onset hypertension after 20 weeks of gestation plus proteinuria or evidence of end-organ compromise including renal insufficiency, thrombocytopenia, pulmonary edema, CNS symptoms, or liver dysfunction[1]. In the absence of either proteinuria or hypertension patients with the aforementioned findings are considered to have an atypical variant of preeclampsia. Eclampsia is a new-onset generalized seizure in patients with preeclampsia. Retinal detachment is one of the rare complications of preeclampsia, affecting only 1-2% of patients and 10% of those with eclampsia[2]. The majority of patients who present with retinal detachment during pregnancy have a complete recovery after delivery, following conservative management.

Case Report

A 20-year-old, primi female, housekeeper, resident of the rural village of Barak valley with no history of hypertension presented to the labor room of the Maternal and Child Health Department at 36 weeks with headache, lower limb edema, and blurred vision.

She also had two episodes of generalized seizure on the way to the hospital. On examination, her Blood pressure was 170/100 mmHg. The urine analysis showed proteinuria but other laboratory exams didn't show Liver enzymes elevation, Thrombocytopenia, or hemolysis.

Editor's Comment :

- Thorough eye examination is a must for patients presenting with dimness of vison along with Antepartum Eclampsia, as this can be due to Retinal Detachment in some cases.
- Proper management of eclampsia, regular fundus examination and follow-up is the key management strategy.

She was started on a magnesium sulfate regime, and vitals fluid output monitoring was done. She had blurred vision and she could see only hand movement hence ophthalmology opinion was taken and on examination, the external eye looked normal with normal shape and reaction of pupils. Funduscopic examination revealed a reduced arteriolar caliber and arteriovenous ratio, edema, cotton wool spots right eye (Fig 1), and serous retinal detachment of the left eye (Fig 2). She underwent a cesarean section and a healthy baby was delivered. In the postpartum period, the patient was continued on magnesium sulfate for 24 hours and she

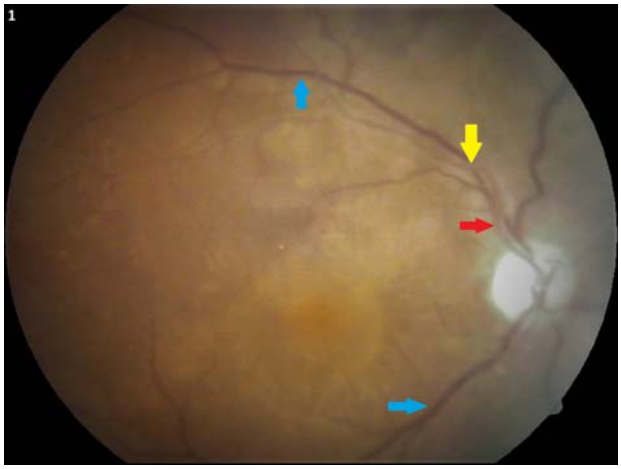

Fig 1 — Reduced arteriolar calibre and arteriovenous ratio (blue and yellow arrows), AV crossing

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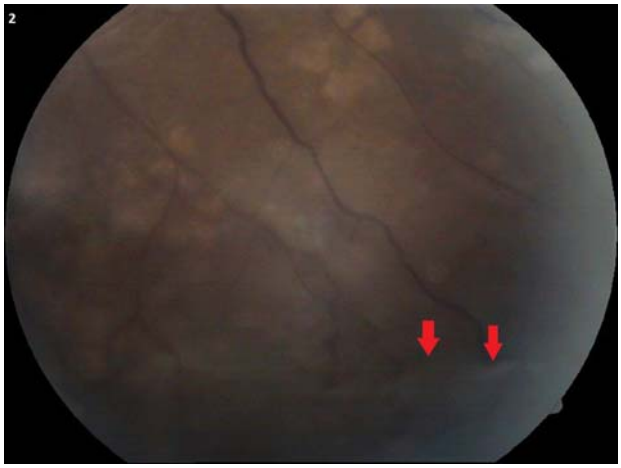

Fig 2 — Arteriolar attenuation, sub-retinal fluid collection with peripheral retinal detachment

was stable with the gradual improvement of vision. Periodic ocular examination showed complete reattachment of the retina in the post-partum period.

Discussion

In patients with pre-eclampsia vision is affected in up to 30 to 100%. Blurred vision is the most common symptom followed by Photophobia, spots in the visual field and diplopia and this may be attributed to preeclampsia/eclampsia associated retinopathy which is due to generalized retinal arteriolar narrowing resulting from Central Retinal Artery Vasospasm[3]. This may cause damage to the Retinal and choroidal Vasculature and the Retinal Pigmented epithelium. This ischemic state manifests as reduced arteriolar caliber, reduced arteriovenous ratio, edema, cotton wool spots, peripheral retinal neovascularization, choroidal neovascularization, macular edema, macular ischemia, and serous retinal detachment[3], all these can be diagnosed on fundoscopy. Serous retinal detachment occurs in about 1% of cases of preeclampsia. Retinal detachment is caused by the accumulation of serous fluid in the subretinal potential space due to local necrosis of the choriocapillaris and Retinal Pigment Epithelium Secondary to chronic occlusive changes of arterioles and choriocapillaris, arteriolar vasoconstriction, and hyperpermeability of the choroid[4].

As there is no retinal tear, reattachment surgery is not needed. Instead, the focus of treatment should be on eliminating the underlying cause, which involves maternal stabilization and delivery[5]. Patients with a serous and haemorrhagic Retinal Detachment can be left with extensive degenerative changes in the RPE and Retina following recovery.

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Case Report

Rare Possible Complications : Pneumothorax and Subcutaneous Emphysema In COVID-19 Patients

Atul Verma[1], Pritish Mahanta[1], Smriti Khari[2], Jaideep Singh[3], Himanshu Chaudhary[4], T R Sirohi[5]

Coronavirus Disease 2019 (COVID-19) is a Respiratory Tract Infection (RTI) caused by a newly emergent Coronavirus, that was first recognized in Wuhan, China, in December 2019. Genetic sequencing of the virus suggests that it is a Beta Coronavirus closely linked to the SARS virus[1]. By the end of 2019, several cases of Pneumonia with unknown aetiology were reported in Wuhan, China[2-5]. Most cases progressed to Acute Respiratory Distress Syndrome (ARDS)[2].

As the second wave surge of COVID-19 has occurred, most of the patients already suffered from dyspnoea but rare complications also seen more frequently in respiratory presentation. Cases of Pneumothorax and Subcutaneous emphysema is not seen frequently in COVID-19 patients so far. Here we are presenting two unusual complications in COVID-19 patients of our COVID facility. The possibility of spontaneous Pneumothorax/Tension Pneumothorax should be kept in differential diagnosis in COVID-19 patient presented with severe breathlessness and on higher settings of Non-invasive ventilation and on higher respiratory assistance can cause Subcutaneous emphysema.

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Key words **: Case report, Spontaneous pneumothorax, Subcutaneous emphysema, COVID 19 corona virus SARS CoV2 complication, CT**

Since the second wave of COVID-19 in India from early April 21 to May 21 due to Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2), surge of cases occurred and has hit India badly.

Cases discussed in this report were admitted in primary care facility (covidsection) Lokpriya Hospital, Meerut (Reg No : RMEE1900995) in Western Uttar Pradesh which is primarily a sugarcane belt of India where most patients belong to lower socioeconomic status and not adopting COVID appropriate behaviour.

Reports of spontaneous pneumothorax, tension Pneumothorax as a result of COVID-19, in the absence of underlying lung disease before COVID Pneumonia or barotrauma due to mechanical ventilation are rare. Therefore, we describe a case of secondary Pneumothorax in a COVID-19 patient in our COVID facility.

Editor's Comment :

- Rare possible complications Pneumothorax and subcutaneous emphysema in COVID-19 patients.
- COVID Pneumonia is common I. COVID-19 presentation but pleural complications should be considered if patients deteriorates.

Case Reports

Case 1 :

A 71-year-old male (UHID No 12493) was brought to our Emergency Department with complaint of severe shortness of breath, chest pain, fever and generalized weakness.

COVID-19 Rapid Antigen Test from nasal swab came positive at the time of admission. High-resolution Computed Tomography (HRCT) chest done one day prior to admission S/O

CT severity index 18/25.

SpO_2 at the time of admission 60% on room air hence supplemental O_2 support @ 20L/min started with Bains circuit, resulting in peripheral SpO_2 saturation reached 97%.

On examination PR 108/min BP 104/68mmhg RR 40/min Temp 99.4-degree Fahrenheit. On examination of respiratory system bilateral decreased air entry with right sided crepts present (Fig 1).

Fig 1 — Urgent chest x-ray done. s/o left pneumothorax

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Investigation —

Hb	13.6	PT TEST	13.8
TLC	14.9	PT INR	1.17
NEUTROPHIL	97	PT CONTROL	12
LYMPHOCYTE	2	RBS	195
PLT	1.1	HbA1C	7.3
ESR	35	PCT	0.43
UREA	32	LDH	1157
S. CREAT	0.47	Ddimer	>10000
S.NA	147	ABG	
S. K	5.5	pH	7.376
S. Ca	7.8	pCO2	45.7
S.BIL	0.83	pO2	53.8
AST	40		
ALT	22		
ALK	179		
Pro T	7.58		
Alb	4.31		
A/G RATIO	1.32		

Immediately ICD insertion done successfully between 4th and 5th intercostal space along the upper border of 5th rib in mid axillary line, in ICU setting. Saturation start improving reached 94%. finally, patient shifted to upgraded respiratory facility for further management.

Case 2 :

A 32-year-male (UHID No. 11764) patient brought to our Emergency Department with complain of fever since last 7 days. Patient also developed shortness of breath which was progressively increasing and more with physical activity.

Patient's RT PCR for COVID-19 came positive.

On examination patient was tachypnoeic with respiratory rate 40/min pulse rate was 120/min and BP 110/70 mmHg. Patient is febrile having axillary temperature 101.4 degree Fahrenheit. Patient saturation came 80% on room air, so supplemental Oxygen support given via non-rebreather mask. On examination of respiratory system Bilateral decreased Air entry with basal crepts.

Blood investigations —

Hb	13	ABG	
TLC	10.4	pH	7.44
NEUTROPHIL	92	pCO2	46.9
LYMPHOCYTE	6	pO2	86.4
PLT	1.5		
ESR	52		
UREA	36		
S.CREAT	1.4		
S.NA	149		
S.K	4.5		
S.Ca	6.7		
S.BIL	0.43		
AST	81		
ALT	77		
ProT	5.1		
Alb	3		
A/G RATIO	1.43		

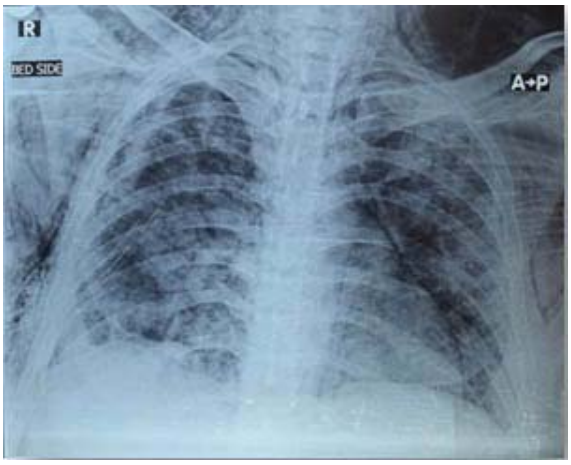

Fig 2 — CT severity index 18/25.

Chest X-ray after Non-invasive ventilation shows Bilateral Lung Infiltrates and diffuse subcutaneous emphysema in the subcutaneous tissues of chest. Both domes and costophrenic angle are partially obscured. (Fig 2).

In view of not maintaining saturation patient taken on BiPAP after which saturation improving but patient develops Subcutaneous emphysema. After which BiPAP removed and taken on double Oxygen support @30L/ min via nasal prongs and Bains support and patient maintain saturation of 94%. Subcutaneous emphysema resolves with this Conservative management within 24-48 hours.

Finally, patient expired 5 days later on after diagnosis due to respiratory arrest.

Conclusion

These cases show that in COVID-19 Pneumonia patient, possibility of spontaneous Pneumothorax/ tension Pneumothorax due to variable etiology. High pressure non-invasive ventilation is a risk factor of subcutaneous emphysema in COVID Pneumonia patients. So, possibility should keep in diagnosis and need prompt investigation and management.

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Case Report

Iatrogenic Isolated Ruptured Dorsalis Pedis Artery Pseudo Aneurysm : A Rare Case Report

Meenakshi Yeola (Pate)[1], Sushanth R Nayak[2], Namrata Singh[3], Amit Kumar Singh[4]

A Dorsalis Pedis Artery (DPA) pseudo aneurysm is one of the most uncommon peripheral arterial aneurysms. These aneurysms can cause distal embolization and thrombosis, leading to limb loss. However, their rupture is unusual[1].

Any type of injury or perhaps an iatrogenic intervention can cause a pseudo localized swelling of the dorsalis pedis artery, which is a relatively unusual condition. Whenever it presents as a non-pulsatile soft tissue mass in the presence or absence of a specific predeceasing event, it can lead to a difficult diagnostic dilemma[2].

The rare instance of an iatrogenic pseudo aneurysm of the dorsalis pedis artery which mimicked cellulitis of the right foot is discussed in this case report. Coil embolization of the proximal artery, and the aneurysm was successfully done by the intervention radiologist. After the procedure, collateral circulation was maintained.

No ischemic symptoms such as intermittent claudication or pain at rest were observed. This approach may be useful in treating similar cases.

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Key words **: Ruptured dorsalis pedis artery aneurysm, coil embolization, Dorsalis pedis artery, Peripheral artery, Pseudoaneurysm, Surgery.**

Case Report

A 72-year-old man presented with a one-month-old swelling on the dorsal aspect of his foot (Right side). (Fig 1).

The agony was increasing as the vague bulge on his right foot grew. After regular physical activity and at the end of the day, the pain would be the worst. There was relief found on elevation. The patient reported suffering from hypo pigmented skin lesions over the anterior aspect of the same ankle joint causing itching over the area, diagnosed as eczema,since last two years, for which he had undergone repeated steroid injection, leading to temporary relief from the skin lesions. He later developed a swelling over the same ankle joint which was later misdiagnosed as cellulitis of the right foot and underwent incision and drainage for the swelling 1 month back.The patient again observed the swelling over the same region following the incision and drainage in a span of 1 week. There was no history of recent trauma or change in lifestyle. Past medical history was insignificant; there was no history of diabetes mellitus, cardiac disease, or peripheral vascular disease.

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Editor's Comment :

- Carrying out unnecessary invasive procedures without complete evaluation is not ethical.
- The Imaging studies may not always prove to be helpful in the diagnosis of the disease conditions that we face. Even the experience of the clinician matters.
- A good surgeon is the one who knows when not to operate.
- Multi-disciplinary approach always helps to diagnose a rare or a misdiagnosed case, leading to a better outcome and a feasible solution.
- Ultimate goal in the management is patient safety.

On local examination there was diffuse swelling without local tenderness. All movements at the ankle joint

Fig 1 — Pre-intervention image showing swelling around the right ankle region

Fig 2 — X-ray Right Foot AP and Lateral View revealing soft tissue swelling anteriorly without any bony involvement

Fig 3 — Aspiration of the cystic swelling

Fig 4 — Post coil embolization image of the local site which was suggestive of significant regression in the subcutaneous blood collection in the dorsum of the foot and medial aspect of the ankle.

were normal. A non-pulsatile, non-tenderfullness, was present antero medially on his right foot. Dorsalis pedis pulse was present bilaterally with equal volume. Peripheral Neurological examination was normal. Radiograph of right foot demonstrated soft tissue swelling anteriorly without any bony involvement (Fig 2).

With clinical diagnosis of the loculated fluid collection along the anteromedial aspect of the right ankle joint, corroborated by local site ultrasonography, aspiration of the content of the swelling was done (Fig 3).

The aspirate was haemorrhagic to dark brown colored and hence the diagnosis of haematoma was made. As duplex scan of the local site and the affected limb was unremarkable, right lower limb angiography was done to know the cause of the recurrent hematoma formation.

Angiogram was suggestive of ruptured pseudo aneurysm of right dorsalis pedis artery.

Coil embolization with the MWCE-18-14-3-NESTER was done for the ruptured DPA pseudo aneurysm. Following coil embolization, subsequent ultrasonography of the region revealed considerable decline in subcutaneous hematic collection in the dorsal aspect of the foot and medial portion of the ankle[3] (Fig 4).

Discussion

The DPA pseudo aneurysms are uncommon. Piercing injury, injection, aspiration or surgical intervention are all possible causes[3].

The obvious diagnosis that we reach for a patient who comes with a narrative of trauma and pulsating, painful mass might hardly vary.

On the other hand, soft tissue swellings on the dorsal aspect of the foot, can be difficult to distinguish, since the above mentioned obvious signs were absent. Hence, the differentials in the diagnosis of the condition get broadened and will be including of both benign and malignant conditions[3].

This patient presented with a spontaneous swelling over the ankle that was getting worse by the end of the day and was not associated with any other local abnormalities.

The clinical signs and symptoms, along with the radiological imaging were pointing towards soft tissue cellulitis, which is one of the most commonly affecting diseased state of the foot or the ankle.

The Imaging studies may or may not prove to be helpful in all the disease conditions that we face[3]. The soft tissue oedema was confirmed by plain radiographs in this case. Had there been clinical suspicions of a vascular lesion, then the vascular sequences would have been performed earlier, hence preventing the unnecessary invasive procedure the patient underwent before.Even in retrospect, we were yet to demonstrate any form of relationship between the swelling and the DPA, despite the fact that Doppler is considered sensitive.

Treatment options for pseudo aneurysms include of repair, or reconstruction or embolization. Since many consider the dorsalis pedis artery to be unnecessary, there are various studies proposing its ligation. Current revelations in small-vessel arterial reconstructive procedures, on the other hand, have made repair or restoration a reasonable choice" and our belief, that conservation of the vessel is the perfect alternative when possible[3].

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Short Communication

The Use of Aspirin in Patients Suffering from COVID-19 Disease

Arvind Nath[1]

Aspirin, in moderately higher doses, can be considered with close monitoring for COVID-19 as this is a relatively inexpensive and a promising therapeutic alternative to save lives.

[*J Indian Med Assoc* 2022; **120(5):** 58]

Key words **: Aspirin, COVID-19, Thrombus.**

The COVID-19 Pandemic has taken place nearly a hundred years after the Spanish Flu Pandemic of 1918-1920. Despite the advancement of Medical Technology, COVID-19 has distorted the Globe. As of 17 November, 2021, there have been 255,225,685 cases of COVID-19 in the World and 5,132,675 persons had died of the disease[1]. According to Ministry of Health & Family Welfare's website, as on 17 November, 2021, 8 AM, in India there were 128555 active cases, 33873890 were discharged and 464153 had died[2]. Though these numbers are insignificant when compared to India's 1.3 billion population, still some preventable control measures can be taken. Of course, life is priceless.

An article published last year elaborately described various treatment modalities which, despite not being definite curative measures, were prescribed for the management of COVID-19[3]. One of the suggested Therapies was that of Paracetamol and it was suggested that it may be preferred over NSAIDs in the management of COVID-19. However, in postmortem studies carried out last year in Italy, Platelet-fibrin thrombi were found in the Lung which would now invite the use of NSAIDs, preferably Aspirin, as the first line of treatment in COVID-19 patients[4].

Aspirin has been prescribed in India as an emergence intervention to be taken in the case of a suspected Heart attack in the form of giving chewable or sub-lingual 300mg Aspirin[5]. This treatment option, in moderately higher doses, can be considered with close monitoring for COVID-19 as this is a relatively inexpensive and a promising therapeutic alternative to save lives.

Conflicts of Interest : None

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Short Communication

Disulfiram Induced Mania — A Case Report

Mamidipalli Sai Spoorthy[1], Parul Gupta[2]

Disulfiram has been most widely used in patients suffering from alcohol dependence. When taken along with alcohol it can cause various side effects like flushing, drowsiness, rashes, hyperventilation, palpitations etc. Mania due to Disulfiram is an uncommon side effect and there are only a few reports of it. We hereby report a case of the development of Mania in an individual with alcohol dependence following 2 months of treatment with a therapeutic dose of Disulfiram. Before the onset of mania, the patient was abstinent from alcohol for about 2 months, which made substance-induced mania unlikely. The possible mechanism for this is the dopamine hypothesis which suggests that Disulfiram inhibits dopamine-Beta-hydroxylase which is responsible for the conversion of dopamine to Nor-adrenaline and increases the dopamine level which is responsible for psychotic and mania symptoms. This possibility of Disulfiram induced mania should be assessed whenever clinicians encounter patients with dual diagnosis, as this might change the management as such.

[*J Indian Med Assoc* 2022; **120(5):** 59-61]

Key words **: Adverse effect, Disulfiram, Mania.**

Disulfiram which is also known as tetraethylthiuram disulfide is commonly used for patients suffering from alcohol dependence for de-addiction treatment for the past 50 years. Disulfiram inhibits aldehyde dehydrogenase which affects the metabolism of alcohol and increases the level of acetaldehyde in the blood. There are many adverse reactions reported due to Disulfiram which include dermatological, hepatological, neurological and psychiatric conditions like psychoses, confusion, delirium, loss of memory, mania. Among the psychiatric side effects, psychosis is more common than any other condition[1].

There is a known dopamine hypothesis that suggests that Disulfiram inhibits the dopamine-Beta-hydroxylase which converts dopamine to Nor-adrenaline and increases the dopamine level which is responsible for psychotic and manic symptoms[2]. By reviewing the relevant literature, we came across a few case reports about psychotic and mood disorders caused by Disulfiram. However, the prevalence of Disulfiram induced mania as such is unknown and rare. In a review, after a study of 52 patients, it was reported that 4 out of 52 patients reported mania or hypomania symptoms on Disulfiram[3]. Murthy *et al*, 1997 followed up 51 patients with alcohol abuse for 4 weeks receiving 250 mg of Disulfiram twice daily and found out that Mood disorder developed in 6 patients. The authors also found out that the mood symptoms resolved shortly after discontinuation of Disulfiram[4]. In one of the case reports authors have suggested the possibility of manic episodes as a consequence of Disulfiram ethanol reaction[5].

In this case report, we describe the presentation of 39 yrs old male who developed mania without any psychotic symptoms after administration of a therapeutic dose of Disulfiram. Informed consent was obtained from the patient.

Case Report

A 39-year-old married male, educated up to BA 1st year, auto driver cum fruit seller, Buddhist by religion, living in a joint family, belongs to a low socio-economic status, resident of Wardha.

He presented with an illness duration of 12 years, with precipitating factor of financial stress, a predisposing factor of mental illness in the family, illness was insidious in onset, continuous and fluctuating in course with alcohol use in the form of craving, tolerance, withdrawal, use despite harm, the usual amount being 500ml- 1L in a day of the country made liquor, the last intake of alcohol was 2 months back.

His history suggested 1 episode of sadness of mood, irritability, death wishes with an aborted suicide attempt under the influence of alcohol 1 year

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back. From the last 6 days patient presented with a new set of complaints with abrupt onset and continuous course characterized by irritability, big talks, over talkativeness, smiling to self, aggressive behaviour, sleep disturbance.

The patient was taking treatment for de-addiction from a private psychiatrist for 2 months. For 2 months patients received tab. Sodium valproate 200mg HS, tab. Disulfiram 250mg OD initially then gradually over 15 days increased to 500mg in divided doses, tab. Olanzapine 5mg HS (poor compliance for olanzapine due to increased sedation). 2 days prior to admission in our psychiatry ward patient went to a private psychiatrist and received tab. Escitalopram 10mg in combination with Clonazepam. He consumed half tablet for 2 days only. There was no history of any other substance abuse. No history of any other medical co morbidities.

Family history was suggestive of Alcohol dependence in father and psychosis in elder sister. Personal history was suggestive of well adjusted pre-morbid personality. Physical and systemic examination was unremarkable; his haematological and biochemical indices were found within normal limits. MSE revealed uncooperativeness, aggressive behaviour, increased psychomotor activity, increased rate, amount, volume of speech, decreased reaction time, irritable affect, ideas of grandiosity, attention and concentration- arousable and ill sustained, insight being 2/5.

The patient was hospitalized and the possibility of Mania induced by Disulfiram (F30.8) was kept. All the medications patient received from outside were stopped including Disulfiram. Young Mania Rating Scale (YMRS) was applied on the day of admission and the score was 26 (moderate mania).

Tablet Sodium Valproate was started at 500mg twice a day and along with this patient was kept on Inj. Haloperidol 10mg and Inj. Promethazine 50mg IM BD for the initial 2 days in view of his irritable behavior. After that Tablet Quetiapine 50mg BD was added and Tab. Sodium Valproate continued at 1gm/day. The patient gradually improved within 4 days after stopping Disulfiram.

No evidence of alcohol withdrawal was seen (CIWA-Ar at baseline), so detoxification was not done and patient was put on thiamine supplementation. No signs and symptoms of disulfiram-ethanol reaction were observed during hospitalization. The patient was discharged within 7 days and before discharge Young Mania Rating Scale (YMRS) was again applied and the score came to be 5 (Normal) and On further follow-up after 15 days patient was asymptomatic and abstinent to alcohol.

Discussion

Our patient was a young male who developed manic features without any psychotic symptoms who was on continuous treatment with Disulfiram while completely abstinent on alcohol for 2 months.

Because of the 2 months alcohol abstinent period, we attribute it is not due to Disulfiram-alcohol reaction but due to Disulfiram itself. The initial recommended dosage of Disulfiram usually is 500 mg per day for the first 1 or 2 weeks, which should be followed by a maintenance dosage of 250 mg per day[6]. The development of Disulfiram related mania or psychosis is usually seen on either therapeutic or higher than recommended dosages[1,6,7]. Our patient developed mania symptoms with the dose of 500 mg per day of Disulfiram. Rapid response to the mood stabilizer and low dose Quetiapine after discontinuation of Disulfiram (within 3-4 days of stopping) also suggests that the manic episode was secondary to Disulfiram use.

Naranjo Adverse Drug Reaction probability scale was applied to the patient. This scale explains the probability of an adverse event that is related to drug therapy and is based on a list of ten questions[8,9]. In this patient, the total score was 7. Hence, Disulfiram can be considered as the probable cause of mania in our patient.

A study reported irritability (1.9%) and over talkativeness (3.8%) as psychiatric side effects which our patient has[5,10]. In one similar case report of 40yrs old male developed mania on the maintenance dose of Disulfiram and improved after stopping the drug[11]. As per the literature review of 52 patients, the development of mania symptoms was seen only in 4 patients on Disulfiram which also suggests that the development of only mania symptoms is less as compared to mania with psychotic symptoms or psychosis[3]. The risk factors for the development of Disulfiram related psychiatric symptoms include a past history or family history of psychiatry illness which our patient has[12].

What is unique in this case is that patient developed mania without any psychotic symptoms and there were only a few case reports on developing only manic symptoms due to Disulfiram use.

Finally, we would like to recapitulate that Disulfiram induced mania is a rare entity and due to these reports, a clinician must not restrict themselves to prescribe Disulfiram, where it is otherwise required and should recognize the risk factor before prescribing.

Declaration of patient consent :

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understand that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Pictorial CME

Those white Spots in the Brain

Rudrajit Paul[1]

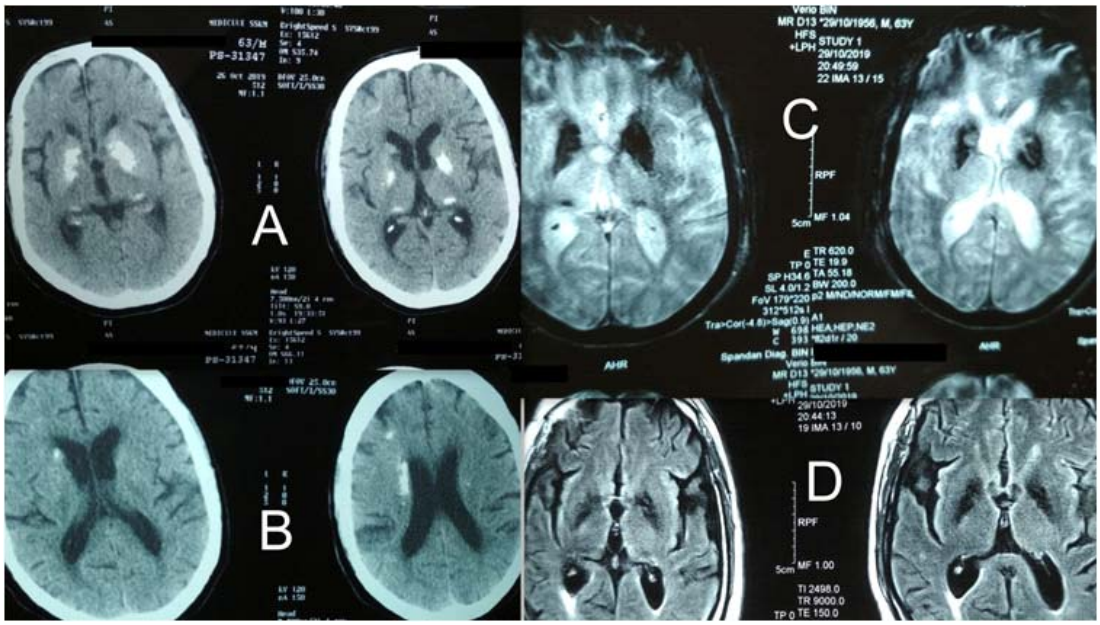

Fig 1 — CT scan of brain (Panels A and B) showing extensive calcification in bilateral basal ganglia and periventricular regions. Panels C and D show the MRI appearances with blooming in GRE

A 63-year-old man was admitted with sudden onset dizziness. At admission, a CT Scan of brain was done. When certain abnormalities were found in that scan, an MRI scan was also done. Both are shown in Fig 1. The patient had since recovered with no neurodeficit. Blood tests done at the time of hospital stay were all normal.

(1) What is the diagnosis?
(2) What are the usual clinical features?
(3) What are the genetic links of this condition?

Answers :

(1) The brain imaging shows areas of bilateral calcification in the brain, especially in and around the basal ganglia. In view of the normal blood tests, this is most probably idiopathic brain calcification or Fahr disease.

(2) As in our case, the patients with limited cerebral calcification may be completely asymptomatic. However, in more severe cases, there may be extrapyramidal features with motor impairment, dementia, dysarthria or movement disorders like athetosis. Neuropsychiatric manifestations may be the dominant presenting symptom in many cases. In addition to the periventricular region (as shown in this Figure), the calcification spots may be located in the cerebellum, hippocampus, thalamus etc. Many patients are asymptomatic in childhood or young adulthood and present with progressive neurodeficits in the 4th and 5th decades of life.

(3) The disease may be sporadic or may be inherited in autosomal dominant manner. The exact gene responsible for the syndrome in unidentified in 50% of the cases. However, some candidate genes which have been proven to be associated with the disease include PDGFB, PDGFRB, SLC20A2 (Chr. 8), XPR1 etc.

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Special Article

Artificial Intelligence in Medicine Avatar — A Promise for Healthcare

R Rajasekar[1], M Gowri Sankar[2]

Artificial Intelligence (AI) is an integration of computer science, data analytics, and pure mathematics, which enable computer systems to mimic human cognitive skills to simulate intelligent behavior and critical thinking comparable to a human being[1]. Today it is blended with our daily living and revolutionizes every part of our life in the form of navigation, computer gaming, the personal voice assistant in smartphones for hands-free mobile usage, facial recognition biometric technology, precise weather forecasting, pop up of recommendations of our interest in Netflix, YouTube, Flipkart, and Amazon-like websites, etc.

The emergence of AI-powered apps in smartphones, wearables (smart electronic devices) like smartwatches, smart wrist bands, epidermal electronics like continuous glucose monitoring devices, and biosensors has revolutionized medicine for better health care for the patients. We are at the beginning of a new era in medicine, where AI-powered medical technologies are widely used in all medical fields to improve the different aspects of clinical practice. This paper aims to discuss the evolution of AI, common AI algorithms used in healthcare and its use in various fields of medicine, and the limitations of AI in clinical practice.

Evolution of AI[2]

In 1950, the English mathematician **Alan Turing** was one of the founders of Modern Computers, and Artificial Intelligence described a test known as the "Turing test" to determine whether computers were capable of human intelligence. Later in 1956, American computer scientist **John McCarthy** coined the term "*Artificial Intelligence*" and described it as *"the science and engineering of making intelligent machines, especially intelligent computer programs".* Over the past 70 years, computing power has evolved dramatically in both hardware and software technologies and AI technology evolved as a powerful tool and led to the fourth industrial revolution in the 21st century (Fig 1). It is on its way to shaping our present generation as well as the future generation.

Based on the level of intelligence revealed by the machine, AI is broadly divided into 3 stages[3]

First stage: Artificial Narrow Intelligence (ANI)

ANI also called weak AI that has focused on single or specific narrow range task

eg, Machines with speech recognition- Google Maps

Second stage: Artificial General Intelligence (AGI)

AGI is also called strong AI, the intelligence of a machine that mimics human intelligence, which has the power to create its programs

eg, Robotic technology.

Third stage: Artificial Super Intelligence (ASI)

In the future, the intelligence of machines will surpass the human intelligence.

Types of AI used in Healthcare[2]

Like specialties in medicine, there are different modalities in AI but the following three are widely used in healthcare

Machine Learning (ML)

ML uses mathematical algorithms to compile data and makes inferences based on preset criteria. It is used in managing medical data, helping in the diagnosis and early detection of diseases, personalized medicine, and analysis of errors in prescriptions.

Deep Learning (DL)

DL is a subfield of ML that requires less human supervision. It is an upgraded version of ML that can solve the problem which is unsolvable by ML. It is used in medical imaging, analyzing a large amount of data, and predicting adverse outcomes.

Natural Language Processing (NLP)

NLP is another sub-discipline of AI and ML. It is related to text and speech recognition and makes decisions based on that information. It improves clinical

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documentation, helps the healthcare provider to review massive quantities of unstructured data, identifies candidates for the clinical trial, and facilitates root cause analysis.

Common AI Algorithms used in Healthcare[4]

Algorithms are a set of rules that a machine can follow to learn how to do a task. AI enlists an endless number of algorithms. Some of the algorithms used in the medical field are

- Artificial Neural Networks
- Logistic Regression
- Support Vector Machines
- Random Forests
- Naive Bayes Classifier

Reasons for the Rising of AI in Healthcare

- Increasing demand for healthcare services and facilities
- Shortage of healthcare providers, especially specialty physicians
- High expectations from patients in terms of service and outcomes
- Availability of AI to perform at par or even better than humans in terms of analysis of medical images, correlating biomarkers, etc.

AI-based Algorithms used in Medical Disciplines[1,2,5,6]

Over the last 10 years, several AI-based algorithms have been approved by the Food and Drug Administration (FDA). It has wide clinical adoption for early detection, disease diagnosis, its management, medical data management, and drug development. Some of the AI-based algorithms used in medical disciplines are (Table 1).

Table 1 — *AI-based algorithms used in medical disciplines*

Discipline	Application of AI (with some examples)
Cardiology	The Kardia app in smartphones or tablets is designed to monitor ECG and helps in the detection of arrhythmias. The Apple Watch Series 4 to Series 7 has an electrical heart rate sensors that detect atrial fibrillation
Pulmonology	AI-based software provides a more accurate interpretation of pulmonary function tests to diagnose respiratory diseases
Diabetology	• Wearable real-time Continuous Glucose Monitoring (rt CGM) measures interstitial glucose by small transcutaneous electrodes placed under the skin of the abdomen or the arm and tracks glucose levels. This device alerts the patient by vibratory or auditory mode if reaches the preset hypoglycemia and hyperglycemia thresholds. • AI-enhanced "Noninvasive" glucose monitoring is successful by a skin patch that transmits readings to a smartphone, wristband with a build-in biosensor, and wearable wristwatch by using optical sensors • Smart insulin pens which have a tiny screen display to view the last dose, when connected with the app, help to track insulin dosing and timing. • Many mobile apps for diabetes address caloric counter, carb counting, exercise tracker, calculating calories burned, tracking blood glucose, insulin calculator, medication reminder, monitoring sleep habits and log-book.
Artificial Pancreas / Automated Insulin Delivery	New generation Insulin pumps automatically adjust the dose of both basal and bolus insulin according to measured glucose concentration and achieves better diabetes control.
Hypertension	AI-enhanced Blood Pressure (BP) monitoring devices like Smart wireless BP devices, and cuffless wireless wearable devices measure BP easily. When connected with the app, it helps to track BP history.
Ophthalmology	Diabetic retinopathy screening in adults is done by AI programed IDx-DR software system which analyzes the retinal images taken with a fully automated digital fundal camera. It helps to detect diabetic retinopathy within minutes and leads to a reduction in diabetes-related ophthalmic complications.

Discipline	Application of AI (with some examples)
Nephrology	AI programmed software and algorithms help to predict the decline of estimated glomerular filtration rate based on serum creatinine concentration in patients with kidney disease and predict acute kidney injuries. Image analysis by computer-aided diagnosis helps in categorizing kidney tumors as cancerous and non-cancerous lesions.
Gastroenterology	Convolutional neural networks are widely used in medical image analysis. By colonoscopy, image analysis detects abnormal structures such as colonic polyps. Endoscopy and ultrasound image analysis is been used to diagnose various gastrointestinal diseases like gastritis, gastroesophageal reflux disease, esophageal cancer, inflammatory bowel disease, and metastasis in colorectal cancer.
Neurology	An AI-enabled wearable smartwatch detects seizures and sends an alert to caregivers and information about the patient location. Also, proven useful to quantitatively assess gait, posture, tremor, sleep, and medication reminders in patients with neurological diseases like Parkinson disease, Parkinsonism, and Huntington disease. AI-based automated seizure detection algorithms help in speedy and accurate interpretation of electroencephalography (EEG).
Pathology	Digitalized Whole Slide Image Technology is capable of diagnosing cancer with great accuracy, allowing the pathologist to focus on important slides as well as speed up the reporting time.
Radiology	Deep learning software revolutionizing all imaging modalities including X-ray, ultrasound, CT scans, MRI scans, and PET scans to diagnose various diseases.
Newer Drugs and Vaccines	AI-based sophisticated algorithms create new opportunities to speed up the drug discovery and vaccines and shorten the longest steps in the discovery process.
Surgery	The Da Vinci Surgical Navigation System- a Robotic surgical system assisting in minimally invasive surgical approach for many surgical procedures.
Medical Virtual Reality	Virtual reality and three dimensional (3D) aid in teaching and training of medical school curriculum. Virtual reality headsets use during surgical procedures or during labor pain make the patient feel more relaxed with less anxiety.
Healthcare Administration	Clinical documentation, health record management, billing, and insurance claiming process can be done by Robotic process automation. Natural Language Processing based application can understand and respond to text or voice and make simple transactions like refilling prescriptions and for appointments. Ambient Clinical Intelligence-based application analyzes the interview and automatically fills the patient's electronic health records.
Electronic Medical Record (EMR) / Electronic Health Record (EHR)	Both EMR and EHR digitalize the patient's health details including demographics, history of illness, lab and imaging reports, and medications. Unlike EMR, EHR records can be shared with all treating physicians wherever the patient goes, thereby facilitating healthcare outcomes more efficiently and less costly.
Adherence to Therapy	A mobile phone-based AI application reminder system improves drug adherence and acts as a tool for patient empowerment, which leads to better clinical outcomes and enhances the quality of life.

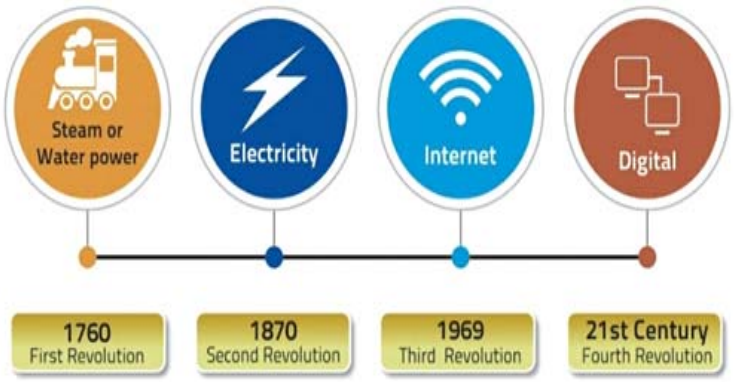

Fig. 1 - FOUR INDUSTRIAL REVOLUTIONS

Limitations of AI in Clinical Practice[5,7]

Technical Aspects :

- Challenges of the application
- Validation of the algorithms
- High cost for updating on the latest hardware and software
- Need frequent up-gradation of software
- For digital experience, proper training and knowledge are needed in computational sciences, coding, algorithmic, and mechatronic engineering
- Lack of clarity for some AI algorithms
- Lack of medical curriculum based teachings
- Electronic waste or e-waste, the harmful materials like lead, beryllium, and cadmium in electronic items are a hazard to the environment and human health

Psychological aspects :

- Fear of slow replacement of job opportunities of physicians and other health staff
- Empathy, trust, and moral support for treating patients would be compromised by using AI
- Negative impact on vulnerable age group
- Reduction of human contact and negative impact on health due to AI dependence and addiction

Ethical and Security issues :

- Lack of personal data privacy and misuse of personal information
- Risk for criminal and malicious use
- Lack of transparency
- Lack of informed consent

Though AI has limitations in various aspects like technology, ethical issues, security issues, and psychological which should be addressed by further studies, proper regulations, and a legal framework, AI technologies certainly improve physician performance by reducing the burden of clerical work and allowing them to spend more time with patients and the healthcare team.

Conclusion :

"Necessity is the mother of all innovations"

The European Union High-Level Expert Group on AI (2019) clearly states that *"AI is not an end in itself, but rather a promising means to increase human flourishing, thereby enhancing individual and societal well-being and the common good, as well as bringing progress and innovation.[7]"* Today high-quality medical care requires strong clinical skills along with appropriate tests and technology like AI. At the beginning of a new era in medicine, the integration of digital medicine is an essential part of the growth and development of medicine, which was accepted as complementary to physicians. AI is a Stethoscope of the 21st century that cannot replace physicians but rather helps physicians to create a paradigm shift toward precision diagnosis, risk prediction, prognosis, and management.

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Drug Corner

Long COVID : New Treatment Perspective Using Nutraceuticals

Hemant P Thacker[1], Anish Desai[2]

Coronavirus disease (COVID-19) is an ongoing worldwide pandemic affecting a large population regardless of gender, age, and ethnicity. The persistence of the COVID-19 symptoms has become a significant health issue and is collectively called "Long COVID." It can be described as the presence of symptoms of COVID even after the recovery from the viral infection. The prolonged symptoms in the patients could be due to various reasons and factors. Prolonged fatigue is a common symptom of Long COVID in patients even after they have recovered from the viral infection. Currently, only rehabilitation has shown promising results in managing the symptoms of Long COVID. Although pharmaceutical drugs have shown potential in treating the symptoms of Long COVID, more clinical evidence is required to confirm its treatment with less to no side effects; since it's a new disease, the in-depth knowledge of the same is still evolving. Another healthier approach to treating the symptoms of Long COVID could be dietary supplements or "Nutraceuticals," identified as an alternative to pharmaceuticals, including nutritional supplements, derived nutrients, and dietary and herbal products that display physiological advantages. Nutritional strategies can also play a role in treating hospitalized patients as maintaining the immune system is critical to combat viral infection.Nutraceuticals may be a practical and healthier approach to managing the symptoms of Long COVID or COVID-19. Although ample clinical evidence is present for the treatment of symptoms of COVID-19, further studies in treating Long COVID or its symptoms are required.

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Key words **: Long COVID, Headache, Pain, Curcumin, Ginger, Nutraceutical etc.**

Severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), a virus that first appeared in December 2019, led to an ongoing pandemic[1]. A pathogenic virus causing severe respiratory issues. It has been reported as a significant ongoing pandemic that has cost millions of lives worldwide. Around 80% of the population has experienced mild to moderate symptoms of COVID-19, and among those who experienced the disease in severity, 5% were victims of critical illness[3]. It was noted that the virus primarily causes gastrointestinal and respiratory tract infections. A small number of clinical trials have reported the active virus, and fecal dissemination has been detected in some patients[2]. A new development that was observed was the persistence of the COVID -19 symptoms that lasted up to weeks or even months; called "Long COVID," "Long Haulers," or "Post COVID syndrome"[2].

Editor's Comment :

- The transmission of acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is fatal as it affects thousands of people daily and can produce long COVID symptoms even after the treatment. The management of long COVID symptoms after COVID is difficult as no definitive therapy is available, and symptoms varies from patients to patients. Nutraceuticals such as CoQ-10, Ginger, Zinc, n-acetylcysteine etc. found to be effective in the treatment of symptoms observed in Long COVID. Current review article helps to identify symptoms occurring during long COVID and the role of nutraceuticals in their management.

LONG COVID-19 :

The persistent presence of symptoms of COVID-19 can be termed "Long COVID" or "Post COVID syndrome."The symptoms can last from weeks to months after acquiringSARS-CoV-2 infection, irrespective of the viral status (Fig 1). It can be continuous or relapsing and remitting in nature. The relative symptoms are not limited to just one, as this viral infection is still an ongoing pandemic; we still lack in-depth knowledge of the working of the virus in the body and any other new budding symptom that could randomly pop up. COVID-19 illness is poorly understood because it affects survivors at all disease severity levels, including younger adults, children, and those not hospitalized[5]. The most observed post-COVID symptoms are fatigue, dyspnoea, olfactory and gustatory dysfunction, chest pain, myalgia, and sleep and mental disorders[4]. The possible working of how the virus affects the body could be that the virus invades

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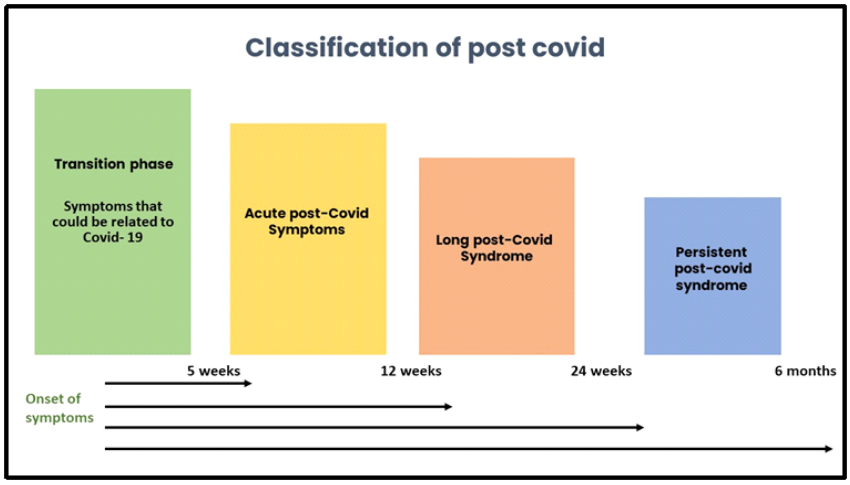

Fig 1 — Classification of Long COVID

many tissues and has a multiorgan and multisystem impact. Angiotensin-Converting Enzyme 2 (ACE2) receptor is expressed in many tissues, leading to oxidative stress and inflammation, leading to weak immunologic response, and incomplete virus eradication[5,6]. Long hauler's symptoms should not be ignored in patients, and proper care should be sought as soon as possible to help them achieve a better quality of life. A personalized and comprehensive approach to manage the symptoms is advised[9].

Prevalence of Long COVID :

The heterogeneous nature of long covid has made it difficult to estimate its prevalence, thereby lacking a precise case definition[1]. A patient-led survey found that the European population was suffering self-reported long covid. Among the patients who reported Long COVID, over 697,000 were suspected of having COVID-19 at least 12 weeks previously.Studies suggest that the symptoms of Long COVID may persist forsix months to over a year. The patients aged 35-49 or 50-69 were more prone to experience these symptoms. The prevalence rate was statistically significantly higher in females (1.9%) than in males (1.5%). Moreover, health and social care workers demonstratedthe highest prevalence rates of self-reported long COVID[11].

Clinical manifestation :

Long-term COVID may occur due to lasting tissue damage (eg, lung, brain, and heart) and pathological inflammation (eg, viral persistence, immune dysregulation, and autoimmunity). Prolonged inflammation could be the significant reason forneurological and cognitive dysfunctions in the body, along with several other symptoms.A diverse array of less prevalent symptoms and signs, including sweating, chest pain, sore throat, anxiety, and headaches, have also been reported[1]. Frequently observed symptoms include cognitive and mental impairments, chest and joint pains, palpitations, myalgia, smell and taste dysfunctions, cough, headache, and gastrointestinal and cardiac issues. Less frequently observed symptoms were sweating, chest pain, sore throat, anxiety, headaches, joint pain, hair loss, etc[3]. One bemusing factor about long covid is that patients who have recovered from COVID -19 are more prone to it[8]. Children are also vulnerable to developingLongCOVID, including those who wereinfected with asymptomatic COVID-19. The symptoms seenin children were dyspnoea, fatigue, myalgia, cognitive impairments, headache, palpitations, and chest pain that lasted for at least six months[9]. The most common symptom of Long COVID was fatigue ranging from 17.5% to 72% among hospitalized patients, which persistedeven after seven months resulting in severe disability[10].

Pathophysiology of Long COVID :

How Long COVID affects the host remains unclear. However, possible speculation suggests that the persistence of infection is due to viremia in patients with modified immunity, re-infection, or relapse[11]. The continuation of symptoms can be the consequence of organ damage, the degree of the organ damage and the time it would be required to recover from the injury, (chronic inflammationor immune response/ autoantibody generation, rare persistence of the virus in the body, the nonspecific effect of hospitalization, sequelae of critical illness, post-intensive care syndrome complications related to comorbidities) or adverse effects of medications used[12]. An unresolved source of inflammation could be in the gut. It was observed thatthe COVID virus could replicate in the gut quite efficiently due to the elevated levels of ACE2 receptors, thus leading to increased fecal shedding of SARS-CoV-2 in patients (Fig 2)[13].

The other possible mechanisms of Long COVIDcan be classified into :

- Persistent tissue/organ injury following the acute phase.
- Other unresolved, ongoing, or recurrent reactions without evidence of classically recognized tissue/organ injury. Table 1 describes the possible mechanisms involved in Long COVID[14].

Table 1 — *Possible mechanisms involved in Long COVID*

S. No	System	Involved Symptoms	Possible mechanism
1	Neurologic	Headache and pain	• Inflammation in various tissues can lead to aggravation of tissue damage in joints and muscles and trigger pain-related symptoms. • Activation of nerves can lead to vasculopathy i.e., unbalanced vasoconstriction, oxidative stress, Nerve viral invasion, hypoxia, and pro-inflammatory cytokines. • Neurological complications leading to pain such as a stroke, Guillain Barré syndrome, and myelitis. • Glymphatic-lymphatic system congestion hypothesis. olfactory nerves damage might lead to a reduced outflow of cerebrospinal fluid through the cribriform plate, toxic build-up within the CNS, congestion of the lymphatic system with secondary cranial hypertension.
		Olfactory Dysfunction	• Viral invasion • Subsequent cell inflammation and injury • Presence of ACE2 in epithelial cells of olfactory mucosa (Mechanism unclear)
		Persistent fatigue	• Neuro-inflammation and subsequent neurotransmission disorders • Psychological factors (neurotransmitters levels can vary after COVID-19 and give • rise to psychological disorder accounting for fatigue worsening) • Peripheral factors (musculoskeletal impairment) in chronic fatigue • Environmental factors (social isolation temperature, humidity) • Mitochondrial dysfunction leading to Bioenergetic disorders (muscle)
		Psychiatricdisorders (anxiety, depression, trauma-related disorders)	• Persistent inflammatory process secondary to the viral invasion or dysregulated immunity processes can cause brain dysfunction neuronal injury leading to: ✓ The blood-brain barrier (BBB) is disrupted by the Pro-inflammatory cytokines which increase its permeability to cytokines and leucocytes transmigration • Inflammation processes may induce: • Activation of the coagulation and the formation • of micro thrombosis impairing tissue vascularization and neurotransmission due to the release of cytokines. • Potential involvement of gut-brain axis • Metabolic brain disorder: ✓ Mitochondrial dysfunction leads to reduced energy metabolism and neuro-inflammation ✓ Cytokine-induced activation of IDO-1 leads to depression. ✓ Virus residual: incomplete immune response causes residual virus, and/or antigen load remains to contribute to a low-grade smoldering inflammatory response. • Autoimmunity: Inflammatory can favor an aberrant immune response against the nervous system • Secondary brain disorder: Indirect nervous system damage via the systemic complications of acute illness (Haemodynamic and coagulation disorders, arrhythmia, severe systemic inflammation, delirium)
2	Cardiorespiratory	Cardiorespiratory dysautonomic symptoms (palpitations, post-exertional malaise, exercise intolerance,breathlessness, chest pain)	• Disruption of the autonomic nervous system (autoimmunity, microcirculation disorders) due to virus or immune dysfunction leading to various symptoms such as dizziness andother cardiovascular symptoms, hypoperfusion of different organs
3	cardiovascular	Thromboembolic complications (Stroke, pulmonary embolism)	• These cardiovascular issues can lead to chronic symptoms, associated with organ damage: • Direct complement activation (inflammation)loss of endothelial homeostasis and integrity • viral-induced activations of platelets (ACE2 receptor) leading toinflammation and coagulation activation • Antiphospholipid antibodies • Systemic cytokines release leading to coagulation activation
		Heart disorders (Impaired contractility, dyspnoea, arrhythmia)	• Residual inflammation could lead to fibrosis • Interactivity with adipose tissue of epicardium points towards long-term arrhythmia and coronary disease • Heart tissue inflammation and account for contractility impairment:acute or subacute myocarditis
4	Respiratory system	Dyspnoea, Cough, Chest pain, Exercise limitation	• Pulmonary alveolar inflammation after the viral invasion • Degeneration of alveolar epithelial lining with the emergence of hyaline membranes • Excessive cytokines production (host inflammatory response) and enhanced influx of inflammatory cells • Decreased expression of ACE2 receptor and angiotensin 1,7 peptides • Greater oxidative and contribute to inflammation and fibrosis stress due to high supplemental oxygen concentration • Unresolved (micro-) vasculature damages may be a potential precursor to chronic thromboembolic disease and pulmonary hypertension.
5	Immune system	Wide range of symptoms	• Inflammation could be responsible for persistent symptoms • Autoimmunity phenomena may result from inflammation and dysregulated immune responses. • Genetic polymorphism in the cytokine genes' regulatory regions can account for inter-individual differences in the severity and occurrence of symptoms • Mast cell activation syndrome hypothesis: The mast cell would be activated via the release of the cytokine. This could lead to lung fibrosis via stimulation of fibroblast activity. • The natural downregulation of the strong initial inflammatory response could allow the virus to persist and replicate in the body with ongoing inflammation and autoimmunity phenomena.
6	Gastro-intestinal and hepato-biliary system	Gastrointestinal symptoms: anorexia, dyspepsia, nausea/vomiting diarrhea abdominal pain	• Hypothesis of the gut as an undetected virus reservoir • Contributions of genetic predisposition and interaction between the gut and environmental and psychological factors • Viral invasion-local inflammation followed by leucocytes infiltration in the digestive mucosa generating a local inflammation • Immune-mediated disruption leading to gut motility disruption
7	Multisystem Inflammatory Syndrome in Children (MIS-C)	Fever, Multiple organ dysfunction, Mucocutaneous Disorders, Abdominal Symptoms, Cardiovascular disorders, Neurological disorders	• Genetical predisposition host factors • Uncontrolled T-cell immune response (triggered by SARS-CoV-2) • Complement activation • Molecular mimicry between antigens and host tissues.
8	Musculoskeletal system	Muscular weakness, Bone and joint disorders (pain, mobility)	• **Muscle:** ✓ Pro-inflammatory cytokines-induced disruption of myocytes ✓ Cytokines-induced muscle fibroblast activation leads to fibrosis ✓ Neuronal demyelination • **Bone:** ✓ leukocyte aggregation, and vessel inflammation that contributes to the development of osteonecrosis • **Joints:** ✓ Autoimmunity (virus persistence, dysregulated immune response, triggering of connective tissue diseases) and NETs activation
9	Endocrine system	Thyroid disorders Diabetes	• **Thyroid** ✓ Direct damage to the thyroid gland ✓ Low-T3 syndrome in hospitalized subjects (inflammation due to severe COVID-19) ✓ Subacute thyroids • **Diabetes** ✓ Possible viral invasion of the pancreatic β cell that precipitates new-onset diabetes

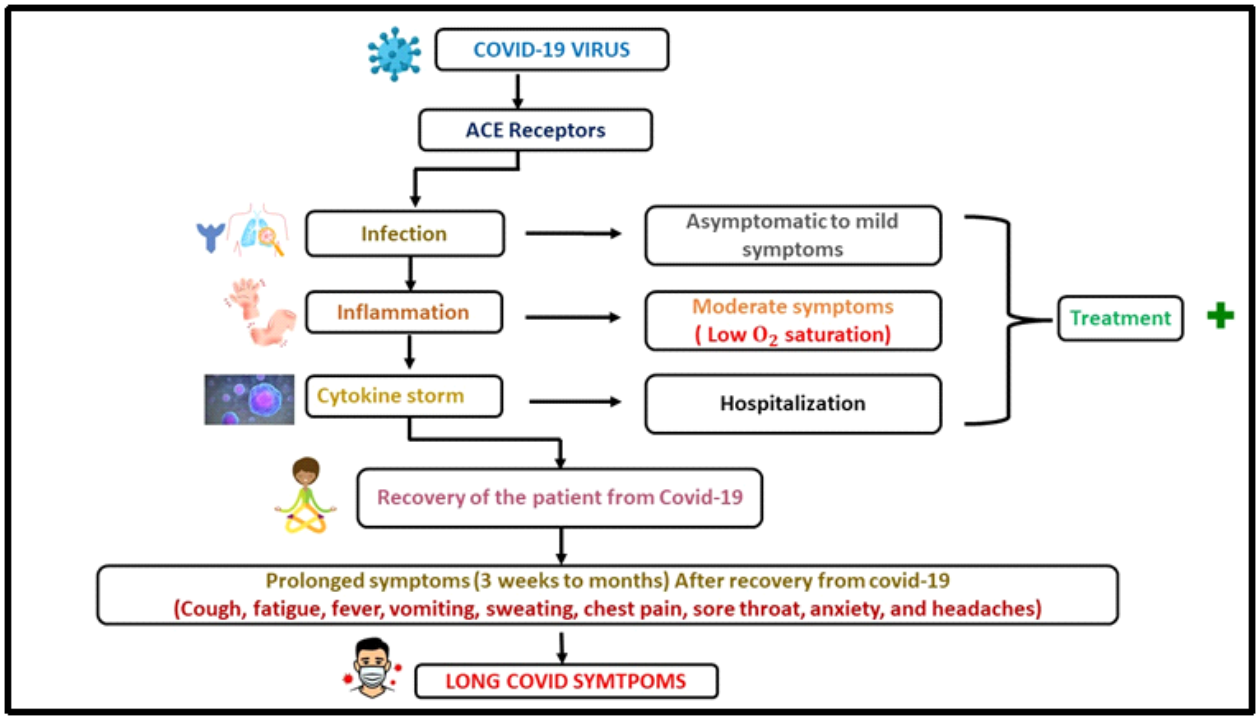

Fig 2 — Pathophysiology of "Long COVID[2]

Possible Risk factors :

Major risk factors include female sex, more than five early symptoms, early dyspnoea, prior psychiatric disorders, and specific biomarkers (eg, D-dimer,C-Reactive Protein (CRP), and lymphocyte count)[3]. Patients who had more than five symptoms in the first week of COVID-19 were four times more vulnerable to developing Long COVID. Fatigue, headache, shortness of breath, hoarse voice, myalgia, older people, and obese patients were more susceptible to Long COVID[15].

Biomarkers :

Among COVID-19 survivors, the risk factors for pulmonary dysfunction were elevated Blood Urea Nitrogen (BUN) and D-dimer levels[16]. Radiological abnormalities of the heart, liver, and kidney were correlated to inflammatory markers such as CRP, procalcitonin, and neutrophil count[17]. Increased D-dimer and CRP levels and decreased lymphocytes were more common in long COVID-19[18].

Mental health :

Post-traumatic Stress Disorder (PTSD) and psychological distress were common in health workers compared to patients suffering from Long COVID. The higher the exposure,the greater the incidence of subsequent PTSD. Young women and those carrying heavy responsibilities and concern for others are more bound to develop Post-traumaticsymptomatology (PTS) following COVID-19 exposure, and hence, they deserve more attention[29].

POTENTIAL INTERVENTION :

Rehabilitation :

Rehabilitation includes various breathing exercises to strengthen respiratory muscles, especially the diaphragm. Positive outcomes of rehabilitation were observed for the treatment of Long COVID patients. Patients were advised to practice light aerobic exercises accordingly to their possible capacity. The exercise level was gradually increased until improvements in fatigue and dyspnoea wereobserved. Physical rehabilitation has its drawbacks, too[18], which should be considered. Rehabilitation may not be suitable for all critical COVID-19 survivors, especially those with serious pulmonary or cardiac damage[20].

Pharmaceutical treatment :

Pharmaceutical drugs are used to manage specific symptoms such as fever; however, drugs having similar treatment properties might hold the potential to be repurposed for Long COVID. At the same time, no pharmaceutical drug ameliorates or attenuates the symptoms of Long COVID so far[20]. Collective studies have proposed that mast cell activation syndrome (MCAS) may also underlie Long COVID pathophysiology; studies have shown to trigger inflammatory mast cell responses alongside other immune cells in COVID-19 patients[23]. Another hurdle

in the treatment approach is the heterogeneous nature of Long COVID, which involves multiple subtypes complicating the accurate diagnosis[3].

Nutraceuticals :

Nutraceuticals are the combination of nutrition and pharmaceuticalsthat popularly speculate about food and its medicinal benefits[22]. They are one of the promising new alternatives to pharmaceuticals that may include nutritional supplements, derived nutrients,and dietary and herbal products that display substantial physiological advantages that potentially could play a significant role in reversing many inflammatory surrounding diseases[23]. Besides the conventional treatments, nutraceuticals could be highly beneficial in treating and preventing COVID-19[22].

The nutraceuticals that could benefit in long covid are **:**

***Coenzyme Q10 (CoQ10)* —** It is rich in antioxidants, prevents oxidative stress, mitigates hyper-immune response, and directly inhibits viral replication and entry[24]. CoQ10 attenuates the action of genes involved in inflammationand controls the release of pro-inflammatory cytokinesin various disorders[25]. It also assists in the regeneration of other antioxidants. In addition, it is a crucial factor in the respiratory chain of the inner mitochondrial membrane and is very much vital to energy metabolism.A double-blinded, placebo-controlled, three crossover study was conducted. The study included 17 healthy volunteers who were randomized to receive oral supplementation of Coenzyme Q10 (100 or 300 mg/d) or placebo administration for eight days. Subjects were made to perform workload trials on a bicycle ergometer at fixed workloads twice for two hours and then were made to rest for four hours. During the physical tasks, subjects performed non-workload trials with maximum velocity for 10 s at 30 min (30-min trial) after physical tasks and 30 min before the end of the tasks (210-min trial). Oral CoQ10 supplementation improved subjective fatigue sensation and physical performance during fatigue-inducing workload trials[26]. The protective role of CoQ10 in improving viral myocarditis and drug-induced cardiotoxicity introduces this supplement as an appropriate choice for the prevention of COVID-19 cardiovascular complications, which are generally influenced by two factors: cytokine storm and adverse effects of the medications. The hyper-cytokinemia caused by SARS-COV-2 infection could lead to fulminant myocarditis, a lethal condition caused mainly by a hyper-inflammatory state and cytokine storms, particularly during viral infection[27,28].Another randomized controlled multicentre trial was conducted on 420 patients with moderate to severe Heart Failure (HF). The patients were randomly assigned in a 2-year prospective trial to receive CoQ10 100 mg 3 times daily or placebo, in addition to standard therapy. The test results demonstrated that long-term CoQ10 treatment of patients with chronic HF was safe, improved symptoms, and reduced major adverse cardiovascular events[29]. Studies suggest that CoQ10 crossesthe Brain Blood Barrier (BBB) easily. CoQ10 can reduce oxidative stress and modulates immunologic reactions as a neuroprotective agent. These properties may help to reduce CNS inflammation and prevent BBB damage and neuronal apoptosis in COVID-19 patients[30-32]. Similarly, CoQ10 could improve the interference in the RASsystem caused by COVID-19 infection by exerting anti-Angiotensin II effects and decreasing oxidative stress. The antihypertensive effects of CoQ10 are not entirely confirmed, and more well-designed clinical trials are needed to verify it. Moreover, CoQ10 can not solely reduce blood pressure but could be beneficial against hypertension in the context of metabolic diseases like diabetes as adjunctive therapy to adjust blood pressure[33,34].

***Ginger* —** Ithas anti-inflammatory and antiviral properties, making it beneficial in treating COVID-19 symptoms[22]. A clinical trial with suspected COVID-19 outpatients as participants was conducted. The results of the studydemonstrated that Zingiber officinale and Echinacea alleviated and controlled the clinical symptoms in COVID-19 outpatients[35].

***Glutathione* —** Glutathione (GSH) exerts anti-inflammatory effects by inhibiting ACE activity, decreasing Reactive Oxygen Species (ROS) production, and inhibiting NF-kB activation. The oxidized form of glutathione (GSSG), renin, and viral infection shift the ACE/ACE2 balance toward ACE. Data from a published report suggests thatfor two COVID-19 patients, 2 g of PO or IV glutathione improved the dyspnea within one hour of use, and it regularly alleviated respiratory symptoms[36].

***Zinc* —** It is the second abundant trace element and an essential dietary supplement used to preserve immunity. Zinc helps treat upper respiratory tract viral infection and hence can also be beneficial in managing COVID-19. Moreover, it may also inhibit the attachment of the virus to nasopharyngeal mucosa and inhibit viral replication. In vitro studies have demonstrated that zinc may inhibit template binding and elongation of SARS-COV-1 RNA-dependent polymerase, which helps prevent viral replication. A studyshowed that patients with COVID-19 who had zinc deficiency required more corticosteroid management and were also associated

with a prolonged hospital stay[22]. Moreover, the reports suggest the use of zinc salt in managing the COVID-19 symptoms[37].

Curcumin — It is Turmeric's active ingredient that has anti-inflammatory properties. In clinical trials, curcumin has been shown to be an effective treatment for COVID-19[38]. The intervention of nano-curcumin resulted in a significant increase in the mRNA expression and cytokine secretion of IL-1β, IL-6, TNF-α, and IL-18 in the COVID-19 patients. Ultimately, nano-curcumin may modulate inflammatory cytokines and cytokine secretion in COVID -19 patients, leading to an overall recovery[39].

N-Acetylcysteine (NAC) — Glutathione is a cofactor for various peroxidase enzymes and a catalyst in reactions that reconvert oxidized cysteine groups to their native form. NAC can enhance the production of glutathione. N Acetyl l cysteine increases the influenza virus-specific lymphocyte proliferation and interferon (IFN) γ production at a concentration of 1.0 mmol/l. Furthermore, N acetyl l cysteine enhanced a specific activity of two influenza-specific CD8+ cytotoxic T lymphocyte clones directed towards HLA A*0201 and HLA B*2705 restricted epitopes[40]. In a clinical trial conducted on COVID-19 patients, NAC helped significantly lower the influenza-like symptoms, which resulted in a shorter hospital stay. Likewise, NAC supplementation could be beneficial in reducing the severity of the illness.

Vitamin D3 — Besides known antimicrobial and anti-inflammatory effects, vitamin D metabolites directly impact ACE2, which serves as the cell surface entry receptor for SARS-CoV-2 infection. In preclinical studies, vitamin D metabolitesincrease ACE2 expression in pulmonary microvascular endothelial cells. Although increased ACE2 expression may theoretically increase viral entry into cells, it may benefit the already infected patients because SARS-CoV-2–mediated downregulation of ACE2 may perpetuate lung injury[41]. A randomized clinical trial on reverse transcriptase-polymerase chain reaction (RT-PCR) SARS-CoV-2 positive adults was conducted. 5000 IU daily oral vitamin D3 supplementation reduced the time to recoverfrom cough and gustatory sensory loss among patients with suboptimal vitamin D status and mild to moderate COVID-19 symptoms. Moreover, Vitamin D3 supplementation could serve as adjuvant therapy for COVID-19 patients[42].

Vitamin C — Vitamin C or ascorbic acid is a water-soluble vitamin that possesses antioxidant, anti-inflammatory, and immunomodulatory properties. It acts as an enzyme cofactor for several biosynthetic processes and may increase the endogenous synthesis of catecholamines[22]. A randomized clinical study conducted on hospitalized critically ill COVID-19 patients showed that vitamin C supplementation significantly increased the survival duration of COVID-19 patients during the post-supplementation period[43].

CLINICAL EVIDENCE :

Table 2 describes the clinical evidence of nutraceuticals in the management of COVID-19.

CONCLUSION :

COVID-19 is an ongoing pandemic mainly affecting the respiratory organs of patients. Long COVID or Post COVID is the persistence of symptoms after the patient has recovered from COVID -19 infection. Fatigue and various other symptoms such as dyspnoea, olfactory and gustatory dysfunction, chest pain, myalgia, sleep, and mental disorders were the most common symptoms of Long COVID. Currently, rehabilitation is the most promising approach tomanaging the symptoms of Long COVID. Similarly,nutraceuticals could be another healthier and potential intervention to manage the symptoms. In conclusion, our review highlights the potential benefits of a variety of nutraceuticals in treating COVID-19. Although ample clinical evidence is present for managing the symptoms of COVID-19, further studies are required to clarify their potential therapeutic value.

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Table 2 — *Clinical evidence of nutraceuticals in the management of COVID-19*

Nutraceutical	Study design	No of subjects	Duration	Intervention	Results	References
Coenzyme Q10 (cardiovascular)	randomized controlled multicenter trial	420	2 years	CoQ10 100 mg 3 times daily or placebo, in addition to standard therapy.	Long-term CoQ10 treatment of patients with chronic HF is safe, improves symptoms, and reduces major adverse cardiovascular events.	(33)
Coenzyme Q10 (Fatigue)	A double-blinded, placebo-controlled, three crossover study	17	8 days	Coenzyme Q10 (100 or 300 mg/d) or placebo	Oral Coenzyme supplementation improved subjective fatigue sensation and physical performance during fatigue-inducing workload trials and might prevent unfavorable conditions because of physical fatigue	(34)
Ginger	Clinical trial	100	2 weeks	concurrent Zingiber officinale (Tablet Vomigone 500 mg II TDS) and Echinacea (Tablet Rucoldup I TDS) The control group only received the standard treatment (Hydroxychloroquine).	Zingiber officinale and Echinacea alleviated and controlled the clinical symptoms in COVID-19 outpatients	(35)
Glutathione	Case report	2		2000 mg of oral or IV glutathione, zinc, 40–50 mg per day, and Vitamin C 1–2 g TID	Oral and IV glutathione, glutathione precursors (N-acetylcysteine), and alpha-lipoic acid may represent a novel treatment approach for blocking NF-κB and addressing “cytokine storm syndrome” and respiratory distress in patients with COVID-19 pneumonia.	(36)
Zinc	Report	4	2 weeks	Patients 1,2 were treated with zinc citrate lozenges (23 mg of elemental zinc); patient 3, zinc citrate/zinc gluconate (23 mg); patient 4, zinc acetate (15 mg).	high dose supplemental zinc may have a role in the management of COVID-19	(37)
Curcumin	Randomized clinical trial	80	2 weeks	160 mg of Nano-curcumin in four 40 mg capsules and placebo capsules daily. Additionally, the covid-19 patients receivedBetaferon 300 ìg subcutaneously every other day until 5 days, Bromhexine 8 mg tablets every 8 h, and Atrovastatin 40 mg daily was also given to the patients.	Nano-curcumin can modulate the inflammatory cytokines, especially IL-1β and IL-6 mRNA expression and cytokine secretion in COVID-19 patients	(39)
Vitamin D3	A Randomized Clinical Trial	69	2 weeks	5000 IU oral vitamin or 1000 IU oral vitamin D3 (standard control) once daily	A significant increase in 25(OH)D levels in the 5000 IU group only, the 5000 IU group had a significantly shorter time to recovery (days) than the 1000 IU group in resolving cough	(42)
Vitamin C	A randomized clinical trial	120	2 weeks	one capsule of 500 mg of vitamin C daily	Vitamin C supplementation could potentially increase the survival duration of covid-19 patients	(43)

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Drug Corner

Safety & Efficacy of a Fixed Dose Combination of Paracetamol (125 mg), Phenylephrine (2.5 mg) and Chlorpheniramine Maleate (1mg) [Flucold Drops] in the Treatment of Common Cold and Flu Syndrome in Children : Postmarketing Surveillance Study

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Background :The common cold and flu syndrome primarily affects the upper respiratory tract, along with a low fever and some systemic symptoms such as sore throat, cough, nasal decongestion, headache, and so on. Several clinical studies have shown that combining analgesics, antihistaminics, and decongestants provides better symptom relief in the common cold. The current post-marketing surveillance study was designed to look into the safety and efficacy of commercially available Flucold Drops in the Indian population.

Methodology :A current prospective, single arm, multicenter, post-marketing clinical study included 224 subjects, 220 of whom completed the study. All patients were given Flucold Drops for three days and then monitored for the next six days. During the study, the incidence of adverse events (AE) and serious adverse events (SAE) was assessed. The efficacy of the Flucold Drops was evaluated using VAS score changes from the beginning to the end of the treatment. The product's safety was also evaluated using blood biomarkers such as haemoglobin, platelet count, SGOT, SGPT, and creatinine level.

Results : Results show the reduction in symptomatic score of common cold and flu syndrome observed after 2rd follow-up visit (0.202±0.325 to 0.139±0.231). During the study, no intervention-related adverse events were observed. Furthermore, no Serious Adverse Events (SAE) were observed in the study or follow-up period. The study found no changes in the levels of blood biomarkers (haemoglobin, platelets, SGOT, SGPT, and creatinine).

Conclusions : Flucold Drops are safe and effective in the treatment of common cold and flu syndrome in Children and infants.

[*J Indian Med Assoc* 2022; **120(5):** 75-9]

***Key words* : Flucold Drops is a fixed dose combination of paracetamol (125 mg), phenylephrine (2.5 mg) and chlorpheniramine maleate (1mg), SGOT, SGPT, Flu syndrome, Congestion, Haemoglobin.**

The common cold and flu are an acute viral infection occur in the upper respiratory tract which involves the nose, sinuses, pharynx and larynx. The virus is propagated by when person comes in contact with secretions from an infected patient and virus[1]. The period require for incubation varies but it is two days for rhinovirus[2]. Symptoms of common clod and flu are associated with infected mucosa usually peak within 1 to 3 days and remain for at least 7 to 10 days however they persist for 3 to 5 weeks[1,3-5]. They consist of rhinitis, sore throat, malaise and cough[1,4]. The severity and variety of symptoms will differ within individuals and with several infective agents. For example, fever is observed commonly in children but rare and comparatively mild in adult[1]. The common cold occurrence decline with age[5-7]. In terms of infection frequency, children under two years of age have about 6 infections a year, adult 2 to 3 and old age people about one every year[5-9]. Factors such as stress and poor sleep pattern elevated the risk of common cold and flu in adults whereas attendance at day care center increases risk in preschool children[10-12].

Because of its high prevalence, particularly among children, the common cold imposes a significant economic and social burden[13,14]. Symptoms of the common cold in children usually peak shortly after the onset of illness[15]. The duration of the symptoms is approximately 7-10 days, but it can range from 2-14 days[16]. The common cold can be difficult to diagnose and treat in young children and infants who are unable to communicate their symptoms.

Treatment of cold and flu in children involves use of conventional medicines such as antipyretics, cough suppressants and decongestant. These agents expected to rapidly improve the comfort of ill child,

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cough and antiviral medicines. Symptomatic treatment of common cold and flu have been evaluated by meta-analysis and found that use of monotherapy is not efficient in enhancement of symptoms in children and adult[17]. In another meta-analysis, investigators evaluated the use of nasal decongestant in 286 subjects and no beneficial effect in nasal decongestion[18,19]. Effectiveness of combination comprised of antihistamine-decongestant-analgesic in reducing duration of symptom of common cold was evaluated in children and adult using Cochrane meta-analysis. The results of the study showed that combination provide general benefits in adults however no evidence of effectiveness is available in children[20].

The current study investigated the safety and efficacy of Flucold Drops [Fixed dose combination of paracetamol (125 mg), phenylephrine (2.5 mg), and chlorpheniramine maleate (1mg)] in the treatment of common cold and flu syndrome in children.

Currently, no clinical trial assessed for the efficacy and safety of Flucold Drops (Wallace Pharmaceuticals) in the treatment of common cold and flu syndrome in infants and children. This was the first clinical trial conducted in India designed to assess the adverse events associated with fixed-dose combination.

Material and Methods

Study Design & Participant :

In a prospective, interventional, multicenter, post marketing study, 224 participants were enrolled.

Study was conducted in accordance with the ICMR guidelines, New Drugs and Clinical Trial Rules 2019 India, & the Declaration of Helsinki (Brazil 2013) & the ICH E6, R2, "Guidance on Good Clinical Practice" (GCP). Furthermore, the trial was approved by Royal Pune Independence Ethics Committee, Prakash Institutional Ethics Committee & SPARSH Hospital Institutional Ethics Committee (ICBio/CR/WPPL/0309/109).

Total 224eligible participants with common flu and cold were treated with Flucold Drops (WALLACE Pharmaceuticals). The total duration of the study for the patient was 9 days (03 days medications with 6 days of follow-up).Study included patients between the age of 6 month to 12 years with recent onset of symptoms not less than 72 hrs such as common cold (with symptoms such as sneezing, rhinorrhea, nasal congestion, headache, discomfort in throat) & flu syndrome (with symptoms such as high-grade fever, headache, chest discomfort, dizziness). Patients with known hypersensitivity, seasonal perennial allergic rhinitis, recent history of influenza vaccination, severely immune compromised patient excluded from the study.

Participant removal or withdrawn criteria :

The investigator has the authority to withdraw a patient from the study for any of the following reasons: the occurrence of an adverse event associated with the administration of the IP, necessitating its cancellation; the emergence of any diseases or conditions during the study that worsen the patient's prognosis and make it impossible for the patient to continue participating in the clinical study; the need for a prohibited concomitant therapy; Patient pregnancy; research protocol violations; inappropriate inclusion of a patient who did not fulfil the inclusion criteria and/or met the applicable exclusion criteria; other serious protocol violations, according to the investigators; The patient withdraws his or her informed consent. Four patients were removed from the study due to absenteeism during the follow up.

Recruitment :

Suitable subjects, who agree to participate in the study were recruited from 3 sites (Jyothi Multispecialty Clinic, MAVEN's Hospital&Basaveshwara Medical College and Hospital Chitradurga. Each site recruited the participants who have voluntarily visited each trial site for enrollment.

Intervention :

After selection of the subjects, all were treated with FLUCOLD drops (consisting of a fixed-dose combination of Paracetamol 125 mg + Phenylephrine HCl 2.5 mg + Chlorpheniramine maleate 1 mg/ml)(Wallace Pharmaceutical Pvt. Ltd.) for three days and follow up of performed for the next 6 days (Fig 1).

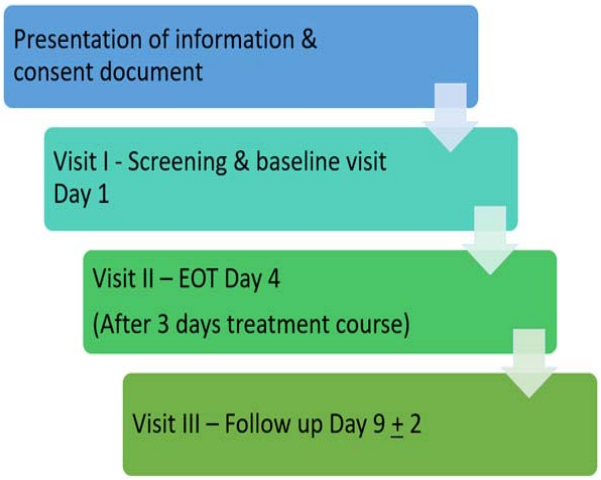

Fig 1 — Study Flow Chart

Outcome Measures :

Primary outcome measure

To evaluate the safety of fixed-dose combination Flucold Drops (Paracetamol 125 mg + Phenylephrine HCl 2.5 mg + Chlorpheniramine maleate 1 mg /ml) from Wallace Pharmaceutical Pvt Ltd in the treatment of common cold and flu syndrome in the children and infants. During the study, Treatment-emergent Adverse Events (TEAE) and serious adverse events were reviewed.

Secondary outcome measures

Subjects were evaluated for secondary outcome which included evaluation of relief from common cold and flu syndrome, significant changes in Visual Analogue Score (VAS) & safety of drops measured in terms of hemoglobin, platelet, SGOT, SGPT & creatinine levels.

Statistical Analysis :

Data analysis was performed using ANOVA & $\div^2$ test &SAS version 9.1 INC, CARY, USA used during the analysis. Efficacy analysis was performed for the per-protocol (PP) population. Primary efficacy was based on PP patients' samples.

Results

During the study, total of 224 patients were enrolled in the study from 3 sites out of which 4patient withdrew from the study (Fig 2).

The mean age of the participants included in the study was 4.711±3.251 years whereas average weight & height was 17.519±8.247 kg & 100.511 ±25.943 cm respectively. The average BMI calculated during the study was found to be at 15.828±2.44 kg/m^2.

Table 1 — *Demographic data of the patient*

Demographics of patient	Values
Age	4.711 ± 3.251
Weight	17.519 ± 8.247
Height	100.511 ± 25943
BMI	15.828 ± 2.440

During the study, no intervention-related adverse events were observed. Furthermore, no treatment related & Serious Adverse Events (SAE) were observed during the study and follow-up period.

During the study, reduction in total symptom score from day 1 to day 4 and during follow up was assessed by using a 4-point scale (0- No symptom, 1-Mild, 2-Moderate, 3-Severe). Study results indicated that use of Flucold Drops in children total symptom score reduced significantly ($p<0.001$) from 0.302 ± 0.325 (visit 1) to 0.000 ± 0.000 (Visit 3) (Fig 3).

Severity of the flu and syndrome was assessed by using change in Visual analogue score (VAS) in children. Treatment with Flucold Drops in children leads to significantly ($p < 0.05$) change in VAS score from 4.532 ± 1.438 (Visit 1) to 0.000 ± 0.000 (Visit 3)(Fig 4).

Flucold Drops tolerability was analysed during the study in each subject& tolerability scale was used during the analysis. During the study, it was observed that no side effects were observed and Flucold Drops was well tolerated in children (Table 2).

Further safety of the product was evaluated by analysing biomarker levels such as haemoglobin, platelet, liver and kidney function test at the end of the study. No effect was exerted by Flucold Drops on haemoglobin (11.950 ± 0.739) and platelet (210.214 ± 119.047) count during the study (Table 3). Liver biomarkers such as SGOT and SGPT levels analysed and found to be at 21.809 ± 5.978 and 22.610 ± 7.321 respectively in children (Table 3). The levels of liver biomarker were not elevated after the intervention indicating the safety of Flucold Drops in subjects. Kidney function was analysed using serum creatinine level and no elevation

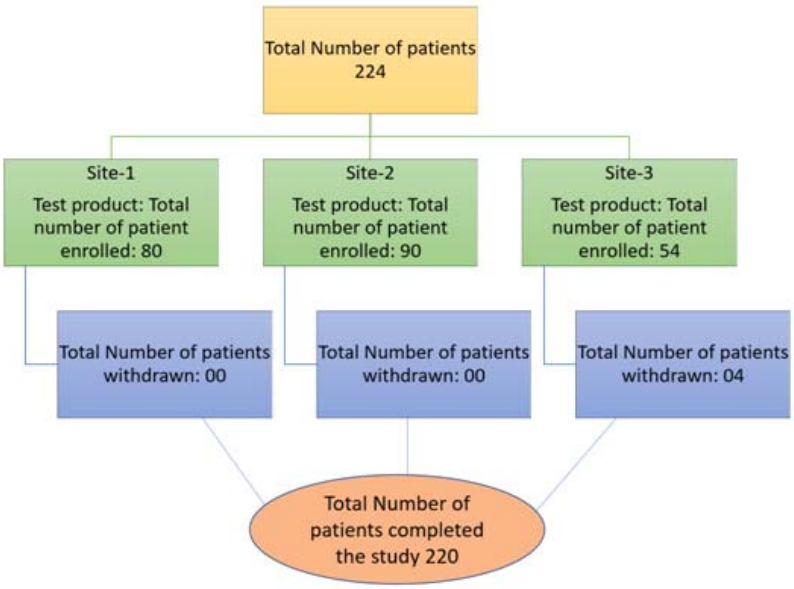

Fig 2 — Deposition of the patient

Table 2 — *Frequency count for FLUCOLD Drops tolerability*

Scale	No. of Subjects
Very good (No Side effects)	220
Good (insignificant side effects which do not cause serious problems to the Patient)	0
Satisfactory (side effects which affect the patient's condition, but do not necessitate discontinuation of the formulation)	0
Unsatisfactory (adverse side effect which significantly affects the patient's condition and necessitates discontinuation of the formulation)	0
Highly unsatisfactory(adverse side effect which necessitates Discontinuation of the formulation and use of additional clinical measures)	0

in creatinine levels (0.603 ± 0.1845) was observed after intervention (Table 3).

Table 3 — *Biomarkers of systemic safety after FLUCOLD treatment*

Demographics of patient	Values
Haemoglobin	11.950 ± 0.739
Platelet count	210.214 ± 119.047
SGOT	21.809 ± 5.978
SGPT	22.610 ± 7.312
Creatinine	0.603 ± 0.1845

Discussion

In a current prospective, multicentre, single arm, post-marketing surveillance study efficacy and safety of Flucold Drops was analysed in Children. The study results revealed that Flucold Drops is effective in reducing symptoms of cold and flu syndrome from baseline in children within 3 visits. The mean score changes from 0.302 ± 0.325 to 0.00 ± 0.00 during the retreatment. Biomarker evaluation demonstrated that Flucold Drops have no effect on liver and kidney function parameters of the subject. No major changes were observed in haemoglobin (11.950 ± 0.739) and platelet count (210.214 ± 119.047) after administration of Flucold Drops. Liver and kidney function test parameters indicate that Flucold Drops are safe to use in infants and children. During the study no treatment emergent adverse events (TAEs) and Serious Adverse Events (SAEs) was reported during the study demonstrate that Flucold Drops are safe in the children.

Currently no study available on effectiveness and safety of paracetamol, phenylephrine and chlorpheniramine combination in children with common cold and flu symptom.However different studies conducted on adult shows that combination of chlorpheniramine maleate, paracetamol, and phenylephrine is effective in the treatment of common cold and flu symptoms.

The effectiveness and safety of chlorpheniramine maleate, paracetamol, and phenylephrine combination evaluated by Picon et al in 146 subjects. Study findings revealed that after treatment with fixed dose combination for 10 days reduced symptom score from 14.09 to 3.54 and no adverse effects observed in the subjects[21]. The results of the study are in line with current study.

Similarly, a phase IV open labelled multicentre study was conducted in 159 patient and found that mean TSS reduced from 6.62 (Day 1) to 0.69 (Day 5). Mist patient included in the study had more than 50% reduction in total symptom score at visit 3 and 58.49% patient had complete relief from symptom[22].

Eccles et al. suggested the combination of products to treat the symptoms of the common cold and flu. When used as directed, multi-ingredient combination products for multi-symptom relief are formulated to

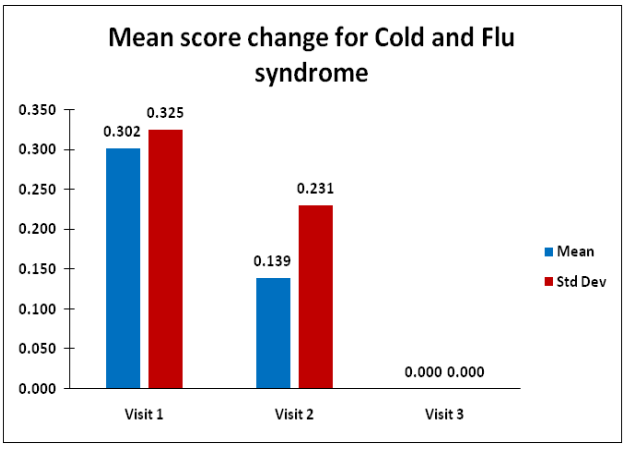

Fig 3 — Mean score change for cold and flu syndrome after Flucold Drops

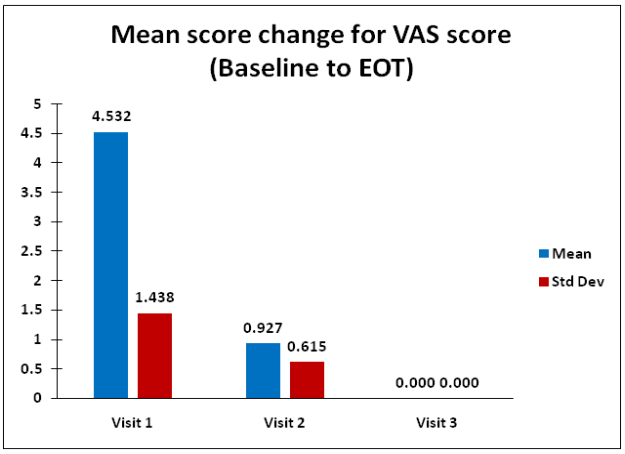

Fig 4 — Significant changes in VAS score from baseline to EOT

safely, simply, and simultaneously treat multiple symptoms. As a result, the rationale for the formulation for common cold and flu is practical, logical, and reasonable. There is no evidence that multi-symptom relief medications are inherently less safe than single-active ingredient medications. When used as directed, multi-symptom relief combination products containing several active ingredients provide a safe, effective, cost-effective, and convenient way of treating the multiple symptoms of the common cold and flu[23].

Our study results showed that symptoms of common cold and flu syndrome were resolved mostly on the second visit and no drug-related side effects were observed during the treatment and follow-up in children and infants.

Conclusion :

After 5 days of treatment with FLUCOLDdrops, substantialdevelopment in symptomatic relief of common cold and flu syndrome was observed in children and infants. Our study demonstrated that fixed dose combination of Paracetamol 125 mg, Phenylephrine 2.5 mg, Chlorpheniramine maleate 1mg per ml, provides optimum symptomatic relief and is safe for use in the symptomatic management of common cold and flu.

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Image in Medicine

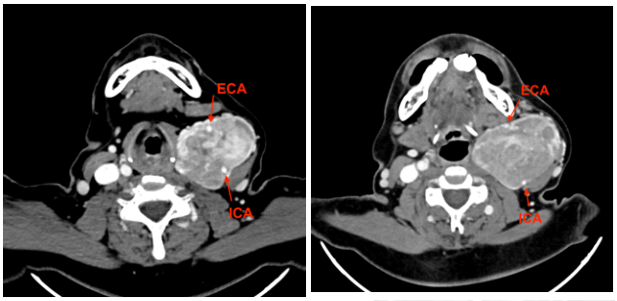
Bhoomi Angirish[1], Bhavin Jankharia[2]

Quiz 1

A 48-year-old male presented with increasing swelling in lateral aspect of neck since 10 months.

Questions :

(1) What is the diagnosis ?
(2) What are paragangliomas ?
(3) What are common differential diagnosis ?



Answers :

(1) Well defined, intensely and homogenously enhancing soft tissue density lesion is seen within the carotid space at carotid bifurcation causing splaying of the internal and external carotid artery – is highly suggestive of carotid body tumour / chemodectoma / carotid body paraganglioma. The characteristic splaying of ICA and ECA is known as lyre sign.

(2) Paragangliomas, the tumors of the paraganglia (extra-adrenal neuroendocrine system), can occur at any site along the specific locations of paraganglia tissue within the body. In the head and neck, the four most common sites are the carotid body at the Common Carotid Artery (CCA) bifurcation, the jugular foramen, along the vagus nerve, and within the middle ear.

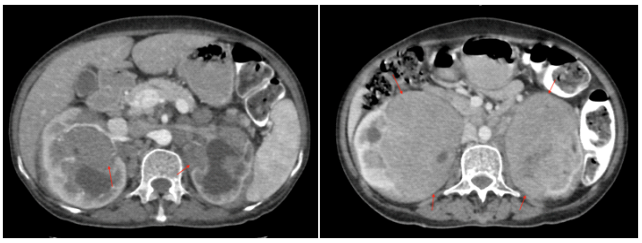
(3) The common differentials include nerve sheath tumors, nodal metastasis, glomus vagale tumor and carotid bulb ectasia. Nerve sheath tumors displace the carotid arteries anteromedially and the IJV posteriorly. Nodal metastases infiltrate more into the surrounding soft tissues. Glomus vagale are located more rostrally. Carotid bulb ectasia has well defined continuation with wall of carotid artery.

Quiz 2

A 43-year-old female presented with bilateral flank pain, weight loss and hematuria.

Questions :

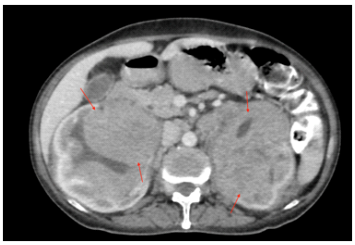
(1) What is the diagnosis?
(2) What are extra-nodal lymphomas ?
(3) What are the common differentials ?



Answers :

(1) Multiple poorly enhancing (in relation to renal parenchyma) retroperitoneal soft tissue density lesions directly invading the kidneys, causing bilateral renal enlargement, and associated with peri-renal soft-tissue masses. These findings are in favour of **renal lymphoma**, which was further confirmed on biopsy. Renal involvement in lymphoma is common in the presence of widespread nodal or extranodal lymphoma, known as secondary renal lymphoma. Rarely, lymphoma may involve the kidneys alone, this presentation is termed primary renal lymphoma.

(2) Extranodal involvement can be seen with lymphoma in approximately 25-40% of cases and almost any organ can be involved. Extra-nodal lymphoma commonly involve the genitourinary system, with the kidneys being the most commonly involved organs. Contrast CT scan remains the modality of choice for the detection, diagnosis, staging, and monitoring of renal lymphoma.



(3) The common differentials are :

(A) Renal cell carcinoma – are usually unilateral, appear heterogeneous and show intense enhancement (as compared to renal parenchyma) and also show vascular invasion.

(B) Acute pyelonephritis – focal wedge shaped areas which appear swollen and show reduced enhancement compared with the normal renal parenchyma. During excretory phase, a straited nephrogram may be seen.

(C) Xanthogranulomatous pyelonephritis : There is loss of normal renal outline and enlargement of kidney wih contracted renal pelvis. On contrast scan, the calyces are dilated giving a multiloculated appearance.

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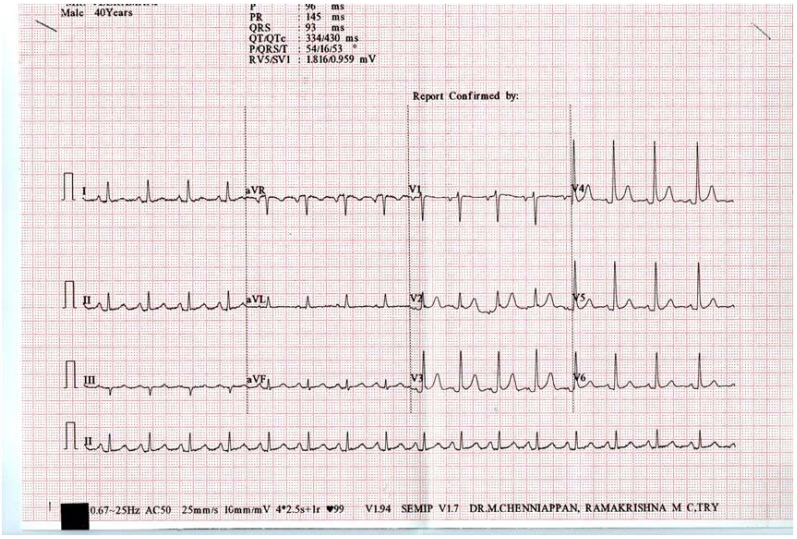
Student's Corner

Become a Sherlock Holmes in ECG

M Chenniappan[1]

Series 5 :

"Don't Let Depressions to Depress You"



This is the ECG of 40 years patient who presents withchest pain and dyspnea. This is the first ECG taken for him and it is a routine ECG.

Questions :

(1) What are the ECG findings?
(2) What are the causes of these ECG findings?
(3) Why is this clue?

Answers :

(1) The striking feature in this ECG is PR depression especially in leads V4, V5, V6 with no significant ST elevation and PR changes in other leads especially limb leads

(2) There are 3 differential diagnosis for PR depression.

1. Normal Variant 2. Atrial Infarction 3. Acute pericarditis

Normal variant of PR depression is less than 1mm. In this ECG it is 1 mm and above, which makes normal variant unlikely.

Atrial infarction almost always is accompanied by Acute Inferior Wall Infarction or lateral infarction. If PR depression happens in chest leads it should be more than 1.5mm (LIU's criteria). In this ECG, there is no acute inferior or lateral infarction and PR depression is not more than 1.5mm in chest leads.

In acute pericarditis, PR depression is usually accompanied by concave ST elevation in all leads except in lead avR and possibly V1 and at this stage most often clinical evidence of pericarditis in the form of pericardial rub is present. This patient had no pericardial rub and the chest pain is not suggestive of acute pericarditis.

Then what is the cause of PR depression in the absence of normal variant, atrial infarction and acute pericarditis?

There are 4 stages of ECG signs in pericarditis

Stage 1: Classical ST elevation concavity upwards in all leads except lead avR which shows reciprocal depression with PR depression and Spodick's sign of down sloping TP segment

Stage 2: In stage 2 ST elevation settle down with normal T wave. In early stage 2, ST may settle down, but PR depression may take more time to normalize. So early stages of stage 2, there may be only PR depression. But our patient had no previous history suggestive of pericarditis, and the chest pain he had is typically non cardiac.

Stage 3: the T wave gets inverted with normal ST and PR

Stage 4: there is normalization of ST and T waves

The second and most probable possibility of PR depression in this ECG is asymptomatic pericardial effusion. PR depression finding alone has been noted in asymptomatic pericardial effusion with no clinical signs of pericarditis (JACC 2002). Our patient had mild but significant pericardial effusion which is the probable cause of PR depression.

(3) This rare sign of pericardial effusion (PR depression) has taken away our concentration from the most important but subtle sign of LA abnormality in V1 in form of deep negative force of P wave. This may be the only sign in some of the patients in mitral stenosis or LV dysfunction which is due to left atrial hypertension in the absence of classical wide and bifid p wave in L II. This patient had moderate to severe Mitral Stenosis of VA of 1.2cm2. He may need an intervention for this finding rather than PR depression.

Sometimes, rare signs of ECG may take our attention away from a subtle butthe most important sign in the ECG which is more crucial in the management of the patient. This ECG is typical example of this phenomenon. So don't get depressed because you may have missed LA abnormality due to your concentration on rare sign of PR depression. There is always other time!

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Letter to the Editor

[The Editor is not responsible for the views expressed by the correspondents]

Amitraz Poisoning : A Case Report of an Unusual Pesticide Poisoning

Sir, — Amitraz, a widely available insecticide, is a highly under-recognized poisoning in humans and often mistaken as organophosphorus poisoning, resulting in mismanagement, and causing the suboptimal clinical outcome. We present a case of a 24-year-old male who was admitted following self ingestion of Amitraz and presented to emergency three hours Postingestion. Although there is no specific antidote for humans in Amitraz poisoning but has an excellent clinical outcome with appropriate supportive management. Misdiagnosis results in multiorgan failure causing respiratory failure and coma leading to the fatal outcome.

A 24-year-old Indian male presented to emergency following self-ingestion of an unknown quantity of amitraz following a family dispute leading to the compulsive act. He got restless and irritable after thirty minutes and was admitted three hours following ingestion. On admission, his Glasgow coma scale was 7/15, pupils were equal, 2 mm in size. His pulse was not palpable and blood pressure was not recordable with respiratory rate 30/min. Systemic examination revealed coarse breath sound in right infraclavicular and mammary region. Neurological examination revealed diminished superficial and deep tendon reflexes.

Gastric lavage was done along with intravenous fluid boluses. He was intubated and put on a mechanical ventilator with inotropic support (NorAd@20ml/hr, Adr@18ml/hr). Initial laboratory investigation revealed neutrophilic leucocytosis with normal liver and renal profile. Arterial blood gases revealed mild respiratory alkalosis with respiratory depression (pH 7.47, PCo2 54 mmHg, PaO2 84 mmHg, O2 saturation 82%). ECG revealed sinus bradycardia, 2D-ECHO showed no RWMA, LVEF 55%, RVSP35mmHg. Chest x-ray showed ill-defined linear opacities in the right upper zone with endotracheal tube in situ. USG whole abdomen and NCCT head showed no abnormality. Other supportive measures like IV antibiotics, proton pump inhibitor, antiemetics, and hydrocortisone were given. His inotropic support was gradually tapered and stopped and was extubated 36 hours after admission. He was discharged 4 days after admission and was doing well 15 days after discharge.

Amitraz is a member of the formamidine family of pesticides, commonly used as an agricultural insecticide and an acaricide for dogs and livestock,[1] first case of poisoning in humans has been reported in 1983, however, the incidence of amitraz poisoning has increased in recent years due to easy accessibility and availability of the product[2]. Pharmacologically, it stimulates alpha-2 adrenergic receptor in the Cranial Nervous System (CNS) and alpha-1 and alpha-2 adrenergic receptor in the periphery. It also acts by inhibiting monoamine oxidase enzyme activity and prostaglandin E2 synthesis[3]. Ingestion is the commonest route of exposure followed by percutaneous, inhalational, and IV injection[4]. Accidental and suicidal are the common manner of poisoning. Clinical manifestations occur within 3 hours of exposure, earlier in oral ingestion compared to another route of exposure. The lethal dose of the toxin is 200 mg/kg[5]. It affects the Cranial Nervous System, Cardiovascular System, Respiratory System, Gastrointestinal System, Liver, Metabolism and Homeostasis. Common neurological abnormality manifests as sleepiness, drowsiness, or complete loss of consciousness depending on the amount of toxin consumed. Cerebral Edema, Seizures, Ataxia, hallucination have been reported rarely. Due to the short half-life of the toxin, consciousness is regained within 48 hours in most of cases. Stimulation of presynaptic alpha-2 adrenergic receptors manifests commonly as bradycardia. Hypotension occurs in a small proportion of cases along with atrial fibrillation and ventricular arrhythmias. Nausea, vomiting is the most common gastrointestinal manifestation with asymptomatic transaminitis. Dry mouth, abdominal distention, and decreased intestinal motility rarely manifest. Bradypnea, respiratory acidosis, and arrest occur due to the direct effect of poison leading to intubation and mechanical ventilation in around 20% of cases, to prevent aspiration. Due to the lack of a specific antidote, supportive management with IV fluids, vasopressors/inotropes are the mainstay of therapy[6].

Due to similarity in clinical features, Amitraz poisoning is often misdiagnosed as organophosphorus poisoning. Meticulous history and retrieval of the container or proper questioning of attendant regarding the consumed substance is required to avoid misdiagnosis and planning proper management. Management is mainly conservative as there is no specific antidote and caries excellent prognosis with no long-term morbidity.

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