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ASSAM JOURNAL OF INTERNAL MEDICINE

Official Journal of Association of Physicians of India, Assam Chapter

Editor in Chief : DR. S. M. BARUAH

C O N T E N T S

EDITORIAL

- COVID-19 : A Perspective 5
Prof. A. K. Das

ORIGINAL ARTICLE

- A Study on clinico-epidemiological characteristics and psychological aspects of COVID-19 patients of two covid care centres in northeast India: A retrospective cross-sectional study 8
S K Das, A Basumatary, M Rabha, S Biswas
- Study of demographic profile of chronic kidney disease patients undergoing haemodialysis in a tertiary care center of Tripura and evaluation of the causative factors for chronic kidney disease 16
A Dasgupta, P Chakraborty, N Das, D Pal
- Outbreak of Scrub Typhus in Manipur Experience at a Tertiary Care Hospital 23
K S Ngulani, S Kakati, S Hussain, M U Singh, K Kaguilan
- Mycological and Clinical Correlation of Dermatophytic Infection in Tertiary Care Hospital of North East India 29
R Nath, M Katakai, A K Borah

REVIEW ARTICLE

- Mechanism of Hypoxia in Covid : A Review of It's Physiological Derangement 32
T Dutta

CASE REPORT

- Erythema Nodosum : An Unusual Chronic presentation Secondary to Latent Tuberculosis 37
C Baruah, T Joseph, S Mitra
- Fracture Shaft of Femur in PwH (person with haemophilia): Surgery or conservative?? 40
B S Dhal, A Dutta, M Buragohain, A D Rajan
- Sudden loss of vision – a rare presentation of Fahr's disease 45
U K Nath, U R Pegu, R K Bora, D Saikia, K Lahan, R H Ahmed

MEDI-QUIZ	47
LETTER TO EDITOR	
■ Covid 19 vaccine needed or not. If yes which one to choose in Indian context <i>Noni Gopal Singh</i>	49

OBITUARY



Prof. Ratan Kr. Kotokey (1953-2020)

API Assam chapter deeply mourns the sudden unexpected demise of Prof. Ratan Kr. Kotokey on 28.09.2020 at Dibrugarh. He retired from Assam Medical College as Principal-cum-chief Superintendent in the year 2017. He has been an excellent teacher and guided many students who are now established in their fields. Prof. Ratan Kr. Kotokey will be remembered for his pleasing personality, loving smile, soft spoken and caring nature. His fatherly nature will always be remembered by the students. API, Assam Chapter offers deep heartfelt condolences to the bereaved family members and prays for the eternal peace of the departed soul.

COVID-19 : A Perspective

Prof. A. K. Das*

The world is experiencing a global SARS-COVID-19 pandemic (of zoonotic origin) along with a number of challenges. As in all outbreaks, there is an urgent need to develop effective diagnostics, therapeutics, and vaccines. The whole-genome sequence of SARS-CoV-2 had been obtained and shared widely by mid-January, a feat not possible at such speed in previous infectious disease outbreaks. Of course, now newer mutations are being reported from UK and South Africa with uncertain implications. Internationally, we have seen rapid generation and sharing of knowledge to the benefit of the outbreak response, but also counter-productive actions by some countries, including limiting trade and shutting of borders, to its detrimental effects – mainly economical drawbacks. With the increasing frequency of zoonotic spillovers leading to human infections and transmission, it's apparent that pandemic preparedness has become a priority for the global health agenda.

This single stranded RNA virus spreads by droplet transmission and from fomites. Patients can be asymptomatic or present with respiratory and gastrointestinal symptoms, and even multiple organ failure which can lead to death. It is highly infectious, causes primarily fever, sore throat and malaise but shows a wide non-uniformity of symptoms. With an average of 2 to 14 days incubation period additional symptoms are headache, anosmia and ageusia plus diarrhea. The significant complications include ARDS and sepsis.

The global death rate is 0.035 in those >60 years of age. Those with co-morbidities (CKD, Diabetes Mellitus, Cardiac, Hepatic, Chronic respiratory, Nervous system disorders, smoking, obesity) represent 23-48% of overall cases and have poorest prognosis. The mortality rate of severe COVID-19 disease can be as high as 49%, based on a recent epidemiological study by China CDC. When the age of patients with a severe disease increased by 5 years, the risk increased by 15.15%. Currently Remdesivir and Dexamethasone plus Heparin are licensed in treatment, which primarily is supportive in nature. But Understanding the inflammatory response of COVID-19 patients is essential for the development of better therapeutic and management strategies. Understanding the cell-mediated or humoral immune response to COVID-19 infection is crucial from this perspective, because differences in host immune response to COVID-19 may play an important role in heterogenous manifestations of this disease.

With a normally functional immune system, infections such as COVID-19 go unnoticed. The 3 types of immunity are innate immunity (rapid response), adaptive immunity (slow response), and passive immunity. Passive immunity has two types: natural immunity, received from the maternal side, and artificial immunity, received from medicine/vaccine. However, when the body encounters germs or viruses for the first time, the immune system cannot work properly, and illness can occur. Almost all immune cells are equipped with the protein complex that constitutes the inflammasome. When one of these proteins identifies a viral or bacterial particle, for example,

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the defense mechanism is activated. As a result, the cell enters a process of programmed death (a type of inflammatory death called pyroptosis) and releases into the bloodstream signaling molecules called cytokines that attract to the site a veritable army of white blood cells. This is the onset of an inflammatory response that is ultimately designed to destruct the potential threat to the organism.

Commonly after an infection, the B cells are assisted by T (CD4 & CD8) cells to differentiate into plasma cells, to produce antibodies specific to a viral antigen. A neutralizing antibody is efficient in fully blocking the virus from entering into host cells to limit the infection (*primary phase*) and plays a very intense protective role at the later stage of infection and prevents relapse of infection (*secondary phase*). By contrast, a cellular immunity response can be observed inside the infected cells, which is mediated by T-lymphocytes. The overall adaptive immune response is directed by helper T cells, and cytotoxic T cells play a vital role in the clearance of viral-infected cells. But this is not the story in COVID-19. The disease will be mild for 80% of the infected patients and mostly restricted to the upper and conducting airways. Still, there are more questions need to be answered in the role of immune response than we can prove, since COVID-19 does not seem to follow the laws of common virological infection that we know.

COVID-19 essentially starts with a strong humoral and cell mediated immune response followed by an uncontrolled adaptive response in symptomatic patients resulting in tissue damage. Approximately 20% of the infected patients develop pulmonary infiltrates and some of these develop very severe disease. The mortality rate of severe patients with COVID-19 can be as high as 49%, based on a recent epidemiological by China CDC. The leading cause for mortality of patients with COVID-19 is respiratory failure from acute respiratory distress syndrome. Secondary hemophagocytic lymphohistiocytosis (sHLH) is characterized by fulminant and fatal

hypercytokinemia with multiorgan failure, and it is underrecognized. sHLH, resembled by a cytokine profile, is associated with COVID-19 disease severity, characterized by increased interleukin (IL)-2, IL-7, interferon-inducible protein 10, granulocyte-colony stimulating factor, macrophage inflammatory protein 1-, monocyte chemoattractant protein 1, and tumor necrosis factor- (TNF-). However, the exact pathways of signaling, generation of cytokines and hyper-stimulation of immune system in SARS COVID is not fully known.

A new variant of SARS COVID has emerged from UK since last November and elsewhere, including India, and is said to be 70 times more contagious than the original COVID 19 virus. It is named as SARS-CoV-2 VOC 202012/01 and has a major mutation in the receptor binding domain of the spike protein at position 501, where amino acid asparagine(N) is replaced by tyrosine(Y). Therefore, in shorthand it is referred to as N501Y mutation. But there are reportedly other mutations too, since regular mutation can occur in SARS CoV 2 virus but remain silent. This new UK mutation may have occurred spontaneously by chance but speculations are on whether it is somehow related to use of convalescent plasma therapy. Exact clinical, epidemiological and other characteristics of this variant is yet to be elucidated. There is no evidence that it causes more severe disease, but may spread more quickly. These variants can still be diagnosed by present PCR assays. As for evading vaccine induced immunity by this variant it remains to be seen in the future, what happens to the theoretical possibility of emergence of "escape mutants". Similarly, treatment need not be modified for this variant.

With the repeat waves of SARS COVID-19 sweeping across the world it is unlikely that COVID-19 will be eliminated completely in near future. We have witnessed a year of pandemic but we know much less about it. Mass vaccination is a welcome step to counter these waves of epidemics but

sticking to basics of personal and respiratory hygiene must be strictly followed. Policymakers and health-workers need to act and plan in tandem with proper logistic support to keep all hospitals in an “emergency mode” if and when cases surge suddenly. A balance between battling COVID-19 and resuming daily activities is a priority. In addition, post-covid complications are increasing, with sometimes severe disability, that we have to look out for and deal with increasingly. Many are also predicting a post-covid era of high Antimicrobial Resistance (AMR) scenario that may adversely affect our abilities to deal with other infections, including Avian flu, causing SARI as these cases are increasing all over India this winter.

In our country dry run for vaccination against COVID-19 has already started, but a rise of

imported UK variant cases, relaxing mood of the general population and rise in new active cases in several states is a worry. Post vaccination surveillance and its implementation will be a necessary, but herculean task. The health care system is unlikely to get a break from the high-alert mode in the near future.

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A Study on clinico-epidemiological characteristics and psychological aspects of COVID-19 patients of two covid care centres in northeast India: A retrospective cross-sectional study

S K Das*, A Basumatary**, M Rabha***, S Biswas****

ABSTRACT

Introduction: COVID-19 has now become a pandemic. It has spread from Wuhan, China in 2019 to all over the world. The outbreak and spread of Severe Acute Respiratory Illness related to COVID-19 has led to global health and economic crisis. **Aim :** The present study was done to understand the clinical epidemiological and laboratory characteristics of COVID-19 patients that could give an insight of the disease and help in evolving management strategies in terms of diagnosis, isolation and prevention of further spread. **Methodology :** This is a descriptive cross sectional study of COVID-19 patients admitted in 2 COVID care centres from 1-6-2020 to 31-7-2020. The patients were diagnosed with RT-PCR. Demographic clinical and laboratory data were collected. Presence of fear, awareness, emotional and financial impact was interrogated. **Results :** There was a male preponderance with the disease mainly infecting adolescent and younger adults. There was positive correlation of the disease exposure with travel history, occupation and, disease severity with co-morbidities, vaccination and leucocyte counts. Extra pulmonary symptoms like anosmia, diarrhoea, myalgia and also predominance of fear emotion and financial insecurity were present among the study subjects. **Conclusion :** Active targeted surveillance among elderly and those with comorbidities for early detection and avoiding COVID-19 complications, adequate awareness in public and workplace with proper SOP (standard operating procedure), early isolation with medications for suspected patients with extra pulmonary symptoms and total counts based on clinical epidemiological guidance even before arrival of COVID-19 reports should be done. Addressing the psychological aspects of the disease with due equality.

Keywords : COVID-19, clinic-epidemiological profile, leukopenia, anosmia, diarrhoea, vaccination, psychological aspects

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INTRODUCTION :

On January 7, 2020, a novel coronavirus was isolated and named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses (ICTV) in the wake of an outbreak of pneumonia of unknown cause in Wuhan city, China.^{1,2} This pneumonia was called Coronavirus Disease 2019 (COVID-19) by the World Health Organization on February 11, 2020. Generally, coronaviruses were not considered to be highly pathogenic to humans until the outbreak of SARS in 2002 and 2003 in Guangdong, China.^{3,4} Another highly pathogenic coronavirus, Middle East respiratory syndrome (MERS) coronavirus, emerged in Middle Eastern

countries in 2012.⁵ COVID-19 is one more highly pathogenic coronavirus to humans in history. COVID-19 has caused severe illness and has impacted multiple countries in the world, and sustained human-to-human transmission has made it a worldwide concern and serious public health threat.⁶ COVID-19 has spread all over the world and so far, it is unclear when this virus will end. However, the symptoms of the virus are similar to those of influenza (e.g. fever, cough, or sore throat), and the outbreak is occurring during a time of year when respiratory illnesses from influenza, respiratory syncytial virus, and other respiratory viruses are highly prevalent. It is very important for clinics to identify the infected patients. Human-to-human transmission via droplets as well as through contact with fomites seems to be the critical route of the virus spread.⁷ Since 80% of

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the infected population are either asymptomatic or have mild disease, people have been going to their workplaces and even traveling internationally. Nevertheless, even though the virus is causing mild disease in many, the course of illness may be severe, leading to hospitalization and even death in elderly or those with comorbid conditions⁸.

The present study was done to understand the clinical epidemiological and laboratory characteristics of COVID-19 patients that could give an insight of the disease and help in evolving management strategies in terms of diagnosis, isolation and prevention of further spread.

AIMS and OBJECTIVES :

- To understand the prevalence of COVID-19 among various age group and gender.
- To understand the epidemiological characteristics.
- To understand the various clinical presentations.
- To understand the prevalence of comorbidities among study subjects.
- To correlate the role of Prophylactic medicines and BCG/MMR vaccines.
- To correlate the presence of leucopenia/lymphocytopenia and COVID-19.
- To correlate the Chest X-ray findings with the disease.
- To understand the prevalence of factors like fear, awareness, financial impact and daily life impact on patients
- To compare the data with existing literatures.
- To extend suggestions and recommendation based on the study.

MATERIALS AND METHOD :

Study setting- The present study was conducted at a COVID care centre.

Study period- The present study was conducted for a period of 2 months from 1st June 2020 to 31st July 2020.

Sample size- A total of 150 COVID-19 patients diagnosed by RT-PCR, were included in the study.

Study design- The study was a descriptive retrospective cross-sectional analytical study.

Data collection- We reviewed clinical charts, nursing records, laboratory findings, and Chest X-rays for all the 150 patients included in the study. To ascertain the epidemiological and symptom data, which were not available from medical records, we also directly communicated with patients or their families to ascertain epidemiological or symptom data. The purpose of the study was explained to the participants in Assamese/Hindi.

Study variables-

1. Demographic and socio-economic variables like name, age, sex, locality, occupation.
2. Types of exposure (family/workplace), recent travel history, exposure to pets/domestic animals.
3. Presence or absence of smoking.
4. Various symptoms like anosmia, dysgeusia, decreased appetite, G.I. symptoms (pain abdomen/diarrhoea/vomiting), fever, headache, joint pain, cough & sore throat, difficulty in breathing
5. Presence or absence of comorbidities like diabetes, hypertension, chronic obstructive lung disease, cancer, immunocompromised state etc.
6. Case severity- mild/ moderate/ severe.
7. Presence or absence of BCG/ MMR vaccination.
8. Prophylactic medicines taken/ not taken.
9. Laboratory parameters like Blood group, TLC, DLC, other significant test reports
10. Presence or absence of Chest X-ray findings.
11. Presence or absence of factors like fear, awareness, financial or emotional impact of the disease on study subjects.

Statistical analysis- A descriptive analytical study was conducted on the data collected. 150 patients from COVID CARE CENTRE were enrolled

in the study to find out the various aims and objectives of the study. The quantitative variables were defined with mean and standard deviation (SD), whereas qualitative measures were defined as proportions. The correlation between quantitative variables was performed. Statistical significance for Pearson's correlation coefficient was tested with Student's t test, and for qualitative variables, Statistical significance was tested with the Chi square test at 5% level of significance. Statistical analysis was performed using Microsoft excel version 2010.

RESULTS AND OBSERVATIONS :

Among the study subjects, the median age group was 48 years. 45 patients were in age group (20-40) years, 75 patients were in age group (41-60) years, 30 patients were 60+ years of age. There was a male preponderance with 108 (72%) male patients. While reviewing locality, it was found that 60 (40%) patients were outsiders and 55 (37%) study subjects had recent travel history.

Out of 150 subjects, 109 (73%) worked in industry/business establishment/office, 16 (11%) were health care workers, 11 (7%) were farmers, rest 14 (9%) stayed in house. And, on going through exposure history, 90 claimed workplace exposure, 24 (16%) claimed exposures through family member, 36 (24%) couldn't specify. Out of 150 patients, 114 (76%) were symptomatic, with fever and cough being the most common presenting symptoms present in 85 patients, 25 patients had joint pain and myalgia, 17 patients complained of diarrhoea. Anosmia was reported by 42 patients along with dysgeusia. 8 patients reported difficulty in breathing.

In the 150 study subjects, a total of 64 (43%) had co morbidities. 54 patients had hypertension, 20 had diabetes, 10 had COPD/pre-

existing lung problems, 12 patients reported having cardiovascular problems, 13 had hypothyroidism, 15 had other co morbidities like kidney disease, arthritis, and liver disease.

Symptoms were mild in 94 (66%) cases, 15 (10%) had moderate symptoms and 36 (24%) had no symptoms.

Only 38 patients could give history of vaccination, while the rest could not specify.

On reviewing the lab reports of patients, 80 patients could provide blood reports. Out of these 80 patients, leukopenia was present in 18 patients reports, 12 were asymptomatic and the rest 6 were symptomatic. 36 patients reports showed leucocytosis, however all of them had co-morbidities.

58 (39%) patients could specify their blood groups, 34 (23%) patients had Blood grp A, 32 (21%) patients had Blood grp O 14(9%) reported having Blood grp AB and 12 (8%) mentioned Blood grp B.

X-ray was done in 46 patients, all were symptomatic, out of which, 28 showed positive findings.

On reviewing the psychological status of patients, fear and awareness was present in 120

Table 1: Clinical and demographic profile and distribution of subjects based on symptom severity.

Baseline characteristics	Case confirmed	No Symptom s	Mild Symptom s	Moderate Symptom s	Total cases	Proportion	χ^2
20-30	8	1	7	0	n = 150	0.053	<0.05
31-40	37	17	20	0	n = 150	0.246	
41-50	51	14	36	1	n = 150	0.34	
51-60	24	1	19	4	n = 150	0.16	
60+	30	3	17	10	n = 150	0.2	
Male	108	28	75	5	n = 150	0.72	<0.05
Female	42	8	24	10	n = 150	0.28	
Industry/Service	64	18	43	3	n = 150	0.426	<0.05
Farmer	11	2	9	0	n = 150	0.073	
Labour	19	4	14	1	n = 150	0.126	
Home	14	0	5	9	n = 150	0.093	
Health Workers	16	3	12	1	n = 150	0.106	
Office Workers	26	9	16	1	n = 150	0.173	
Local	90	N/A			n = 150	0.60	
Outsider	60				n = 150	0.40	
Yes	55	N/A			n = 150	0.36	
No	95				n = 150	0.63	
Family Exp.	24	2	13	9	n = 150	0.16	<0.05
Work Exp.	90	23	63	4	n = 150	0.60	
Unknown Exp.	36	11	23	2	n = 150	0.24	
Fear/Awareness	120	N/A			n = 150	0.80	
Emotional Impact	129				n = 150	0.86	
Financial Impact	100				n = 150	0.66	

(80%) of the study subjects. 100 (67%) patients reported having financial impact owing to continuous lockdown. 129 (86%) had emotional stress due to no firm estimate on how long the pandemic will last and how long their and their loved ones' lives will be disrupted.

Table 2: Blood Group distribution among study subjects.

Groups	A	O	B	AB	Unknown
Number	34	32	12	14	58

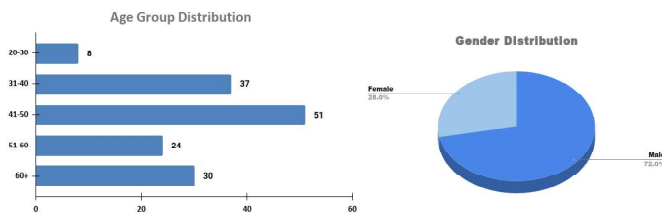


Fig 1: Graphs showing Age groups distribution and Gender distribution.

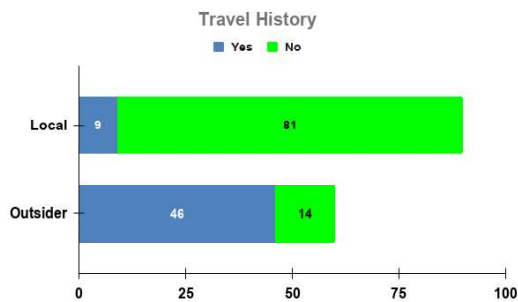


Fig 2: Graph showing correlation between Locality and Travel history.

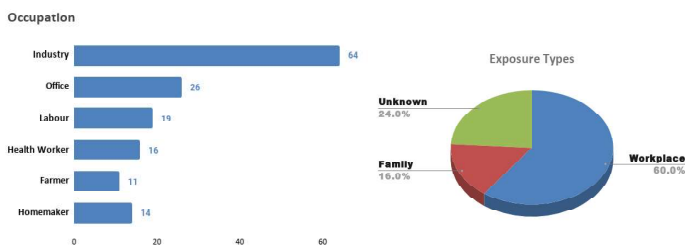


Fig 3: Graphs showing various occupations and types of exposure.

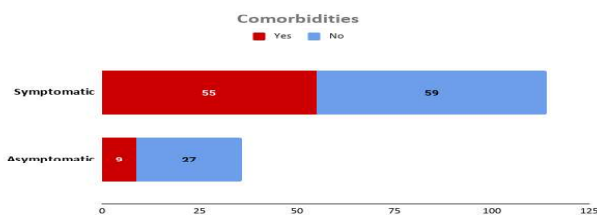


Fig 4: Graph showing symptomatic and asymptomatic patients with/without comorbidities.

DISCUSSION :

In our study population, we found that the disease has a male preponderance and the infection was observed in adolescent and elderly groups with predominance in younger adults (Fig.1). This may be correlated to limited travel history and not venturing unnecessarily out of house in very young, very elderly and female population and not related to susceptibility of these population groups.^{9,10}

Out of 60 outsiders 46 (77%) had travel history (Fig.2). Such an observation mandates an urgent need of limitation of interstate travel and also stronger tracking of the contacts along with appropriate quarantine measures.¹¹

In our study 90 (60%) gave history of workplace exposure (Fig.3). Occupational exposure is a crucial contributor in disease outbreak. Labourers, industrial workers are at increased risk both for contacting the disease and being hospitalized. It has been established in many studies that some occupation and industries are at increased risks especially those employed in healthcare and other essential industries.^{12,13,14}

Protecting frontline workers is essential in current crisis as these groups are more vulnerable at the same time they are the much needed working force, this should include adequate PPE, preliminary medication and isolation including paid sick leave.

Our study revealed that apart from fever cough and respiratory distress, symptomatic patients also presented with anosmia, dysgeusia and myalgia, joint pain and diarrhoea (Fig .5). GI symptoms like diarrhoea, dysgeusia and sudden onset anosmia have been reported in many studies in presenting complaints.^{15,16,17,18} This is important because if clinicians solely monitor for respiratory symptoms, they may miss cases with extra pulmonary symptoms, thereby decreasing early detection and prompt medication.

It was seen in our study that, among 114 symptomatic patients, 55 (48%) had comorbidities,

Fig 5: Graphs showing frequency of various symptoms and comorbidities.

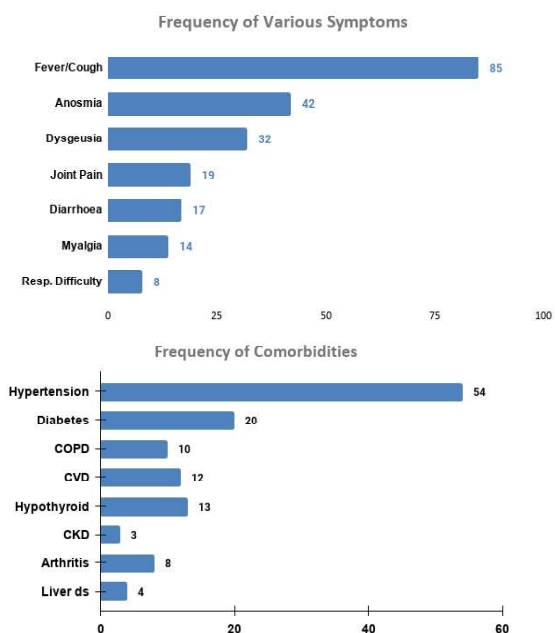


Fig 6: Graph showing correlation between case severity and BCG/MMR vaccination.

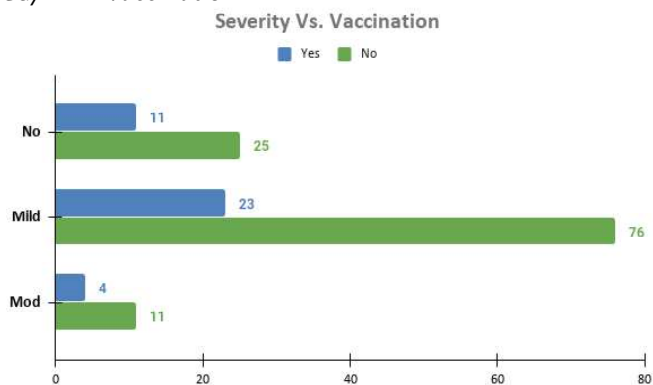
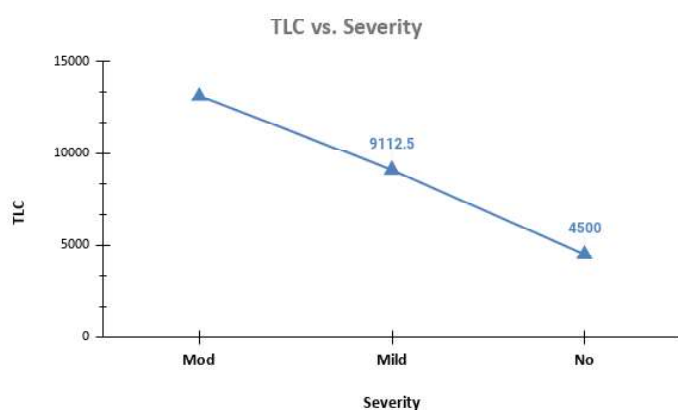


Fig 7: Graph showing correlation between TLC and case severity.



hypertension being present in 54 cases and 20 having diabetes. 13 patient had hypothyroidism. (Fig.5)

Evidences convincingly attest that both pulmonary and systemic HTN is risk factor for unfavourable progression in patients with pneumonia,¹⁹ ARDS,^{20,21} MOF(multi organ failure).²²

A relationship between diabetes and infection has long been clinically recognized.²³ Infections, particularly influenza and pneumonia, are often common and more serious in older people with type 2 diabetes mellitus (T2DM).^{24,25}

Hypertension and diabetes should be considered a clinical predictor of COVID-19 severity in elderly people and this elderly population with comorbidities should be screened and monitored for early detection and treatment.

Going through BCG/MMR vaccination which could be provided by only 38 patients, it was found that 11 were asymptomatic, 23 had mild symptoms and 4 had moderate symptoms (Fig.6). In our study 6 patients mentioned being under Anti tubercular drugs and all 6 of them were asymptomatic. This relates to the fact that many studies have discussed the plausible BCG vaccination cross protection from COVID severity.^{26,27,28}

Studies also correlate to the fact noting homology in the amino acid sequence in SARS-CoV2, measles, rubella possibly explaining crossover reactivity of the vaccines. The variety of epidemiologic associations clearly suggest a plausible indication that the MMR vaccine may confer protection to the COVID-19 virus as well.^{29,30,31,32}

Right now, it is a national priority to develop a safe and effective vaccine for the COVID-19 virus, and the race is on to do this, with dozens of companies and millions of dollars spent in this effort. As part of this effort, there should be an immediate investigation of using the already available BCG and MMR vaccine in controlled studies to show a protective benefit.

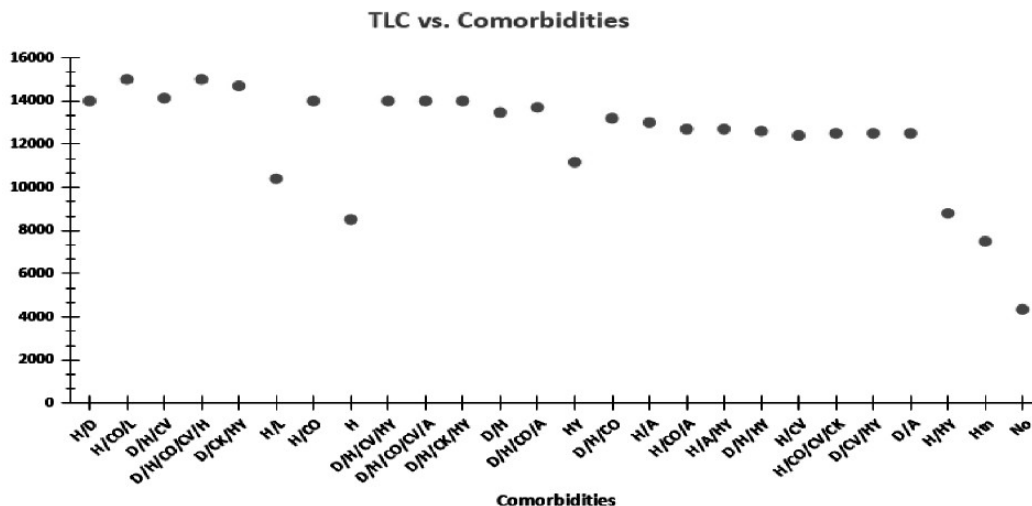
Our study showed that most of the asymptomatic and mild symptomatic patients had a low total leucocyte count, and the counts

increased with the increase of symptoms (Fig.7). These findings were similar to those of Zhang *et al.*³³ Guan *et al.*³⁴ that showed that leukopenia was a common laboratory finding in asymptomatic young individuals and thereby marking them a potential carrier.

Although more in-depth research on the underlying aetiology is necessary, several factors may contribute to COVID-19 associated leukopenia. It has been shown that lymphocytes express the ACE2 receptor on their surface; thus SARS-CoV-2 may directly infect those cells and ultimately lead to their lysis and ultimately decreasing the total counts.³⁵

It was also seen in our study (Fig.8) that people with comorbidities tend to have an increased total counts thereby indicating a more

Fig 8: Graph showing correlation between TLC and comorbidities.



severe infection or aggravation of the infection. These findings were similar to those of Li T *et al.*³⁶ Xu H *et al.*³⁷ which showed that following viremia, SARS-CoV-2 primarily affects the tissues expressing high levels of ACE2 including the lungs, heart and gastrointestinal tract. Approximately 7 to 14 days from the onset of the initial symptoms, there is a surge in the clinical manifestations of the disease with a pronounced systemic increase of inflammatory mediators and cytokines, which may even be characterized as a “Cytokine storm”.

Thus, these findings suggests considering leukopenia as an important findings indicating viremia in asymptomatic patients and their potential to be a carrier and transmitter of the disease. The findings also suggest serial monitoring total counts in vulnerable groups with comorbidities for early detection of cytokine storm and deterioration of clinical conditions.

Our study also showed a prevalence of psychological impact with prevailing fear, emotional stress and financial insecurity among patients (Table.1). This were similar to studies in many other countries.^{38,39,40}

The proliferation of fear and emotional stress resulting in erratic behaviour among people amidst infectious outbreaks is an understandably not

u n c o m m o n phenomenon as also seen in previous pandemic⁴¹ and anyone of any gender, and socio demographic status can be infected. This is especially true for COVID-19 when there is much speculation surrounding the mode and rate of transmission, with the disease spreading at such an unparalleled

magnitude. The psycho-emotional impact of the COVID-19 pandemic on patients is indeed multifaceted; it influences both their ability to work and their ability to cope with mental health issues.⁴²

It is pivotal, therefore, that we do not ignore the psychological impact that the outbreak has on individuals and the society, which is often the limiting factor for the nation to overcome the crisis. Social media is to be used in good sense, to educate people on transmission dynamics, symptoms of disease, and time when exact medical consultations are needed.

CONCLUSION :

This descriptive retrospective cross-sectional analytical study showed that the virus tended to infect mainly the middle aged and older people with underlying comorbidities and as the disease is already in Stage 3-4 of disease transmission, so, an active surveillance with targeted population being individuals aged more than 65 years and individuals with comorbidities should be done. This will help in early diagnosis, isolation and prevention of complication including death. Secondly, we concluded that travel history and occupational exposure are playing a crucial role in disease spread and therefore awareness among general population should be increased and proper standard operating procedure(SOP) should be maintained by all to contain the spread. Thirdly, patients with extra pulmonary symptoms and patients with leukopenia should also be suspected for COVID-19 and isolated early along with initial medications even before the test results arrive. Fourthly, although COVID-19 vaccines are at different phases of clinical trials, BCG/MMR vaccination programs should also be strengthened. Fifthly, psychological conditions of patients and care givers should also be addressed properly in order to strengthen health system. Stigma and blame targeted at communities affected by the outbreak may hinder daily life, finance and relationships, instigating further unrest. Due care needs to be taken to erase the stigma associated with disease. Finally to conclude, the COVID-19 pandemic has clearly shown us how a “virus” can negatively impact our lives even in the 21st century and simultaneously made us realize that the greatest assets of mankind are health, peace, love, solidarity, ingenuity, and knowledge.

LIMITATIONS OF THE STUDY :

The study limitations include the inclusion of cases treated in only two Covid care centres. It is possible that this group of patients does not completely represent the characteristics of

infections diagnosed across the nation. Its value is in providing early patient and epidemiological data that add to what is known of this emerging viral disease and will be of use in the on-going effort to control this pandemic.

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Study of demographic profile of chronic kidney disease patients undergoing haemodialysis in a tertiary care center of Tripura and evaluation of the causative factors for chronic kidney disease

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ABSTRACT

Introduction : The world is suffering from a hike in the cases of Chronic Renal Disease (CKD), India alone contributes about 55,000 patients on haemodialysis each year. CKD affects every system of body and results into multiple abnormalities which increases both morbidity and mortality. The demographics of people with CKD vary from region to region and also the causative factors leading to CKD are multiple. In this study an attempt was undertaken to evaluate the causative factors leading to CKD among the patients undergoing haemodialysis and the demographics of the patients were studied simultaneously. By calculating the sample size 100 patients undergoing haemodialysis were undertaken as study subjects. **Aims and objectives:** To study the demographics of patients undergoing haemodialysis and evaluation of precipitating factors leading to CKD. **Methodology:** 100 patients under haemodialysis were selected as cases of study based on defined inclusion and exclusion criteria. History taking was done in detail and data collection done to highlight the demographic of each and every patient. Previous record scanned to look for the causative factors leading to CKD and investigations as per requirement done for the same. **Results:** The mean age of involvement of CKD patients undergoing haemodialysis was 50.49(\pm 15.31) years. At the time of diagnosis, 5% of the patients were in Stage1 CKD. Maximum patients report late. 29% of cases was diagnosed in stage3 and also 29% in CKD Stage4. 25% were diagnosed in Stage5. Maximum patients were diagnosed in the age group of 46-60 years(39%). This is the productive period of life and it results in human resource burden and simultaneously economic burden for society and government. For evaluation of causative factors hypertension is the most important factor (49%) followed by diabetes mellitus (33%). **Conclusion:** The study was undertaken to evaluate the causative factors of CKD which leads to haemodialysis for survival and like other studies uncontrolled hypertension and diabetes mellitus are found to be primary causes; early diagnosis and continuous uninterrupted treatment of which might retard the process of development of CKD; which is always diagnosed late when the disease had already advanced.

Keywords : chronic kidney disease; haemodialysis; demographic profile; causative factors for CKD.

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INTRODUCTION :

The clinical practice guidelines of the US-based National Kidney Foundation Disease Outcome Quality Initiative defined chronic kidney disease (CKD) as kidney damage or an eGFR measurement of lower than 60ml/min/1.73m² that persists for three months or longer.¹

According to the Global Burden of Disease Study, CKD ranks 18th in the list of deaths with an annual rate of 15.7 deaths per 100,000 people.²

The demographics of people having CKD varies from region to region; the mean age of 9614 patients in one Indian study was 51(\pm 13.6) years where as a similar study from China shows mean age at 63.6(\pm 14.7) years.^{3,4}

In Africa younger aged people in between 20 to 50 years are more affected owing to uncontrolled and poorly treated hypertension and glomerulonephritis.⁵

The progressive renal disease usually leads to a common end point End Stage Renal Disease (ESRD) of a shrunken fibrotic non functioning kidney.¹ CKD affects 5 to 15 % of the adult population of developed world. Patients reporting

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late for medical help develop complications and need interventions with emergency admissions which are cost-effective. The burden of treatment of ESRD economically is too enormous to afford for middle class people.⁶

In India too, there is a significant burden of CKD. But due to limited access of health care services and lack of awareness, CKD is diagnosed in advanced stages. Cost of treatment of advanced CKD is substantial and beyond the reach of common Indian resulting into only 10% of Indian CKD population can afford for renal replacement therapy.⁷

The National Institute of Health have recommended a smooth transition of patients of CKD from Medicine discipline to a multi-staffed pre-dialysis team in order to ensure a reduction in patient's morbidity and mortality for which recommendation of haemodialysis is mandatory.⁸ Components of work of this team are many: among which insertion of a permanent access for dialysis and timely outpatient based haemodialysis initiation are of prime importance. Hence timely referral for haemodialysis initiation is associated with decreased risk of adverse outcomes at the time of dialysis initiation.⁹ Amongst the common methods available for renal replacement therapies like haemodialysis, peritoneal dialysis and kidney transplantation; haemodialysis aims at providing a near normal life of the afflicted patients.¹⁰ Haemodialysis protects human lives and aims for increasing life expectancy however never could replace the functioning of a normal kidney and hence the purpose of such treatments is to reach the highest level of function and patients well being, which in current scenario is far from reality.¹¹ 90.6% of ESRD patients are undergoing haemodialysis. The difficulties faced by these patients are countless; the way they relate and end up with physical impairment and emotional difficulties.¹²

In a state where resources are limited and lack of awareness of people to diseases and disease

modifying factors it is only appropriate that focus is directed towards the prevention of CKD rather than its treatment as the economic burden is huge both for the patient and the government. Studies on prevalence will give attention to the magnitude of the disease and will offer platform for planning.¹³

High risk predisposing factors for CKD can be identified and addressed with an aim for necessary modifications which might retard the progression of the disease towards ESRD.¹⁴ ESRD is associated with co morbid health conditions, poor quality of life and high health care costs.¹⁵

Diabetes mellitus and hypertension are the leading cause of CKD in developing nations; however primary diseases like glomerulonephritis are more common in Asian countries and Africa. This difference of burden of CKD in populations of developed and developing nations is due to the moving away from infections towards lifestyle diseases but in low income groups CKD often arises as an infectious disease.^{16,17}

In western countries diabetes and hypertension accounts for 2/3 rd cases of CKD¹⁸. In India too both these two disease today are responsible for 40 to 60 % of the causes for CKD. It's a known fact that 50% of the diabetics and hypertensives in India are not aware that they are harbouring the disease and in targeting for screening of CKD in the high risk groups these 50% of cases will be missed.¹⁹

Medical complications, economic pressure, marital discord, sexual dysfunction, emotional stress and fear of death continue to be present regardless of ongoing dialysis and the greatest potential to return to a healthy life never comes.²⁰

There is a paucity of published Indian data on the demographic profile along with socioeconomic conditions of patients with CKD & also the social factors associated with the acceptance of the prescribed treatment.²¹

Hence this study was carried out with an aim to look for the demographic profile of the patients undergoing haemodialysis in our institute and also

in our state. In this study an attempt was also adopted to search for the causative factors of development of CKD by questionnaire and investigations.

AIMS AND OBJECTIVES :

1. To study the demographic profile of patients with chronic kidney disease undergoing haemodialysis.
2. To evaluate the causative factors leading to chronic renal failure.

METHODOLOGY :

The study was carried out in the Dept of Medicine at Agartala Government Medical College Agartala Tripura for a period of one and half years. It's a cross sectional study. The study was done after taking permission from Institutional Research Committee and Institutional Ethics Committee. The patients of chronic kidney diseases under maintenance haemodialysis fulfilling the inclusion criteria; attending the hospital both as an in-patient or out-patient in the Dept of Medicine for haemodialysis during the study period are included as cases. A total of 100 cases of chronic kidney disease patients under haemodialysis have been taken as total number of cases by calculating the sample size.

Inclusion criteria: All 100 patients of chronic renal failure undergoing haemodialysis at Agartala Govt Medical College are included as cases. They are selected by systemic random sampling by sample interval of one.

Exclusion criteria: Patient refused to be a part of the study.

All cases were fully informed about the study protocol and pattern and they participated willingly and consent in written has been taken from all of them. All 100 cases after selection were examined clinically and investigated. Routine blood and biochemistry investigations which includes Hb, TLC, DLC, Blood Sugar, blood urea, serum creatinine, Glomerular Filtration Rate , electrolytes (Na⁺, K⁺, Ca⁺) , lipid profile, liver function tests were

done. ECG and ultra-sound of Abdomen were done in all 100 cases. Chest X-ray was done when clinically indicated.

An attempt was taken in all 100 cases to find out the cause leading to chronic renal failure. History taking was done in detail to document the demographic parameter of each and every patient. Clinical examination was done to assess the status of the patient and also to highlight the cause leading to CKD. Accordingly the past history, occupational history, lifestyle history and treatment history was also recorded to reveal any clues leading to CKD. The previous treatment history and past case records were studied for the same. The determination of the primary cause of renal failure was based on history taking, clinical examination and laboratory investigations like blood biochemistry, urine analysis which included albuminuria and culture, ultrasonography and serology. Histological documentation of primary renal disease was not done here but such results already done were collected as a part of data collection.

RESULTS :

Out of 100 patients under haemodialysis in this study there are 61(61%) male patients and 39(39%) female patients. In this study, there are 39(39%) patients from urban population and rest 61(61%) belonged to rural population. The age group of patients undergoing haemodialysis showed maximum patients in 46 to 60 ages. The mean age of involvement was 50.49(±15.3) years. The minimum age of involvement was 18 yrs and maximum age was 82 yrs.

The age group of involvement showed:

The age group of involvement showed:

Age group	Frequency	Percent
≤ 30 yrs	10	10%
31 to 45 yrs	29	29%
46 to 60 yrs	36	36%
61 to 75 yrs	22	22%
≥ 76	3	3%

TABLE 1: Distribution of age of patients.

The distribution of tribal and non tribal Bengali population of the state showed:

Non tribal (n=75)		Tribal (n=25)	
Male	Female	Male	Female
48	27	13	12

TABLE 2: Distribution of gender & categorization of tribal vs non tribal population.

The religion status of the patients showed the following distribution:

Sl no	Religion	Frequency	Percent
1	Hindu	76	76%
2	Muslims	14	14%
3	Christians	8	8%
4	Others	2	2%

TABLE 3: Distribution of patients according to religion.

The socio-economic status of the patients showed the following distributions:

BPL card holder	Free	RSBY	APL card holder
41	6	11	42

(BPL= below poverty line; RSBY= rastriyo swastho bima yojana; APL=above poverty line)

TABLE 4: Distribution of patients according to socio-economic status.

Educational status of the patients revealed 84 patients are literate and rest 16 are illiterate.

Educational Status	Frequency	Percent
Literate	84	84%
Illiterate	16	16%

TABLE 5: Distribution of patients according to educational status.

The age of diagnosis of chronic renal failure showed the following distribution:

Age group	Frequency	Percent
≤ 30 yrs	7	7%
31 to 45 yrs	32	32%
46 to 60 yrs	39	39%
61 to 75 yrs	21	21%
≥ 76	1	1%

TABLE 6: Distribution of patients according to age of onset of disease.

Classification of patients at the time of diagnosis according to Glomerular Filtration Rate:

CKD stage	GFR ml/min/1.72m ²	Frequency	Percentage
Stage1	≥ 90	5	5%
Stage 2	60-89	12	12%
Stage3	30-59	29	29%
Stage 4	15-29	29	29%
Stage5	≤ 15	25	25%

TABLE 7: Classification of patients according to GFR.

Age groups	Total	CKD Stage1	CKD Stage2	CKD Stage3	CKD Stage4	CKD Stage5
≤ 30 yrs	7	2	0	2	2	1
31 to 45 yrs	32	2	2	3	13	12
46 to 60 yrs	39	1	5	15	12	6
61 to 75 yrs	21	0	5	9	2	5
≥ 76	1	0	0	0	0	1
Total	100	5	12	29	29	25

TABLE 8: Distribution of ages in different stages of CKD n=100 at the time of diagnosis of CKD.

The age of initiation of dialysis of the 100 patients showed the following distribution:

Age group	Frequency	Percent
≤ 30 yrs	8	8%
31 to 45 yrs	20	20%
46 to 60 yrs	41	41%
61 to 75 yrs	22	22%
≥ 76	9	9%

TABLE 9: Distribution of patients according to the age of initiation of dialysis.

The commonest complaints and sign the patients presented with are:

Slno	Symptoms & signs of patients	Frequency	Percent
1.	Hypertension	66	66%
2.	Swelling of body	62	62%
3	Anaemia	100	100%
4	Breathlessness	58	58%
5	Loss of appetite with nausea	65	65%
6	Recurrent urinary tract infections	11	11%
7	Reduced urine output	62	62%
8	Pericardial rub	3	3%

TABLE 10: Distribution of signs and symptoms of patients.

The mean laboratory value findings of the patients are :

Slno	Laboratory findings	Mean value	Frequency	percentage
1	Proteinuria	Present	85	85%
2	Serum creatinine	8.75	100	100%
3	Anaemia	8.23.	100	100%
4	Hypocalcaemia	7.96	82	82%
5	Hyperuricemia	7.7	90	90%
6	Increased blood urea	104	100	100%
7	Hyperkalemia	7.4	8	8%
8	GFR	35.36	100	100%

TABLE 11: Distribution of laboratory findings of patients.

A study into the causative factors leading to chronic renal failure in these 100 patients undergoing haemodialysis revealed:

Sl. no	Causative factors	Frequency	Percentage
1	Hypertension	49	49%
2	Diabetes mellitus	17	17%
3	Both hypertension & DM	16	16%
4	Recurrent UTI	4	4%
5	NSAID induced	2	2%
6	Interstitial nephritis	1	1%
7	Lupus nephritis	8	8%
8	Carcinoma cervix with obstructive uropathy with bilateral hydronephrosis	1	1%
9	Adult polycystic kidney disease	2	2%

TABLE 12: Distribution of causes for development of CKD.

DISCUSSION :

Chronic renal failure leading to end stage renal disease requires haemodialysis for survival. In this study 100 cases of CKD patients taking haemodialysis are included. The demographic profiles of the patients are studied and an attempt was made to search for the causative factors that lead to the development of chronic renal failure. Among the 100 patients, there are 61 male patients

and 39 female patients.

Tripura is a land lock state of northeast India inhabited by

tribal and non tribal population. The study reveals that there are 75 non tribal patients who mainly included the Bengali speaking group and 25 tribal patients. Gender study showed 12% of the tribal patients are females where as 27% of non tribal patients are females.

The state being a Hindu dominated state maximum patients (76%) are Hindus. Rural-urban categorization reveals 61% of patients belonged to rural population. Study of socio-economic status revealed 58% belonged to poor socio economic status and carrying a BPL card. Most of the patients are literate and only 16% are illiterate.

The study revealed patients seek medical advice late. Only 5% of the patients took medical advice in CKD stage 1. Most of the patients came for medical advice in stage 3 and stage 4; 29% each. It's a matter of concern that as many as 25% of the patients attended for the first time for medical help when the disease has already reached stage 5. Studies of distribution of age in different stages of CKD showed maximum number of patients are diagnosed for CKD in stages 3 and 4 in the age group of 46 to 60 years; 29% of cases. It's alarming that in the age group 31 to 45 years 25 % of cases are diagnosed in stage 4 and 5. These are all productive age of life and the disease had already crossed stage 3. Renal replacement therapy is the only treatment option.

Age of onset of the disease showed maximum patients is in age group 46 to 60 years (39%) followed by 32% of patients in age group 31 to 45 yrs. So it's a disease affecting the persons when they are building up carrier and incoming for family and the ailment causing an enormous human resource burden for the society. It's also a concern that 7% of the patients belonged to age group below 30 years.

Parameters	Present study	African study	Developing nation study	Developed country registry ANZ-Data
Mean age	50.49±15.31	43.7±17.8	42.6±15.4	65
Peak age	46 to 60 ages.	40 to 49	36 to 60	65 to 74
Time of presentation according to eGFR	58% in Stage 3 & 4	85.8% in CKD stage 4 & 5	CKD stage 4 & 5	Less than 25 % , 3 months prior to first dialysis

A comparison of this study with another study done at Africa's Ghana which compares the data collected from other developing and developed countries reveals the following:²²

A possible explanation for young age preponderance and in productive time of life in this study which matches with study done at Africa and developing nations is due to inadequate knowledge of patients about the precipitating diseases along with lack of preventive care. There is definitely a rejection from the patients who are from low socioeconomic group to adapt to curative medical care for the predisposing diseases from an early age.

The age of initiation of haemodialysis reflects the same distribution. 41% started dialysis in between 46 to 60 years. 8% of the patients need to start haemodialysis early in life (< 30 years). The percentage of patients initiating dialysis late in life is also quite high; 31% after the age of 60 years. A study into the various complaints and signs as examined by us revealed that maximum patients had an elevated blood pressure as a presenting symptom and also a clinical finding. 66% of the patients were found to be hypertensive. 62% had swelling in the form of edema feet or generalised anasarca. Loss of appetite with vomiting feeling is an important complaint and is present in 65% of

the patients. All 100 patients are found to be anaemic. 58% had breathlessness as a presenting feature.

Study of the laboratory results shows the mean serum creatinine value being 8.75 ± 2.1 mg%. All patients are anaemic and mean Hb value is 8.23 ± 2.08 gm%. Proteinuria seen by dip-stick test was present in 85% patients. Hypocalcaemia and hyperurecemia are two important associated laboratory findings. Mean Ca^{++} value was 7.96 ± 0.9 and mean serum uric acid level was 7.7. The mean GFR value was 35.36 ± 27.16 ml/kg/m².

An attempt was made to search for the cause of development of chronic renal failure. We found hypertension being the major cause for development of CKD. 49% of the patients attributed for hypertension for the cause of development of CKD. 17% of the patients developed CKD due to diabetes mellitus. Among them 16% have both hypertension and diabetes mellitus as the causative factors.

Rest 18% are attributed to other causes. It has been found that recurrent urinary tract infection also contributes for development of CKD & it amounts to 4% of cases. Lupus nephritis is another important cause for development of ESRD at an early age and required haemodialysis for survival. They accounted for 8% of cases. All these cases are females from tribal population and had initiation of haemodialysis also early in life, below 40 years of age.

The study concludes with the finding that patients seek medical help late when the disease had already advanced and that time the patients are in their productive life. Haemodialysis causes economic loss for the family and it's a burden for the family and society. Early diagnosis and adequate treatment of hypertension and diabetes mellitus the principal two precipitating factors for CKD might prevent the development of CKD in latter life.

CONCLUSION :

The present study was conducted in a tertiary care center of Tripura to study the demographic

profile of patients undergoing haemodialysis and to study the causative factors responsible for development of CKD.

There are 100 patients in this study and it was seen that there are more number of patients from rural background with poor socio-economic status. Non tribal patients are more. Most importantly the patients are seeking medical help late when the disease had already advanced to stage 4 or 5. Unfortunately the age of involvement shows that patients are affected in their productive life when they are earning. It's a big economic and human resource burden both for family and society.

Study also reveals lack of early diagnosis and inadequate treatment of hypertension and diabetes mellitus are the two important causes for development of CKD. Proper management and treatment of the precipitating causes might retard the process of development of CKD.

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Article Submission

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Outbreak of Scrub Typhus in Manipur Experience at a Tertiary Care Hospital

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ABSTRACT

Aim: To describe the clinical features, laboratory manifestations, complications in patients diagnosed with scrub typhus at a tertiary care hospital in north east India. **Material and Methods:** All cases of acute onset fever diagnosed to have scrub typhus from August 2017 to December 2018 were analysed. Cases of scrub typhus with a positive immunochromatography test were studied. **Results:** 176 confirmed cases of scrub typhus were studied over a period of 18 months. Majority (96.6%) of patients are from rural background. Farmers constituted 59% of the patients. Most common symptoms were fever with headache 100 (56.8%) and due to the involvement of respiratory tract in the form of cough in 94 (53%) patients followed by breathlessness in 84 (47.7%). Signs of consolidation were seen in 80 (45.5%). Central nervous system involvement in the form of altered sensorium was seen in 43 (24.4%) and seizures in 11 (6.3%) patients. Eschar was seen in 23 (13%) patients. Transaminases were elevated in 153 (86.9%) patients, serum alkaline phosphatase in 110 (62.5%) patients. Renal failure was seen in 49 (27.8%) cases and respiratory failure was seen in 11 (6.2%). 8 (4.5%) patients died in our study. **Conclusion:** Scrub typhus should be suspected in patients with rural background with fever and multi system involvement. The predominant symptoms were headache, cough and breathlessness. Central nervous system abnormalities in the form of altered sensorium was seen in 43 (24.4%). Most common laboratory abnormality noted in our patients with scrub typhus was elevated liver enzymes which were seen in 153 (86.9%) cases.

Keywords : Scrub Typhus, Outbreak, Acute Onset fever, Laboratory abnormalities

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INTRODUCTION :

Scrub typhus is caused by *Orientia tsutsugamushi* (*O. tsutsugamushi*) an obligatory intra-cellular gram negative bacterium. It is transmitted to humans by the bite of larval mites (chiggers) of *Leptotrombidium deliense*.¹ Scrub typhus, if undiagnosed or diagnosed late, or untreated, may prove fatal. The clinical manifestations of this disease range from sub-clinical disease to organ failure.^{2,3} Fever is the most common feature of scrub typhus and due to lack of awareness among clinicians the condition is labelled as "fever of unknown origin".⁴ Scrub typhus has protean manifestations which can mimic conditions like pneumonia, meningoencephalitis,

acute hepatitis, acute renal failure, loose motions and occasionally joint pains. Scrub typhus may occasionally present as fever of unknown origin and due to lack of awareness of the disease, clinicians spend a lot of time and resources during the work up. The clinical course of the disease and the prognosis vary depending on the character of the endemic strain.⁵ Lack of access to specific laboratory tests is another problem in developing countries like India for the under diagnosis of several infectious diseases including scrub typhus. Recent reports from several parts of India, including north east India, indicate that there is a resurgence of scrub typhus.^{2,6,7} There are very few publications on scrub typhus from the state of Manipur.^{8,9} We present our experience on clinical and laboratory features of patients with scrub typhus.

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MATERIAL AND METHODS:

This is a retrospective observational study of patients with scrub typhus who were admitted between August 2017 and December 2018 in the Medicine department of JNIMS, Porompat. Data of clinical and laboratory features of patients aged more than 12 years, with fever, and confirmed diagnosis of scrub typhus was collected and analysed. Scrub typhus cases confirmed by a positive immunochromatography test were included in the study. Patients with other established causes of fever were excluded from this study.

RESULTS:

Study population was recruited after the start of the monsoon season in 2017 August to the end of December 2018. Patients with scrub typhus were identified on the basis of clinical features and serology. Data of 176 patients with scrub typhus were recorded from the case records and were analysed. Most of the cases are seen in months of monsoon and post monsoon period i.e., August, September and October. The baseline characteristics of the study patients are shown in Table 1. Mean age of the study population is 41 years (± 16). There were 105 (59.7%) males and 71 (40.3%) females in our study. Most of the patients are from rural background with history of working in open fields. 170 (96.6%) patients are from the rural part of Manipur and the rest of the patients, i.e. 6 (3.4%) patients visited rural parts of the state in the recent past.

Table 1: Showing baseline characteristics of the patients.

Characteristics of the patients	No. of patients (%)
Male	105 (59.7%)
Female	71 (40.3%)
Rural background	170 (96.6%)
Urban	6 (3.4%)
Farmers	104 (59%)
Housewife	36 (20.5%)
Others	36 (20.5%)

The clinical features of the patients are shown in Table 2. All patients presented with fever and the average duration of fever was 11.8 days (range 2 to 30 days). Majority of patients i.e. 73 (41.5%) patients presented with fever of 7-14 days duration. 40 (22.7%) patients presented to us as prolonged pyrexia as fever was persisting beyond 14 days. Most common symptom was headache (56.8%), and cough (53.4%). The next most common symptom was breathlessness, which was present in 84 (47.7%) patients. Loose motions were seen in 28 (15.9%) patients. Seizures were present in 11 (6.3%) patients and one patient presented with status epilepticus. Joint pains were seen in 5 (2.8%) patients.

Table 2: showing the symptoms and signs

Symptoms	No. of patients (%)
Fever duration < 7 days	63 (35.8%)
Fever duration 7-14 days	73 (41.5%)
Fever duration > 14 days	40 (22.7%)
Cough	94 (53.4%)
Breathlessness	84 (47.7%)
Jaundice	40 (22.7%)
Diarrhoea	28 (15.9%)
Seizures	11 (6.3%)
Status epilepticus	1 (0.5%)
Joint pains	5 (2.8%)
Hepatosplenomegaly	51 (28.9%)
Altered mental status	43 (24.4%)
Eschar	23 (13.1%)
Crepitations in lungs	80 (45.5%)
Headache	100 (56.8%)

Maculopapular rash was seen in 10 (5.7%) patients. Eschar was seen in 23 (13.1%) patients in our series. The most common abnormality on examination seen was lung involvement in the form of crepitations in 80 (45.5%) patients. Twenty-three (13.1%) patients had altered mental status. The other signs of organ involvement observed were hepatosplenomegaly in 51 (28.9%) patients. Laboratory features are shown in Table 3. Mean haemoglobin was 11.1g/dl (± 2.3). Leucopenia (TLC < 4000/cmm) was seen in 18 (10.2%) patients. Leucocytosis was seen in 42 (23.9%) patients. Thrombocytopenia (platelet count < 100000/cmm) was seen in 53 (30.1%) patients.

Elevation of serum creatinine i.e. 1.6 mg/dl was seen in 49(27.8%) patients. Elevation in serum aspartate transaminase (AST) was noted in 153(86.9%) and serum alanine transaminase (ALT) in 136 (77.3%) patients. Cardiac conduction abnormalities in the form of relative bradycardia (corresponding to temperature record) were seen on electrocardiogram in 6 (3.4%) patients. Dialysis was needed in 5 (2.8%) patients. Ventilatory support was needed in 8(4.5%) patients.

Table 3: showing the laboratory abnormalities

Investigations	No. of patients
Mean Haemoglobin	11.1(±2.3)
Leucopenia	18(10.2%)
leucocytosis	42(23.9%)
Platelet count < 1 lakh	53(30.1%)
Elevated SGOT	153(86.9%)
Elevated SGPT	136(77.3%)
Elevated serum creatinine	49(27.8%)
Elevated serum ALP	110(62.5%)
Infiltrating on chest x-ray	46(26.1%)
Bradycardia	6(3.4%)

Average duration of hospital stay was 7.2 days (SD: ± 3.95). Duration of hospital stay of less than 7 days was noted in 121(68.8%) patients. 46 (26.1%) patients had a hospital stay of 8-14 days. 9(5.1%) patients stayed for more than 14 days in the hospital. All patients were treated with doxycycline orally and supportive care. Out of 176 patients 168 (95.5%) recovered and 8(4.5%) patients died. 1 (0.5%) patient left against medical advice.

DISCUSSION :

It is important to rapidly delineate the cause of fever in regions where several infections like dengue fever, malaria, scrub typhus, and community-acquired pneumonia are common. Finding the exact aetiology is important as treatment is different for each disease and unnecessary use of antimicrobial agents can be avoided. In India, epidemics of scrub typhus have been reported from north east and south India.^{5-7,10} We have observed a sudden outbreak of scrub

typhus from this part of the country.

O.tsutsugamushi, an obligate intracellular bacterium transmitted to humans by the bite of larval mites (chiggers) of *Leptotrombidium deliense*.¹ These larval mites usually feed on the wild rats of the subgenus *Rattus*. The organism is maintained by transovarian transmission in mites. There are several serotypes of *O.tsutsugamushi* and infections with one-serotype gives only transient cross immunity to another.⁷ Man is accidentally infected when he encroaches the mite-infested areas with secondary scrub growth, which grows after the clearance of primary forest. The basic pathologic changes are focal vasculitis and perivasculitis of the small blood vessels in the involved organs, arising from multiplication of the organisms in the endothelial cells lining the small blood vessels.^{11,12,13,14}

In the present study most of the cases were seen during the months of July to November. Scrub vegetation, optimum amount of monthly rainfall, and soil bound moisture are important factors responsible for disease transmission.¹⁵ Consequently, an increase in incidence of cases is seen in the rainy season.¹⁶ One more reason for increased incidence during the months of August to October is that, farmers are involved in the harvesting activity in the fields, where they are exposed to the bites of larval mites.¹⁰ However, there are descriptions of scrub typhus outbreaks in cooler seasons also.¹⁶ This is possibly due to the growth of secondary scrub vegetation, which is the habitat for trombiculid mites (mite islands in the immediate post monsoon period i.e. September to early months of the next year).¹

As described in literature the disease is common in farmers, persons rearing domestic animals and those living close to bushes and woodpiles.¹⁷ Farm work and related activities were noted in 60% in our study and it is comparable to other studies in the literature.^{18,19} Almost all the patients were from rural background in our study. The mean age of our patients is 41 years and majority were men. Age and sex can occasionally influence the incidence of scrub typhus mainly due

to the exposure to outdoor activities in the younger adults. Whether occupational or recreational, more common in 21-50 years and those involved in outdoor activities.²⁰

The classic case description includes an eschar at the site of chigger feeding, regional lymphadenopathy, and a maculopapular rash.^{1,21} An eschar at the wound site is the single most useful diagnostic clue and it is very important to perform a thorough physical examination to look for eschar and signs to exclude other causes of fever. Though eschar was pathognomonic of scrub typhus, it was noted only in 23 (13.1%) of our patients. Similar number of eschars reported in other Indian studies by Mathai *et al* (2003) and Vivekananda *et al* (2010). The reason for the less number of eschar in Indian studies may be due to the high skin colour of the population and due to variation of serotypes among different regions.⁶ Maculopapular rash was seen in 10 (5.7%) patients in our series and is comparable to other Indian studies.^{7,15}

Most of our patients with scrub typhus presented with non-specific symptoms of gastrointestinal and respiratory tract involvement mimicking viral fever. One of the clinical differentiating features in scrub typhus from other viral illnesses like dengue is the duration of fever. Average duration of fever in our study group was 11.8 days (ranging from 2 to 30 days). 40(22.7%) patients presented with prolonged pyrexia i.e., fever more than 2 weeks duration.

Scrub typhus involves multiple organs including the lung, heart, central nervous system (CNS), and is characterised by focal vasculitis or perivasculitis. Such microangiopathies may also involve the kidney (acute renal failure), gastrointestinal tract (gastrointestinal bleeding), liver (hepatic dysfunction and hepatomegaly), spleen (splenomegaly), and lymph node (lymphadenopathy).¹²

Respiratory tract involvement is a common manifestation of scrub typhus and clinicians need to differentiate it from community-acquired pneumonia caused by the usual organisms like streptococcus species. Cough and breathlessness

were present in 94 (53.4%) and 84 (47.7%) patients respectively in our series. Eighty (45.5%) patients had signs of consolidation on clinical examination. Respiratory failure is a common complication of scrub typhus and was reported in 11% of cases in one large series.²²

In our series, 11(6%) patients developed respiratory failure out of which 8 patients required ventilator support and 3 patients needed high flow oxygen support. Chest radiograph abnormalities in the form of reticulonodular opacities, air space consolidation, peribronchial infiltration, pulmonary congestion, pulmonary oedema, acute respiratory distress syndrome (ARDS) and pleural effusion were known to occur in scrub typhus.^{22,23}

Gastrointestinal system symptoms in the form of vomitings and loose motions are common presenting features of scrub typhus. Loose stools were seen in 28(15.9%) patients in our series. Clinician should suspect scrub typhus in a case of fever and diarrhoea if accompanied by symptoms of respiratory or central nervous system symptoms in an endemic area and it helps in differentiating from infective diarrhoea. Hepatosplenomegaly was seen in 51(28.9%) patients of our series. Among the gastrointestinal manifestations, elevated hepatic transaminases are a striking feature in scrub typhus that physicians need to pay attention in an endemic area. We have observed an elevation in transaminases in which ALT was found to be more than AST similar to the reports found in literature. Apart from transaminases, elevated serum alkaline phosphatase and serum bilirubin were seen in 110 (62.5%) and 68(38.6%) patients respectively in our study in comparison to other studies.^{7,15,24}

Renal failure was the next complication after hepatitis in our series. Elevation of serum creatinine > 1.6 mg/dl was seen in 49(27.8%) patients in which 5(2.8%) patients required dialysis. Renal failure was seen in 13- 37%^{7,15} from two different studies from India.

Scrub typhus, as the name suggests is characterised by fever with altered sensorium. In our study, the most common symptom is fever

associated with headache which occurs in 56.8% of patients. CNS involvement ranges from aseptic meningitis to frank meningoencephalitis.²⁵ The pathologic changes in the brain are predominantly vascular in nature and actual tissue destruction is rare and they are potentially reversible despite widespread lesions.²² As reported in other series in literature, 33 (18.8%) of our patients had drowsiness on examination during hospital stay. Seizures were present in 11(6.3%) and one patient presented with status epilepticus. All patients including the one with status epilepticus responded to treatment with doxycycline.

The existence of myocarditis in scrub typhus is easily ignored, because the symptoms of myocardial involvement are usually subclinical and sometimes may lead to heart failure also.²⁶ Cardiac conduction abnormalities in the form of bradycardia were seen on electrocardiogram in 6 (3.4%) patients. and we observed bradycardia on ECG in 6(3.4%) of our patients. Other febrile illnesses with relative bradycardia include dengue fever, brucellosis, chlamydiosis, legionellosis and enteric fever.²⁷

Another feature noted in our series was arthralgia in 8(4.5%) which was rarely reported in literature and only one study from India by Patil *et al* reported in 27% patients in their study from Karnataka.²⁸ Arthralgias are commonly described in other febrile illnesses like dengue fever and chikungunya fever and need to be differentiated from each other as treatment is different for scrub typhus.

Complete blood counts and peripheral smear examination initially help in differentiating aetiology of fever, which is important in developing countries like India where there are limited resources. Among the laboratory abnormalities, most common haematological abnormality noted was thrombocytopenia in 53(30.1%) patients followed by leucocytosis in our series. Similar observation was made by other studies. This helps in clinching the diagnosis to scrub typhus. In complicated falciparum malaria there will be anaemia, leucopenia usually and thrombocytopenia

occasionally. In dengue fever there will be haemoconcentration, leucopenia and thrombocytopenia.

Antibiotics of the tetracycline class (doxycycline in particular) have a high degree of efficacy and low toxicity in treating rickettsial infections, even in children and pregnant women. The treatment of choice for scrub typhus infection is doxycycline 100 mg per dose administered twice daily (orally or intravenously) for adults or 2.2 mg per Kg for children less than 45.5 Kg.²⁹ This treatment should be started empirically as soon as diagnosis is suspected. The optimal duration of treatment has not been established, but current recommendation suggests at least 3-7days for life threatening cases to a maximum of 15 days for severe or complicated disease. Alternatively chloramphenicol (500 mg 4 times a day orally for 7 days in adults or 150 mg per kg per day for 5 days in children) in endemic areas has been proven effective in treating scrub typhus and preventing relapse.²⁹ Rifampicin or azithromycin are effective in doxycycline resistant strains of scrub typhus.

Outcome of the patients admitted with scrub typhus was studied. All our patients are treated with doxycycline and supportive care. Doxycycline was given for 7 days in mild disease and 14 days for patients with multiorgan disease. Out of 176 patients 168 (95.5%) recovered, 1 (0.5%) patient left against medical advice and 8 (4.5%) patients died. The main cause of death is ARDS and the mortality in our study is comparable to other Indian studies.^{7,16,30} and a large study from Taiwan reported less (2-3%) mortality. The low mortality in Taiwan may be due to the endemicity of the disease and familiarity of the disease among the clinicians. The deaths in our series are possibly due to delayed diagnosis, late presentation and multiorgan dysfunction.

CONCLUSION :

Scrub typhus clinically mimics infections like dengue viral infection, leptospirosis, malaria, pneumonia as all of them may be associated with

sudden onset fever, mild hepatitis and thrombocytopenia. Associated headache, respiratory involvement, gastrointestinal symptoms, altered sensorium and hepatitis should prompt physicians for a diagnosis of scrub typhus. Majority of our patients with scrub typhus are from rural parts of Manipur. Though eschar is pathognomonic of the disease, it was noted in 23 (13.1%) patients and its absence does not rule out scrub typhus. Fever with headache are the most predominant symptoms while transaminases are the most predominant laboratory abnormality in our series. We conclude to say that in rural Manipur patients who present with fever, headache, respiratory symptoms and hepatitis scrub typhus should be suspected. As delay in treatment may lead to complications and higher mortality, empiric treatment with doxycycline or macrolides may be given in cases where scrub typhus is suspected and facilities for diagnosis are not available.

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Mycological and Clinical Correlation of Dermatophytic Infection in Tertiary Care Hospital of North East India

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ABSTRACT

Introduction: Dermatophytosis is the common and most significant superficial fungal infections of keratinized tissues, namely the skin, nails and hairs because of their widespread involvement among the people all over the world. **Objectives:** To study the clinical profile of dermatophytic infections and to identify the causative fungal species in the various clinical presentations. **Materials and methods:** A retroactive observational study was done on the basis of medical records admitted to Assam Medical College and Hospital during 01-03-2018 to 31-03-2019. Direct microscopy in 10% potassium hydroxide (KOH) and culture was done in each case. **Results:** A total of 845 cases were found during the study period of which 497(59%) were males and 348(41%) were females. Highest cases were seen in the age group from 21-30 years. *Trichophyton* was the most common clinical type (72.7%) followed by *Scopulariopsis* (22.7%) and *Trichosporum spp.*(4.6%). Overall positivity by culture was 1.4 % and by direct microscopy 28.3%. Among the total cases highest cases of Skin(71%) were seen. **Conclusion:** *Trichophyton* was the commonest agent of Dermatophytosis and overall predominance in the study was male with 21-30 being most affected age group. Due to poor hygienic status and lack of knowledge on fungal infection was possible cause of Dermatophytic infection.

Keywords : Dermatophytosis; Dermatophytic; Trichophyton; Dermatophyte Testing Media(DMT).

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INTRODUCTION :

Dermatophytosis is the most common disease in human beings mostly affected areas are scalp, skin and nails of the body. Dermatophytes are closely related to fungi that have the capacity to invade the keratinized tissues.¹ Dermatophytes are hyaline septate moulds with more than 100 species. According to Emmon's morphological classification, on the basis of conidial morphology dermatophytes are classified into three major genera, including Epidermophyton, Microsporum, and Trichophyton.² Dermatophytes are mainly aerobic fungi. They produce enzyme-like proteases that digest keratin and permit colonization, invasion, and infection of the scalp, skins and nails. Dermatophytosis is restricted to the nonliving superficial cornified layers because

its fungal agents are not able to penetrate into the deeper tissue or organ of a healthy host.³ The dermatophytosis depends on a variety of factors- the fungi, immune status of the host, and site of infection. Host reactions to the metabolic products of the fungi, virulence of pathogenic species of particular strain, and local environmental risk factors.⁴ Dermatophytosis can spread easily by direct contact with the infected humans and animals or through fomites. Dermatophytic infections are widespread and cause discomfort. Dermatophytosis is common in tropical countries like India and may reach epidemic proportions in areas with high rate of humidity, over population and poor hygienic conditions. Reactions to dermatophyte infection may range from mild to severe. The present study was designed to determine the risk factor, clinical patterns, prevalence and the most common fungal pathogen.

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MATERIALS AND METHOD :

A total of 845 samples including 601 skin samples, 222 nail samples and 22 hair samples from clinically suspected to have dermatophytosis were collected. A detail history regarding age, sex, occupation, social status, duration of complaint and others were taken.

Samples were collected from skin lesions, scales after cleaning the affected surface with 70% alcohol using a sterile blunt scalpel and hair were plucked with a sterile blunt scalpel. Collected samples were transported to the laboratory in sterilized Whatman filter paper envelope to resist drying of fungal spores.

Direct microscopic examination of the collected samples was done by using 10% KOH mount respectively. All samples were cultured on Sabouraud's dextrose agar (SDA) with gentamicin and cycloheximide (SDA with actidione) and dermatophyte test medium (DTM) (Hi-media). They were inoculated in two sets of these culture media, was incubated at 37°C and at 25°C in BOD incubator. Cultures were examined thrice weekly for the appearance of growth. Cultures were incubated for 1-month before discarding them as negative. Fungal growth was identified by colony morphology, pigment production and microscopic examination by tease mount technique in lactophenol cotton blue. Urease test and *in-vitro* hair perforation tests were also performed to differentiate *Trichophyton rubrum* and *Trichophyton mentagrophytes* when there was difficulty in identification by microscopic and macroscopic examination.

RESULTS :

A total of 845 clinically suspected cases of superficial mycosis enrolled for the different types of dermatophytic infections. Out of 845 cases, 601 samples from skin, 222 from nails and 22 from hairs were collected (Table 1)(Fig 1).Maximum number of fungal isolates were positive in skin

samples by KOH microscopy culture which is similar to other studies.^{5,6} Out of 26 clinically suspected samples of nails 22 samples were cultures positive. Among 845 patients 497(59%) were males and 348(41%) were females. Maximum number of cases were in the age group of 21-30, 31-40 (Table 2). Our study revealed that *Trichophyton*(72.7%) is the most common isolated species in the

Table 1: Categorical distribution of clinical samples

Types of Specimens	Number of cases	Percentages
Skin scrapings	601	71.1
Nail clippings	222	26.3
Hair stubs	22	2.6
Total	845	100

Table 2: Age wise distribution of cases

Age	Number of cases	Percentages
0-10	55	6.5
11-20	87	10.3
21-30	207	24.5
31-40	203	24.02
41-50	133	15.7
51-60	80	9.46
61-70	61	7.21
71-80	19	2.25
Total	845	100

Table 3: Distribution of identified dermatophytes

SL No	Name of isolate	Number of isolate	Percentage
1	<i>Trichophyton</i>	16	72.7
2	<i>Scopulariopsis</i>	5	22.7
3	<i>Trichosporum</i>	1	4.6
	Total	22	100

Fig 1: Categorical distribution of clinical samples of study period

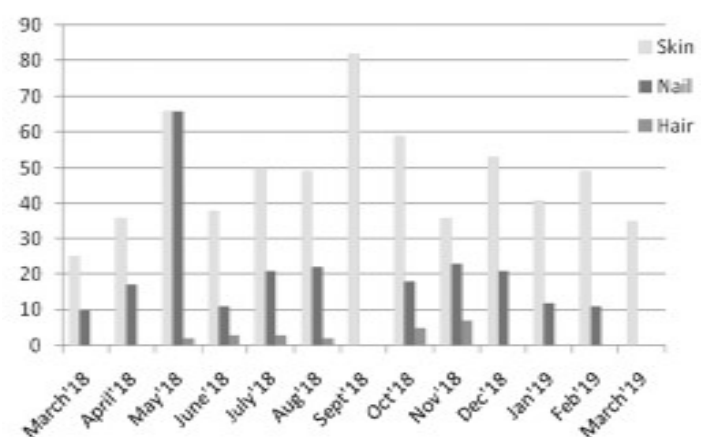
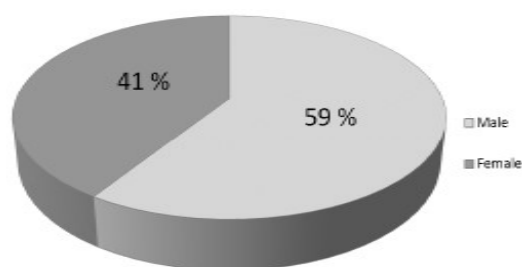


Fig 2: Distribution of male and female patients



laboratory followed by *Scopulariopsis*(22.7%), *Trichosporum*(4.6%)(Table 3).

DISCUSSION :

Dermatophyte infections are widespread and cause significant distress to the patients socially, emotionally and financially. Recurrent dermatophytosis is fast emerging as a challenge for dermatologists in India.⁷ The incidence of dermatophytosis is undoubtedly very high. However, neither the medical profession nor the research workers paid any attention toward the investigations of these important human infections. In our study the maximum numbers of infection were seen in the age group of 21- 40 years. Similar findings have been reported in a study conducted by Kamothi where 39% of the patients were seen in the age group of 21-30 years.⁸ In our present study, most of dermatophytic infections were seen in male patients could be due to greater physical activity and increase sweating. Similarly Hassan *et al* in his study observed a male preponderance of dermatophyte infection, with a male: female ratio of 2:1.⁹ Our results also agree with Kumar *et al*, who reported that the percentage of males affected with ringworm infections was only marginally higher than females.¹⁰ In our study the major clinical isolate is *Trichophyton* and the second common isolate is *Scopulariopsis*. 22 samples of nails were culture

positive. Specimens of skin and hair were frequently negative on direct microscopy.

CONCLUSION :

Dermatophytosis is the most common infection found in tropical and subtropical region. Our present study gives an insight about the etiological agents of dermatophytosis in the part of north east. Lack of knowledge about this disease differed from other areas in chronicity and involving mixed sites. In case of commonest lesion, species isolated and other variables it is similar to the other parts of India. *Trichophyton* is the most common causative agent of dermatophytosis in this region.

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Mechanism of Hypoxia in Covid : A Review of It's Physiological Derangement

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INTRODUCTION :

The pandemic of coronavirus disease 2019 (COVID-19) have become the greatest threat to public health and several waves have already caused a significant morbidity and mortality globally. It has a predilection to cause hypoxia in almost all infected, although it has multi-system damaging effect since widespread microthrombi in blood vessels is almost universally present in the severe disease. However, systemic hypoxemia and acute respiratory distress syndrome (ARDS) remain the primary manifestations in SARS-Cov 2 infection. They precede cytokine storm and inflammation due to various patho-physiological disturbances that may lead to a lethal outcome. Increased risk of death is associated with increasing age, associated co-morbidities, male sex, presence of inflammatory biomarkers, and hypoxemia/dyspnea.^{1,2,3} The key to successful management of COVID primarily rests on early recognition and prompt correction of hypoxemia. A study from China reported that an SpO₂ value of 90% or less was strongly associated with death, independent of age and sex (multivariable HR, 47.41; 95% CI, 6.29 to 357.48; $P < .001$).³ Most importantly this study demonstrated an independent mortality risk associated with two

simple features: dyspnea and hypoxemia (SpO₂ < 90% despite oxygen supplementation) that can be assessed by primary health care givers.

COVID, RESPIRATORY PHYSIOLOGY AND HYPOXIA :

The exact pathophysiological alteration of pulmonary functions in COVID-19 leading to hypoxemia is largely unknown and likely to be multifactorial. They include pneumonia, ARDS, intrapulmonary vasodilatation and shunting, vascular microthrombi, hyluronic acid deposition, and loss of lung compliance in varying degrees. Early recognition of hypoxemia and its correction has been shown to reduce ICU admission thereby reducing health care burden in addition to predicting mortality in symptomatic COVID-19.^{4,5} Significant hypoxemia is commonly seen COVID-19 patients presenting with dyspnea and leads to a suspicion of moderately severe or critical disease. However, there have been reports of some patients with significant arterial hypoxemia but without proportional respiratory distress, therefore presenting without dyspnea.⁶⁻¹⁰ Hence, the term *Silent or Happy Hypoxia*. In one Chinese study only 18.7% of 1099 hospitalized COVID-19 patients reported dyspnea, despite associated low PaO₂/FiO ratios, abnormal CT scans in 86% and need for supplemental oxygen in 41% of patients¹¹ while the rest had minimal or no dyspnea.

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Respiratory drive is dependent upon the respiratory centres in brainstem (medulla and pons) to meet the metabolic demands of the body. To co-ordinate respiration, these centres receive chemical inputs from peripheral and central chemo-receptors. Other inputs influencing respiratory drive also include higher brain cortex, hypothalamic integrative nociception, feedback from mechanostretch receptors in muscle and lung, and metabolic rate.¹² The resultant outputs ultimately influence the rate of respiration and the pattern or rhythm of respiration, *viz.* tachypnea, hyperpnea, irregular breathing etc.¹³ Conscious awareness of the activation of respiratory muscles is absent in healthy breathing. Dyspnea will occur as a distressing or uncomfortable sensation if the demand for ventilation exceeds the physiological responses, in various grades. Therefore, if and when the respiratory muscles are fatigued due to deranged lung mechanics (e.g. decreased thoracic/lung compliance), bronchoconstriction and inputs from mechanoreceptors from thoracic wall, dyspnea may become prominent too.¹⁴

The primary dominant determinant of respiratory drive is dependent however, on the central and peripheral chemoreceptors which are highly sensitive to alterations in PaCO₂ (partial pressure of dissolved carbon dioxide in the blood), resulting in pH changes. Compared to hypercapnia, hypoxemia causes less dyspnea¹⁵ occurring only if the PaO₂ drops below 40 mm Hg. The normal response to hypoxemia is a rise in minute ventilation/hyperventilation, by increasing tidal volume and respiratory rate. Increased respiratory rate (tachypnea) and tidal volume (hyperpnea) and not dyspnea, are the most important clinical features of impending hypoxemic respiratory failure.¹⁶ Hyperventilation causes decreased PaCO₂ leading to arterial vasoconstriction thus lowering cerebral blood flow and intracranial pressure. Conversely, increase in PaCO₂ leads to increased intracranial pressure ultimately resulting in deteriorating level of consciousness, altered

brainstem reflexes, and altered postural and motor response. So, a detailed understanding of the pathophysiological determinants of respiratory drive and hypoxemia may provide a more clear comprehension of a COVID-19 patient's clinical presentation and timely management¹²

CAUSES OF HYPOXIA IN COVID-19

Early in the diseases, arterial hypoxemia is due to V/Q mismatch and persistent pulmonary arterial blood flow to non-ventilated alveoli, reflected by a marked increase in P(A-a)O₂ gradient. The infection leads to a modest local interstitial edema, particularly located at the interface between lung structures with different elastic properties, where stress and strain are concentrated.¹⁶ Due to increased lung edema (leading to ground-glass opacities and consolidation on chest imaging), loss of surfactant and superimposed pressure, alveolar collapse ensues and a significant fraction of the cardiac output is perfusing non-aerated lung tissue, resulting in ***intrapulmonary shunting***.¹⁶ Then tidal volume increases during the shunting leading to rising negative inspiratory intrathoracic pressure. The latter, in combination with increased lung permeability due to inflammation, will eventually result in progressive, interstitial and alveolar edema.¹⁷ Later, the increased edema will further enhance lung weight, alveolar collapse, and dependent pulmonary collapse, resulting in progressively increasing shunt fraction and further decline of oxygenation which cannot be corrected completely by increasing FiO₂.

Normally, intrapulmonary vasoconstriction to non-aerated alveoli is the rule as a ***regulatory mechanism in lung perfusion***. But recently it has been shown that bradykinine and other cytokine release in SARS Covid may predispose to persistent blood flow (*hyperdynamic pulmonary flow*) to non ventilated alveoli, thereby aggravating hypoxemia.¹⁸ Lung perfusion may also be disturbed in Covid-19 associated lung injury by dysregulation of the

renin-angiotensin system (RAS) system. ACE2 receptors are used by Covid virus for cell entry, thereby reducing ACE2 levels. Conversion of (a vasoconstrictor), to Angiotensin I is mediated by ACE2 which also degrades bradykinin. Therefore a rising level of Angiotensin II can lead to pulmonary vasoconstriction in Covid pneumonitis and is associated with increasing viral load and lung injury.¹⁹ Hence there seems to be a complicated irregularity in V/Q physiology in Covid lung.

COVID virus directly infects pulmonary capillary endothelial cells expressing ACE2 receptors leading to **Intravascular microthrombi** — the net result of an imbalance between procoagulant and fibrinolytic activity in acute inflammation and endothelial injury. Lung autopsy in severe disease showed fibrin deposition, diffuse alveolar damage, vascular wall thickening, and frequently occurring complement-rich microthrombi occluding lung capillaries and larger thrombi causing pulmonary artery thrombosis and embolism.²⁰ The procagulant activity may be due to multiple reasons e.g. *a)* complement system-mediated activation of clotting, or thrombotic microangiopathy (TMA), *b)* inhibition of plasminogen activation and fibrinolysis via increased activity of plasminogen activator inhibitor (PAI-1 and -2) which are induced as acute-phase proteins under the influence of IL-6 and *c)* activation of C-reactive protein and resultant complement activation and hepatic synthesis of fibrinogen as an acute phase protein in COVID-19.^{13,21} Diffuse intravascular coagulation (DIC) also seen in patients with severe COVID-19, is mediated via endothelial release of tissue factor and activation of clotting factor VII and XI. Many patients with COVID-19 develop elevated D-dimers suggesting the formation of blood clots. Hypercoagulable state due to any cause leads to further deterioration in V/Q mismatch, hypoxemia and pulmonary tissue damage in COVID.

Impaired diffusing-capacity was detected in 30.4% in mild illness, 42.4% in pneumonia and 84.2% in

severe pneumonia²² especially with exercise. Immune response mediated destruction of infected alveolar type II epithelial cells and a pro-coagulant state cause the denuded basement membrane to be covered with debris, consisting of fibrin, dead cells, and complement activation products, collectively referred to as hyaline membranes.²³ In the background of an intrapulmonary hyperdynamic state, this can result in impairment in gas diffusion and arterial hypoxemia with raised P(A-a)O₂ gradient mostly with exercise.

THE ENIGMA : “HAPPY” HYPOXEMIA IN COVID 19

The disparity between significant hypoxemia and relatively mild respiratory discomfort (dyspnea) in some cases of COVID are not exclusive to Covid and has been reported in patients with atelectasis, intrapulmonary shunt (i.e. arterio-venous malformations) or right-to-left intracardiac shunt.¹³ The lung mechanics in COVID remain relatively normal in presence of increasing hypoxemia, without any associated increased airway resistance, and no increases in anatomical or physiological dead space ventilation, and effort of breathing is low in absence of a pre-existing lung disease. This implies preserved lung compliance, especially in early stages of the disease and in resting state. However, lung compliance can still be near normal in critically ill patients as reported recently²⁴, which is highly unusual for most forms of disorders that lead to acute lung injury and ARDS. But contradictions exist in this regard.²⁵ But in all cases as the disease progresses, dyspnea becomes increasingly apparent as well as decreasing lung compliance. Hypoxemia-driven tachypnoea, hyperpnea and altered oxygenation predict clinical deterioration and this underscores the importance of silent hypoxemia in COVID, which can progress rapidly to critical states within a short period. Understanding of the respiratory mechanics found in COVID-19 will continue to evolve as further research is reported.

The oxygen dissociative process in COVID due to hypoxemia is altered too. Normally all COVID patients are monitored for hypoxia by SpO₂ measurement. However, the sigmoid shaped **oxyhemoglobin dissociation curve** shifts to the left, due to induced respiratory alkalosis (low PaCO₂) because of hypoxemia-driven tachypnea and hyperpnea. During hypocapnia, the affinity of hemoglobin for oxygen and thus oxygen saturation increases for a given degree of PaO₂, and SpO₂ can be well-preserved in the face of a profoundly low PaO₂.²⁶ Other workers have suggested that due to direct viral interaction with heme fraction of hemoglobin, there is a rise in serum ferritin plus hemoglobin to neutralize harmful iron ions that are generated during inflammation to protect against tissue damage.²⁴ Overall, we have to be cautious while interpreting SpO₂ values through pulse oximetry, since hyperventilation induced drop in alveolar partial pressure of CO₂ may actually increase alveolar partial pressure of oxygen which can lead to normal/high SpO₂. In these situation, arterial blood gas estimate is accurate to diagnose hypoxemia, in absence of dyspnea. Combination of hypoxia and dyspnea therefore will be a most dangerous clinical situation suggestive of very advanced disease process.

CONCLUSION :

The respiratory symptoms in early and late stages of COVID lung involvement depend upon different multiple physiological changes. Hypoxemia and hypoxic respiratory failure may be associated with no dyspnea especially at rest. Although multifactorial, the primary denominator of hypoxemia is physiologically either due to intrapulmonary vascular shunting or V/Q mismatch. The former does not respond properly to O₂ supplements while the latter does. Since clinicians monitor hypoxemia by pulse oximetry (SpO₂), it may remain normal in presence of significant hypoxemia, and dyspnea is not a

prominent feature of early hypoxemia (silent or happy hypoxia). Therefore tachypnea and hyperpnea should be taken as a warning for impending respiratory failure rather than dyspnea. These patients can deteriorate rapidly and show a high mortality once admitted to ICU. Assessment by arterial blood gas analysis coupled with careful clinical monitoring of respiration alongwith SpO₂ interpretation should be carried out at regular intervals in such patients.

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Erythema Nodosum : An Unusual Chronic presentation Secondary to Latent Tuberculosis

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ABSTRACT

Introduction: Erythema Nodosum (EN) is a form of panniculitis (inflammation of the fat layer beneath the skin) that produces tender red or violet subcutaneous nodules usually on lower legs, but also on upper extremities. The causes are infections [streptococcal infections, upper respiratory viral infections, bacterial gastroenteritis (*Yersinia, Salmonella*), coccidioidomycosis, tuberculosis, histoplasmosis, brucellosis], sarcoidosis, inflammatory bowel disease in addition to drugs (OCs, sulphonamides, penicillins, bromides, iodides). **Case Report:** An 18 year old unmarried female presented with recurrent history of erythematous painful non-ulcerating nodules for 7 years on extensor surfaces of lower limbs and occasionally upper limbs for which she had consulted medical advice on several occasions and received symptomatic treatment. She presented to Medicine OPD of GMCH for exacerbation of her same symptoms for last 6 months and also had history of fever and bilateral ankle joint pain for last 1 month. She had a contact history of Open Tuberculosis in family 8 years back. MANTOUX test was found to be positive (70 mm induration). She was thought to be a case of Latent Tuberculosis with Erythema Nodosum. However HRCT Thorax revealed bronchiectatic changes and mucus plugging in left upper lobe of lungs with multiple centriacinar nodules, suggestive of infective etiology. Quantiferon TB Gold test was also found to be positive. A diagnosis of Pulmonary Tuberculosis with Erythema Nodosum was made and patient was started on ATT. **Conclusion:** Though Erythema Nodosum usually resolves in 6 weeks, this is an uncommon case of Chronic Erythema Nodosum, secondary to Latent Tuberculosis which lasted for 7 years and subsequently presented as Pulmonary Tuberculosis. Anti Tubercular treatment started and nodules resolved gradually after 3 weeks of treatment. Patient has completed 4 months of Antitubercular treatment and no relapse was seen.

Keywords : Erythema Nodosum, Panniculitis, Latent Tuberculosis.

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INTRODUCTION :

Erythema Nodosum (EN) is a form of panniculitis, which is inflammation of the fat layer beneath the skin. Erythema Nodosum produces large, violaceous, nonulcerative, subcutaneous nodules which are tender and usually present on lower legs, but also on upper extremities. Erythema nodosum is more common in women and occurs three to five times more often in female patients. In erythema nodosum, the nodules are initially red but then develop a blue colour as they resolve. The shin is the most common location for the nodules of erythema nodosum. Erythema Nodosum shows histopathological diversification, including vasculitis, septal interlobular inflammation,

haemorrhage, varying degrees of acute or chronic panniculitis, and Miescher's radial granulomas. Patients with erythema nodosum can have fever, malaise, leucocytosis, arthralgias and/or arthritis. However, the possibility of an underlying illness should be always excluded.

The common associations with Erythema Nodosum are streptococcal infections, upper respiratory viral infections, sarcoidosis and inflammatory bowel disease, in addition to drugs (oral contraceptives, sulphonamides, penicillins, bromides, iodides) in developed countries. Less common associations include bacterial gastroenteritis (*Yersinia, Salmonella*) and coccidioidomycosis followed by tuberculosis, histoplasmosis, brucellosis and infections with *Chlamydia pneumoniae* or *Chlamydia*

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trachomatis, Mycoplasma pneumoniae or hepatitis B virus.

But in developing countries like India, Tuberculosis is much more common than in developed countries and hence it is a more common association with Erythema Nodosum.

CASE REPORT:

An 18 year old unmarried female presented with recurrent history of erythematous painful non-ulcerating nodules for 7 years on extensor surfaces of lower limbs and occasionally upper limbs for which she had consulted medical advice on several occasions and received symptomatic treatment.

She presented to Medicine OPD of GMCH for exacerbation of her same symptoms for last 6 months and also had history of fever and bilateral ankle joint pain for last 1 month.

Past history: The patient had a contact history of Tuberculosis in family 8 years back. Her grandfather had open Pulmonary Tuberculosis.

No H/o- Intake of any drugs

No H/o Travel

Examination revealed:

B.P. = 110/70 mm Hg,

PR = 86/min, regular

Body Temperature = 100.2°C

RR = 16/min

SpO₂ = 98%

Multiple erythematous subcutaneous nodules were seen on the anterior aspect of tibia and extensor surface of elbow which were non ulcerating and painful and bilateral ankle joint arthralgia.

No pallor, icterus, cyanosis, clubbing, pedal edema and lymphadenopathy.

Respiratory System: Bilateral vesicular breath sounds present, no added sounds.

Cardiovascular and GI system examination did not reveal any abnormality.

Investigations revealed: TC=6200, Hb=10.5

ESR =66mm. RBS=105, Urea=20 Creat= 0.6. LFT - TSB 1.30 Direct 0.4 Indirect 0.9, ASO TITRE

=Insignificant; Viral Markers =Negative; ANA; Anti CCP =Negative; Throat Swab =Negative; MANTOUX TEST -Positive(70 mm)

ACE Test-Negative.

CXR PA View-Normal

Quantiferon TB GOLD- Positive

Provisional Diagnosis was made as Erythema Nodosum secondary to Latent Tuberculosis.

D/D -Sarcoidosis

Chronic Erythema Nodosum

Lupus Panniculitis

After hospitalisation she started coughing and subjected to HRCT Thorax.

HRCT THORAX revealed Bronchiectatic changes and mucus plugging in left upper lobe of lungs with multiple centriacinar nodules, suggestive of infective etiology.

Patient was diagnosed to be an uncommon case of Chronic Erythema Nodosum due to Latent Tuberculosis, which lasts for 7 years and subsequently landed up with Pulmonary Tuberculosis. Anti Tubercular treatment started and nodules resolved gradually after 3 weeks of treatment. Patient has completed 4 months of Antitubercular treatment and no relapse was seen.

DISCUSSION :

Panniculitis, an inflammation of the fat, also presents as subcutaneous nodules and is frequently a sign of systemic disease. There are several forms of panniculitis including Erythema nodosum, Lupus panniculitis. Except for erythema nodosum, these lesions may break down and ulcerate or heal with a scar. The shin is the most common location for the nodules of erythema nodosum.

Lesions in Sarcoidosis arise as asymptomatic macules and papules ranging in colour from redbrown to purple and in size up to 5 mm. The commonest areas of involvement are the face and extensor aspects of the limbs.¹ Chest roentgenogram will show bilateral hilar adenopathy in sarcoidosis patients, which was absent in our patient.

Erythema Nodosum usually resolves in 6-8 weeks without any ulceration or scar formation. But according to a study conducted by Robert M. Fine *et al*², there is a Chronic form of Erythema Nodosum, which has a varied clinical presentation but a common histology typical of Erythema Nodosum. This form of Erythema Nodosum can continue for years. Patients with this condition are generally healthy and do not have any serious associated systemic disease.

Lupus panniculitis is characterized clinically by painful (later asymptomatic) subcutaneous, nodules and plaques that may later adhere to the overlying skin. Histology shows lobular panniculitis with a dense inflammatory infiltrate of lymphocytes and plasma cells as well as mucin deposits between fat cells. The sites of predilection in Lupus Panniculitis are the gluteal region and thighs as well as the upper extremities.³

In regions such as India, *Mycobacterium tuberculosis* may be the most important factor in Erythema Nodosum.⁴ Our patient who was having recurrent episodes of erythematous nodules was diagnosed to be a case of Latent Tuberculosis, who subsequently revealed evidence of pulmonary involvement. Other causes for Erythema Nodosum were ruled out with proper history taking, clinical examination and blood investigations.

Our patient is an uncommon case of Chronic Erythema Nodosum due to Latent Tuberculosis, which lasts for 7 years.

CONCLUSION :

The association of Tuberculosis with Erythema Nodosum is uncommon in developed countries as the prevalence of Tuberculosis is low in these countries. But in developing countries like India, the prevalence of Tuberculosis is much higher. Therefore, Tuberculosis is a much more common cause of Erythema Nodosum in India.

There has not been any study in North Eastern India about the association between Erythema Nodosum and Tuberculosis, but the prevalence of tuberculosis is higher in northeastern states.⁵ Therefore, all cases of Erythema Nodosum are to be screened for both latent and active Tuberculosis in this region of the country.

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Fracture Shaft of Femur in PwH (person with haemophilia): Surgery or conservative??

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ABSTRACT

Haemophilia is uncommon and therefore fractures in haemophilic patients are not often met. In severe haemophilia, a minor injury can lead to hemorrhages, sometimes spontaneously the patient can bleed. While undergoing any surgical procedure proper haemostatic management is needed along with the other measures. Persons with Haemophilia (PwH) are more prone to post operative complication like infection, bleeding, decreased flexibility of muscles and joints. So, it's always been a debate and challenge for the surgeon and hematologists to opt for surgery in a person with haemophilia. Here we present a case report of 9 year old Haemophilia. A patient with fracture shaft of femur managed conservatively without surgery.

Keywords : Person with Haemophilia (PwH), Haemophilia A, Factor VIII.

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INTRODUCTION :

Haemophilia A is a X-linked recessive disease due to mutations in F8 gene. Haemophilia affects 1 in 10,000 males worldwide in all ethnic groups and haemophilia A represents 80% of all cases.¹ In our two previous publications, haemophilia A was recorded at 81 %² and 79.7 %³ respectively. The incidence of fracture in PwH population is very low. This low incidence is related to both the lower rates of daily activities and the slower movements that go hand in hand with the condition of the muscles and joints⁴. On the other hand joint deformation, osteoporotic bones, and poor musculature increase the fracture risk in hemophiliac individuals, after a trivial trauma in these patients⁵. However, in a recent study, Gay and co-workers reported a higher incidence of fractures in PwH compared to a population without haemophilia (24.8 fractures per 1000 patient-

years vs. 9.6 fractures per 1000 patient years in the control group)⁶. In the mid 20th century, the mortality of up to 66% has been reported for patients with haemophilia undergoing minor and major surgical procedures.⁷ Due to improvement of perioperative haemostatic management using clotting factor concentrates, a reduction in the mortality rate to 4.5% was achieved.⁸ Nevertheless, treatment of persons with haemophilia (PwH) remains a challenge for surgeons and haematologists even in elective surgery.⁹ This can only be ensured by a close interdisciplinary cooperation between surgeons and haemostaseologists guaranteeing timely and individualized factor replacement. Here we mentioned a patient of haemophilia A with closed fracture of shaft of left femur managed conservatively.

PRESENTATION OF THE CASE :

A nine (9)year old boy suffering from severe Hemophilia A came across a RTA and presented with fracture shaft of left femur to AMCH

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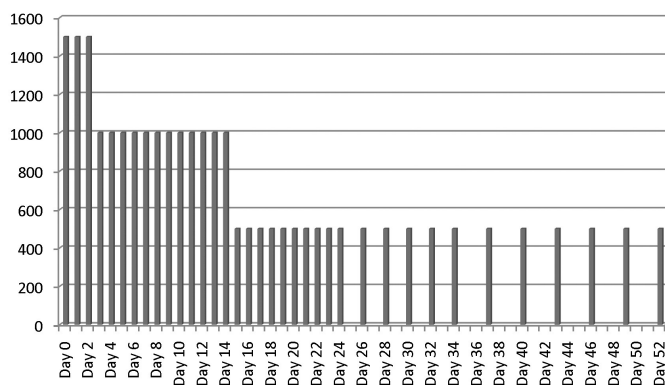
casualty. On examination, patient's vitals was stable and GCS was within normal limit. There were many abrasion marks over the hands and legs. On examination of local site there was redness, swelling, tenderness, crepitation, acute deformation and integration of shaft of femur was lost, looked like a closed fracture. X-Ray showed fracture of shaft of femur (Image 1).



Image 1:
Day of Accident
X-ray done on day of presentation (19/10/2019) with Thomas splint.

1500 IU of factor VIII stat dose was given as per his body weight and after stabilizing the patient by initial management (ice pack, splinting, necessary analgesia) from the orthopedics side, The patient was hospitalized for further management and observation. 1500 IU of factor VIII was given daily for the first 3 days, 1000 IU factor VIII every day for the next 2 weeks, 500 IU daily from day 15th -24th and on alternate day from day 25th -34th (Figure 1) was given to make

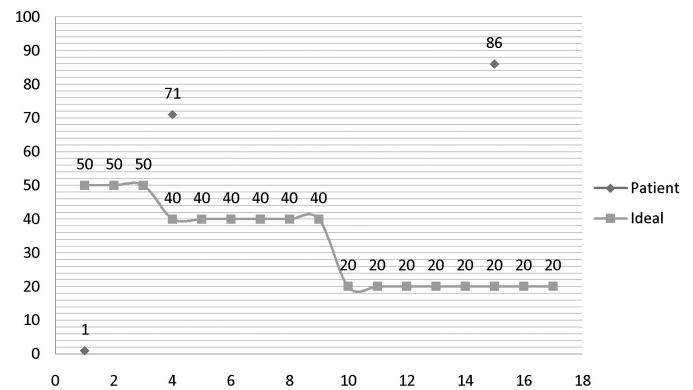
Figure 1 : Factor VIII (International Unit) given during hospitalization and during follow up.



sure that fracture heals properly without any risk of fresh bleeding as the level of factor should be e+50% during the closed reduction and within first 48 hours, e+40% in the next 4-8 days,

e+30% in the following 9-15 days of fracture, then the prophylaxis dose of 500 IU twice weekly was applied to maintain the factor level at e+20% . Factor assessment was done on day 3rd and 14th as shown in Figure 2. Orthopedics consultation was being taken regularly during the hospital stay.

Figure 2 : Factor levels (%) of the patient recorded on Day 3 (71%) and day 14 (86%) were quite higher than the desired trough levels.



From the orthopedics side conservative management was planned. Initially limb was stabilized with Thomas splint and skin traction. Closed reduction was done and hip spicacast was applied under GA. X-ray was repeated after one week (Image 2). Patient was discharged on 29th oct , 2019 after taking the clearance from orthopedics and secretary of haemophilia society.



Image 2:
One week later
X-ray taken after 7 days of presentation on 25/10/2019 with Hip spica cast

On discharge patient was advised to do active toe movements, limb elevation, to take care of plaster, to consume syrup calcitonin 5ML once daily for 45 days, syrup cefixime for 14 days, to take factor VIII as per the schedule mentioned earlier and to review after 2 weeks.

After the discharge patient was being followed up multiple times and multiple X-rays were

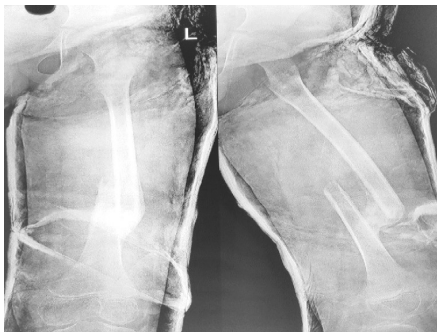


Image 3:
One month later
X-ray done on 18/12/2019 after one month of fracture.



Image 4:
Removal of plaster
X-ray done on 13/01/2020 after removal of plaster.



Image 5:
Five months follow-up
X-ray done on 6/3/2020 showing malunion of fracture in one plane.

Image 6:
shoe raise



taken as shown in Image 3,4,5. Plaster was removed on 13/1/2020. Latest X-ray done on 6/3/2020 showed malunion of the shaft of femur only on lateral view. Though Left leg is a bit shortened Quality of life is least affected. He can walk and do day to day work without assistance. He is on maintenance dose of factor replacement therapy now, 500 IU of factor VIII twice weekly, is advised to consult orthopedician .

Future plan of management : Since the fracture is malunited in one plane, Patient will be followed up to the age of skeletal maturity ,and residual limb shortening will be calculated and adequate amount of shoe raise (Image 6) will be given and patient will be encouraged to ambulate under physiotherapy guidance .

DISCUSSION :

Every fracture in PwH should be managed as per the normal fracture management protocol. The neurological and vascular status of the region should be recorded before and after dealing with the fracture. The aim of modern fracture treatment is both the union of the fractured bone in the correct anatomic position, and the functional healing of the adjacent soft tissues and joints. Treatment begins with re-alignment of the fracture and immobilization of the extremity with splint. However in PwH temporary splinting and appropriate doses of factor replacement should be performed with necessary doses of analgesics and sedatives given before reduction of fracture. Ibuprofen and paracetamol can be safely used. Surgery is required if unacceptable reduction and shift in alignment of fracture occurs.²

Haematologic treatment :

The appropriate dose of factor changes according to the weight of patient and the level. The factor level should be raised to above 50% during closed reduction, and should be kept above 50% in the first 48 hours. The factor level should be kept above 40% between day 3 and 8, and 30% between day 9 and 15. During the later period of immobilization, it will be safe to keep the factor level above 20%.⁴

For surgical procedures factor level should be raised above 50% during operation, maintained above 50% during first 4 days after the surgery, and above 40% , 30% in the next 4-8 days, 8-15days respectively. Then the prophylaxis dose should be applied. Tranexamic acid can be used as an adjunct therapy during the operation as IV

infusion, can be used orally also. Tranexamic acid treatment should begin 12 hour prior to the operation and continue for 5-7 days. 10mg/kg single iv stat dose can also be given during the operation. FFP can be used if there is no other option is left⁴

Compartment syndrome:

Fracture hematoma due to damaged periosteal and endosteal vessels can occurs and tends to be larger in PwH. If the fascia around the fracture space is still intact, the pressure in the compartment increases. If it lasts for longtime Muscles, nerves, vessels get compromised. Irreversible damage such as muscle necrosis, nerve palsies can occur. So, compartment syndrome should be diagnosed as earliest as possible and early intervention should be taken. Treatment of choice is fasciotomy in both haemophilic and non-haemophilic patients.^{10,11}

Orthopedics management:

Fracture treatment of PwH in an acute trauma situation is challenging due to a high risk of bleeding as clotting factor levels may not be adequate at the time of trauma. While the indications and the principles of surgical fracture treatment are similar in PwH and non-haemophilic patients, maintenance of haemostasis plays a major role for injured patients with a coagulation disorder.¹² For both methods, it is important to prevent further bleeding during the process of fracture healing. It is important to keep in mind that an osteoporotic bone can be so fragile that it will not allow stabilization by either internal or external fixation.¹³ Infection rates after osteosynthesis or endoprosthesis operations are known to be higher in hemophiliac patients than in the general population.¹⁴ The muscles' flexibility around the fracture is likely to have decreased, and the scar tissue after the surgical dissection can therefore further negatively affect the muscles' flexibility in that area. Percutaneous pins during external fixation might loosen prematurely because of minor bleeding around the pins.¹⁵ Pin tract infections in

external fixators can cause more serious problems for hemophiliac patients. Taking all of these factors into consideration, one has to be careful when applying surgical treatment in hemophiliac patients. Circumferential plaster should be avoided; splints are preferred. In hemophiliac patients, rehabilitation is a "sine qua non" due to associated factors like hemophilic arthropathy and muscle contractures. When treating fractures in hemophiliac patients, rehabilitation should be slow enough not to negatively affect the healing of the fracture and cause further bleeding. It should, however, be fast and aggressive enough to avoid joint adherence and muscle atrophies.⁴ Physiotherapy should be started as soon as the fracture is stabilized to restore range of motion, muscle strength, and function.¹⁶

CONCLUSION :

Currently, internal stabilization is indicated in most displaced fractures in the children, whereas external fixation remains the best choice for initial stabilization when the fracture is complicated by severe soft-tissue injuries. If a fracture is promptly treated in a haemophilia patient, it will progress to healing in a similar time frame to those occurring in the general population. Though rigid internal fixation is preferred to external fixation, but this has to be done under recombinant factor VIII concentrate cover, which is not readily available in our environment and it is quite expensive and there is a risk of complications. Hence conservative management is one of the better choice.¹⁷

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Sudden loss of vision– a rare presentation of Fahr’s disease

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ABSTRACT

Abstract : Fahr’s disease is a rare neurodegenerative disorder. Most commonly transmitted as autosomal dominant trait. The clinical course of the disease has a degenerative component, often slowly progressive and lasting for many years. Although behavioural impairments and dementia is a common manifestation, we report this case of Fahr’s disease in a young female with secondary amenorrhea and sudden onset loss of vision which is a very rare presentation.

Keywords : Fahr’s disease, loss of vision, secondary amenorrhea

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CASE REPORT :

A 30 year old female came to our casualty in the last week of September, 2020 with 3 days history of sudden loss of vision of both the eyes and 1 days history of irrelevant talk and abnormal behaviour associated mild headache and giddiness. According to the attendant she had no h/o fever, head injury or any substance abuse. She was non hypertensive, non diabetic, no h/o thyroid disease, autoimmune disease or no past history of stroke. She was having secondary amenorrhea for last 14 years. No family history of any neurodegenerative and movement disorders.

On examination, the patient was confused, not oriented to time, place and person. The pulse rate was 96/min, regular. BP – 110/70 mmHg, Spo₂- 98% on room air. The respiratory, cardiovascular and abdominal examinations were found to be normal. On neurological examination, bilateral extensor plantar reflex and exaggerated jerks were found. There was no neck rigidity. Ophthalmology examination showed - B/L

congested eyes, Visual Acuity could not perform. Fundoscopic examination revealed mild temporal pallor in B/L optic disc. Biochemical reports showed RBS-124mg%, S.creat-0.86mg%, S.Na-135.97mmol/L, potassium -4.93mmol/L, Serum calcium – 9.3mg%, AST-51 U/L, ALT-67 U/L, total bilirubin-0.61mg/dl, TSH -2.93 IU, Hb%- 13.7gm%, TC-13,640/cumm, N-76.2%, L-17%. E-1.8%, M-5%, ESR-5mmAEFH. RTPCR for covid was negative. The Computed Tomography scan of brain showed bilateral basal ganglia and cerebellar hemisphere calcification- possible Fahr’s disease / inherited mitochondrial disorder. She had abnormal awake EEG suggestive of diffuse cerebral dysfunction. Her ultrasonography of whole abdomen showed focal bladder wall thickening with echogenic debris suggestive of cystitis; uterus appears small and atrophied, with minimal free fluid in pouch of Douglas.

She developed several episodes of seizure during the period of hospitalization for which she had to be shifted to ICU and treated accordingly. The patient was diagnosed to be a case of Fahr’s disease based on the CT findings. Patient’s general condition improved except the visual loss. She was referred to higher centre for further management and did not come back for follow up till now.

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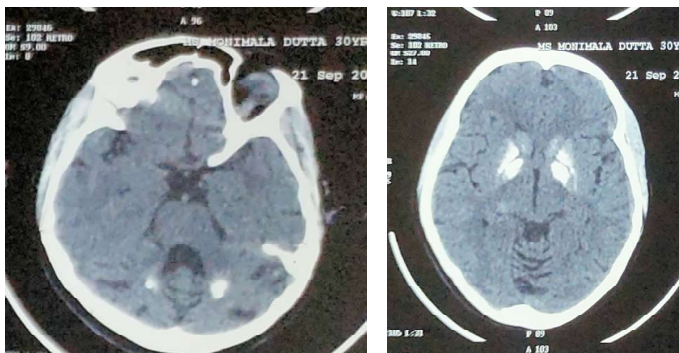


Figure: CT Brain showing calcification in basal ganglia and cerebellum.

DISCUSSION :

Fahr's disease (striato-pallido-dentate calcifications) is a rare neurodegenerative disorder characterised by bihemispherical and symmetrical calcium deposits in certain areas of the brain, particularly in the basal ganglia.¹ It is an inherited or sporadic neurological disorder with a prevalence of 1/10,000; most commonly transmitted as an autosomal dominant trait.² It is reported that Fahr's disease commonly affects people in their 40s and 50s.³ With aging, over 50 years a certain degree of calcification of basal ganglia can be considered "physiological", and it could be an incidental finding in 15–20% of asymptomatic patients undergoing computed tomography scan.^{4,5} This rare condition is associated with specific neuroradiological features but numerous clinical manifestations. Most cases present with extrapyramidal symptoms initially. They may present with cerebellar dysfunction, speech difficulty, dementia and neuropsychiatric symptoms also.⁶ The clinical course of the disease has a degenerative component which is often slowly progressive, lasting for many years. The mineral deposition may lead to cell loss in the cerebral cortex, basal ganglia, dentate nucleus or subthalamus. Clinical diagnosis is facilitated by the presence of bilateral and symmetrical calcifications in the basal ganglia in cranial CT. Detection of intracranial calcifications in CT scan is more sensitive comparing with skull X-ray or MRI.⁷ The term "Fahr's syndrome" has been suggested when a secondary, and potentially treatable, cause is found such as

hypoparathyroidism, and other genetically determined conditions, brain infections, or toxic exposure. Fahr's Disease is an incurable disease. So, management and treatment strategies mainly focus on symptomatic relief and eradication of causative factors; however certain evidence suggest that early diagnosis and treatment can reverse the calcification process leading to complete recovery of mental functions.⁸

CONCLUSION :

Although behavioural impairments and dementia is a common manifestation in Fahr's disease, the presentation with sudden onset visual loss associated with secondary amenorrhoea is very rare. Indeed to the best of our knowledge rarely any case with the same clinical features have been reported so far. Herein, we report this case of a 30 year old female with Fahr's disease presenting with sudden onset visual loss in both eyes, so to emphasize that though rare, the Fahr's disease should be considered in differential diagnosis in patients presenting with sudden onset blindness and behavioural abnormalities.

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Medi-Quiz

T K Das*

1. A 23 year old female, developed sudden onset excruciating pain starting at her legs and then shooting up her body to her jaws after she had a run for 5 kilometres, was associated with cola-coloured urine. Initial evaluation showed an increase in creatinine kinase enzyme along with a normal rise in venous lactate as tested during forearm exercise. She was treated symptomatically and discharged without any complication. She had similar attacks in the past, however her laboratory work-up including EMG was normal in between attacks. What could be the probable cause?

 - A. Myophosphorylase Deficiency (McArdle's Disease)
 - B. CarnitinePalmitoyltransferase 2 Deficiency
 - C. Acid Maltase Deficiency (Pompe Disease)
 - D. None of the above
2. A 24 year old man presented with foot drop. The weakness was more in his right leg. He informed that his father and paternal aunt have some sort of weakness in their lower extremities as well. His father was 54 years old and developed the weakness for the last two years. On examination, distal leg weakness along with reduced sensation to light touch in both legs was found. Muscle bulk was decreased in both calves, and knee and ankle jerk were diminished. Upper extremity examinations were within normal limits. Which of the following is the most likely cause?

 - A. Hereditary Neuralgic Amyotrophy
 - B. GuillianBarre Syndrome
 - C. Charcot Marie Tooth Syndrome
 - D. Hereditary Sensory and Autonomic Neuropathy
3. A 45 years old man developed sudden onset chest pain in a restaurant after swallowing a piece steak and was rushed to the emergency department. After the situation was dealt with, he informed that he had been suffering similar episodes for the last 2 and a half years which he described as meat getting stuck at his lower chest, but none was as severe as this one. On being asked about food regurgitation or heart burn, he denied suffering from either of them. There was no history of weight loss and he can swallow liquids without any difficulty. Which of the following is the most likely diagnosis?

 - A. Schatzki Ring
 - B. Achalasia
 - C. Plummer-Vinson syndrome
 - D. Adenocarcinoma of Esophagus
4. A 37-year-old man presents with a 5-day history of haematuria. Abdominal examination is unremarkable. Urine analysis reveals hypercalciuria and excretion urography reveals small calculi within the papilla of the patient's right kidney. The patient has presented several times in the past with UTIs and renal stones, but is otherwise healthy. The most likely diagnosis is:

 - A. Medullary sponge kidney
 - B. Renal cell carcinoma
 - C. Medullary cystic disease
 - D. Horse-shoe kidney
 - E. Tertiary hyperparathyroidism
5. A 37-year-old man presents with symptoms of an acute headache, vomiting, malaise and visual disturbance. A neurological examination reveals a bitemporal superiorquadrantanopia. A CT scan shows a hyperdense area within the pituitary gland. The most likely diagnosis is:

 - A. Kallman syndrome
 - B. Septo-optic dysplasia
 - C. Sheehan's syndrome
 - D. Empty sella syndrome
 - E. Pituitary apoplexy

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6. A middle aged woman presents complaining of dark stools and painful fingers on both hands. She appears plethoric and complains of severe itching, often when she is washing. A large liver and spleen is palpable. You suspect features of polycythaemia rubra vera and measure red cell mass and erythropoietin levels among other tests. Which of the following is likely to be most accurate in this patient?
- Low erythropoietin and low red cell mass
 - Normal erythropoietin and normal red cell mass
 - Raised erythropoietin and low red cell mass
 - Raised erythropoietin and raised red cell mass
 - Low erythropoietin and raised red cell mass
- 7.. A healthy 60 year old female patient on routine check up was found to have a hemoglobin of 10.2 g/dl, creatinine of 1.5 mg/dl, calcium of 10.2 mg/dl, a high protein with 11g/dl, of which serum albumin is 4.4 g/dl. protein electrophoresis shows IgG kappa monoclonal peak. Its concentration is 50 G/L. A skeletal survey and MRI shows no lytic lesion and bone marrow biopsy shows plasma cell population of 55%. Which of the following management options is next
- Antimyeloma treatment
 - PET scan to guide next step of treatment
 - Observation with regular follow up
 - Obtain a heavy light assay.
- 8.. A 45-year-old woman was referred to higher for bilateral ductal cancer. She had a history of intussusception at the age of 12 years. On examination, it was also observed that she had blue/black hyperpigmented macules on her lips, buccal mucosa, and finger tips. What is she suffering from?
- Hereditary BRCA 1 syndrome
 - Hereditary BRCA 2 syndrome
 - Peutz-Jeghers syndrome
 - Cowden syndrome.
9. A 36 year old male patient suffering from HIV/AIDS presented with aplastic anemia and it was seen that parvovirus B19 was the causal agent. Most likely route of transmission is
- By contact with skin rash
 - Through sexual activity
 - Through recent blood transfusion
 - By contact with respiratory secretion or droplets.
- 10.. A 41-year-old teacher presents to her GP with a 5-day history of fevers, headaches, lethargy and muscle aches. She also mentions that she is developing an expanding red rash on her left thigh. On further questioning, she mentions that she has been on a school camping trip the previous week. She is otherwise fit and well. What is the most likely diagnosis?
- Lyme disease
 - Sarcoidosis
 - Brucellosis
 - Syphilis
 - Erythema ab igne
11. A 42-year-old man presents to accident and emergency with a 1-day history of headache and fevers. He presents with his partner who says he has been becoming increasingly confused and disorientated. On examination, his temperature is 38.5°C. On cranial nerve examination there is a right-sided superior quadrantanopia. An urgent CT scan of the head is organized which shows multiple ring enhancing lesions. What is the most likely diagnosis?
- Toxoplasmosis
 - Meningitis
 - Cryptosporidiosis
 - CMV encephalitis
 - Histoplasmosis

Covid19 vaccine needed or not. If yes which one to choose in Indian context

To the Editor ,

Where does the coronavirus SARS-CoV-2 lie along the spectrum of natural infection versus vaccine-induced protective efficacy? The answer to this question will be known only as more data are collected from ongoing natural infection and vaccine studies; the initial results from interim analyses by Pfizer/ BioNTech and Moderna of mRNA vaccines against SAR-CoV-2 showing a reduction in infections of around 95% are very encouraging. There are a number of other promising signs for vaccines. Protection against infection and disease has been associated with neutralizing antibodies in both vaccine studies and passive-antibody-transfer studies in animal models. Furthermore, passive antibodies seem to have beneficial effects on established early SARS-CoV-2 infection in humans, which suggests that they can contribute to protection.

Among viruses, two classic cases in which vaccines generate immunity superior to that generated by natural infection are varicella zoster virus, which can lead to shingles, and human papillomavirus (HPV), some strains of which cause various malignancies, including cervical, penile and oropharyngeal cancer. Varicella zoster virus typically causes chickenpox in children and young adults and is resolved but rendered latent so that when re-activated in later life, it can lead to shingles. Immunity arising from the primary infection does not prevent the disease in those who develop shingles. However, the recently developed vaccines do offer protection against shingles. Varicella vaccine protects around 90% vaccinees across all age groups, and it is suggested for an extended time period. Protection seems to be antibody based but with important contributions from CD4+ T cells. The quintessential example of immunity superior to that induced by infection is the vaccine against HPV. The HPV strains that cause genital cancers enter the body via genital mucosal surfaces, and the antibody responses induced are low and take a long time to develop—more than 8 months in one study. In

contrast, two or three sequential intramuscular injections of one of the vaccines against HPV induce potent neutralizing antibody responses that have been shown directly in an animal model to prevent entry of the virus into target cells and the establishment of infection. The vaccines against HPV are based on the incorporation of a single viral surface protein into virus-like particles. They have been shown to offer complete protection against cervical cancer.

Antibody produced in Covid-19 against spike protein by natural infection is short and start fading after 3 month and do not lived more than 6 month from studies. Hence, cell mediated immunity is important. Vaccines of Covid-19 will help in development of cell mediated immunity. So vaccine seems to have a role in preventing incidence and complications of Covid 19. Now several vaccines has been developed and even some completed phase 3 trial and UK has started giving Pfizer /BioNTech vaccine to its people . Now question is which vaccine to be taken? Covid vaccine mainly are mRNA (carried by liposomes), Adenovirus vectored DNA Vaccine (which contain viral genome code for viral spike protein), live attenuated vaccines (Oxford vaccine, Sputnik vaccine) mRNA enters our body when we get a natural infection but only issue is that this mRNA vaccine is made genetically so future side effects is uncertain.

Advantage of mRNA vaccine are non replicable and non infectious hence can be given to immunosuppressed but immune response may be lower . mRNA vaccines need -70⁰ C storage which may not be possible in India.

Pfizer moderna vaccine also needs -20⁰ C which also may not be possible in remote areas of our country. Oxford vaccine uses chimpanzee adenovirus while Sputnik vaccine uses human adenovirus 26. These two vaccines are stable at freezer temperature so it will feasible to maintain this temperature in country like ours thereby maintaining efficacy . Moreover we are quite experienced in using live attenuated vaccines like MMR, Varicella vaccine.

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Q.1. Ans:-	B. CarnitinePalmitoyltransferase 2 Deficiency
Q.2. Ans:-	C. Charcot Marie Tooth Syndrome
Q.3. Ans:-	A. Schatzki Ring
Q.4. Ans:-	A. Medullary sponge kidney
Q.5. Ans:-	E. Pituitary apoplexy
Q.6. Ans:-	E. Low erythropoietin and raised red cell mass
Q.7. Ans:-	C. Observation with regular follow up.The patient is suffering from Smoldering multiple myeloma. Presently patients with smoldering multiple myeloma requires treatment only when myeloma defining events are identified
Q.8. Ans:-	C. Feutz-Jeghers syndrome
Q.9. Ans:-	D. By contact with respiratory secretion or droplets
Q.10. Ans:-	A. Lyme disease
Q.11. Ans:-	A. Toxoplasmosis

CONSENT FORM FOR CASE REPORTS

For a patient’s consent to publication of information about them in a journal or thesis

Name of person described in article or shown in photograph : _____

Subject matter of photograph or article : _____

Title of article : _____

Medical practitioner or corresponding author : _____

I _____ [insert full name] give my consent for this information about MYSELF OR MY CHILD OR WARD/MY RELATIVE [insert full name]: _____, relating to the subject matter above (“the Information”) to appear in a journal article, or to be used for the purpose of a thesis or presentation.

I understand the following :

1. The Information will be published without my name/child’s name/relatives name attached and every attempt will be made to ensure anonymity. I understand, however, that complete anonymity cannot be guaranteed. It is possible that somebody somewhere - perhaps, for example, somebody who looked after me/my child/relative, if I was in hospital, or a relative - may identify me.
2. The Information may be published in a journal which is read worldwide or an online journal. Journals are aimed mainly at health care professionals but may be seen by many non-doctors, including journalists.
3. The Information may be placed on a website.
4. I can withdraw my consent at any time before publication, but once the Information has been committed to publication it will not be possible to withdraw the consent.

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_____ Date: _____