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From the Editor

As internists, we all are in the eye of the Covid-19 storm, which I am sure will subside in the days to come. Sadly, the Covid-19 pandemic has taken its toll not only on human lives, but also on almost every sphere of human activity. The *JIACM* has been no exception. All editors – past or present – of any medical journal worth its name, will admit that bringing out a quality medical journal with clock-work regularity is no child's play. More than anything else, the financial robustness of any journal which is having a print edition is of paramount importance. For finances, most journals largely depend on advertisements from pharmaceutical companies, and contributions from the proprietors, i.e., the medical associations which publish the journal. Indirectly, Covid-19 has affected the *JIACM* too by denting its advertisement revenues. Even though some issues of the *JIACM* could not come out in time, we have spared no efforts in ensuring that the scientific quality of articles published conformed to international benchmarks. Sometimes, to compensate for delay in publication, we have had to club two issues together – including this issue – with more pages and more articles.

As I complete my three-year stint as Editor of the *JIACM*, I would like to thank Associate Editor Dr. Sumeet Singla who worked shoulder-to-shoulder with me at all times. I am indebted to the IACM President Dr. Subhash C. Gupta and all office bearers and members for guidance and support in these trying times. My Special thanks go out to the technical team of the JIACM – Mr Yashpal Satmukhi (Circulation and advertising), Mr Vijay Shankar Vashisht (Type setting) and Mr Avinash Kumar (Printing) – for their Untiring efforts.

Dr Amit Aggarwal, Senior Physician in ABVIMS and Dr RML Hospital has joined the editorial team as Secretary, JIACM and I am sure he will put in his best efforts.

As always, the *JIACM* has spared no efforts in catering to the clinically relevant academic needs of our internist members – our esteemed readers. The variety on our menu has always been clinically relevant and refreshing – Original Articles, Update Articles, PG Clinics, Case Reports, Pictorial CMEs, Viewpoint, etc. Now what more can an internist want!

It is always the readers and contributors who are the real audience and artists respectively of any journal. Our readers too have always been supportive and indulgent by providing regular doses of healthy criticism and suggestions which we have always welcomed, and whenever possible, incorporated. Finally, dear readers, I wish to personally thank you all for your support and encouragement. Good bye and stay safe.

– MPS Chawla
drmpschawla@gmail.com

ORIGINAL ARTICLE

JIACM 2020; 21(1): 7-11

Study of Antibody-based Rapid Card Test in COVID-19 Patients Admitted in a Tertiary Care COVID Hospital in Southern Rajasthan

Mahesh Dave, Lakhan Poswal**, Vikram Bedi*, Lalit Regar***, Rahul Vijayvargiya****, Mayank Sharma****, Narendra Deval*****

Abstract

Background: COVID-19 also known as SARS C0V-2, is now a pandemic which started in December 2019 in China. RT-PCR based nucleic acid detection is currently the standard diagnostic method for COVID-19, but certain shortcomings make it unfeasible for use as a screening test.

Aims and objectives: To study the dynamics of IgM and IgG antibody, establish its role in diagnosis and prognosis of COVID-19 patients.

Methods: It was a cross-sectional study conducted over 100 RT PCR confirmed COVID-19 patients admitted in various wards of a dedicated Corona hospital, RNT Medical College, Udaipur, Rajasthan, India over a period of 2 months – from April 2020 to May 2020.

Results: We performed an anti-SARS-CoV-2 IgG/IgM test on 100 confirmed COVID-19 patients and found that 61% patients had antibody positivity. Dynamics of antibody show that seroconversion, peaking, and disappearance of IgM antibody occur at end of 1st week, 2nd week, and 3rd week respectively, while for IgG seroconversion was seen at the end of 2nd week, and was persistently positive up to 32nd day of illness in our study. Patients with development of anti-SARS-CoV-2 antibodies had a mild degree of illness with positive outcome and vice versa.

Conclusion: Our study concludes that serological responses have been observed in COVID-19 patients, and the dynamic pattern of these responses is consistent with acute viral infection which is useful to see the immune status of these patients and diagnosis of COVID -19.

Keywords: COVID-19, RT PCR, antibody-based card test.

Introduction

Several cases of pneumonia of unknown aetiology have been reported from Wuhan, Hubei province, China, in December 2019[1]. It was later named COVID-19 (corona virus disease 2019) after genomic sequencing. COVID-19 also known as SARS C0V-2 is caused by an enveloped, positive sense, single-stranded RNA with a size varying between 26 kb and 32 kb[2]. The name corona was derived from the Latin word coronae or crown which means a coloured circle around a luminous body such as sun or moon. Current evidence suggests spread to humans occurred via transmission from wild animals illegally sold in the Huanan Seafood Wholesale Market[3].

Up till now, 6 human corona virus species were known among which HCoV 229E, HCoV OC43, HCoV NL63, and HKU1 cause only mild upper respiratory disease[4]. Two recent outbreaks of beta corona viruses had seen, causing epidemics were SARS-C0V and MERS-COV. In 2003, the world had experienced the Severe Acute Respiratory Syndrome (SARS) caused by a new corona virus (SARS-COV) whose outbreak started in Guangdong, South china, resulting in 8,700 cases and 744 deaths with case fatality rate of 9.5%[5]. In June 2012, another respiratory illness outbreak occurred named as MERS (middle-east respiratory syndrome) started in Saudi Arabia with the total of 2,040 cases and 712 deaths with case fatality rate of 34.90%[6].

WHO declared COVID-19 as a pandaemic on 11th March, 2020, and In India the first case was reported on 30 January, 2020 from Kerala. As on 01 June 2020, the total number of cases reported was 6,057,853 with 3,71,166 deaths worldwide, whereas in India the total number cases was 1,90,535 with 5,394 death[7].

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Transmission of the corona virus is usually via airborne droplets to the nasal mucosa in closed environments and through close contact between people and touching contaminated surfaces, with an incubation period of 2 - 14 days and basic reproduction ratio of 2.2[8]. It causes a spectrum of clinical features which ranges from asymptomatic or mild symptom such as cough, cold, sore throat to acute respiratory distress syndrome, and multi-organ failure. COVID-19 affects people of all ages, but older people (more than 60 years) and those with underlying medical illness are at higher risk of getting severe infection with the death rate at 3.4%. Poor prognosis calculated by Mulbsta score[9].

Diagnosis of COVID-19 is clinically done by history of contact and clinical features, while laboratory confirmation is done by RT-PCR (reverse transcription polymerase chain reaction) based oropharyngeal swab testing.

RT-PCR based nucleic acid detection is currently the standard diagnostic method for COVID-19, but certain shortcomings mentioned below make RT-PCR unfeasible to use as a screening test, which limit our COVID-19 containment efforts:-

1. Long turnaround time (2 - 3 hour).
2. The RT-PCR tests require certified laboratories, expensive equipment, and trained technicians to operate.
3. High false-negative results.
4. Expensive costing around INR 4,500 (Indian rupees) per test.

Therefore, there is an urgent need for a rapid, simple, sensitive, cheaper, and accurate test to quickly diagnose COVID-19 infected patients and to see the immune status, and to establish usefulness in prognosis and outcome of these patients.

Aims and objectives

1. To study antibody status in RT-PCR confirmed COVID-19 patients.
2. To establish timeline of IgM and IgG in RT-PCR confirmed COVID-19 patients.
3. To establish relation between antibody appearance and clinical features, severity, and outcome in RT-PCR confirmed COVID-19 patients.

Material and methods

Definition of confirmed case

A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.

RT-PCR testing

Oropharyngeal/nasopharyngeal swab samples were taken of suspected patients and transported via virus transport medium (VTM) for RNA extraction. In the microbiology lab, the sample is tested by RT-PCR based technique as directed by the National Institute of Virology, Pune.

Antibody-based card testing

Principle: Immune chromatographic assay.

Test kit: Provided by SIDAK Life Care Ltd.

Procedure:

1. Place test kit on flat surface.
2. Load 2 drops of blood into the sample well, then add 1-2 drops of buffer.
3. Interpret the result at 15 - 20 minutes.

Interpretation of results: as shown in Fig. 1.

1. Negative Result: if only C band is visible. The absence of any pink line in zones 1 and 2 indicate that no antibodies are present.
2. Positive result:
   a. Along with C band if band at zone 1, indicates presence of IgM antibodies.
   b. Along with C band if band at zone 2, indicates presence of IgG antibodies.
   c. Along with C band if band at both zones 1 and 2, indicates presence of both IgM and IgG antibodies.
3. Invalid

If C band does not appear, the assay is invalid.

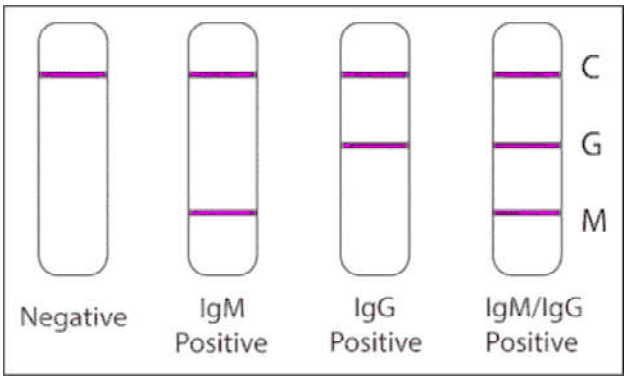

Fig. 1: *Showing interpretation of antibody-based rapid card test.*

Data collection and study design

It was a cross-sectional study conducted over 100 RT PCR confirmed positive. COVID-19 patients admitted in various wards of the corona dedicated hospital, RNT Medical

College, Udaipur, Rajasthan, India, over a period of 2 months – from April 2020 to May 2020.

Inclusion criteria

1. All RT PCR confirmed symptomatic and asymptomatic COVID-19 patients above the age of 18 years.

Exclusion criteria

1. COVID-19 patients already on chronic steroid, immunosuppressants and chemotherapy.
2. Known case of PLHA and other immune-deficient diseases.
3. COVID-19 patients not giving consent for study.

All these patients included in the study were evaluated by a set protocol in the form of detailed history, physical examination, systemic examination if needed.

All patients underwent routine investigations which included complete blood count, renal function test, liver function test, chest X-ray, electrocardiography.

These patients were divided into 4 groups according to duration of illness, i.e., 0 - 7 days, 8 - 14 days, 15 - 21 days, > 21 days.

Data analysis

The collected data were entered in a Microsoft Excel Sheet. Graphs and tables were generated using Microsoft Word and Microsoft Excel. Quantitative data were studied using Mean, Median, Mode and Standard Deviation (SD).

Results and observation

In our study, out of 100 patients 45 were male and 55 were female having mean age of 37 years with 22 (22 %) patients having co-morbidities which included type 2 diabetes mellitus, thyroid disorder, hypertension, and malignancy. In view of residence, 88 patients (88 %) were from urban locality while the rest of 12 (12%) were from rural areas. Clinical features as depicted in Fig. 2, show that 76 patient were asymptomatic and diagnosed because of contact tracing. In 24 symptomatic patient, 6 (25%) had cough, 5 (20%) had fever, 5 (20%) had both cough and fever, 7 (30%) patients had shortness of breath, 1 (5%) had other features.

Table I shows that out of 100 patients, 61 tested positive and 39 negative for antibodies. Among 61 antibody positive patients, IgM positivity is seen in 21 patients (34%), IgG positivity in 30 patients (49%), both IgM and IgG positivity in 10 patients (17%).

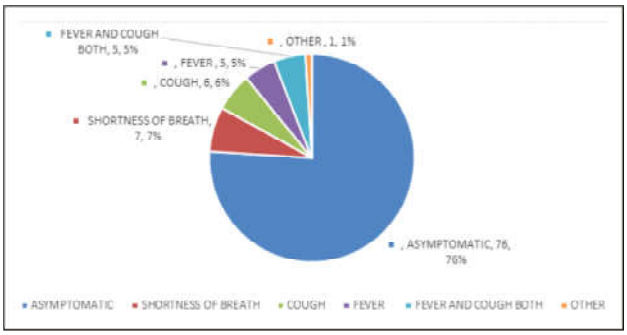

Fig. 2: *Clinical presentation of COVID-19 patient.*

Table I: Categorisation of total patients tested according to positivity.

S. No	Category of patients	Number	%
1.	Total number of patients tested	100	
2.	Total patients having positivity	61	
	1. IgM positive patients	21	34
	2. IgG positive patients	30	49
	3. Both IgM and IgG positive patients	10	17

Table 3 and Fig. 3 show that between 0 to 7 days of illness, out of 23 patient tested only 2 (8.69%) patients developed IgM antibody and none of them had IgG antibody test positive. In the next 7days (between 8 - 14 days) of illness, among 27 patients tested, 11 (40.2%) patients developed IgM and 9 patients (33.3%) developed IgG. In 15 - 21 days group of illness, out of 36 patients tested 8 (22.2%) developed IgM where rest 12 patients (33.3%) developed IgG and 10 patients (27.7%) developed both IgM and IgG antibody. In the later days of illness, i.e., beyond 21 days, on testing 14 patients, only 9 patients (64.2%) developed IgG and no one had IgM antibody.

Table II: Timeline of IgM and IgG antibody with duration of illness.

Days of illness	Total patients tested	Patients having IgM positive	Patients having IgG positive	Patients having both IgM and IgG positive	Total patients positive
0 - 7	23	2 (8.69%)	0 (0%)	0 (0%)	2 (8.69%)
8 - 14	27	11 (40.2%)	9 (33.3%)	0 (0%)	20 (74%)
15 - 21	36	8 (22.2%)	12 (33.3%)	10 (27.7%)	30 (83.3%)
> 21	14	0 (0%)	9 (64.2%)	0 (0%)	9 (64.2%)

Table III given below showing correlation between IgM and IgG antibody with severity of disease.

Out of 100 patients studied, 76 patients were in the asymptomatic group where 17 patients were in the mild-

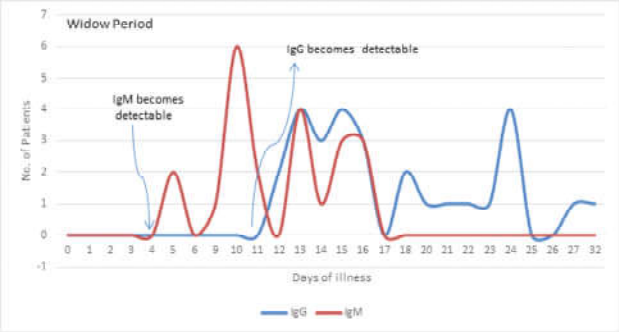

Fig. 3: *Timeline of antibody response in COVID-19 patient.*

to-moderate symptom group and 7 patients were in the severe symptom group; when studied further, it was found that antibody positivity in these group was 65%, 59% and 29% respectively. In respect to antibody type specific, IgM antibody positivity in asymptomatic, mild-to-moderate and severe group was 26%, 5.5% and 0%, while for IgG it was 26%, 48% and 29% and for both IgM and IgG it was 13%, 5.5%, 0% respectively.

Table III: Antibody positivity and disease severity.

S. No	Disease severity	Total patients	IgM positive	IgG positive	Both IgM and IgG posiitve	Total positive	Total negative
1.	Asymptomatic	76	20 (26%)	20 (26%)	9 (13%)	49 (65%)	27 (35%)
2.	Mild-to-moderate	17	1 (5.5%)	8 (48%)	1 (5.5%)	10 (59%)	7 (41%)
3.	Severe	7	0 (0%)	2 (29%)	0 (0%)	2 (29%)	5 (71%)

Table IV shown below depicts the co-relation between disease severity, antibody response and outcome of these patients in the form of death or discharge. In asymptomatic, mild and moderate symptom group, total antibody response was found 65% and 59% respectively and outcome was noted in form of 100% discharged, whereas in severe symptom group, antibody response was only 29% and major outcome was death (5 out of 7 patient studied) which was 71%.

Table IV: Correlation between disease severity, antibody response, and outcome.

S. No	Disease severity	Total number of patients	Patients with antibody response positive	Outcome (death/ discharge)
1.	Asymptomatic	76	49 (65%)	100% discharge
2.	Mild-to-moderate	17	10 (59%)	100% discharge
3.	Severe	7	2 (29%)	5 deaths (71%)

Discussion

Started as an epidemic in China, and then spreading to other countries quickly, COVID-19 pandemic is an unexpected global health issue. Day by day COVID-19 information and understanding about its diagnosis, treatment and containment is changing.

Our study was aimed mainly to observe the antibody response, its dynamics and its clinical application in COVID-19 patients.

In the present study, a total of 100 RT-PCR confirmed cases were taken, out of which 45 (45%) were males whereas 55 (55%) were females with a median age of 37 years. Huang *et al*[10] did a similar type of study and found mean age of patients to be 49 years which was not resembling with our study due to the sample size which was smaller in our case. Among 100 patients studied, 76% patients were asymptomatic and the rest 24% patients were in the symptomatic group. The study done by Tian *et al*[11] and Wang *et al*[12] demonstrated 90 - 95% patients were symptomatic. These studies contradict the present study because of the fact that the clinical presentation, severity, and mortality varies from country to country and region to region because of the different viral strain , immunity status, age, co-morbidities, and various other epidemiological factors among peoples, which are not known to us.

The present study was carried-out over 100 patients. 61 (61%) patients had positive antibody response whereas 39 (39%) patients had no antibody response. Among these 61 antibody positive patients, IgM positivity was seen in 21 patient (34%), IgG positivity was in 30 patients (49%) and both IgM and IgG antibody positivity was in 10 patients (17%). Long *et al*[13] observed antibody response in 96.8% patients and the proportion of patients with positive virus-specific IgM and IgG seen in 94%, and 100% patients respectively. Higher percentage of positivity in the Long *et al* study is because of multiple times antibody testing in a single patient during the course of illness while we conducted it only a single time.

The present study was carried-out in 100 COVID-19 patients and correlated with duration of illness and antibody response. These patients were grouped according to duration of illness, i.e., o to 7 days, 8 - 14 days, 15 - 21 days and more than 21 days respectively. Between 0 to 7 days of illness out of 23 patients tested only 2 (8.69%) patients developed IgM antibody. In next 7days (between 8 - 14 days) of illness among 27 patients tested, 11 (40.2%) patients developed IgM and 9 patients (33.3%) developed IgG. In 15 - 21 days group of illness, out of 36 patients tested 8 (22.2%) developed IgM where the rest 12 patients (33.3%) developed IgG, and 10 patients (27.7%) developed both IgM and IgG antibody. In the later days of illness, i.e., beyond 21 days, on testing 14 patients, only 9 patients (64%) developed IgG whereas no one had IgM antibody.

Regarding antibody response and peaking, it was observed that IgM appearance was noted after 7 days with peak in between 10 to 14 days, and IgM disappeared by the end of 3rd week, while IgG seroconversion was seen at the end of 2nd week and it persistently remained positive up to 32nd day of illness. Similar type of results were observed by a study done by Hou *et al*[14].

Comparing antibody positivity with severity of illness and outcome, we observed that, as severity of illness increases antibody detection decreases and outcome worsens, i.e., % of antibody positivity in asymptomatic, mild and severe disease is 65%, 59% and 29% respectively and outcome was observed in form of 100% discharged in asymptomatic, and mild/moderate symptomatic group whereas 71% mortality observed in severe symptomatic group in which antibody response was only 29%.

In respect to antibody type specific, IgM antibody positivity in asymptomatic, mild-to-moderate and severe group is 27%, 5.5% and 0% while for IgG it is 26%, 47% and 29% and for both IgM and IgG it is 12%, 5.5%, 0% respectively which is contrary to the study conducted by Hou *et al* in which mild, severe and critical groups IgM was detected in 81.3%, 82.9% and 82.7% of cases, IgG was detected in 90.6%, 92.7% and 88% of cases, and both IgM and IgG were detected in 79.7%, 77.9% and 80% of cases.

Our results may explain that patients who develop protective antibody IgM and IgG had a mild severity, early RT-PCR negativity, short course of illness, rapid recovery and better outcome while vice versa for those who do not develop antibody. The significance of antibody response in COVID-19 is important, not only in the diagnosis but also prognosis. Specific antibodies, including IgG antibodies and neutralising antibodies, are important for protecting the host from infection by blocking viral entry into host cells after viral infection[15].

As greatly said "Sky has no limit" this study is our little contribution from our clinical experience to add ot the literature of COVID-19, a novel disease with ab evolving course.

Conclusion

From the present study, we conclude that like other viral diseases, significant antibody response was observed in COVID-19 patients and its positive response can be directly correlated with severity and outcome of disease. Further antibody detection by rapid card may be a useful diagnostic tool which provide valuable information regarding diagnosis, severity, and outcome of COVID-19 patients. Moreover, it is a less expensive, less time consuming, easy to perform, and least cumbersome tool in this pandemic scenario.

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ORIGINAL ARTICLE

JIACM 2020; 21(1-2): 12-15

The new Scandinavian Five-Point Classification of Diabetes Applied to an Indian Population: A Pilot Study from Eastern India

Rudrajit Paul, Kunal Som**, Dipanjan Bandyopadhyay****

Abstract

Background: Diabetes is a major public health problem all over the world. It is a heterogeneous disease and the patients have different degrees of metabolic control and other complications. Recently, there have been attempts to classify diabetes into further sub-groups which can give better prognostic information. The present study is aimed to test one such classification in a sample Indian population.

Material and methods: Diabetic adult patients coming to medicine department were the subjects for this cross-sectional pilot study. Parameters like HbA1C %, Body Mass Index (BMI), HOMA-2 IR and HOMA-2B scores were collected. Then, the patients were classified into clusters according to the scheme proposed by Ahlqvist et al in 2018. Appropriate India/South Asia specific cut-offs were used to define obesity and insulin resistance. Presence of specific complications like fatty liver and microalbuminuria in different clusters was studied.

Results: There were 64 diabetic patients with male: female ratio 41: 23. According to this classification system, 10.9% of the subjects had SIDD, 26.6% had SIRD, 31.3% had MOD and 4.7% had MARD. 26% of the patients remained unclassified and there was no SAID. Average HbA1C of SIDD and SIRD groups were higher than study average. In the unclassified group, HbA1C was lower (p = 0.013). Urine ACR was higher in the MOD group.

Conclusion: This study gives an idea of the relative percentage of different clusters in Indian diabetic subjects. A higher percentage of MOD was found in this study, compared to other European data. However, the classification may need some modification in the Indian context to account for the unclassified section.

Keywords: Diabetes; cluster; HbA1C; insulin resistance; HOMA.

Introduction:

Diabetes is a complex metabolic disorder with multi-organ involvement[1]. By some accounts, diabetes is the fastest increasing disease worldwide and the economic impact of the disease will adversely affect all health systems[1]. The management of diabetes involves managing the metabolic parameters as well as dealing with the long-term complications like blindness or nephropathy.

Diabetes has been traditionally classified broadly into type 1 and type 2[2]. There are also other types like MODY, pancreatic diabetes and gestational diabetes. However, this classification system may sometimes look inadequate as newly diagnosed diabetics can't always be put into a definite box. Also, among patients of type 2 diabetes, there are wide variations in complications, metabolic control, and prognosis[1]. The same treatment algorithm may not benefit all type 2 diabetes patients and a nuanced approach may be necessary. Some authors have expressed an opinion that type 2 diabetes is not a single disease entity but a heterogeneous combination of different syndromes. Thus, the present classification of diabetes is not always appropriate in correctly prognosticating all patients after diagnosis and there is scope of revision.

In this background, in 2018, Ahlqvist *et al* proposed a new classification of diabetes[1]. Based on certain variables in addition to blood glucose, they attempted to classify diabetes phenotypically into five types[1]. Later, they used independent cohorts to replicate the clusters and found that the classification is robust. This classification can give a better idea of the prognosis and various systemic complications.

This new classification is just two-years-old. Thus, it is still early days to comment on its usefulness. But in general, there are attempts to reclassify diabetes[3]. For example, with the availability of continuous glucose monitoring, there is a new concept of "glucotypes"[3]. Improved use of statistical methods and genetics will probably lead to more such attempts in the future. In 2019, the German diabetes study group published a study on this novel classification[4]. They reported that the phenotypic classification, as proposed by

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Ahlqvist *et al* was, in fact, able to predict systemic complications in their cohort too[4]. Thus, this new classification can be the first step in precision medicine for diabetes.

There are no published studies on this new classification of diabetes from India. However, India is experiencing a rapid rise in the number of diabetics (probably the highest in the world) and this will be a significant burden on the health system in the future[5]. Thus, there is an urgent need of research into the biological characteristics of diabetics in India so that better management decisions can be made. The present study is a small attempt in this regard.

The aim of this study is to analyse the metabolic parameters of diabetic patients and classify them according to the novel classification system as mentioned above.

Material and methods

This was a cross-sectional observational study conducted in a tertiary care private hospital of Eastern India. Diabetic patients coming to the medicine OPD were screened for inclusion in the study. Exclusion criteria included anyone with drug-induced diabetes, genetic form of diabetes, pregnancy, anyone below 18 years of age, autoimmune diseases, on-going steroid or other immunosuppressive therapy, known haemolytic disorders and cirrhosis of liver. Also, anyone with an active infection like tuberculosis was excluded.

The patients were explained about the study in their native language and written informed consent was obtained. Necessary approval for the study was obtained from the medical superintendent.

The aim of the study was to classify the diabetic patients according to scheme suggested by Ahlqvist *et al*[1]. For this, the parameters as mentioned in this Scandinavian study, were analysed.

To characterise insulin resistance, the HOMA-2 scoring system was used. Software for this scoring system has been developed by the Diabetes Trials Unit of the University of Oxford[6]. This software is freely downloadable.

The HOMA-2 IR score cut-off to define insulin resistance in different populations is a matter of intense research. In a study from Iran, the cut-off points for HOMA-2 IR was determined to be 1.4 (men), 1.18 (women) and cut-off for HOMA-2B was found to be 72 - 74% respectively[7]. In another recent study from Asia (China), the HOMA-2 IR cut-off point has been determined to be 2[8]. The optimum HOMA-IR score cut-off must be calculated for each population separately. In India, there are not many studies on the HOMA-2 scoring. In a 2013 study from North India, the optimum HOMA-2IR cut-off for adolescents of both sexes was determined to be 2.5[9]. But adolescents have higher insulin resistance than adults. In the present study, adolescents were excluded. In another recent study from India, the HOMA-2 IR cut-off for insulin resistance has been taken as 2[10]. Thus, considering the Chinese and Indian study methodology, the HOMA-2 IR cut-off in the present study has also been taken as > 2. A recent Venezuelan study has also proposed the same cut-off value[11]. However, whether there are grades of insulin resistance with higher IR scores, indicating higher resistance, is again a matter of debate.

According to this study, diabetes has been divided into five types[1]:

Cluster	Characteristics					
	BMI	Age of onset	GAD antibody	Insulin secretion	HbA1C	Insulin resistance
Cluster 1: SAID: Severe Auto-immune diabetes	Low	Early	Positive	Low	High	None
Cluster 2: SIDD: Severe insulin-deficient diabetes	Low	Early	Negative	Low	High	None
Cluster 3: SIRD: Severe insulin-resistant diabetes	High	Variable	Negative	Normal	Variable	High
Cluster 4: MOD: Mild Obesity-related diabetes	High	Variable	Negative	Normal	Moderate	None
Cluster 5: MARD: Mild age-related diabetes	Normal	Delayed	Negative	Normal	Moderate	None

To define obesity, body mass index has been used. For this purpose, the Asian/Indian population specific standards have been used[12]. Thus, BMI $\geq$ 25 kg/m^2 has been considered as obese.

To define beta cell failure and low insulin secretion, the HOMA-2B score was used. This reflects the release of insulin under basal conditions. Any exogenous insulin or insulin secretagogues would falsely change the serum insulin levels and thus, the HOMA scores. Thus, patients on sulfonylurea or basal insulin treatment were excluded from this study. However, there is no single cut-off for HOMA-2B score which can define beta cell failure. So, in this study, to define insulin deficiency or beta cell failure, we considered the lowest quartile of the HOMA-2B scores.

To define age-related diabetes, a cut-off age of 60 or above was considered.

Blood glucose was checked by the hexokinase method, HbA1C was checked according to NGSP standards, fasting insulin was checked by Chemiluminescence and urine ACR was checked by Immunoturbidimetry (urine microalbumin) and Modified Jaffe method (urine creatinine). The GAD-65 antibody in serum was calculated only for patients with low HOMA-2B scores.

Since this was a pilot study with no Indian precedence, there was no reference value to determine sample size. Hence, a sample size of at least 50 was targeted. Consecutive sampling technique was used. The data was entered into Microsoft Excel worksheet and standard statistical tests were used. The data is expressed as percentage with 95% confidence interval (CI). $P < 0.05$ was considered significant.

Results

We had a total of 64 diabetic patients in this pilot study. Male: female ratio was 41: 23. Average age was 58.6 ± 11.1 years. In HOMA-2B score, the median was 42.65, first quartile was 23.3.

Based on the methodology described above, the patients were classified (Fig. 1). It is seen that there were no patients with severe autoimmune diabetes. SIDD was present in 7 (10.9%; 95% CI: 4.5 - 21.2%), SIRD was present in 17 (26.6%; 95% CI: 16.3 - 39.1%), MOD was present in 20 (31.3%; 95% CI: 20.2 - 44.1%) and MARD was present in 4.7% (95% CI: 1 - 13%). But 26.6% of the patients could not be classified into any of the 5 categories. These were the subjects who had BMI below 25, HOMA-2IR score below 2, age of diagnosis between 30 and 50 and HOMA-2B score in the 2nd or 3rd quartiles. They are hereby referred to as "unclassified".

The average HbA1C% of the SIRD group was higher than other subjects (8.8 ± 1.9 vs 8.2 ± 2.5%) but the difference was not statistically significant ($p = 0.2$). In the unclassified group, average HbA1C was 7 ± 1.1%, which was lower than the average HbA1C of study population (8.3%; $p = 0.013$; $t = -2.26$). In the SIDD group, average HbA1C was 9.5%, which was higher than the study average ($p = 0.11$).

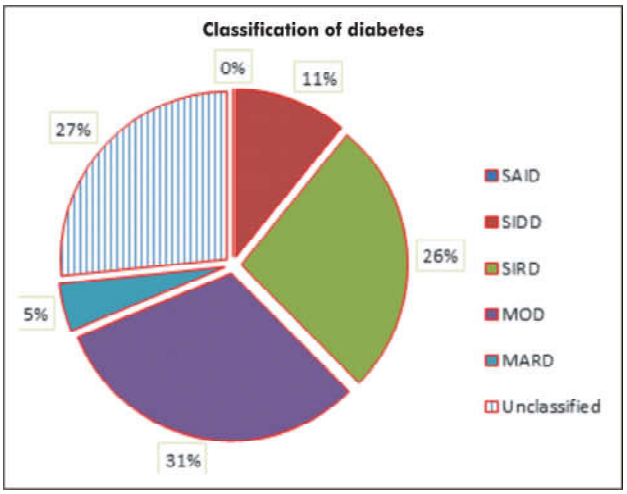

Fig. 1: *Pie chart showing the various categories of diabetic patients in the study.*

Average urine ACR of study subjects was 125.9 ± 326.1 µg/mg. But in the unclassified group (n = 17) it was 45 ± 42.4 ($p = 0.17$) and in the MOD group (n = 20) it was 256.3 ± 579 ($p = 0.13$). Thus, obese patients tended to have higher degree of proteinuria. Fatty liver by ultrasonography was found in 12 subjects (18.8%). There was no difference among the categories regarding occurrence of fatty liver.

Discussion

In this pilot study, we have attempted to apply the recently published Scandinavian classification of diabetes on a sample adult Indian population. It was found that 26% of the diabetic subjects remained unclassified. This unclassified group had better metabolic control (as determined by the HbA1C%) and lower incidence of proteinuria.

In the Scandinavian study mentioned in "introduction", the relative percentage of diabetic subjects in each category was as follows: SAID: 6.4%, SIDD: 17.5%, SIRD: 15.3%, MOD: 21.6%, MARD: 39.1%[1]. In the present study, SIDD was 10.9%, SIRD was 26.6% and MOD was 31.3%. We did not find any SAID and MARD was only 4.7%. We may have missed the SAID cases as our study population involved only adult subjects (> 18 years) and autoimmune diabetes cases are usually diagnosed at younger age. Also, our study area was medicine OPD and indoors; but autoimmune diabetes cases tend to attend the endocrinology speciality clinics.

Recently, the classification system of Ahlqvist *et al* was applied to a UK population[13]. Here, it was found that SIRD was 20%, MOD was 22% and MARD was 34%[13].

Ahlqvist *et al* identified that the different clusters had different prognosis and occurrence of diabetic complications. For example, they found that clusters 1 and 2 had higher HbA1C and cluster 3 had the highest incidence of fatty liver[1]. In the UK study, some difference in treatment response was also seen among the clusters[13]. In the present cross-sectional study, treatment response was not assessed.

Thus, there seems to be some evidence that this cluster-driven approach in diabetes may be useful for clinical purposes also, like deciding on therapy. But the specific elements which make up the clusters, like HOMA2 scores are not meant for clinical use and are difficult to interpret for an individual patient. Thus, how this clustering will become clinically applicable is a matter of future research.

Another similar classification of diabetic subjects based on this model was done in Germany recently[4]. They found that the SIRD cluster had the highest prevalence of fatty liver and also, hepatic fibrosis on follow-up[4]. This group also had the highest fasting adipose tissue-insulin resistance index. Diabetic polyneuropathy was more prevalent in SIDD[14]. In

the current study, the number of fatty liver cases was too small for any comment or inference.

As this present study shows, the cluster-driven classification of diabetes may not be the same in Indian patients. We found that about a quarter of our patients did not fulfil the criteria for any cluster. This unclassified group also had metabolic parameters like urine ACR different from other diabetics. There are two possibilities here. One is: for Indian patients, the description of clusters may have to be changed or a new cluster introduced. The second is, on longitudinal follow up, these patients may show new features and thus, may become eligible for one of the existing clusters. Also, this Scandinavian classification has "severe" for the first three clusters and "mild" for the last two clusters. There is no "moderate" category. May be some of these unclassified patients of the present study will fall into that moderate grade. Some Indian authors are quite sceptical of this new classification[14]. They raise a lot of issues like lack of availability of suitable tests in this country and lack of inclusion of South Asian variety of diabetes like Flat-bush diabetes[14]. Also, since this new clustering cannot predict cardiovascular mortality, they are not hopeful about its prognostic role. Some authors have proposed that this new classification of diabetes should also include parameters like family history and lipid profile.

However, this novel classification of diabetes is just in its infancy. These are early days and it is difficult to comment on their merits with the current meagre data. There is need of more data from different ethnic groups.

Limitations

The present study is limited by small number of subjects. But this was meant mainly as a pilot study. A larger study is planned in the future. Also, a cross-sectional study is not appropriate to assess parameters like treatment response or progression of specific complications like neuropathy. For that, a cohort study would be appropriate.

Secondly, there is much controversy regarding the cut-off for HOMA scores. This study has used a certain cut-off based on available literature. But there are other proposed values also. The whole idea of division into clusters is based on these cut-offs and thus, the relative percentage of subjects in each category will change significantly if cut-off references are changed.

Finally, the present study also did not study genetic markers in the different sub-groups for want of funds.

Conclusion

Diabetes is a major public health problem of modern times. There is need of newer research into the types of diabetes and their prognostic value. However, whether novel classification systems proposed from other parts of the world will be applicable in the Indian context is a matter of further deliberation.

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ORIGINAL ARTICLE

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Assessment of Fracture Risk and its Predictors in Patients with Axial Spondyloarthritis using the Fracture Risk Assessment (FRAX) Algorithm

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Abstract

Background: Ankylosing spondylitis (AS) is a chronic inflammatory disease primarily affecting the axial skeleton. Increased prevalence of low bone mineral density in patients with AS has been reported by studies but data on fracture risk in these patients is scarce. The present study was undertaken to find the risk of fracture and predictors of fracture risk in patients with Axial spondyloarthritis (AxSpA) using FRAX algorithm.

Methods: 40 consecutive adult patients with AxSpA attending the Rheumatology clinic of our Institute were included in this cross-sectional observational study. Bone Mineral Density (BMD) was measured at femur neck, lumbar spine and forearm, and T-scores were taken. FRAX score was calculated using FRAX calculator for Indian cohort and results showed 10-year probability of major osteoporotic and hip fractures in percentage.

Results: Out of total 40 patients, 34 (85%) were males, and 6 (15%) were females with a mean age of 34.98 ± 9.29 years and a mean disease duration of 5.14 ± 4.47 years. Osteoporosis was found in 17 patients (42.5%) at lumbar spine, 10 (25%) at forearm, and 6 (15%) at femur. Overall prevalence of OP in the study population was 55%. The mean FRAX score for major osteoporotic fracture was 1.53 ± 1.04% and for hip fracture 0.54 ± 0.82%. On multivariate analysis, femur BMD showed independent association with risk of major osteoporotic fracture; while age, BASDAI and femur BMD with the risk of hip fracture.

Conclusion: Prevalence of osteoporosis was high in AxSpA patients. Though a trend of higher FRAX score was seen with loss of BMD, its absolute values did not exceed prescribed cut-off for intervention. The independent predictors for the risk of fracture in AxSpA patients were age, BASDAI and low BMD at femur neck.

Key words: Axial spondyloarthritis, ankylosing spondylitis, osteoporosis, FRAX.

Introduction

Axial spondyloarthritis (AxSpA) is an immune-mediated chronic inflammatory arthritis predominantly involving the spine and/or the sacro-iliac joints. It shows a strong association with HLA B-27 and mainly affects young males. AxSpA include ankylosing spondylitis (AS) and non-radiographic spondyloarthritis depending on the presence or absence of radiographic sacro-iliitis. The hallmark of AS is syndesmophytes formation and ankylosis of spine and sacroiliac joint leading to pain and severe disability.

Increased prevalence of low bone mineral density (BMD) in patients with AxSpA has been reported in studies with a reported prevalence ranging from 19% to 62% for osteoporosis (OP) in AxSpA[1,2]. The pathogenesis of OP in AS is, perhaps, multifactorial involving different mechanisms at different stages of disease[3]. Risk of radiographic or clinical vertebral fracture is increased in AS even in early disease[4,5]. Literature about the risk of fracture is limited but suggests increased prevalence of vertebral fracture in AS with loss of BMD. The prevalence of vertebral fracture is 0 - 20% in various studies; however, most of them remain unrecognised[6].

DEXA is a cost-effective, easily available test with low radiation, rapid scan time, and reproducible results[7] and has become the gold standard in clinical practice to assess BMD in different patient populations including AS. FRAX is a web-based algorithm (www.shef.ac.uk/FRAX) designed to calculate the 10-year probability of major osteoporosis related fractures and hip fracture in men and women based on easily obtained clinical risk factors and bone mineral density[8]. Though, FRAX tool has been used for fracture risk assessment in Rheumatoid arthritis (RA) patients by some authors, such data in AxSpA is scarce.

The present study was done to assess the risk of fracture and to determine its predictors in AxSpA patients using FRAX algorithm.

Material and methods

40 consecutive patients aged > 18 years and diagnosed

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with AxSpA as per ASAS criteria[9], attending the Rheumatology clinic of our institute were included in this cross-sectional observational study. Patients with chronic liver or renal disease, hypogonadism, or those taking treatment for osteoporosis were excluded.

Detailed history regarding inflammatory back pain (IBP), joint pain, extra-articular symptoms, and treatment were obtained. History of fracture in self or parents was taken. Detailed musculoskeletal examination was done and disease-specific measures like Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI) and Bath Ankylosing Spondylitis Metrology Index (BASMI) were estimated. HLA B-27, ESR, haemogram, liver and kidney function tests, and X-rays of pelvis, spine and peripheral joints, as indicated, were done. BMD was measured by densitometer (HOLOGIC, INC. 35 CROSBY DRIVES BEDFORD, Model ASY-00409) at 3 sites: left femur neck, lumbar spine (L_1 to L_4) and non-dominant forearm; and values of T-score were obtained.

As per WHO criteria, BMD was classified on the basis of T-score of femur neck/lumbar spine/forearm as below:-

Osteoporosis	:	T-score < -2.5
Osteopenia	:	T-score < -1 and > -2.5
Normal bone density	:	T-score > -1

The FRAX scores were calculated using FRAX calculator for Indian cohort. The results were obtained in % as 10-year probability of major osteoporotic fracture or hip fracture. The WHO task force has identified eight individual risk factors for fracture (entered in a questionnaire form in FRAX calculator), independent of BMD and they have added country-specific fracture incidence rate for each country to these risk factors to give a 10-year probability of fracture. According to the National Osteoporosis Foundation (NOF) recommendation, 10-year probability of major osteoporotic fracture > 20% and hip fracture > 3% is considered to be significant for intervention[10,11].

Results

Out of 40 patients, 34 (85%) were males and 6 (15%) were females with a mean age of 34.98 ± 9.29 years and disease duration of 5.14 ± 4.47 years. The Mean BMD of femur, lumbar spine and forearm were -1.5 ± 0.82 gm/cm^2, -2.2 ± 1.23 gm/cm^2 and -1.99 ± 1.19 gm/cm^2 respectively. The mean BMD of lumbar spine was the lowest among the three sites, followed by forearm and femur. BMD of femur was normal in 9 (22.5%), whereas osteopenia in 25 (62.5%) and osteoporosis in 6 (15%) patients was seen. Lumbar spine showed osteoporosis in 17 (42.5%) patients, osteopenia in 14 (35%) patients, and normal BMD in 9 (22.5%) patients. DEXA scan of forearm showed osteopenia in 23 (57.5%) patients, osteoporosis in 10 (25%) patients while BMD was normal in 7 (17.5%) patients. Thus, osteoporosis was seen in 42.5% for spine, 25% for forearm and 15% for femur. Overall, the prevalence of osteoporosis in our study was 55% (22 out of 40 patients had osteoporosis at least at one site). The mean of FRAX score for major osteoporotic fracture was 1.53±1.04 % (0.8 - 6.3 %). The FRAX for hip fracture was 0.54 ± 0.82% (0 - 4%). We found only one patient with a ten- year hip fracture risk of > 3% and no patient had a ten-year risk of a major osteoporosis-related fracture of > 20%.

Table I: Patient characteristics between the groups on the basis of BMD T-score/

Patient characteristics	Normal BMD (N = 9)	Osteopenia (N = 25)	Osteoporosis (N = 6)	P - value
Age (years)	37 ± 9.8	32.32 ± 7.99	43 ± 9.7	0.027
*Sex (male)	7 (78%)	23 (92%)	4 (67%)	0.233
Disease duration (years)	2.92 ± 2.78	4.94 ± 4.07	9.33 ± 5.85	0.019
Height (cm)	163.11 ± 5.75	165.76 ± 7.01	161 ± 4.65	0.225
Weight (kg)	64.11 ± 13.11	61.16 ± 11.49	56.83 ± 7.94	0.49
BMI (kg/m^2)	24.42 ± 4.2	22.75 ± 2.87	22.02 ± 3.31	0.313
Chest expansion (cm)	4.12 ± 0.88	4.25 ± 0.91	3.63 ± 0.51	0.298
*Uveitis	2 (22%)	3 (12%)	0	0.440
*Current smoker	1 (11%)	6 (24%)	1 (17%)	0.692
BASDAI	3.57 ± 1.68	3.67 ± 1.28	4.72 ± 1.86	0.262
BASFI	3.28 ± 1.3	3.48 ± 1.32	4.23 ± 0.95	0.341
BASMI	2.73 ± 1.91	3.14 ± 1.87	4.5 ± 1.44	0.177
ESR (mm/hr)	21.22 ± 11.32	25.56 ± 9.44	34 ± 6.2	0.049
FRAX score for Major osteoporotic fracture	0.97 ± 0.16	1.29 ± 0.23	3.45 ± 1.73	< 0.001
FRAX score for hip fracture	0.1 ± 0.09	0.3 ± 0.19	2.03 ± 1.29	< 0.001

*Continuous variables have been presented as mean ± SD. *Categorical variables have been presented as numbers with percentages in brackets.*

Patient characteristics were compared after dividing them into 3 groups based on the BMD T-score of femur. Age, disease duration, ESR as well as FRAX score for major osteoporotic and hip fractures were higher in patients with osteoporosis (P value < 0.05). However, sex, anthropometric measurements, BASDAI, BASFI, BASMI, uveitis, and smoking status were comparable between the groups.

Univariate regression analysis was done for FRAX score with different variables to determine the factors associated with fracture risk in these patients. It was found that higher age, disease duration, BASDAI, BASFI, BASMI and lower femur BMD were associated with risk of major osteoporotic fracture or hip fracture. High ESR was associated with risk of

hip fracture only. These factors were then included for Multivariate regression analysis to determine the independent risk factors for major osteoporotic fracture or hip fracture.

Table II: Univariate analysis of FRAX score for major osteoporotic fracture and hip fracture.

	Major osteoporotic fracture		Hip fracture	
	Standardised Beta-co-efficients	P value	Standardised Beta-co-efficients	P value
Age (yrs)	.422	.007	.412	.008
Male gender	-.153	.347	-.115	.479
Disease duration (yrs)	.501	.001	.469	.002
Body mass index				
Normal				
Underweight	.124	.446	.161	.322
Overweight	-.151	.351	-.154	.341
Obese	-.086	.596	-.089	.584
Weight (kg)	-.051	.753	-.046	.780
Height (cm)	-.095	.558	-.083	.613
Chest expansion (cm)	-.289	.071	-.276	.085
Uveitis	-.197	.223	-.175	.280
Current smoker	.071	.662	.117	.474
BASDAI	.361	.022	.398	.011
BASFI	.332	.036	.330	.037
BASMI	.428	.006	.423	.007
ESR (mm/hr)	.311	.051	.318	.045
Femur BMD (gm/cm^2)	-.755	<.001	-.748	<.001
Lumbar-spine BMD (gm/cm^2)	-.213	.187	-.243	.132
Forearm BMD (gm/cm^2)	-.284	.076	-.276	.085

Table III: Multivariate linear regression for FRAX score for major osteoporotic fracture.

	Beta	P - value
Age (yrs)	.246	.055
Duration (yrs)	.078	.549
BASDAI	.249	.093
BASFI	-.037	.774
BASMI	.029	.824
Femur BMD (gm/cm^2)	-.591	<.0001

On multivariate regression analysis, only femur BMD was found as the independent predictor for major osteoporotic fracture. With the decrease in femur BMD by 1 gm/cm^2, FRAX for major osteoporotic fracture increases by 0.755 units (p value < .0001).

Table IV: Multivariate linear regression for FRAX score for hip fracture.

	Beta	P - value
Age (yrs)	.276	.034
Duration (yrs)	.035	.793
BASDAI	.337	.030
BASFI	-.071	.594
BASMI	.000	.998
ESR (mm/hr)	-.019	.869
Femur BMD (gm/cm^2)	-.600	< .0001

On multivariate regression analysis, age, BASDAI and femur neck BMD were found to be independent predictors of hip fracture. With the decrease in femur BMD by 1 gm/cm^2, FRAX for hip fracture increases by 0.595 units (p value < .0001). Similarly, hip fracture risk increases by 0.024 units (p value = .034) and by 0 .186 units (p - value .030) for 1 unit increase in age and BASDAI respectively.

Discussion

Bone mineral density in our patients with AxSpA was estimated using DEXA scan at 3 sites: femur, lumbar spine and forearm. The overall prevalence of osteoporosis in our study was 55%. It was similar to other studies showing the prevalence of osteoporosis in AS as 19 - 62%[1,2].

In our study, BMD was reduced in the majority of patients, in spite of relatively short disease duration (mean 5.14 ± 4.47 years) and low disease activity (BASDAI of 3.8 ± 1.48). The mean BMD of lumbar spine was the lowest among the three sites, followed by forearm and femur. Similar findings were reported by Davogelaer *et al* showing a decrease in the lumbar spine BMD in mild AS[12].

Overall, the prevalence of osteopenia was more at femur (62.5%) and prevalence of osteoporosis at lumbar spine (42.5%). Vasdev *et al* also found that AS patients had significantly lower BMD at the spine and femur as compared with controls (P < 0.001); with OP in spine and femur neck seen in 28.75% and 11.54% respectively[13]. They also found increased prevalence of osteopenia at femur and osteoporosis at lumbar spine similar to our study.

In our study, the mean FRAX score for major osteoporotic fracture was 1.53 ± 1.04 % and for hip fracture 0.54 ± 0.82%. We found only one patient with a ten-year hip fracture risk of > 3%, and no patient with major

osteoporosis-related fracture of > 20% on FRAX algorithm. In the study by Meng *et al* on RA patients, OP was found in 41.1% patients, 10-year risk of hip fracture was 0.62 ± 0.11% and for major osteoporotic fracture 4.04 ± 0.83%[14]. These values were higher as compared to controls; however, both the values were below the NOF treatment cut-offs (i.e., 10-year risk of > 20% and > 3% for major osteoporotic and hip fracture respectively) in spite of the fact that RA had been included as a risk factor in FRAX algorithm, and steroid use was prevalent in RA. In our study, though a trend of increasing FRAX score was seen with reduced BMD; absolute values of FRAX scores were not found higher than cut-off set by NOF. Thus, FRAX algorithm did not appear to predict the increased fracture risk requiring intervention in Ax SpA patients. However, this observation could be due to younger age group of Ax SpA patients, small sample size, one time FRAX scoring without follow-up and FRAX calculator not considering Ax SpA as a risk factor (unlike Rheumatoid Arthritis).

To determine predictors of fracture risk in Ax SpA patients, logistic regression analysis was done between various clinical parameters and FRAX score for major osteoporotic fracture and hip fracture. On univariate analysis, age, disease duration, BASDI, BASFI, BASMI, were found to be associated with FRAX scores for hip fracture and major osteoporotic fracture ($P < 0.05$). ESR showed correlation only with FRAX score of hip fracture and not with major osteoporotic fracture. No correlation was found with sex, anthropometric measurements, uveitis, smoking and BMD of forearm and lumbar spine. On multivariate regression analysis, only femur BMD showed independent association with FRAX score for major osteoporotic fracture. However, the FRAX score for hip fracture showed age, BASDAI and femur BMD as its independent predictors. A significant negative correlation was shown between BMD of femur neck and risk of hip fracture and major osteoporotic fracture ($P < 0.05$). This finding was consistent with other studies that showed BMD of femur to be better correlated with risk of vertebral fracture[15,16]. In a meta-analysis, Cara Pray *et al* found that age, male sex, disease duration, low BMD at femoral neck were associated with the increased risk of vertebral fracture in AS while BMI, uveitis, serum ESR, BASDAI, BASFI were not significantly associated[17].

We conclude that prevalence of osteoporosis and hence fracture risk is higher in AxSpA patients despite younger age and early disease; though we could not show high FRAX scores in absolute terms. The independent predictors for increased risk of fracture in AxSpA patients are increasing age and disease activity and loss of BMD at femur neck.

The present study has several limitations. It was a small cross-sectional observational study with no controls. FRAX – as an algorithm – itself suffers from various drawbacks and limitations. It does not utilise AxSpA or BMD of sites other than femur as a factor in its calculator.

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ORIGINAL ARTICLE

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Evaluation of Renal Functions in Tropical Acute Febrile Illness

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Abstract

***Introduction:** India is endemic for dengue, malaria, typhoid and scrub typhus infections. Acute kidney injury (AKI) is one of the most challenging problems faced by clinicians in tropical acute febrile illness. Due to emerging and re-emerging diseases, population growth, urbanisation, migration, international travel, pandemics, and global warming, the incidence of tropical acute febrile illness is continuously increasing. The spectrum of tropical acute febrile illness is also changing. While some infections like malaria are contained because of effective implementation of national programmes, various febrile illnesses like scrub typhus and dengue have shown a resurgence. There is a scarcity of literature available from developing countries like India. This study was planned to know the spectrum of tropical acute febrile illness and its association with AKI.*

***Methods:** The present study is a prospective observational study conducted on 100 adult patients of tropical acute febrile illness who reported to the medicine department at Pt. B.D. Sharma PGIMS Rohtak, Haryana. A detailed history and clinical examination was done in all subjects included in the study. Patients who fulfilled case definition criteria were evaluated for AKI as per definitions of KDIGO classification on day of admission and then subsequently on day 3, 7, and 14 with laboratory investigations, i.e., serum creatinine, blood urea, urine output, and eGFR.*

***Results:** The most common tropical acute febrile illness (TAFI) diagnosed in the current study was dengue in 43% cases. The spectrum of TAFI was dengue (43%), followed by malaria (23%), scrub typhus (19%), enteric fever (9%), and mixed pattern (6%). The febrile illnesses causing AKI in decreasing trend in present study was malaria (40.6%), scrub typhus (31.2%), dengue (12.5%), mixed disease pattern (9.4%) and enteric fever (6.3%). The proportion of AKI was highest among the subgroup with malaria (56.5%), followed by scrub typhus (52.63%), mixed infections (50%), enteric fever (22.22%), and dengue fever (9.30%). Among the subtypes of malaria, 64.7% of Plasmodium vivax cases and 50% of falciparum cases had AKI; but none of the mixed cases had AKI. In the present study; none of the patients with Dengue, enteric fever, or mixed disease pattern had undergone dialysis. Only one patient of Scrub Typhus with AKI underwent dialysis. 38.46% cases required dialysis of malaria subgroup. Total cases of AKI were 32, out of these 18.75% were dialysed and in-hospital mortality was none.*

***Conclusion:** In the present study, the proportion of AKI in tropical fever was 32%. Serum blood urea, serum creatinine, urine output, eGFR and hospital stay were statistically significantly different between AKI and non AKI. The most common cause of AKI in TAFI was malaria followed by scrub typhus and mixed infection. Long-term studies are needed to know the exact spectrum of AKI in TAFI, so that an effective strategy can be implemented to prevent this recoverable complication.*

***Key words:** Tropical acute febrile illness (TAFI), acute kidney injury (AKI).*

Introduction

Infectious diseases are a major cause of acute kidney injury (AKI) in tropical countries during the monsoon season. Tropical acute febrile illness (TAFI) is defined as all acute febrile syndromes with oral temperature over 37.5° c within the last 24 hours and less than 2 weeks with nonspecific symptoms like fever, generalised body pain, loose stools, vomiting, swelling of legs, generalised swelling of body, decreased urine output, breathlessness, cough, chest pain, altered sensorium, headache, and nonspecific signs like tachycardia, myalgia, conjunctival congestion, rashes, joint pains, etc.[1-3]. Epidemics of acute febrile illness have been causing major concerns in India. Every year during and after the rainy season an epidemic of acute febrile illness is witnessed in Northern India, but the relative contribution of various aetiological agents remains unknown[4-6].

Acute kidney injury in tropical fever is characterised by abrupt deterioration in kidney function which clinically manifests as acute increase in nitrogen waste products, measured by blood urea nitrogen and serum creatinine levels with or without reduced urine output over the course of hours to weeks. Renal abnormalities in tropical infections range from asymptomatic urinary abnormalities to severe forms of AKI necessitating emergent renal replacement therapy. These can be either related to direct involvement of the kidneys and urinary tract via tubulointerstitial toxicity and injury to glomerular endothelium or indirect consequence of systemic effects of infection, i.e.,

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haemolysis, rhabdomyolysis, hypovolaemic shock, septic shock, and immune complex deposition in glomeruli[7]. Direct invasion of the tubules in the kidney and resultant tubulointerstitial inflammation leading to AKI has been demonstrated in patients infected with leptospirosis and scrub typhus. *Plasmodium falciparum* has been shown to affect the glomerular endothelium through cytoadherence of infected red blood cells in circulation. In addition, the kidneys are susceptible to damage by various other mechanisms. Glomerular damage secondary to immune-complex deposition or activation of complement can also occur in some infections, e.g., mesangiocapillary glomerulonephritis seen in quartan malaria.

There is a paucity of data in the northern part of India on the spectrum and renal involvement in patients of tropical fever. In a recent study from a tertiary care hospital in North India, dengue (71.2%) was the most common cause of tropical acute febrile illness, followed by malaria, enteric fever, scrub typhus, and mixed infection[8]. Due to emerging and re-emerging diseases, population growth, urbanisation, migration, international travel, pandemics and global warming, the incidence of tropical acute febrile illness is continuously increasing. The spectrum of tropical acute febrile illness (TAFI) is changing and various febrile illnesses such as scrub typhus and dengue have shown resurgence. Some infections like malaria are contained because of effective implementation of national programme. Moreover, as already stated the spectrum of tropical acute febrile illness is different from developed countries.

Material and methods

The present study was a prospective observational study conducted on 100 adult patients aged more than 18 years of tropical acute febrile illness who reported between October 2017 and October 2018 to the medicine department at Pt. B.D. Sharma, PGIMS Rohtak, Haryana. All the patients were admitted with fever of less than 2 weeks duration with signs and symptoms suggestive of tropical acute febrile illness like generalised body pain, nausea, and vomiting, loose stools, myalgia, joint pain, conjunctival congestion, pedal oedema, generalised swelling of body, cough with expectoration, chest pain, shortness of breath, headache, and altered sensorium were screened. Patients aged less than 18 years or more than 75 years, patients having nosocomial infections, chronic infections, fever due to noninfectious aetiologies were excluded from the study. Patients of chronic kidney disease, acute kidney injury secondary to noninfectious aetiologies, urosepsis, lower respiratory tract infections, haematological malignancies, immunocompromised or immunosuppressed individuals, and pregnant females were also excluded from the study.

All patients were evaluated by a set of routine blood and urine investigations, peripheral blood smears for malaria, chest radiograph, abdominal ultrasonogram, blood cultures, IgM typhidot test for enteric fever, leptospiral IgM ELISA (PAN Bio Ltd, Brisbane, Australia), dengue IgM (PAN Bio Ltd, Brisbane, Australia) and arterial blood gas. KDIGO guidelines were used for AKI diagnosis and classification[9]. The tropical acute febrile illness was considered in patients who had clinical and laboratory diagnostic features suggestive of malaria, dengue, scrub typhus, leptospirosis, and enteric fever. The patients positive for more than one tropical infection by specific investigation were considered as having mixed infections. All patients were evaluated for AKI on day of admission and then subsequently on day 3, 7 and 14 with laboratory investigations, i.e., serum creatinine, blood urea, urine output, and eGFR.

Statistical analysis

AKI was considered as explanatory variable. Descriptive analysis was carried-out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. Categorical outcomes were compared between study groups using Chi square test/student's t test. The trend of laboratory values from admission to final follow-up, at different time intervals was assessed by comparing the mean values, using one-way repeated measures ANOVA. Data were analysed and statistically evaluated using SPSS 22.0 software.

Results

The present study included 100 adult patients of tropical acute febrile illness. The mean age was 34.9 ± 13.01 years. The spectrum of TAFI was dengue (43%) followed by malaria (23%), scrub typhus (19%), enteric fever (9%) and mixed pattern (6%) (Table I). Among the study population, 32% people developed AKI. Out of which 7% had AKI stage I, 16% had AKI stage II and remaining 9% had AKI stage III (Table II). Patients of tropical acute febrile illness showed increasing trend of blood urea and serum creatinine up to 7 days and then it started decreasing after treatment. eGFR also showed similar trends (Table III).

Out of 32 patients with AKI, 13 patients had AKI due to malaria (40.6%), followed by 10 due to scrub typhus (31.3%), 4 due to dengue (12.5%), 3 due to mixed pattern disease (9.4%), and 2 due to enteric fever (6.2%). The proportion of AKI was highest among people with malaria – 13 cases (56.5%), followed by scrub typhus – 10 cases (52.63%), and 3 cases of mixed infections (50%). Among people with Dengue fever, 9.30% had AKI and 22.22% of enteric fever patients had AKI. Among the subtypes of

malaria, 64.7% of *Plasmodium vivax* cases and 50% of falciparum cases had AKI but none of the mixed cases had AKI (Table I). Dialysis was required in one patient of scrub typhus and 5 patients of malaria with AKI. None of the patients with dengue, enteric fever, or mixed disease pattern needed dialysis (Table II).

Table I: Causes of acute kidney injury in tropical acute febrile illness (N = 100).

Diagnosis	Total n - 100	AKI	
		AKI n - 32	No AKI n - 68
Dengue	43	4 (9.302%)	39 (90.69%)
Scrub typhus	19	10 (52.63%)	9 (47.36%)
Malaria	23	13 (56.5%)	10(43.5%)
• Malaria (vivax)	17	11 (64.70%)	6 (35.29%)
• Malaria (falciparum)	4	2 (50%)	2 (50%)
• Malaria (vivax + falciparum)	2	0 (0%)	2 (100%)
Enteric Fever	9	2 (22.22%)	7 (77.77%)
Mixed Pattern Disease	6	3 (50 %)	3 (50 %)
• Scrub typhus with enteric fever	2	0 (0%)	2 (100%)
• Dengue with malaria (vivax))	1	1 (100%)	0 (0%)
Enteric Fever with malaria (vivax)	1	1 (100%)	0 (0%)
• Scrub typhus with leptospirosis	2	1 (50%)	1 (50%)

Table II: Distribution of patients in relation to diagnosis and AKI staging (N = 32).

Diagnosis	AKI stage			Dialysis required	
	I	II	III	Yes	No
Malaria (N = 13)	3	5	5	5	8
Scrub typhus (N = 10)	3	5	2	1	9
Enteric fever (N = 2)	0	1	1	0	2
Dengue (N = 4)	0	3	1	0	4
Mixed disease pattern (N = 3)	1	2	0	0	3
Total (N = 32)	7	16	9	6	26

Amongst the AKI patients, complications in the form of thrombocytopenia were present in 19 patients, anuria in 3 patients, and ARDS in 2 patients. The mean duration of hospital stay in patients with AKI was 10.75 ± 5.58 days as compared to 6.88 ± 0.76 days in patients without AKI and this difference was statistically significant (p value < 0.001). Age, diagnosis, SpO_2, temperature, haemoglobin, total leucocyte count, neutrophils, lymphocytes, absolute platelet count, blood urea, serum creatinine, corrected serum calcium, serum uric acid, serum albumin, urine output, eGFR, and hospital stay were statistically significantly different between AKI and non AKI (p value < 0.05) (TableIV). Hence, these factors can be the influencing factors in occurrence of AKI among patients presenting with TAFI.

Table III: Comparison of haematological and renal parameters in tropical acute febrile illness patients on follow-up (100).

Parameter	Baseline	Day 3 follow-up	Day 7 follow-up	Day 14 follow-up	P* value
Haemoglobin (g/dl)	13.48 ± 2.25	13.42 ± 2	12.98 ± 1.7	12.74 ± 1.41	> 0.05
Total leucocyte count	6528 ± 3789.33	6591 ± 2178.83	6254 ± 1569.05	6498 ± 1096	*> 0.05*
Absolute platelet count	68910 ± 58408.19	100580 ± 44514.25	158990 ± 32417.57	267200 ± 46233.49	< 0.001
Blood urea (mg/dl)	45.59 ± 57.84	42.49 ± 42.55	30.37 ± 25	19.42 ± 14.3	< 0.001
Serum creatinine (mg/dl)	1.52 ± 1.38	1.45 ± 1.26	1.07 ± 0.89	0.89 ± 0.55	< 0.001
Corrected serum calcium (mg/dl)	9.49 ± 0.53	9.34 ± 0.36	9.26 ± 0.33	9.27 ± 0.26	> 0.05
Serum phosphate (mg/dl)	3.4 ± 0.38	3.4 ± 0.42	3.49 ± 0.41	3.4 ± 0.38	> 0.05
Serum uric acid (mg/dl)	3.4 ± 1.09	3.52 ± 1.14	3.39 ± 0.75	2.84 ± 0.71	> 0.05
Serum protein (g/dl)	7.59 ± 0.29	7.57 ± 0.25	7.55 ± 0.25	7.48 ± 0.32	> 0.05
Serum albumin (g/dl)	3.41 ± 0.24	3.51 ± 0.22	3.69 ± 0.17	3.59 ± 0.21	> 0.05
Serum sodium (meq/l)	141.35 ± 2.99	141.45 ± 2.14	139.22 ± 2.84	140.79 ± 3.39	> 0.05
Serum potassium (meq/l)	3.53 ± 0.31	3.71 ± 0.34	3.81 ± 0.37	3.79 ± 0.31	> 0.05
Urine output (ml)	1236.3 ± 443.89	1328.8 ± 425.58	1501.5 ± 335.48	1784.5 ± 307.95	< 0.001
eGFR (ml/min/ 1.73m^2)	83.66 ± 43.22	87.53 ± 43.64	105.94 ± 43.61	111.94 ± 40.22	< 0.001

**repeated measure anova*

Discussion

India is an endemic country for dengue, malaria, typhoid, and scrub typhus. Tropical acute febrile illness accounts for the majority of hospitalisation in India. There are only limited studies from north India about the spectrum and renal involvement in tropical illnesses. This study was conducted to know the relative contribution of the aetiological agents in an outbreak of acute febrile illness and subsequently their effect on the renal parameters.

The spectrum of TAFI in the present study in decreasing trend was dengue (43%), followed by malaria (23%), scrub typhus (19%), enteric fever (9%), and mixed pattern (6%). The most common cause of tropical acute febrile illness

Table IV: Predictive factors associated with AKI (N = 100).

Parameter	AKI		*P value
	Present (N = 32)	Absent (N = 68)	
	Mean ± SD	Mean ± SD	
Age (Years)	39.88 ± 13.67	32.56 ± 12.09	< 0.01
Gender			#P value
Male	23 (71.87%)	45 (66.17%)	> 0.05
Female	9 (28.12%)	23 (33.82%)	
Diagnosis			#P value
Dengue	4 (9.3%)	39 (90.7%)	< 0.001
Scrub typhus	10 (52.6%)	9 (47.4%)	
Malaria	13 (56.5%)	10 (43.5%)	
Enteric fever	2 (22.2%)	7 (77.8%)	
Mixed disease pattern	3 (50%)	3 (50%)	
Physical examination parameters			
Systolic BP (mmHg)	114.88 ± 7.92	113.85 ± 5.01	> 0.05
Diastolic BP (mmHg)	71.94 ± 6.53	68.74 ± 7.25	> 0.05
Pulse rate (per min)	84.56 ± 10.05	84.06 ± 8.62	> 0.05
SpO_2 (%)	96.03 ± 2.1	97.47 ± 1.2	< 0.001
Temperature (° F)	103.22 ± 0.83	102.32 ± 1.1	< 0.001
Biochemical parameters			
Haemoglobin (g/dl)	12.57 ± 2.8	13.91 ± 1.81	> 0.05
Total leucocytes count (per mm^3)	9615.63 ± 5322.75	5075 ± 1188.42	> 0.05
Neutrophils (per mm^3)	76.47 ± 10.85	60.93 ± 7.62	< 0.001
Lymphocytes (per mm^3)	19.47 ± 10.16	34.1 ± 7.18	< 0.001
Absolute platelets count (per mm^3)	94444.44 ± 59298.68	61852.94 ± 56484.38	< 0.05
Blood urea (mg/dl)	109.97 ± 66.11	15.29 ± 3.17	< 0.001
Blood sugar (mg/dl)	97.56 ± 11.6	99.22 ± 8.23	> 0.05
Serum creatinine (mg/dl)	2.99 ± 1.67	0.83 ± 0.11	< 0.001
Corrected serum calcium (mg/dl)	9.65 ± 0.63	9.41 ± 0.47	< 0.05
Serum phosphate (mg/dl)	3.31 ± 0.43	3.44 ± 0.35	> 0.05
Serum uric acid (mg/dl)	3.73 ± 1.67	3.24 ± 0.62	< 0.05
Serum protein (g/dl)	7.52 ± 0.31	7.62 ± 0.27	> 0.05
Serum albumin (g/dl)	3.49 ± 0.29	3.37 ± 0.2	< 0.05
Serum sodium (meq/l)	141.41 ± 3.71	141.32 ± 2.61	> 0.05
Serum potassium (meq/l)	3.46 ± 0.5	3.56 ± 0.16	> 0.05
Urine output (ml)	732.19 ± 354.5	1473.53 ± 233.48	< 0.001
eGFR (ml/min/1.73 m^2)	32.05 ± 23.31	107.94 ± 25.27	< 0.001
Hospital stay (days)	10.75 ± 5.58	6.88 ± 0.76	< 0.001

**Student's t- test, #Chi square test*

was dengue which was consistent with various other studies conducted attributable to climatic change, rainy season, distinct geography, and resurgence of dengue[8,10,11]. Falciparum malaria was seen in only 4% cases in the present study and this showed a decreasing trend as observed in recent studies as most patients do not report to tertiary care setting and complicated malaria is not so common because of use of antimalarial drug at periphery[12,13].

Table V: Comparison of present study with various other studies.

Study	Basu *et al*[2]	Nair *et al*[14]	Atkar *et al*[15]	Present study
Most common cause of TAFI	Scrub typhus (51.2%)	Malaria (48.17%)	Malaria (31.43%)	Dengue (43%)
Proportion of AKI in TAFI	41.1%	54%	27.86%	32%
Most common cause of AKI in TAFI	Scrub typhus	Leptospirosis	*P. falciparum*	*P. vivax*
Proportion of AKI among malaria patients	57.35%	34.95%	27.87%	56.52%
Proportion of AKI among dengue patients	35.7%	69.4%	27.03%	10.26%
Proportion of AKI among scrub typhus patients	42.6%	40%	25%	52.63%
Proportion of AKI among enteric fever patients	6.3%	42.9%	9.68%	22.22%
Proportion of AKI among leptospirosis patients	50%	98.7%	41.67%	0%

The incidence of AKI in acute tropical febrile illness in the present study was 32%, which was different as compared to the other studies due to reporting of different proportion of critically ill patients of TAFI in the tertiary care centre[2,12-14].

The proportion of AKI among malaria patients was 56.52%. Similar findings were reported by Basu *et al* in their study which was conducted in southern India[2]. However, our findings were contradictory to other studies[12-16]. Aktar *et al* found only 27% malaria patients developed AKI[13]. This difference could be due to geographical variations among different study populations. The spectrum of malarial sub-types in decreasing trend in present study was vivax (73.9%), falciparum (17.4%) and mixed (8.7%). Results were similar to the study conducted by Trivedi *et al*, which concluded that *Plasmodium vivax* was the major parasite type (52.54%), followed by *P. falciparum* (33.75%), and mixed malarial infections (13.69%)[17]. Among the sub-types of malaria, 64.7% of *Plasmodium vivax* cases and 50% of falciparum cases developed AKI but none of the mixed cases developed AKI. AKI develops in falciparum malaria because of the unique properties of the parasite which produces haemorrhagic changes leading to renal ischaemia and rarely rhabdomyolysis. While global incidence of malaria has fallen in the last decade, it continues to be an important cause of mortality and morbidity in acutely ill febrile patients. In the present study, all complications of malaria have been reported in vivax. *P. vivax* malaria is now increasingly

associated with severe disease and high case fatality due to more pronounced inflammatory response and higher cytokine production. A recent retrospective study also concluded that anaemia, hepato-renal dysfunctions were equally frequent in vivax malaria and it can no longer be considered as benign infection[18]. The present study showed that the proportion of AKI in scrub typhus was 52.63% and in a previous study conducted by Aggarwal *et al*, the proportion of AKI in scrub typhus was 40%[19]. In southern, India the studies conducted by Basu *et al*, Nair *et al*, and Aktar *et al*, the proportion of AKI in scrub typhus were 42.6%, 40% and 25% respectively which were lower than the proportion of AKI in scrub typhus in the present study due to more critically ill patients of scrub typhus reporting to our institute which is a tertiary care centre[2,12,13]. AKI was less among dengue patients due to timely diagnosis, fluid management, and ICU care. A few studies have reported very high incidence of dengue-associated AKI[12,20].

In the present study, none of the patients with dengue, enteric fever, or mixed disease pattern had undergone dialysis. Total cases of AKI were 32, out of these 18.75% were dialysed and in-hospital mortality was none. Nair *et al*, in his study found that 10.2% of AKI patients underwent dialysis and in-hospital mortality was 3% among all patients[12]. In another study conducted in southern India, it was found that 19.21% of AKI patients required dialysis[2].

The mean duration of hospital stay was statistically significant in patients with AKI (10.75 ± 5.58 days) as compared to in patients without AKI (6.88 ± 0.76 days). Khalil *et al* demonstrated that patients with AKI had longer duration of hospital stay than patients without AKI[21]. The positive predictors of AKI from this study were comparable to the studies conducted by Saravu *et al*, Basu *et al*, and Nair *et al*[2,12,14].

Conclusion

From this present study it can be concluded that the most common cause of TAFI was dengue followed by malaria, scrub typhus, enteric fever and mixed disease pattern. The spectrum of AKI in TAFI in decreasing trend in the present study was malaria, scrub typhus, dengue, mixed disease pattern, and enteric fever. Long-term studies are needed to know the exact spectrum of AKI in TAFI, so that an effective strategy can be implemented to prevent this recoverable complication. It is necessary to increase public awareness, provide clinical education and training about tropical illnesses, and form specialised renal teams to treat severe AKI patients.

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ORIGINAL ARTICLE

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Spectrum of Infection among Admitted Systemic Lupus Erythematosus Patients

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Abstract

Background: Patients of Systemic Lupus Erythematosus (SLE) often require hospitalisation due to infections, which remains a major cause of mortality and morbidity in these patients. This study was intended to study the spectrum of infection and clinical profile of SLE patients getting admitted at a tertiary centre in north India.

Methods: This was a cross-sectional observational study done over a period of one year on SLE patients' getting admitted under the department of medicine with suspected infection. The demographic, presenting complaints, duration of SLE, treatment history, clinical parameters, laboratory investigations, SLE-related organ involvement, systemic lupus erythematosus disease activity score (SLEDAI) at admission, type of infection, duration of hospital stay, treatment received, and outcome were recorded.

Results: A total of 27 patients were included in the study and the mean age of the patients was 29.7 ± 10.7 years. The most common symptom at the time of admission in the hospital was fever (74%), followed by cough (55%), dyspnoea (55%), oral ulcers (51%), arthralgia (37%), photosensitivity (33%), oliguria (15%), and psychosis (11%). The common risk factors for infection seen in this study were steroid intake in the last 3 months (51.8%), previous antibiotic intake (18.5%), other immunosuppressant therapy (18.5%), recent hospital stay (7.4%) and past history of tuberculosis (7.4%). Acute phase reactants were significantly elevated and mean SLEDAI score was 11.1 ± 6.8.

The most common infection was bacterial pneumonia (44.4%), followed by tuberculosis (33.3%), fungal pneumonia (7.4%), MRSA bacteraemia (7.4%), acute gastroenteritis (7.4%), urinary tract infection (7.4%), skin infection (3.7%), HIV (3.7%) and infective endocarditis (3.7%). E.coli, Methicillin resistant Staphylococcus aureus (MRSA), A.baumannii and Candida were isolated from various specimens. There were four deaths due to infection.

Conclusion: Bacterial pneumonia and tuberculosis are the leading cause of infection among hospitalised SLE patients.

Key words: Fungal infection, Staphylococcus aureus, tuberculosis.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterised by multiple organ involvement requiring long-term immunosuppressant therapy. SLE patients have two- to five-fold increased mortality as compared to the general population[1-2]. The mortality in SLE has a bi-modal pattern with earlier deaths due to high disease activity and the later deaths related to various complications of SLE like cardiovascular disease and malignancy[3-4]. Infections in SLE can occur during any stage of the disease and often correlate with high disease activity. However, Indian data suggests both high disease activity and infection as the leading causes of mortality in these patients[5]. Impairment of both innate and adaptive immunity in SLE along with use of immunosuppressant therapy predisposes them to various infections[6]. This study was intended to study the spectrum of infection and clinical profile of SLE patients getting admitted at a tertiary centre in north India.

Subjects and Methods

This was a cross-sectional observational study done in the Department of Medicine at the All India Institute of Medical Sciences, New Delhi. The study was approved by the ethical committee of the institute. All patients satisfying either 1997 American College of Rheumatology Modified Classification Criteria or the 2012 Systemic Lupus International Collaborating Clinics Classification Criteria for the diagnosis of SLE getting admitted in the hospital between June 2018 and June 2019 with a provisional diagnosis of infection were included in the study. Patients having overlap syndrome and only flare without any

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infection were excluded from the study. Infection was defined by presence of three of the following clinical criteria: fever, increase in acute phase reactants (CRP, ESR) or procalcitonin, leucocytosis, presence of focal abnormalities (like lung infiltrates, leucocyturia, cellulitis, etc.,) and good response to antibiotics.

The demographic, presenting complaints, duration of SLE, treatment history, clinical parameters, laboratory investigations, SLE-related organ involvement, systemic lupus erythematosus disease activity score (SLEDAI) at admission, type of infection, duration of hospital stay, treatment received, and outcome, were recorded on a pre-designed proforma.

Statistical analysis

The statistical analysis was performed using Stata 13 software. Continuous variables were expressed as mean and standard deviation (SD) or median and range (if any outliers). Qualitative variables were summarised as frequency and percentage.

Results

There were a total of 27 patients in the study; female to male ratio was 26:1. The mean age of the patient was 29.7 ± 10.7 years and mean duration of hospital stay was 12.2 ± 7.8 days. The median duration of SLE was 12 months (range: 0 - 156 months) and 6 patients were newly detected cases of SLE (Table I). The most common symptom at the time of admission in the hospital was fever (74%), followed by cough (55%), dyspnoea (55%), oral ulcers (51%), arthralgia (37%), photosensitivity (33%), oliguria (15%), and psychosis (11%). The most common risk factor associated with infection was steroid intake in the last 3 months (51.8%), followed by previous antibiotic intake (18.5%), other immunosuppressant therapy (18.5%), recent hospital stay (7.4%) and past history of tuberculosis (7.4%) (Table II).

Table I: Demographic and Clinical features of admitted SLE patients.

Variables	Mean ± standard deviation
Age	29.7 ± 10.7 years
Duration of SLE	Range: 0 to 156 months; median: 12 months
Duration of hospital stay	12.2 ± 7.8 days
SLEDAI score	11.1 ± 6.8

The mean haemoglobin level was 7.7 ± 1.9 gm/dl, total leukocyte count (7,441± 7,046), platelet count (1,43,148 ± 1,14,136), urea (77.6 ± 55.8 mg/dl), creatinine (1.3 ± 0.9), ESR (65.7 ± 21.3 mm/hr), CRP (79.9 ± 67.3 mg/l), ferritin (1,840 ± 2,022 ng/ml), n = 15] (Table III). The mean SLEDAI score was 11.1 ± 6.8, suggestive of mild-to-moderate flare. Among the organs affected due to SLE per se, the most commonly affected organ was renal (70.3%), followed by haematological (59.2%), cardiovascular (25.9%) and neurological (22.2%).

Type II: Various risk factors associated with infection in SLE patients.

Risk factors in last 3 months	Number of patients (%) (n = 27)
Steroid intake	14 (51.8%)
Hospitalisation	2 (7.4%)
Antibiotic intake	5 (18.5%)
Cyclophosphamide	1 (3.7%)
MMF	2 (7.4%)

Table III: Laboratory parameter of SLE patients with infection,

Laboratory parameters	Mean ± standard deviation
Haemoglobin (g/dl)	7.7 ± 1.9
Total leucocyte count (cells/cu mm)	7,441 ± 7,046
Platelet count (cells/cu mm)	1,43,148 ± 1,14,136
Urea (mg/dl)	77.6 ± 55.8
Serum creatinine (mg/dl)	1.3 ± 0.9
ESR (mm/hr)	65.7 ± 21.3
CRP (mg/l)	79.9 ± 67.3

The most common infection was bacterial pneumonia (44.4%), followed by tuberculosis (33.3%), fungal pneumonia (7.4%), MRSA bacteraemia (7.4%), acute gastroenteritis (7.4%), urinary tract infection (7.4%), skin infection (3.7%), HIV (3.7%), and infective endocarditis (3.7%) (Table IV). Among tuberculosis, most common type was extra-pulmonary tuberculosis in 4 patients (14.8%), pulmonary tuberculosis in 3 patients (11.1%), and disseminated tuberculosis in 2 patients (7.4%). Urine culture grew *E.coli* in two patients; two positive blood cultures showed MRSA, and one blood culture was positive for Candida. Sputum culture was sterile in all patients; and broncho-alveolar lavage fluid in one patient grew *Acinetobacter baumannii*. Among various antibiotics administered, the most commonly used was cefoperazone-sulbactam (22.2%), followed by teicoplanin (14.8%), ceftriaxone (14.8%) and azithromycin (14.8%). The outcome was favourable in 23 patients (85%) and there were four mortalities (15%).

Table IV: Spectrum of infection among admitted SLE patients.

Infection type	Number of patients (%) (n = 27)
Bacterial pneumonia	12 (44.4%)
Tuberculosis (All)	9 (33.3%)
Pulmonary tuberculosis	3 (11.1%)
Extra-pulmonary tuberculosis	4 (14.8%)
Disseminated tuberculosis	2 (7.4%)
Fungal pneumonia	2 (7.4%)
MRSA bacteraemia	2 (7.4%)
Acute gastroenteritis	2 (7.4%)
UTI	2 (7.4%)
Skin infection	1 (3.7%)
Infective endocarditis	1 (3.7%)
HIV	1 (3.7%)

Discussion

Infections are the leading cause of mortality and morbidity in patients with SLE. The most common infection in SLE is bacterial, followed by viral and fungal due to impaired immune system. In our study too, we found the most common infection to be bacterial pneumonia, followed by tuberculosis and MRSA bacteraemia. The risk factors associated with infection were steroid use, antibiotic use and past history of tuberculosis.

Among bacterial infections, lower respiratory tract infections (LRTI) are the most common among admitted SLE patients[7]. The common pathogen causing LRTI in SLE patients is *Streptococcus pneumoniae*, followed by *Staphylocoocus aureus*. The risk of *S. pneumoniae* is increased in SLE patients due to defective opsonisation and failure in complement-mediated activation of immune system[8]. Patients on long-term steroid and immunosuppressant therapy are at risk for bacteraemia, which are commonly caused by *S.aureus*, *E. coli,* and *Salmonella*[9-10]. Urinary and skin infections are frequently seen in outpatients. *Gram-negative* pathogens like *E. coli, Kleibsella,* and *Pseudomonas* are commonly involved in urinary tract infections[11]. In our study too, bacterial pneumonia was the most common bacterial infection; however, we could not isolate any organism from sputum samples. MRSA bacteraemia was observed in the present study; and among urinary tract infections, *E. coli* was the most common isolate.

SLE patients are also predisposed to *M.tuberculosis* infections due to dysfunctional immune system and long-term immunosuppressive therapy. The prevalence of *M. tuberculosis* in SLE patients ranges from 5% to 30%[12]. Extrapulmonary tuberculosis is more frequent than pulmonary tuberculosis, and a few patients might acquire multidrug resistant tuberculosis infection too[13-14]. We found tuberculosis to be the second most common infection and we also observed more extra-pulmonary and disseminated cases.

The common viral infections observed in SLE patients are *Herpes zoster*, *cytomegalovirus*, *parvovirus*, *hepatitis B* and *C* and *human papillomavirus*. Opportunistic fungal infections commonly seen in SLE patients are Candida, invasive *aspergillosis*, *Pneumocystis jirovecii* and *Cryptococcus neoformans*[15]. The most common risk factor for opportunistic infections is high disease activity. We had two cases of *aspergillu*s pneumonia and one patient had infective endocarditis due to *Candida*. Disease activity was high in all three patients.

Immune dysfunction is a common predisposing factor in SLE patients. T lymphocytes are reduced in number and T-helper cell activity is impaired in SLE patients with flare[16]. Neutropenia, impaired phagocytic activity and complement dysfunction are other immune defects in these patients[17]. The other risk factors associated with infection are high disease activity, low C3 levels, high anti-dsDNA levels, prednisone dose (> 7.5 mg/day), renal activity, intravenous cyclophosphamide[18-19]. The measures that could be taken to prevent infection rate in SLE patients are yearly influenza vaccination, pneumococcal vaccination, low-dose methylprednisolone pulse, low-dose cyclophosphamide regimen, and hydroxychloroquine therapy in all SLE patients.

Conclusion

Bacterial pneumonia and tuberculosis are the leading cause of infection among SLE patients requiring hospitalisation.

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ORIGINAL ARTICLE

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Study of Prevalence of Retinopathy, it's Awareness and Associated Risk Factors in Type 2 DM Patients in Hadoti Region, Kota

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Abstract

***Introduction:** DM is one of the major systemic causes of blindness throughout the world. Diabetic retinopathy can be defined as damage to microvasculature in the retina by prolonged hyperglycaemia. Though multiple studies have been conducted to find out prevalence of DR and its awareness in various parts of India, it remains less explored in Hadoti region, Kota, Rajasthan, India.*

***Study design and material:** This is a hospital-based cross-sectional study conducted on patients attending the diabetic clinic in New Medical College Hospital, Kota. A total of 248 type 2 diabetes mellitus patients were screened with Carl Zeiss Retinoscope after taking informed and written consent. Anthropometric data of each subject was collected. Urine albumin and HbA1C levels were also noted. Furthermore, a special questionnaire was designed to assess awareness about diabetes-related eye disease among the patients.*

***Observation:** The overall prevalence of diabetic retinopathy was 8.87%, out of which 54.54% patients had NPDR and 45.45% patients had PDR. Out of the 22 patients with diabetic retinopathy, 16 had albuminuria, and 14 of them have had diabetes for more than 10 years.*

Out of 248 patients, 178 patients (71.77%) were aware about ophthalmological side-effects of DM, though only 74 of them (41.57%) visited an ophthalmologist for further check-up.

Out of the 70 patients unaware about ophthalmological s/e, 26 patients (37.14%) were illiterate.

***Conclusion:** This study concluded that prevalence of diabetic retinopathy in Hadoti region was 8.87%. and awareness about the illness was seen in 71.77% of the population. Furthermore, in our study educated patients were more aware (94.38%) about diabetic eye disease suggesting an association between the two. Early diagnosis via screening programme may help in formulation and implementation of effective intervention at the earliest. It will also help in reducing the economic burden on the government and society.*

Introduction:

India, the world's second most populous country, now has a greater number of people with type 2 diabetes than any other nation. Calling India the diabetes capital of the world, the 'International Journal of Diabetes in Developing Countries' says that there has been an alarming rise in the diabetic population[1]. The prevalence of diabetes mellitus is growing rapidly worldwide and is reaching epidemic proportions[4,5]. IDF expects a rise in number of people living with diabetes from 366 million in 2011 to 552 million by 2030, if no action is taken. In 2011, IDF estimated that India alone has 61.3 million diabetics[6].

DM is one of the key causes of blindness in the major part of the world. It is a heterogenous group of syndromes in which not only carbohydrate metabolism but metabolism of lipids and proteins is also deranged. This deregulation causes secondary pathophysiological changes in multiple organ systems and ultimately imposes a tremendous burden on the healthcare system. Diabetic retinopathy (DR) however, is an end-organ response to a systemic disease, representing only one of many microvascular and macrovascular diabetic complications. The newer evolving technologies have improved the diagnostic accuracy of screening methods and access of the diabetic patients to specialist care. In spite of this progress, it remains a significant cause of acquired visual loss in working-age adults worldwide. Patients with DR are 25 times more likely to be blind than non-diabetic patients of similar age and gender[7].

Up to 21% of patients with type 2 diabetes have retinopathy at the time of diagnosis and more than 60% of those with type 2 diabetes have some degree of retinopathy twenty years after diagnosis[2]. Although diabetic retinopathy does not cause obvious visual symptoms in earlier stages, it threatens the sight of the patient once Proliferative Diabetic Retinopathy (PDR) or macular oedema develops, according to the global update of available data on visual impairment in the year 2002[3].

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Epidemiologic studies and clinical trials have provided information on the incidence and prevalence of retinopathy and on the associated risk factors of retinopathy. Many important risk factors are identified to be related with progression of DR such as longer disease duration, higher levels of glycosylated haemoglobin, and presence of proteinuria[1,8,9]. Data on other factors including body mass index, male sex, education status have demonstrated varying results[1,8].

Various studies have been conducted to find out prevalence of DR, and its awareness in various part of India, yet it remains less explored in Hadoti region, Kota.

Material and method

This was a hospital-based cross-sectional study carried-out from January to December 2019, in the Diabetes Clinic, New Medical College Hospital, Kota (Rajasthan). The subjects were diabetic patients who were being treated in our clinic and agreed to participate in our study. All patients were diagnosed cases of T2DM and were on treatment.

248 patients were screened via Carl Zeiss Retinoscope machine after taking informed and written consent. Urine albumin and HbA1C levels, along with anthropometric and demographic data were collected for each subject. Besides, a special questionnaire was designed to find out awareness of diabetic-related eye disease among the subjects and association with education status was analysed *ad hoc*.

All patients had pupils dilated with 0.5% tropicamide (two drops in each eye). A single photograph centred on the macula was taken using Carl Zeiss Retinoscope with instantaneous picture development. An ophthalmologist was then given the fundal photographs to look for diabetic retinopathy; and if present, to examine whether it was proliferative or non-proliferative.

Inclusion criteria: Patients diagnosed with type 2 DM, who gave their consents for participation in the study.

Exclusion criteria: Patients with mature cataracts, history of exposure to radiation, hypertensive retinopathy without DM, sickle cell disease, and pheochromocytoma were also excluded, as these conditions could mimic fundus features with diabetic retinopathy.

An approval was obtained from the institutional ethics committee. Informed consents were taken from all the subjects.

Statistical analysis

Data was analysed by using epi-info statistical software. Mean, standard deviation, range and percentage were calculated. Prevalence of DR was calculated as the ratio of the number of participants with DR in one or both eyes to the total number of diabetic patients who were evaluated.

Result

Demographic profile of diabetic population under study (Values in parenthesis indicate age range, * Standard Deviation)

Table I:

No. of Participants (N = 248)	Age in years (Mean ± SD*)	Duration of diabetes in years (Mean ± SD*)	HBA1C (%) (Mean ± SD)
Male (N = 154)	56.80 ± 10.42	7.28 ± 6.51	8.34 ± 1.61
Female (N = 94)	51.32 ± 9.12	6.78 ± 6.74	8.23 ± 1.53

Table II shows the overall prevalence of diabetic retinopathy was 8.87%, out of which 54.54% patients had NPDR and 45.45% patients had PDR.

Table II: Prevalence of DR (total, NPDR and PDR).

Total no. of patients (pts)	Percentage of pts with *DR (Total)	Percentage of pts with #NPDR	Percentage of pts with †PDR
248	22 (8.87%)	12 (54.54%)	10 (45.45%)

*(Values in parenthesis indicate number of patients, *Diabetic retinopathy, #Non-proliferative diabetic retinopathy, †Proliferative diabetic retinopathy).*

Table III and IV show relation of diabetic retinopathy with other risk factors such as urinary albumin, duration of diabetes. 16 out of 22 diabetic patients with retinopathy (72.22%), had albuminuria (detected by spot urine albumin) whereas 90 out of 226 diabetic patients without retinopathy (39.82%) had albuminuria (p - value 0.0029; statistically significant at $p < 0.05$).

14 out of 22 subjects with retinopathy (63.33%) had disease duration of > 10 years whereas only 42 out of 226 patients (18.58%) without retinopathy had had the illness for more than 10 years (p - value 0.00001; statistically significant at $p < .05$).

Table III:

Category	No. of patients with urinary albumin (%)	No. of patients without urinary albumin (%)
Diabetic patients with retinopathy (N = 22)	16 (72.22%)	6 (27.78%)
Diabetic patients without retinopathy (N = 226)	90 (39.8%)	136 (60.18%)

Table V and 6: Out of 248 patients, 178 patients (71.77%) were aware about ophthalmological side-effects of DM, out of which only 74 patients (41.57%) visited ophthalmologist for further check up:

Table IV:

Category	No. of patients with DM duration > 10 yrs	No. of patients with DM duration < 10 yrs
Diabetic patients with retinopathy (N = 22)	14 (63.63%)	8 (36.37%)
Diabetic patients without retinopathy (N = 226)	42 (18.58%)	184 (81.42%)

Table V:

Total patients	Aware patients (%)	Male (%)	Female (%)
248	178 (71.77%)	118 (66.30%)	60 (33.70%)

Table VI:

Total patients (N)	Aware patients about ophthalmologic side-effects (%)	No. of patients who visited an ophthalmologist (%)	No. of patients who did not visit an ophthalmologist (%)
248	178 (71.77%)	74 (41.57%)	104 (58.43%)

Table VII:

Education status	No. of patients aware about ophthalmological side-effects	No. of patients unware about ophthalmological side-effects
Illiterate (N = 36)	10 (5.61%)	26 (37.14%)
Literate (N = 212)	168 (94.38%)	44 (62.86%)

Table VIII:

Education level of literate patients (N = 212)	Aware patients about diabetic eye disease	Unaware patients about diabetic eye disease
Up to primary level (63)	33 (52.38%)	30 (47.62%)
Up to secondary level (47)	36 (76.59%)	11 (23.41%)
Up to higher education or more (102)	99 (97.05%)	3 (2.95%)

Table VII and VIII shows relationship between education level and awareness about diabetic retinopathy which suggests that 168 out of 178 patients (94.38%) (who were aware about ophthalmological side-effects) were literate while 10 out of 178 (5.61%) were illiterate. On the other hand, out of 70 patients (who were unaware about ophthalmological side-effects) 37.14% patients were illiterate while 62.86% were literate. (p value - 0.00001, statistically significant at $p < .05$).

Among literate patients, 63 were educated up to the primary level, 47 up to the secondary level and 102 up to higher education level. Awareness among these group was found 52.38% (33 patients), 76.59% (36 patients), 97.05% (99 patients) respectively, which suggests that awareness increases as education level increases.

Table IX shows the source of information about diabetic eye disease among literate and illiterate patients which suggests that all illiterate patients (100%) got the information from medical personnel or treating doctor while for literate patients the major source was media (51.20%) (e.g., newspapers, magazines, books, etc.), followed by medical personnel (25%) and other patients (23.80%).

Table IX:

Education status (only aware patients)	Source of information about diabetic eye disease or side-effects		
	Other patients	Media	Medical personnel
Illiterate patients (N = 10)	NIL	NIL	10 (100%)
Literate patients (N = 168)	40 (23.80%)	86 (51.20%)	42 (25%)

Discussion

Diabetic retinopathy (DR) is a well-known complication of diabetes mellitus (DM). Prevalence of DR differs in type 1 and type 2 DM and also differs in different populations. Different population and hospital-based studies, which were done to establish prevalence of DR in diabetic populations, have been summarised in (Table X).

Table X:

Study and authors	Year	Region/area and type of population studied	Total No. of cases	% DR, % NPDR and % PDR
Present study Piyush Rameshchandra *et al*	2019 2009	Hadoti region, Kota (Raj) India, urban and rural Western India type 2 DM	248 168	8.87%,54.54%, 45.45%, 33.92 25.59, 8.33
Rema M *et al*[11]	1996	Urban and rural South Indian type 2 DM	6792	34.1, 30.8, 3.4
Agrawal RP *et al*[7]	2000	Urban and rural North India type 2 DM	4067	28.9, 23.06, 5.9
Narendran V *et al*[12]	2002	Urban and rural South India type 1 and type 2 DM	260	26.2, 24.6, 1.6
Rema M *et al*, CURES Eye study I[8]	2005	Urban South India Type 2 DM	1382	17.6, 16.6, 0.9
Mahesh G *et al*[13]	2005	Urban and rural South India type 1 and type 2 DM	323	20.12, 10.84,

Several studies from the world and India have also tried to find out prevalence of diabetic retinopathy, including its stages NPDR and PDR, in different populations from south, north and western India. The present study showed that the prevalence of diabetic retinopathy (DR) was 8.87% (NPDR - 54.54%, PDR - 45.45%) in type 2 DM patients of Hadoti region, Kota (Rajasthan).

Overall, prevalence of DR in our hospital-based study was

lower as compared to other epidemiological studies. This observation may be attributed to the fact that there was a referral bias among the diabetic patients who were reported to our clinic (as our study was mainly OPD based), small sample size, lower mean diabetes mellitus duration (7.28 ± 6.51 in male, and 6.78 ± 6.74 in female) as compared to other studies and lower mean HBA1C (8.34 ± 1.61 in male and 8.23 ± 1.53 in female).

On the basis of the questionnaire designed to assess awareness, we concluded that out of 248 patients, 178 patients (71.77%) were aware about ophthalmological side-effects of DM, out of which only 74 patients (41.57%) visited ophthalmologist for further check-up. Further questioning suggested that all patients who did visit an ophthalmologist were symptomatic, mostly presenting with blurring of vision and the rest who did not visit, were still asymptomatic. So, our study also suggests that the subjects tend to take professional help only after experiencing symptoms despite having knowledge about the disease.

Furthermore, an association between educational status and awareness about diabetic eye disease (DR) was also noted. In our study, literate patients were more informed (94.38% v/s 5.61%) about diabetic eye disease than illiterate patients. The latter group came to know about it from their treating physicians, hence our study suggests that doctors play a great role in enhancing awareness of diabetic related eye disease, especially in the illiterate and socially backward class.

Limitations and strengths of our study

Smaller sample sizes, referral bias and cross-sectional study are major limitations due to which results are difficult to extrapolate to larger populations. Its strength lies in the fact that it was the first of its kind which assessed the prevalence of DR in Hadoti region, Kota, by using retinal photographs.

Conclusion

This study concluded that prevalence of diabetic retinopathy in Hadoti region was 8.87%, and 71.77% were cognizant of the disease. Early diagnosis via screening programme may help in formulation, implementation of effective intervention at the earliest, and reducing the economic burden on government and society.

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ORIGINAL ARTICLE

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Tobacco use Behaviour in the Urban Population: A Hospital-based Study from Eastern India

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Abstract

Background: Tobacco use is a major public health menace in India. As a signatory to the WHO framework convention, the Government of India is trying to battle this problem earnestly. However, tobacco use is still high in India and the consumption pattern in heterogeneous. For proper public health interventions, region-specific data on tobacco use behaviour is thus needed. The present study is a pilot project to generate data from a sample urban population.

Material and methods: Had two sections: one for the tobacco use behaviour and one for nicotine dependence. Subjects greater than 12 years were included in the survey. Anyone with history of tobacco use in the last one month was designated as "user".

Results: There were 299 subjects in the study. Around 47% were below 40 years of age. 51.5% (95% CI: 45.7 - 57.3%) were tobacco users. Biri was the commonest form of tobacco used (51%). 11.7% of the users used more than one form of tobacco simultaneously. The prevalence of use in males was much more than females (P < 0.001) and males were also more likely to be smokers. There was an increasing trend of tobacco use with age. The type of tobacco product used also varied with educational level with cigarette being more common (75%) among those with college education. As a vocation, labourers were the ones with highest rate of tobacco use (81.5%). 35% of the users had started tobacco use before 16 years of age. For male users, peer pressure was the main factor (94%) in initiation of tobacco use while for females, family influence was the main determinant (55%). More males had higher tobacco dependence scores compared to females.

Conclusion: Proper public health measures are needed to address adolescent tobacco use and also tobacco addiction among vulnerable groups like labourers.

Keywords: Tobacco; urban; biri; labourers; adolescent.

Introduction

Tobacco is responsible for many of the public health problems in the world. According to the World health organisation (WHO), tobacco products are responsible for at least six million deaths per year and many of these are premature[1]. A further six hundred thousand are estimated to die annually as a result of second-hand smoke. To curb this menace, in 2003, the World Health assembly adopted the FCTC (Framework Convention on Tobacco Control) which was signed by most countries including India[1]. The government of India has taken many steps for tobacco control, including the banning of advertisements. However, tobacco use is still very high in the Indian population with a sizeable portion starting tobacco use in their teens, and there is considerable scope of stepping up the public health measures to curb this menace.

According to the global adult tobacco survey, 2016 - 17, 28.6% of adult Indians are current tobacco users[2]. There is a marked gender difference, with the use in males three times that of females[2]. However, there is considerable regional difference in the pattern of tobacco use with the prevalence in Tripura being 7 times that of Goa. Thus, one public health programme will not be useful across the country and there is need of regional tobacco prevention programmes, based on local patterns of tobacco use.

Studies have shown that there is wide variation in tobacco use in India, based on habitat (rural vs urban), gender, religion, level of education and other cultural variables[3]. For example, while smoking is still considered as a taboo in many Indian families especially in front of elderly members, chewing forms of tobacco like betel quid enjoy a certain level of acceptance, especially among the females[3]. On the contrary, in most sections of the Indian society, smoking is considered indecent for females, although people tend to tolerate smoking in males. Also, there are certain myths about smokeless tobacco (SLT) like their benefit for dental pain and their role in weight reduction. These are incorrect assumptions but these myths lead to a culture of chewing tobacco for the perceived health benefits[3].

In a recent study from North-east India, Sarkar *et al* found

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that 74% of urban slum dwellers were current tobacco users[4]. SLT was more commonly used compared to smoking, especially in the higher age groups[4]. But in another study from Indore among law students, it was seen that cigarette and hookah were the commonest forms of tobacco used while SLT was very rarely used[5]. In other studies from India, smoking has been found to be the predominant form of tobacco use among college students[5]. Thus, different socio-economic groups in India would require different tobacco control measures.

Tobacco is responsible for a lot of human diseases like coronary artery disease, hypertension, gastric ulcer, and various types of malignancy. Thus, control of tobacco use is an essential preventive programme. But for this to be successful there is need of regional data on tobacco use behaviour from different parts of India. While there is some data from north and south India, there is a dearth of good quality data from Eastern India. The present pilot study is aimed at generating this data from a sample urban population of West Bengal.

Aims

To study the tobacco use behaviour in a sample urban population (including teenagers) with special reference to smokeless tobacco.

To study the level of nicotine dependence in the tobacco users.

Material and methods

This was a hospital-based cross-sectional survey conducted in a tertiary care medical college of West Bengal. The questionnaire for the survey was adopted from the sample questionnaire provided in the document: "Tobacco questions for surveys" by CDC, Atlanta[6]. Since this was a pilot study, all sections of the survey questions were not included and only those which which were relevant for generating initial pilot data were chosen.

In addition to this, to measure the level of nicotine dependence, the revised version of the Fagerstrom Test for Nicotine Dependence (FTND) was also used in the study subjects[7]. Thus, there were two sections: one for the tobacco use behaviour and one for the FTND. The whole questionnaire was made in the local language, Bengali, and checked by an expert in clinical research. Then, the questionnaire was tested in 30 subjects as a pilot project. After validation, the final questionnaire was used for the survey.

For FTND, the total score was analysed as follows[8]: -

Table showing interpretation of FTND scoring system

FND score	Interpretation
1 - 2	Low dependence
3 - 4	Low-moderate dependence
5 - 7	Moderate dependence
8 +	High dependence

Adult (> 12 years) patients and the family members coming to the medicine OPD of the concerned medical college were screened for inclusion in the survey. The legal and medical definition of adulthood varies. In some definitions, adulthood is defined as ≥ 18 years of age. *But in this study, the cut-off limit of 12 years was used as one of the aims of the survey was to find the prevalence of teenage tobacco use.* The prospective participants were explained about the study in their own language. In cases where communication due to language barrier was a problem, help of an interpreter was sought. The exclusion criteria included anyone involved with the tobacco industry, anyone with dementia, and anyone enrolled in smoking cessation programmes. Informed consent was obtained from each study participant.

The study was approved by the institutional ethics committee. All interviews were conducted by the same person (SG). The study was conducted for four months, between May - August, 2019. The participants were taken to a separate place, away from their family members or friends, and then interviewed. The survey questionnaire was read out to the participants and their responses were marked. Then at the end, the responses were verified again. Incomplete responses were rejected. Tobacco use was defined as use of any tobacco product currently or within the last one month.

Sample size

For calculating the sample size, the authors used a well-designed 2013 study from South India[9]. In this study, comparing tobacco use among rural, semi-urban and urban areas, the prevalence of tobacco use in urban areas was found to be 19.4%[9]. Taking this as reference, for 95% confidence interval and an acceptable difference of 5%, the sample size, as calculated by the WINPEPI software, was 241. A 10% margin of error was also considered. Thus, the target sample size was 265.

The data from the survey was first entered in case record forms. Then, this was transferred to Microsoft Excel worksheet. Data entry was cross-checked by another researcher. The data was first checked for normalcy and then analysed using online statistical software like Graphpad. $P < 0.05$ was considered significant.

Full confidentiality was maintained and the data from this survey was not released to any other entity, including the subject's family.

Results

There were a total of 299 subjects in this survey with male: female ratio of 197: 102. Average age was 42.2 ± 16.2 years with a range of 12 - 88 years. Among the subjects, 92 (30.8%) were labourers and 56 (18.7%) were businesspersons. The rest were of diverse occupations. According to educational qualification, 36.8% were educated up to primary level while 28.8% had studied up to the secondary level. Table I shows the demographic characteristics of the subjects.

Table I: Showing the demographic characteristics of the study subjects.

Parameter	Percentage	
Gender	Male	65.9
	Female	34.1
Age (in years)	≤ 20	10.7
	21 – 40	36.8
	41 – 60	39.8
	> 60	12.7
Educational qualification	Illiterate	14.4
	Primary	36.8
	Secondary	28.8
	Higher Secondary + College educated	20
Occupation	Home-maker	19.4
	Labourer	30.8
	Business person	18.7
	Farmer	8.7
	Student	10
	Miscl.	12.4

Among the study subjects, 154 (51.5%; 95% CI: 45.7 - 57.3%) used one or more tobacco products (henceforth called "users"). 136 subjects used one tobacco product, 17 used two products and only one used three tobacco products. Among the tobacco users (n = 154), biri was the most popular (n = 79; 51.3%; 95% CI: 43.1 - 59.4%), followed by guraku (16.2%) and Khaini (13.6%). Snuff and Dokta (2 each) were the least used tobacco products. Among the subjects who used two tobacco products (n = 17), the combination of biri and khaini was the most popular (17.6%).

There was considerable gender difference in tobacco use behaviour. Among males, 63.5% were users, while for females, this figure was only 28.4% ($p < 0.0001$ by two-tailed chi square test). In males (n = 197), biri was the most popular (37.6%) followed by Khaini and Cigarette (10% each). In females (n = 102), Guraku was the most popular (18.6%). Males were also more likely to use two tobacco products simultaneously. Among the persons who used two or more tobacco products, 77.8% were male. Also the smoking form of tobacco (biri or cigarette) was used much more by male users (75.2%) compared to females (20.7%) ($p < 0.0001$ by Chi square test).

Fig. 1 shows the tobacco use behaviour according to the age groups. It is seen that there is an increasing trend of tobacco use in higher age groups with more than 60% of those above 60 being tobacco users ($p = 0.01$, Chi square for trend). Thus, the younger people were less likely to be tobacco users. Gutkha-Guraku use was the highest in 21 - 40 year age group while khaini use was the highest in the over-60 age group.

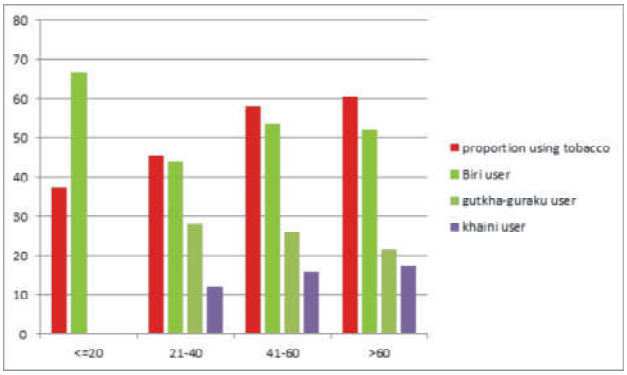

Fig. 1: *Histogram showing trends of tobacco use in different age groups.*

Among the illiterate subjects, 53.5% were tobacco users, among those educated up to primary level, 60% were users and in the secondary-educated group, 52.3% were users. Biri was the commonest form of tobacco used in all these educational groups. However, gutkha and guraku were more commonly used by illiterate or primary educated subjects (34.8% and 28.8% respectively) compared to secondary level educated subjects (17.8%). Among those with higher secondary or college level education (n = 60), 33% were users. Gutkha-guraku was used by only 10%, biri was used by 15% and cigarette was used by 75% of the users. This difference in the type of tobacco product used in different educational groups is shown in Fig. 2. There is a trend of decreasing gutkha-guraku use ($p = 0.01$, Chi square test for trend) and increasing cigarette use ($p < 0.01$, Chi square test for trend) with higher educational qualification.

Among the female subset (n = 102) as a whole, 28.4%

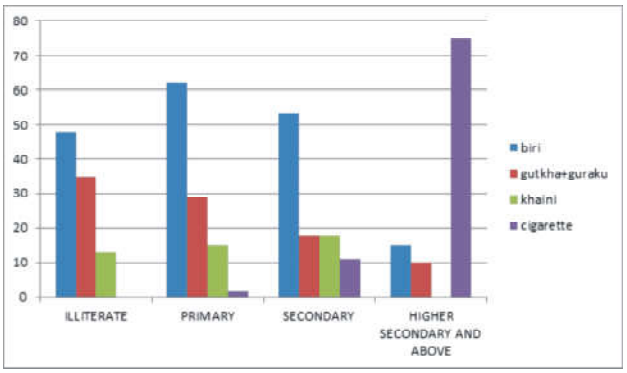

Fig. 2: *Histogram showing the proportion of different tobacco products used by tobacco consumers in different groups according to the educational qualification.*

were users. But among females who were labourers, 50% were users. Similarly among males, tobacco use was seen in 63.5%. But among the male labourers, (n = 70), tobacco use was reported in 91.4%. Thus, labourers, as an occupation, had higher risk of tobacco use (81.5% in labourers compared to 38.2% in non-labourers; p < 0.001 by Chi square test, Two-tailed).

The average age of initiation of tobacco product was 19.7 years with the lowest recorded age being 12 years. Also, among the users, 35.1% reported initiation of tobacco at or before 16 years of age. Fig. 3 shows the age of initiation of tobacco use. Average daily frequency of tobacco product use was 8.4 with 32 of the 154 users (20.8%) reporting a daily frequency equal to or greater than 20. Of these 20, 90% were male. The average daily frequency of tobacco use in males (12.9) was much higher compared to females (6.8) (p = 0.001).

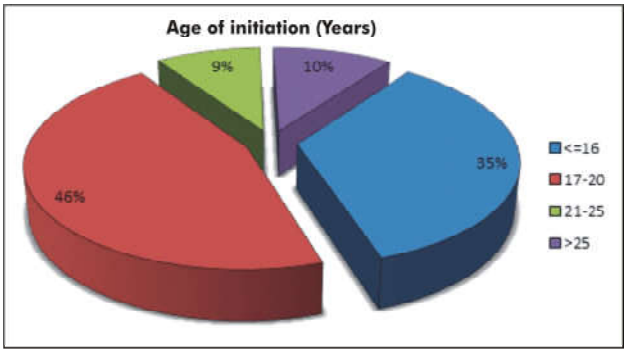

Fig. 3: *Pie diagram showing the age of initiation of tobacco use in the subjects.*

Among the users, 83.1% (95% CI: 76.2 - 88.7%) reported peer group influence as the factor leading to initiation of tobacco use. But there was significant gender difference. In male users (n = 125), peer influence was instrumental in 94.4%, while in female users (n = 29), peer influence was present in 34.5% (p < 0.0001, Fisher's Exact test, two-tailed). For female users, family was the more important influence (55.2%).

Table II shows the distribution of tobacco dependence score (TDS) in the users. It is seen that among the female users (n = 29), 69% had low TDS (≤ 4). Among male users, only 38.4% had TDS ≤ 4. Thus, males had higher TDS compared to females (p = 0.0036, two-tailed Fisher's Exact test). Altogether, 14% of the users had very high TDS (≥ 8) (all male). There was not much difference in average TDS across age groups with the below-20 group having average TDS of 3.6 and above-60 group having average TDS of 3.9.

Among the study subjects, 99% were aware of the harms of tobacco.

Table II: Showing the tobacco dependence scores (TDS) in the tobacco users (n = 154).

TDS	Male	Female	Total (n; %)
1 - 2	13	10	23; 14.9
3 - 4	35	10	45; 29.2
5 - 7	55	9	64; 41.6
≥ 8	22	0	22; 14.3

Discussion

In this hospital-based survey, it was seen that more than 50% of the participants were tobacco users with biri being the commonest form of tobacco used. Men were more likely to use tobacco compared to females and men also used the smoking form of tobacco much more than women. Trend of tobacco use increased with age. Subjects with higher educational qualification were more likely to use cigarette and less likely to use gutkha or guraku. As a vocation, labourers were the ones most likely to be tobacco users. 1 in 3 users had started tobacco use before the age of 16. 1 in 5 tobacco users reported a daily frequency of use in excess of 20 and the daily frequency of use in males was almost double that of females.

In the 2013 study from Chennai, the prevalence of tobacco use in urban wards was 19.4%[9]. But this was a community-based survey while our study is a hospital-based survey. Tobacco use prevalence may be higher in hospital-based surveys as tobacco makes people sick and those people are more likely to turn up in a hospital. Thus, in our study, the prevalence of tobacco use was 51%. But similar to our study, the Chennai study also recorded an increasing prevalence of tobacco use with age, more tobacco use in males and more smoking in males. In this study, 60% had started using tobacco between 15 to 24 years[9]. But in our study, more than 80% had started using tobacco before 20 years of age (Fig. 3). Thus, in our population, initiation of

tobacco use was probably earlier. In the south Indian study, chewing raw tobacco leaves was the most common form of SLT while in our study, guraku and khaini were the most common forms.

In our study, biri was the commonest smoking form of tobacco, except in the college educated group where cigarette was preferred. National surveys from various countries have revealed that cigarette is the commonest form of smoking everywhere in the world except in India and Bangladesh where biri is preferred[10]. This preference for biri in these countries may be due to very low cost (average price of one biri in India is 20 - 30% that of the cheapest cigarette[11]), easy availability, and less regulations on its sale. However, biri is no less harmful than cigarette or other forms of smoking and a recent study from the Indian subcontinent have shown that biri smokers have high-risk of airway obstruction or cardiovascular events[12]. However, still, biri is not given as much importance as cigarette in tobacco prevention programmes in India.

In our present study, it was seen that labourers, as an occupational group, had very high prevalence of tobacco use (81%). In a study among construction site labourers in New Delhi, the prevalence of tobacco use was found to be 91%[13]. Most of them (97%) used tobacco at the workplace with their peers[13]. More than 50% had started smoking before 20 years of age. Tobacco led to considerable expenses for these poor workers[13]. Thus, workplace tobacco prevention programs are needed for such labourers in unorganised sectors. There is a clear relation between presence of workplace smoking rules and the prevalence of smoking in workers[14]. However, in the unorganised sectors of India like construction or goods carriage, such workplace rules are a distant dream. Since peer pressure is a strong influence on tobacco use, the use of peer educators can be an option for tobacco prevention in such vocations.

In another cross-sectional study in urban slums of North-East India, tobacco use prevalence was found to be 74%[4]. However, the type of tobacco product was different from our study with cigarette, Khaini and Betel Quid being the most popular ones. In this study also, an increasing trend of tobacco use with age was observed up to 54 years, after which the tobacco use decreased by 8 percentage points. Labourer and drivers were the two occupations associated with high tobacco use[4]. A study similar to the Chennai project was conducted in Haryana, North India[15]. In this, it was found that the prevalence of tobacco use among urban males was 35% and that among females was 3.5%[15]. The corresponding figures in our study were considerably higher. There was considerable difference in the daily frequency of tobacco use, depending on the actual product, in the study from Haryana. Thus, for biri, daily frequency was 13, while for gutkha, it was 4.3. In our study also, high daily frequency of tobacco use was found in a section of the male subjects.

Limitations

The present study is limited by the small number of subjects. Also, it is a hospital-based survey and thus, the results may not always be extrapolated to the community. Also, some demographic variables like monthly income have not been included in this survey.

However, despite the shortcomings, this pilot survey generates a lot of data which may be used for tobacco prevention programmes in target groups.

Conclusion and recommendation

Tobacco use is very high among the attendees of hospitals in urban areas in Eastern India. Thus, these hospitals can be the sites of tobacco prevention programs. This can be in the form of anti-tobacco billboards and banning of tobacco sale for a specific radius around the hospital. Specific groups like labourers, who are likely to have high-risk of tobacco addiction, should be targeted for the interventions. For this, places frequented by the people of that vocation like railway stations, long distance bus stations or street-side eateries may be used.

Since a large part of the users start tobacco use before the age of 20, the adolescent age group should be a target of tobacco control programmes in urban areas. This can be in high schools and colleges. Physicians should be aware of the population groups with high chance of tobacco addiction and routine medical history must document the tobacco use behaviour in these groups.

Role of authors: SG was involved in data collection; RP was involved in statistical calculation; RP, SG and IT were involved in writing and revision.

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ORIGINAL ARTICLE

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Study of Adiponectin and Leptin Levels in Patients of COPD and its Correlation with Severity and Acute Exacerbation of Disease

Geeta Kampani, Priyanka Singh**, Adnan Khan***

Abstract

***Background:** COPD is associated with inflammation which leads to acute exacerbation and causes extra pulmonary manifestations of the diseases. Elevated levels of CRP, fibrinogen, leukocyte counts are inflammatory markers associated with COPD.*

Adiponectin and leptin are biomarkers of inflammation which can be used to assess disease activity and severity in COPD patients.

***Aims:** To compare the adiponectin and leptin levels during acute exacerbation and remission in patients of COPD and correlate the levels with severity of disease.*

***Methods:** It was a hospital-based case control study conducted in VMMC and Safdarjung Hospital, New Delhi. It was conducted on 60 patients of COPD and 30 controls. Adiponectin and leptin levels were measured on admission and 7 days after discharge during remission. Severity of COPD was assessed by GOLD guidelines. Acute exacerbation was defined by anthonisen criteria. Patients were considered to be in remission if they do not require increased doses of bronchodilator, antibiotics or steroids.*

***Result:** Leptin levels were higher in cases than control on admission 21.12 v/s 4.96. Adiponectin levels were also higher in cases than control on admission 5.91 v/s 3.17. Leptin levels were higher on admission, during acute exacerbation 21.12 than on remission 10.91. Adiponectin levels were higher on remission 7.11 than on admission. L/A ratio was higher on admission 3.71 v/s remission 1.74. Adiponectin levels correlate negatively with FeV_1/FVC with r value of - 0.005 but the correlation was not statistically significant. Serum leptin levels also correlates negatively with FeV_1/FVC r value - 0.051 but was not significant statistically.*

***Conclusion:** Adiponectin and leptin levels are raised in cases of COPD compared to controls. Leptin levels are higher during acute exacerbation than remission whereas adiponectin levels are higher during remission. Adiponectin and leptin levels correlate negatively with severity of COPD but the correlation is not statistically significant.*

Introduction

Chronic obstructive airway disease (COPD) is characterised by persistent airflow limitation that is usually progressive and associated with enhanced chronic inflammatory response in the airway and lungs to noxious particles or gases. COPD is currently the leading cause of death in the world but is projected to be the 3rd leading cause of death by 2020[1]. Patients with COPD are at increased risk of developing heart diseases, lung cancer and stroke[2].

Exposure to inhaled pollutants, primarily cigarette smoke leads to chronic inflammation via activation of structural and inflammatory cells within the lungs. These in turn release chemotactic mediators which recruit additional inflammatory cells in the lung perpetuating a state of chronic inflammation which is thought to cause structural changes in airway and respiratory symptoms. Recently there has been increasing evidence that COPD is a systemic inflammatory disease in which there is systemic inflammation indicated by raised levels of cytokines, acute phase proteins and inflammatory cells. This systemic inflammation may be implicated in the development of comorbidities in COPD such as cardiovascular diseases, diabetes, lung cancer, pneumonia, pulmonary embolism, osteoporosis and depression[3].

Leptin and adiponectin are produced by adipose tissue and both play an important role in energy balance. They are established cytokines in energy and fat metabolism. The association of adiponectin and leptin with COPD is becoming increasingly apparent. These cytokines are related to severity of emphysema[4] as well as to the frequency of exacerbation[5], lower leptin levels have been associated with lower fat mass in emphysematous patients and are thought to be at least partially responsible for pulmonary cachexia[6]. Adiponectin levels have been found to be higher in patients of COPD compared with control patients[7]. It is therefore plausible that dysregulation of these cytokines has an effect on the natural history of COPD. However, there are very few Indian studies to study the association of adiponectin and leptin in COPD during phases of exacerbation, remission and further their association with severity of the diseases.

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Adiponectin and leptin may be used as biomarkers of inflammation to assess disease activity and severity of disease in cases of COPD. With this in mind we thought to analyse the adiponectin and leptin levels in COPD during exacerbation and remission and their correlation with severity of COPD.

Material and Methods

This hospital-based case control study conducted on 60 patients of COPD admitted to the medicine wards of VMMC and Safdarjung Hospital, New Delhi; 30 cases were taken as controls.

Each patient was subjected to a detailed history and examination of past records with special emphasis on records of any intrinsic pulmonary disease, cardiovascular diseases and other co-morbid conditions. Patients of metabolic syndrome, hepatic, renal and heart failure, malignancy, and collagen vascular disease were excluded.

Diagnosis of COPD was based on:-

- Clinical symptoms of dyspnoea, chronic cough with sputum production.
- History of exposure to risk factors (tobacco, smoke from cooking, occupational dust, and chemicals).
- Spirometry (post-bronchodilator FeV1/FVC < 0.7 confirms the diagnosis.
- Severity of COPD was assessed according to GOLD guidelines[8].

Acute exacerbation was defined by anthonisens criteria[9]:-

- Increased sputum volume.
- Sputum purulence.
- Increased dyspnoea.

Remission of COPD was defined as:-

- Asymptomatic patients not requiring increased dose of bronchodilators.
- Does not require antibiotics and steroid.

Adiponectin and leptin levels were done on admission and repeated 7 days after discharge when patients were in remission. Venous blood was drawn in the morning after overnight fast in EDTA containing tubes. Plasma was separated by centrifugation for 10 minutes at 4° C within 1 hour of collection and stored at - 70° C until analysis. Plasma adiponectin and leptin were measured by ELISA kit.

Statistical analysis

Categorical variables were presented in number and percentage and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov Smirnov test. If the normality was rejected then non parametric test was used.

Statistical tests were applied as follows:-

- Quantitative variables were compared using Independent T test/Mann-Whitney test (when the data sets were not normally distributed) between the two groups.
- Quantitative variables were correlated using Chi-Square test/Fisher exact Test.
- Spearman rank correlation co-efficient was used to assess the association of various parameters with each other. A p value of < 0.05 was considered statistically significant.

The data was entered in MS Excel Spreadsheet and analysis was done using statistical Package for Social science (SPSS) version 21.0.

Observations and Result

The study was conducted on 60 cases of COPD after fulfilling the inclusion and exclusion criteria. 30 cases were taken as control . The mean age of the cases was 56.78 ± 6.35 years while controls was 52.17 ± 7.47 years. Majority of cases were in the age group 51 - 60 years while minimum number were in the age group 61 - 70 years. Of the 60 cases, 45 were male and 15 were female whereas 25 were male and 5 female among the controls.

Table I: Comparison of serum leptin, serum adiponectin and L/A ratio in cases versus controls on admission.

Variables	Cases	Control	P value
Serum leptin	21.12 ± 5.13	4.96 ± 1.14	0.0001
Serum adiponectin	5.19 ± 1.36	3.17 ± 0.71	0.0001
L/A ratio	3.71 ± 1.11	1.65 ± 0.58	0.0001

Table II: Comparison of serum leptin, serum adiponectin and L/A ratio during admission and remission in cases.

Variables	Admission	Remission	P value
Serum leptin	21.12 ± 5.13	10.91 ± 3.89	0.0001
Serum adiponectin	5.91 ± 1.36	7.11 ± 2.95	0.0001
L/A ratio	3.71 ± 1.1	1.74 ± 0.76	0.0001

On admission the mean serum leptin was 21.2 ± 5.13, adiponectin was 5.19 ± 1.36 and L/A ratio was 3.71 ± 1.1.

The values were significantly higher when compared to controls with p value 0.0001.

It was observed that serum leptin levels were raised on admission and decreased during remission.

Serum adiponectin levels were higher during remission (7.11 ± 0.95) compared to those on admission (5.91 ± 1.36). L/A ratio was higher on admission (3.71 ± 1.11) compared to remission (1.74 ± 0.76).

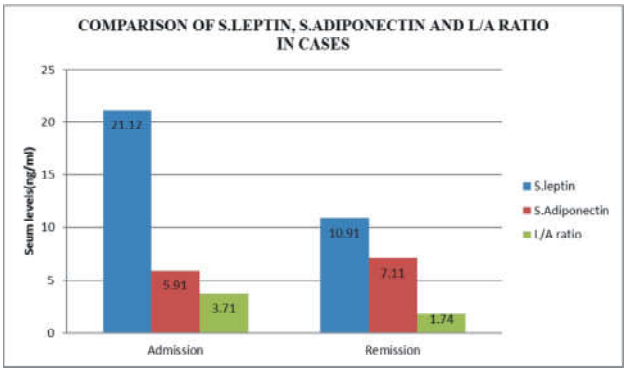

Fig. 1: *Comparison of serum leptin, serum adiponectin and L/A ratio during admission and remission in cases.*

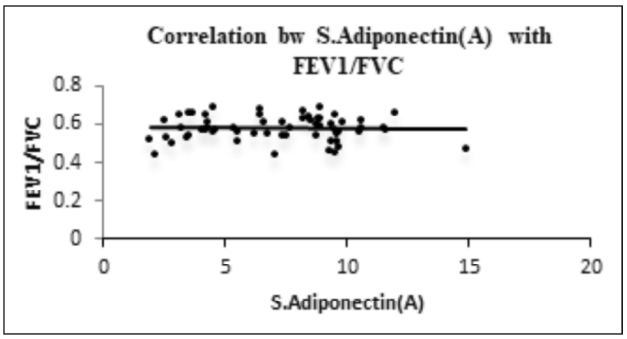

Fig. 2: *Correlation of adiponectin, leptin with FeV1/FVC.*

Table III: Correlation of adiponectin, leptin with FeV1/FVC.

Variables	r value	p values
Serum adiponectin	- 0.005	0.967
Serum leptin	- 0.051	0.699
L/A ratio	- 0.059	0.654

Serum adiponectin corelated negatively with FeV1/FVC .

r value - 0.005, however p value was not significant (0.967).

Serum leptin correlated negatively with FeV1 /FVC. r - 0.051 with a p value of 0.699 (not significant).

14 cases in the study were in stage I COPD while 46 cases were in stage II while no case was in stage 3 and 4.

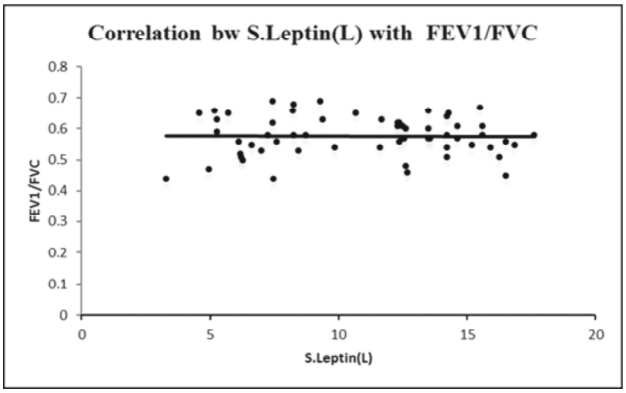

Fig. 3: *Correlation between serum leptin with FeV1/FVC.*

Table IV: Correlation of adiponectin, leptin and L/A ratio with severity of COPD.

Variables	r value	p value
Serum adiponectin	- 0.017	0.897
Serum leptin	- 0.196	0.133
L/A ratio	- 0.138	0.294

Adiponectin, leptin and L/A ratio showed a negative correlation with severity of COPD. However, the p value in all were not significant.

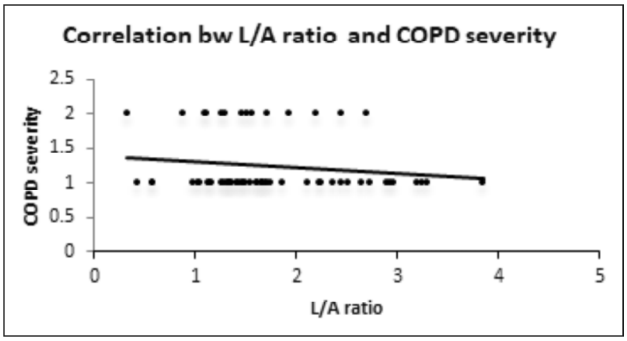

Fig. 4: *Correlation of L/A ratio with severity of COPD.*

Discussion

COPD is a pulmonary disease with systemic involvement of musculoskeletal, cardiovascular, and endocrine system as a consequence of inflammation and increased cytokines. The local inflammatory process in the lungs can effect peripheral tissues by direct effect of released cytokines and indirect activation of peripheral inflammatory cells. Adiponectin is a proteic hormone which exerts its anti-inflammatory properties by inhibiting several proinflammatory mediators TNF α, IL-6 and promoting anti-inflammatory mediators IL-10, IL-1. Leptin is involved in haematopoiesis, angiogenesis, immune and inflammatory response.

In our study adiponectin, leptin and L/A ratio was higher in

cases of COPD compared with controls. The leptin levels were significantly higher during acute exacerbations (21.1 ± 5.13) and reduced on remission 10.91 ± 3.89 whereas adiponectin levels were elevated on remission 7.11 ± 2.95 as compared to admission 3.71 ± 1.1 and the L/A ratio was decreased on remission 1.74 ± 0.76 as compared to admission 3.71 ± 1.1.

These results were in concordance with a study by Georgios *et al*[10] who assessed serum leptin, adiponectin, L/A ratio and other inflammatory biomarkers CRP, TNF α, IL-6 at three points (admission, resolution, and stable state, i.e., 8 weeks after resolution). Georgios *et al* concluded that leptin levels were higher on admission compared to resolution and stable state ($p < 0.0001$). In contrast, adiponectin levels were significantly increased on resolution and in the stable state [8 weeks later ($p < 0.0001$)] compared to the levels on admission. The L/A ratio was also significantly higher on admission (mean L/A 2.6) compared to ratio on remission (mean L/A 1.5) and further decreased on stable state (1.22). There was significant positive correlation between leptin and L/A ratio with CRP, IL-6 and TNFα on admission and resolution. A negative correlation was noted between adiponectin and inflammatory biomarkers on admission and resolution. TNFα and IL-6 had the most significant association with adiponectin and leptin on stepwise multiple linear regression analysis.

Similar results were seen by Chan *et al*[7], they also assessed relationship between serum adiponectin, IL-6, IL-8 and CRP. They found a positive correlation between serum adiponectin and CRP, IL-6 and negative correlation with IL-8.

In our study adiponectin and leptin showed a negative correlation with FeV1/FVC r value of - 0.005 and - 0.051 respectively. However, the p value of all these ventilatory parameters were not significant. Adiponectin and leptin showed negative correlation with severity of COPD (as per GOLD guidelines) though correlation was not stastically significant.

Similar results were seen by Ahmed *et al*[11] who saw a significant negative correlation of leptin with FeV1

($r = -0.523$, $p < 0.005$), change in feV1/FVC ($r = - 0.541$, $p < 0.05$).

This study showed that leptin correlated inversely with severity of ventilatory function. Chan observed a negative correlation of adiponectin with FeV1, FVC and FeV1/FVC with r value of - 0.370, - 0.262 and - 0.302 respectively with significant p values. CRP and IL-6 also showed a negative correlation with above ventilatory parameters. They found that serum adiponectin levels increase with disease severity, and stage 4 COPD had the highest median levels of adiponectin compared with stage 2 and 3 patients. Jaswal *et al*[12] also found a significant negative correlation of serum adiponectin with FeV1 ($r = - 0.580$, $p < 0.001$) thereby suggesting that adiponectin levels have an association with severity of airway obstruction. Kochi Tomoda *et al*[5] observed a positive correlation between residual volume and serum adiponectin but there was no correlation of adiponectin with FeV1. Thereby suggesting that hyperinflation not flow limitation may be leading to adiponectin elevation in COPD.

We thus concluded that serum adiponectin and leptin levels were higher in cases of COPD than in controls. These levels were further raised during acute exacerbation. The levels of leptin and L/A ratio were higher on admission than during remission while the adiponectin levels were higher during remission state. The levels of adiponectin and leptin showed a negative correlation with FeV1/FVC and severity of COPD (as per GOLD guideline) but this correlation was not statistically significant.

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ORIGINAL ARTICLE

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Prevalance of Non-alcoholic Fatty Liver Disease in Hypothyroid Patients and its Correlation with Seruml Ferritin Levels

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Abstract

NAFLD is a relatively newly recognised entity among clinicians, presented with vague symptoms and upper quadrant abdominal pain. With growing epidemic of obesity, more and more cases of NAFLD are seen in clinical practises due to better availability of ultrasonographic facilities. The disease has an unpredictable course, may remain stationary through out life or may progress to hepatic cirrhosis. Search of a biomarker like serum ferritin may be useful in routine clinical practise to predict the natural history of NAFLD. In this small study, 100 patients were included which shows raised TSH in 33% patients of NAFLD, and out of 33 patient 20 patients has raised serum ferritin. To prove that it has more of a prognostic as compared to diagnostic value, a larger sample size is needed.

Key words: Hypothyroidism, NAFLD, serum ferritin, ultrasonography.

Introduction

Nonalcoholic fatty liver disease (NAFLD) comprises a broad spectrum ranging from simple steatosis, nonalcoholic steatohepatitis with fibrosis, which can eventually progress to cirrhosis and hepatocellular carcinoma[1]. Nonalcoholic fatty liver disease (NAFLD) means accumulation of fat mainly triglycerides exceeding 5% of liver weight, affecting approximately 20% of population in developed countries[2]. In recent years, a growing body of evidence has led to speculations on the association between NAFLD and hypothyroidism. Disturbances in thyroid hormone concentrations may promote hyperlipidaemia and obesity, thus contributing to NAFLD[3,4]. Early identification of at-risk patients is important since treatment of hypothyroidism may reduce the risk of NAFLD and potential complications[5].

Hyperferritinaemia with mild hepatic iron accumulation is observed in 20 - 30% of patients with NAFLD, and is commonly referred to as dysmetabolic iron overload syndrome[6]. Iron overload is found in as many as one-third of the patients with NAFLD[7]. To know the actual prevalence of NAFLD in hypothyroid patients, there is a search for various biochemical markers, out of which serum ferritin has emerged to be a promising one which can be easily used in various indoor and out door clinical setting as predictors for the presence of NASH versus simple steatosis[8,9]. The present study also shows its prognostic value in NAFLD.

Material and methods

The study was conducted in the Department of Medicine, SN Medical College and Hospital, Agra, on all newly diagnosed and old cases of hypothyroidism attending the OPD or admitted in the wards. In the present cross-sectional prospective study, demographic, clinical, laboratory, and radiological data of 100 adult patients with hypothyroidism was analysed.

The liver was assessed with respect to size, the presence of focal lesions, the presence of hepatic steatosis, and also whether steatohepatitis has progressed to cirrhosis. Different scoring systems have been designed, hoping to diagnose and stage NASH without histological data, but the debate on their accuracy is still ongoing[10]. On the basis of USG examination, diagnosis of fatty liver disease was made if large fat vacuoles were present in the liver parenchyma, displacing the nuclei to the border of the cells. Steatosis was graded as 1 if less than 33% of the hepatocytes were affected, grade 2 when 33 - 66% of the hepatocytes were affected, and grade 3 if more than 66% of the hepatocytes were affected. Staging and grading were performed according to the Brunt *et al* scoring[11].

Serum ferritin was measured by ELISA method (Monobind, USA) within two weeks after performing the USG. Serum iron and total iron-binding capacity (TIBC) were measured by calorimetric methods at the same time.

Observations and results

The present study consisted of 100 patients of which 67 were female and 33 were male. We tried to correlate the levels of TSH with grading of NAFLD, correlation of serum ferritin with TSH, and correlation of NAFLD and hypothyroidism as shown in the Table I - IV.

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Table I: TSH in patients having non alcoholic fatty liver disease with hypothyroidism (n = 100).

TSH (μIU/ml)	Male		Female		Overall	
	No.	%	No.	%	No.	%
≤ 5.0	0	0.00	0	0.00	0	0.00
5.1 - 20.0	5	15.15	5	7.46	10	10.00
20.1 - 35.0	6	18.18	8	11.94	14	14.00
35.1 - 50.0	11	33.33	22	32.84	33	33.00
50.1 - 65.0	2	6.06	17	25.37	19	19.00
> 65.0	9	27.27	15	22.39	24	24.00
Total	33	100.00	67	100.00	100	100.00

The TSH value in patients of non alcoholic fatty liver disease with hypothyroidism was highest (33%) in the range of 35.1 - 50.0 μIU/ml, followed by 24% in the range of > 65.0 μIU/ml, 19% in the range of 50.1 - 65.0 μIU/ml, 14% in range of 20.1 - 35.0 μIU/ml and 10% in the range of 5.1 - 20.0 μIU/ml. No patient was found to have TSH value ≤ 5.0.

Table II: Grading of fatty liver in non alcoholic fatty liver disease with hypothyroid patients (n = 100).

Grade	Male (N = 33)		Female (N = 67)		Overall (N = 100)	
	No.	%	No.	%	No.	%
Fatty liver grade-I	5	15.15	10	14.93	15	15.00
Fatty liver grade-II	3	9.09	9	13.43	12	12.00
Fatty liver grade-III	5	15.15	1	1.49	6	6.00

chi-square = 6.12, p - value = 0.047.

Out of all the subjects (N = 100) included in our study, most (15%) of the patients had grade-I fatty liver followed by 12% who had grade-II fatty liver, and only 6% had grade-III fatty liver. Grade-I fatty liver and grade-II fatty liver were seen in 15.15% and 9.09% of males respectively. Most (14.93%) of the females showed grade-I fatty liver. Only one female was found to have grade-III fatty liver.

Table III: Correlation of serum ferritin level with serum TSH level.

S. TSH	Serum ferritin level					
	Male			Female		
	N	Mean	SD	N	Mean	SD
≤ 5.0	0			0		
5.1-20.0	5	139.80	95.70	5	36.00	0
20.1-35.0	6	180.33	96.29	8	180.33	63.08
35.1-50.0	11	223.73	170.16	22	208.49	143.66
50.1-65.0	2	503.00	231.93	17	162.71	64.45
>65.0	9	371.11	161.63	15	218.23	189.21
f - value		3.900			2.913	
p - value	0.012			0.028		

The study conducted between serum TSH levels and serum ferritin levels showed that higher levels of serum ferritin were present in patients with raised serum TSH.

Table IV: Correlation between grading of fatty liver and serum ferritin level in non alcoholic fatty liver disease with hypothyroid patients.

Fatty liver Grade	Serum ferritin level					
	Male			Female		
	N	Mean	SD	N	Mean	SD
Grade I	5	163.60	148.28	10	171.68	202.00
Grade II	3	527.33	144.20	9	241.71	105.67
Grade III	5	590.40	110.59	1	364.00	0
f - value		10.076			0.876	
p - value		0.004			0.043	

The study conducted comparing the serum ferritin levels and grades of fatty liver on ultrasonography showed that patients with higher grades of fatty liver on ultrasonography had higher serum ferritin levels too.

Discussion

In the present study, 33% of patients showed fatty liver of variable grades on ultrasonography. From this study, it has been observed that there is high incidence of fatty liver in patients whose TSH level was more than 35. Around 66% patients with fatty liver had TSH more than 35. The value was calculated for the relationship which came to be less than 0.001 which is significant.

In the present study, out of 33 patients of fatty liver of various grades, grade 1 fatty liver is seen in maximum no. of patients. TSH value was found to be more in patients with higher grades of fatty liver. Out of 33 patients of NAFLD with hypothyroidism, it was found that serum ferritin was significantly high in 20 patients, it was shown that serum ferritin level was significantly high with high TSH and higher grades of NAFLD, which is statistically significant with p value < 0.1. In the rest 13 patients, serum ferritin level was normal. Thus it has more of prognostic value as compared to diagnostic value.

Although a role of hypothyroidism in the pathogenesis of non alcoholic fatty liver disease (NAFLD) has not been established, a number of possible mechanisms could be involved. Hypothyroidism has been associated with insulin resistance, dyslipidaemia and obesity, all of which are important components of the metabolic syndrome.

Seyed Reza Modares Mousavi (2018) conducted a prospective cross-sectional study on 30 patients with biopsy proven NAFLD/NASH and found no significant correlation between the histopathological stages of the disease with

serum ferritin levels. The prevalence of NAFLD and its severity increased with age. Our patients were relatively young and with less severe disease as expected.

In his study, it was found that 3 males and 9 females had both hypothyroidism and grade II non alcoholic fatty liver. These subjects showed a mean serum ferritin level of 527.33 and 241.71 respectively with a standard deviation of ±144.20 and ±105.67 respectively. They found 5 males and only 1 female with both hypothyroidism and grade III non alcoholic fatty liver, these subjects showed a mean serum ferritin level of 490.40 and 364.00 respectively with a standard deviation of ± 110.59 and ± 0 respectively. p value of correlation of serum ferritin level in patients of hypothyroidism with non alcoholic fatty liver was found to be 0.004 and 0.434 for males and females respectively.

Out of all the subjects (N = 100) included in our study, most (15%) of the patients had grade-I fatty liver followed by 12% having grade-II fatty liver and only 6% had grade-III fatty liver. Grade-I fatty liver was seen in 15.15% of males whereas only 9.09% of males showed grade-II fatty liver. Most (14.93%) of the females showed grade-I fatty liver. Only one female was found to have grade-III fatty liver.

Conclusion

With increase in obesity and sedentary lifestyle in developing countries like India, more and more cases of NAFLD are reported. More reporting of NAFLD cases is possible due to easy accessibility and sophisticated technique of ultrasonography, but the prognosis and natural history of NAFLD is still unpredictable. A bio-chemical marker like serum ferritin could help in predicting the natural history of NAFLD in hypothyroidism patients. Thus a better and suitable preventive strategy can be formulated to limit the development and progression of hepatic cirrhosis. In the present study, it was found that there was increased prevalence of fatty liver in patients of hypothyroidism and the levels of serum TSH correlated with grades of fatty liver. Also, serum ferritin levels were found to be increased in patients of fatty liver with hypothyroidism which also correlated with the grade of fatty liver.

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REVIEW ARTICLE

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Clinical Update on COVID-19

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Abstract

The rapid spread of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in Wuhan, China prompted an increased surveillance in India since early January 2020. The first laboratory confirmed case of COVID-19 in India was reported from Kerala on 30th January 2020. Since then the novel coronavirus infected pneumonia (NCIP) cases have been presenting to the hospital emergencies as severe acute respiratory illness (SARI) or influenza like illness (ILI). As on 4th June, 2020, about 2,10,000 confirmed cases have been detected in India with around 6,100 reported deaths. The major mode of transmission has been via close contact with infected individuals through respiratory droplets and fomites. The clinical spectrum varies from asymptomatic to mildly symptomatic (fever, myalgia, and sore throat) to acute respiratory distress syndrome as a part of cytokine release syndrome. The diagnosis depends on nucleic acid detection by rRT-PCR for SARS-CoV-2, IgM/IgG antibodies detection and typical radiological appearance in high suspects. Social distancing, isolation precautions, and proper hand hygiene with good cough etiquettes are all very important infection prevention and control (IPC) measures in mitigating the spread of the contagion. Repurposing of old and existing drugs like hydroxychloroquine, lopinavir/ritonavir, favipiravir, remdesivir, interferons have been found to be useful in various trials. Role of convalescent plasma and anti-inflammatory/immune-suppressive therapy is also being tried to some effect in cases with cytokine release syndrome. Personal protective equipments form a crucial part of the management of the affected individuals. Vaccine development and trials are being pursued with aggressive vigor worldwide.

Key words : COVID-19, SARS-CoV-2, COVID-19 therapy, COVID-19 pneumonitis, novel coronavirus, 2019-nCoV outbreak, pandemic.

Introduction

On 11 March 2020, the World Health Organisation (WHO) declared severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) as a pandemic that causes novel coronavirus disease 2019 (COVID-19)[1]. As on 4th June 2020, there have been 6.4 million confirmed cases from over 216 countries worldwide with almost 3,83,000 deaths. India has reported 2,10,000 cases with 6,100 deaths[2]. SARS-CoV-2 is a novel strain of betacoronavirus that has not been previously identified in humans. Phylogenetic analysis suggests that SARS-CoV-2 might have emerged from the zoonotic cycle and rapidly spread by human to human transmission[3]. However, the exact source of SARS-CoV-2 has not been identified yet. Transmission among humans occurs via close contact with an infected individual that produces respiratory droplets while coughing or sneezing within a range of about 2 metres[4]. COVID-19 as an emerging disease has unique pathophysiological characteristics, clinical manifestations, and radiological features. Although very challenging, yet considerable progress has been made on the clinical management aspect of this diseases as the information is being gathered and shared worldwide. This article will summarise the epidemiological, aetiological, clinical, pathological, and radiological characteristics of COVID-19 and review the latest advancements in the treatment.

Epidemiology of COVID-19

The epidemic curves reflect that the current epidemic may be a mixed outbreak pattern with initial cases suggestive of a continuous common source, potentially at Huanan seafood market in Hubei province of Wuhan, China; and later cases suggestive of a propagated source as the virus began to be transmitted from person to person. A phase-adjusted estimation of epidemic dynamics assumed that the effective reproduction number R_0 was 3.1 at the early phase of the epidemic[5]. Despite more than 1.5 million international arrivals to India from January 18 to March 23, India had tested only 5,900 individuals for SARS-CoV-2 up until 13th March, 2020. Since then, testing has been increased, but it has still not reached the desired level of coverage, both in terms of areas as well as numbers. To study the extent of spread of COVID-19 cases, ICMR tested for SARS-CoV-2 in samples from patients admitted with severe acute respiratory illness (SARI) in multiple centres spread across India from Feb 15 to Apr 2, 2020. In this study they estimated a conservative number of possible COVID-19 cases to be 1.8%[6]. SARS-CoV-2 spreads mainly through respiratory droplets or close contact. While in the later stage of infection, the virus is also detectable in anal swabs, suggesting the possibility of oral-faecal route transmission[7]. Significant environmental contamination by patients

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carrying SARS-CoV-2 through respiratory droplets and faecal shedding suggests that the environment serves as a potential medium of transmission and supports the requirement for strict adherence to environmental and hand hygiene[8]. The possibility of SARS-CoV-2 vertical transmission is still controversial. Literature reporting evidence of vertical transmission is limited. Luisa Patane *et al* in one study have described SARS-CoV-2 RNA on the foetal side of the placenta in two cases of mothers infected with COVID-19 and with neonates also positive for the virus at birth[9]. These findings support the possibility of vertical transmission of SARS-CoV-2 from the mother to the baby in-utero. Moreover, the direct visualisation of SARS-CoV-2 RNA in the infected placentas raises the possibility of estimating the viral load in cells with morphological context. In a study of 77 well-characterised infector-infectee pairs in Hong Kong, it was estimated that the serial interval (duration between symptom onset of a primary case to symptom onset of its secondary case) of COVID-19 was 5.8 days (mean), with 7.6% of serial intervals distributed negatively (i.e., the infectee developed symptoms prior to infector), strongly implying pre-symptomatic transmission[10]. Assuming a median incubation period of 5.2 days (based on other studies), the study estimated that the infectious period of SARS-CoV-2 started 2.3 days before onset of symptoms, peaking at 0.7 days and declining within 7 days.

SARS-CoV-2 genome and pathogenesis

SARS-CoV-2 is a single-stranded RNA virus of ~30 kb genome size, which belongs to the genus coronavirus and family Coronaviridae. Six other kinds of coronaviruses are known to cause human disease, including severe acute respiratory syndrome coronavirus (SARS-CoV) and middle east respiratory syndrome coronavirus (MERS-CoV) with high mortality rate. According to the genome characteristics, coronavirus is separated into four genera: α-CoV, β-CoV, γ-CoV and δ-CoV. Genomic sequencing revealed that the novel coronavirus isolated from lower respiratory tract samples of patients with COVID-19 belongs to β-CoV. The genome of SARS-CoV-2 is similar to other coronaviruses and comprises of ten open reading frames (ORFs)[11]. Coronavirus has the appearance of crown under electron microscopy and thus the name. They are enveloped viruses with a single-strand, positive-sense RNA genome, which is the largest known genome for a RNA virus. All coronaviruses share the same genome organisation and expression pattern, with two large overlapping reading frames (ORF1a/b) which encode 16 nonstructural proteins, followed by ORFs for four major

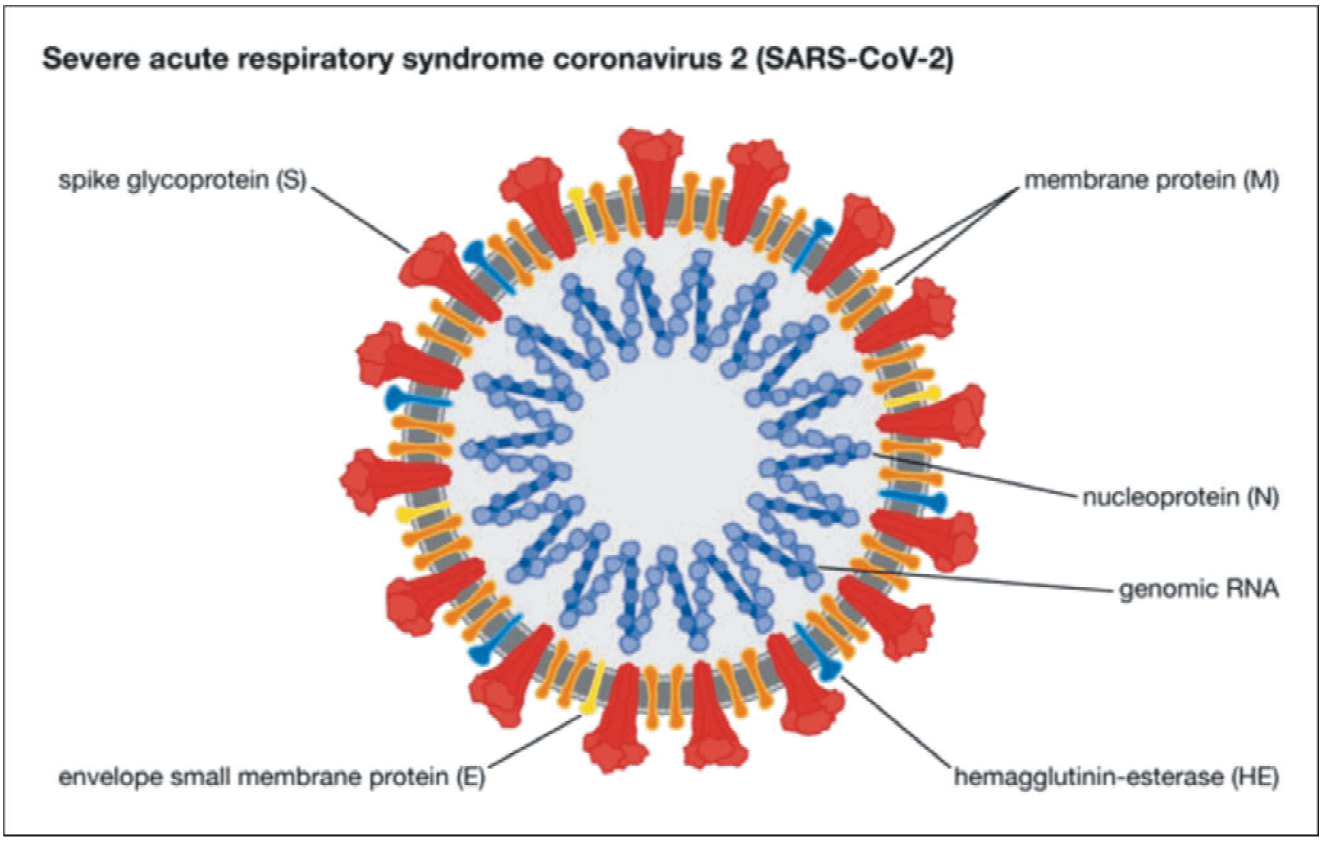
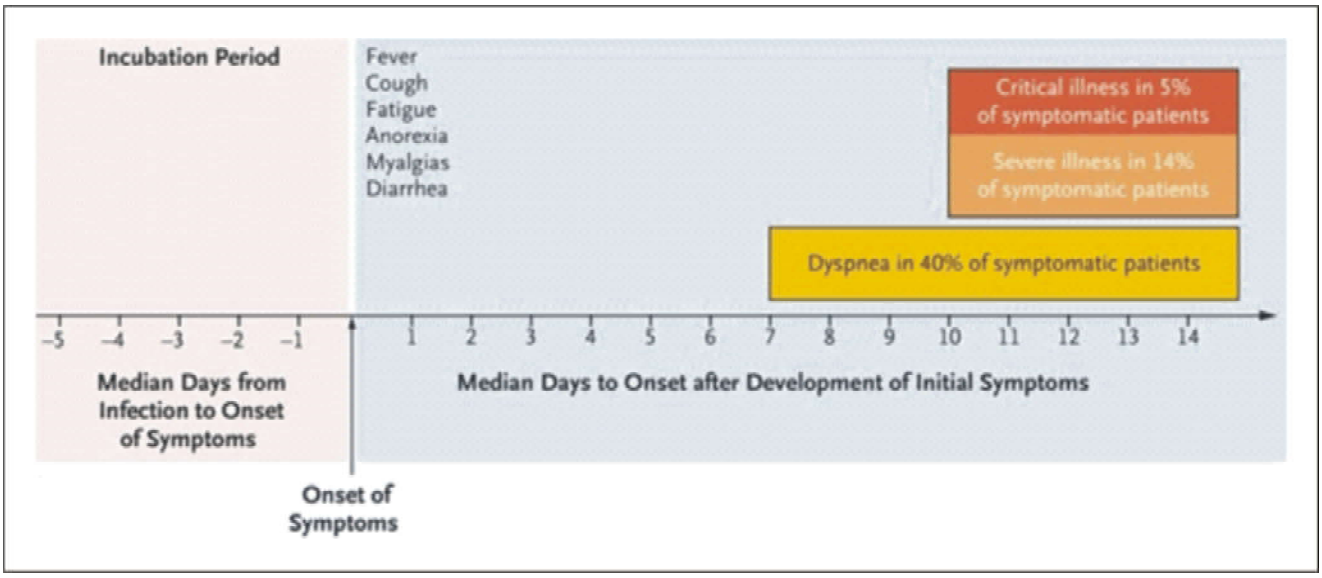


Fig. 1: *Schematic diagram of SARS-CoV-2 viral structure.*

structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N) (Fig. 1). Spike-protein plays an essential role in binding to receptors and is critical for determining host tropism and transmission capacity. It is functionally divided into S1 and S2 domain, responsible for receptor binding and cell membrane fusion, respectively. The receptor binding domain of β-CoV is commonly located in the C-terminal domain of S1. SARS-CoV-2 spike protein has 10- to 20-fold higher binding affinity to human angiotensin-converting enzyme 2 (ACE2) than SARS-CoV. Like SARS-CoV, SARS-CoV-2 uses the ACE2 receptor for internalisation and TMPRSS2 serine proteases for S protein priming[12]. Upon entry into the host target cells, the viral antigens get presented via antigen presenting cells (APCs) to virus-specific cytotoxic T lymphocytes (CTL). Studies have been conducted in SARS-CoV-2 infected patients showing the activation and reduction in CD4+ and CD8+ T cell counts. In addition, SARS-CoV-2 patients have been found to present with acute respiratory distress syndrome (ARDS). ARDS is a cytokine release syndrome (CRS) which is a lethal uncontrollable inflammatory response resulting from the release of large pro-inflammatory cytokines (IL-1β, IFN-α, IFN-γ, IL-12, IL-6, IL-18, TNF-α, IL-33, TGFβ, etc.) and chemokines (CCL3, CCL2, CXCL8, CCL5, CXCL9, CXCL10, etc.) by immune cells. The main protagonist of this storm is interleukin-6 (IL-6). IL-6 is produced mostly by activated leukocytes and acts on a large number of cells and tissues. It is able to promote the differentiation of B-lymphocytes. It also stimulates the production of acute-phase proteins and plays an important role in thermoregulation, bone maintenance and in the functionality of the central nervous system. Histopathological investigation of tissues from SARS-CoV-2 infected patients showed virus-induced cytopathic effect with signs of acute respiratory distress syndrome in both type-I and type-II pneumocytes[13].

Clinical manifestations

COVID-19 has an incubation period of 2 - 14 days, mostly ranging from 3 to 7 days. The clinical spectrum of COVID-19 varies from asymptomatic or pauci-symptomatic forms to clinical conditions characterised by respiratory failure that necessitates mechanical ventilation and support in an ICU, to multiorgan and systemic manifestations in terms of sepsis, septic shock, and multiple organ dysfunction syndromes (MODS) (Fig. 2). In one of the first reports on the disease, Huang *et al* illustrated that patients (n 41) suffered from fever, malaise, dry cough, and dyspnoea. Chest computerised tomography (CT) scans showed pneumonia with abnormal findings in all cases. About a third of those (n 13) required ICU care, and there were 6 (15%) fatalities[14]. As per the CDC list, the symptoms include – fever (85%), dry cough (86%), fatigue (44-70%), anorexia (40 - 84%), sputum production, shortness of breath (80%), sore throat, headache, myalgia/arthralgia (11 - 35%), chills or repeated shaking with chills, nausea or vomiting (24%), nasal congestion, new onset anosmia or dysgeusia, diarrhoea (27%), haemoptysis, conjunctival congestion[15]. Silent hypoxaemia has been a very talked about and commonly observed feature of COVID-19 in which the patient has low blood oxygen saturation level on pulse oximetry but is not apparently dyspnoeic. It is considered to be a clinical manifestation of underlying capillary



(Adapted from Zhou et al, and the Centers for Diseases Control and Prevention).

Fig. 2: *Timeline of symptoms of Severe coronavirus disease 2019 (COVID-19).*

dysfunction or thrombosis.

The authors of the Chinese CDC report divided the clinical manifestations of the disease by severity[5]:

- Mild disease: No pneumonia or mild pneumonia; occurred in 81% of cases.
- Severe disease: Dyspnoea, respiratory frequency ≥ 30/min, blood oxygen saturation (SpO2) ≤ 93%, PaO2/FiO2 ratio or P/F [the ratio between the blood pressure of the oxygen (partial pressure of oxygen, PaO2) and the percentage of oxygen supplied (fraction of inspired oxygen, FiO2)] < 300, and/or lung infiltrates > 50% within 24 to 48 hours; occurred in 14% of cases.
- Critical disease: Respiratory failure, septic shock, and/or multiple organ dysfunction (MOD) or failure (MOF); occurred in 5% of cases.

As per the WHO, COVID-19 disease severity is classified as:[16]–

Mild disease		Symptomatic patients meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia.
Moderate disease	**Pneumonia**	**Adolescent or adult** with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia, including SpO2 ≥ 90% on room air.
Severe disease	**Severe pneumonia**	**Adolescent or adult** with clinical of pneumonia (fever, cough, dyspnoea, fast breathing) plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO2 < 90% on room air.
Critical disease	**ARDS**	As per Berlin definition.
	Septic Shock	As per sepsis-3 guidelines.

As a reference, the criteria for the severity of respiratory insufficiency as in Berlin definition of ARDS and the diagnostic criteria of sepsis and septic shock as in sepsis-3 guidelines, is followed to describe the disease severity in COVID-19. The risk factors for developing into severe to critical cases include advanced age (> 60 years), pregnancy, underlying comorbidities such as hypertension, diabetes, cardiovascular disease, chronic kidney diseases, malignancy, pre-existing pulmonary disease, immunosuppression, cerebrovascular disease and obesity[14].

Coagulopathy and thrombocytopenia are also common complications for COVID-19 infection, which increase the risk of haemorrhage and thrombosis. Mottled skin, petechial or purpuric rash, appearance of melena or haematuria is found in some cases. Patients with the syndrome of persistent hypoxaemia, chest pain, pre-syncope or syncope and haemoptysis should be suspected of having pulmonary thromboembolism (PTE)[17]. The manifestation of limb pain, swelling, erythema and dilated superficial veins should be suspected of deep vein thrombosis (DVT). Nearly 20% of patients have abnormal coagulation function, and most of severe and critical patients present with coagulation disorders and have the tendency to develop into disseminated intravascular coagulation (DIC)[14]. It may be hypothesised that myocardial injury is a result of microthrombus formation in the myocardial vasculature in the setting of a hypercoagulable state like DIC. Numerous studies have reported acute cardiac injury as an important manifestation of COVID-19[18]. AKI is primarily seen in COVID-19 patients with respiratory failure, with 89.7% of patients on mechanical ventilation developing AKI compared to 21.7% of non-ventilated patients. Risk factors for AKI included older age, diabetes mellitus, cardiovascular disease, black race, hypertension and need for ventilation and vasopressor medications. AKI occurs early and in temporal association with respiratory failure and is associated with a poor prognosis[19]. Mechanisms of renal injury have been hypothesised to include both acute tubular necrosis, direct cytotoxic effects of the virus itself and immune-mediated damage[20]. Neurologic manifestations are categorised into 3 categories: central nervous system (CNS) manifestations (dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and seizure), peripheral nervous system (PNS) manifestations (taste impairment, smell impairment, vision impairment, and nerve pain) and skeletal muscular injury manifestations. Impaired consciousness includes the change of consciousness level (somnolence, stupor, and coma) and consciousness content (confusion and delirium)[21].

Laboratory investigations

Whom to test

Most countries are utilising some type of clinical and epidemiologic data to determine who should have testing performed. As per the Indian Council of Medical Research (ICMR) the following categories of individuals should be considered for COVID-19 testing in India:-

1. All symptomatic (ILI symptoms) individuals who have undertaken international travel in the last 14 days.
2. All symptomatic (ILI symptoms) contacts of laboratory confirmed cases.
3. All symptomatic healthcare personnel (HCP)/frontline workers involved in containment and mitigation of COVID-19.

4. All patients of Severe acute respiratory infection (SARI).
5. Asymptomatic direct and high risk contacts of a confirmed case to be tested once between day 5 and day 10 of coming into contact.
6. All symptomatic ILI within hotspots/containment zones.
7. All hospitalised patients who develop ILI symptoms.
8. All symptomatic ILI among returnees and migrants within 7 days of illness.
9. No emergency procedure (including deliveries) should be delayed for lack of test. However, sample can be sent for testing if indicated as above.

As per WHO guidelines:-

- ILI case is defined as one with acute respiratory infection with fever > 38° C AND cough.
- SARI case is defined as one with acute respiratory tract infection with fever > 38° C AND cough AND requiring hospitalisation.
- All testing in the above categories is recommended by real time RT-PCR test only.

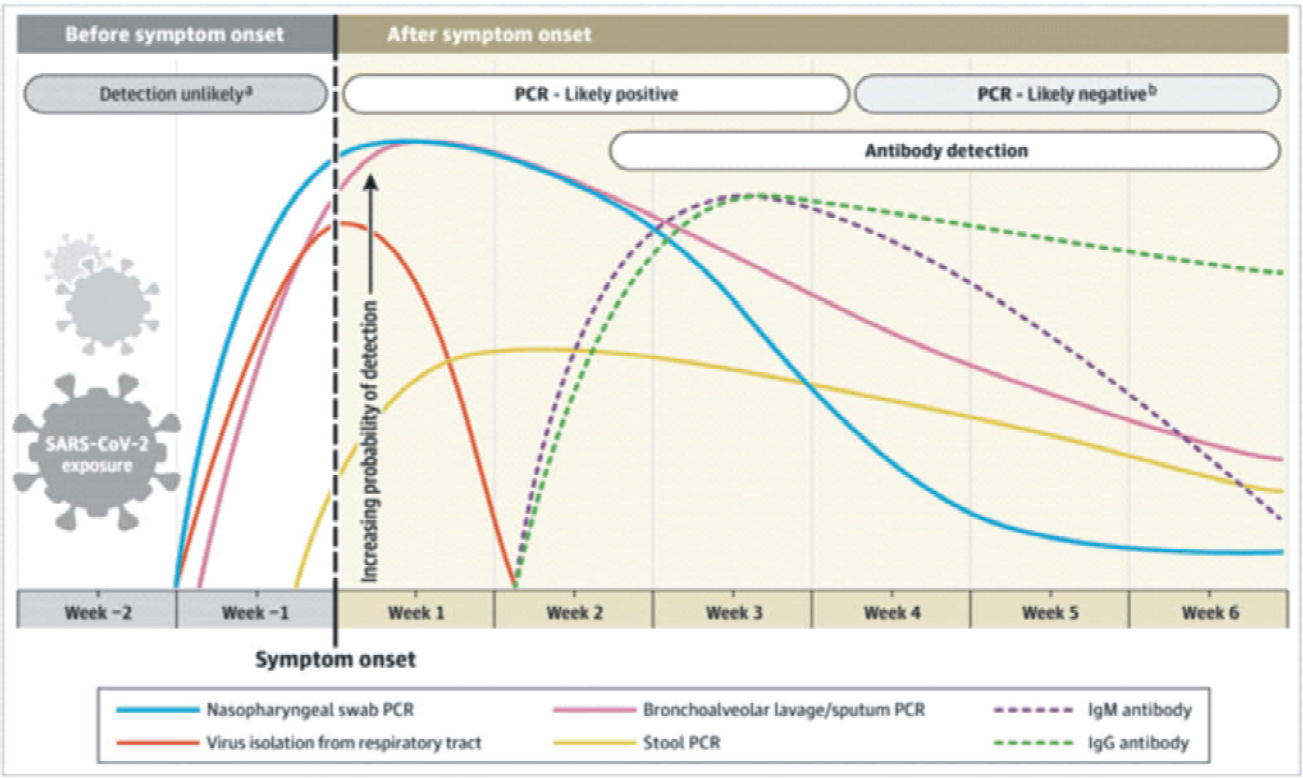
Case definitions (as per WHO)

Surveillance definition of suspect case: A person with acute respiratory infection (sudden onset of at least one of the following: fever, cough, sore throat, shortness of breath) requiring hospitalisation or not, *and*

In the 14 days prior to symptom onset, meets at least one of the following epidemiological criteria:

- Was in close contact with a confirmed or probable case of COVID-19, *or*

Figure. Estimated Variation Over Time in Diagnostic Tests for Detection of SARS-CoV-2 Infection Relative to Symptom Onset



Estimated time intervals and rates of viral detection are based on data from several published reports. Because of variability in values among studies, estimated time intervals should be considered approximations and the probability of detection of SARS-CoV-2 infection is presented qualitatively. SARS-CoV-2 indicates severe acute respiratory syndrome coronavirus 2; PCR, polymerase chain reaction.

[a] Detection only occurs if patients are followed up proactively from the time of exposure.

[b] More likely to register a negative than a positive result by PCR of a nasopharyngeal swab.

Fig. 3: *Estimated variation over time in diagnostic tests for detection of SARS-CoV-2 infection relative to symptom onset.*

(Adapted from Sethuraman N, Jeremiah SS, Ryo A. Interpreting Diagnostic Tests for SARS-CoV-2. JAMA, May 6, 2020. doi:10.1001/jama.2020.8259).

- History of travel to areas with ongoing community transmission of SARS-CoV-2, *or*
- Worked in or attended a healthcare facility where COVID-19 patients were being treated.

Probable case: A suspected case in whom testing for SARS-CoV-2 is inconclusive (result of the test reported by BSL4 lab) or in whom testing was positive on a pan-coronavirus assay.

Confirmed case: A person with laboratory confirmation of SARS-CoV-2 causing COVID-19 infection by rRT-PCR of oropharyngeal or nasopharyngeal swab, irrespective of clinical signs and symptoms.

Diagnosis

Molecular testing

The WHO recommends collecting specimens from both the upper respiratory tract (naso- and oropharyngeal samples) and lower respiratory tract such as expectorated sputum, endotracheal aspirate or bronchoalveolar lavage. The collection of BAL samples should only be performed in mechanically ventilated patients as lower respiratory tract samples seem to remain positive for a more extended period. Lower respiratory tract samples have a higher yield than upper respiratory tract samples, but often they are not obtained because of concerns about aerosolisation of virus during sample collection procedures. Laboratory confirmed COVID-19 patients are those who test positive on real-time reverse transcriptase polymerase chain reaction (rRT-PCR) of nasal and oropharyngeal swabs or sputum specimens. The collected clinical specimens are transported to designated laboratories in viral transport medium (VTM) and extraction of RNA is done, followed by rRT-PCR detection with primers and probes of appropriate sequences[14]. The value of cycle threshold (Ct) is the criterion to determine the detection result, with less than 37 being defined as negative, above 40 as positive and a medium load (37 - 40) calling for confirmation by retesting[22]. The estimated variation over time in diagnostic tests for detection of SARS-CoV-2 infection relative to symptom onset is shown in Fig. 3.

Serology testing

The detection of SARS-CoV-2 specific IgM and IgG antibodies can also be used for diagnosis but it is not recommended by the WHO for disease confirmation[23]. COVID-19 infection can be determined with one of the following criteria: positive specific IgM, the transformation of specific IgG from negative to positive, a 4-fold increase in IgG titre during recovery period compared with the result of acute phase. Although antibody detection is simple, rapid and inexpensive, it is still not widely used due to inherent limitations, like - false negativity resulting from the existence of a window period, limited sensitivity and specificity as compared with rRT-PCR, and absence of exclusion criteria, which makes it an epidemiological tool for sero-surveillance only.

Laboratory parameters

A majority of COVID-19 patients show normal leucocyte count and nearly one-third have leucopenia. Lymphocytopenia, as one of the most typical laboratory abnormalities, is present in 83.2% of patients[24]. Interestingly, lymphocytopenia appears to be a negative prognostic factor. The elevated neutrophil-to-lymphocyte ratio (NLR), derived NLR ratio (d-NLR) (neutrophil count divided by the result of WBC count minus neutrophil count), and platelet-to-lymphocyte ratio, can be the expression of the inflammatory storm[24]. The correction of these indices is an expression of a favourable trend. Many patients have liver function abnormalities with elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), and LDH. Liver damage in mild cases of COVID-19 is often transient and can return to normal without any special treatment. A prominent finding of SARS-CoV-2 is disarray of the coagulation and fibrinolytic system, with > 70% of non-survivors meeting criteria for disseminated intravascular coagulation (DIC)[25]. Hospitalised patients with moderate and severe COVID-19 and those with poorer outcomes are noted to have prolonged prothrombin time, elevated D-dimer and deranged activated partial thromboplastin time. Acute cardiac injury is variably defined as either cardiac troponin elevation > 99th percentile alone or a composite of troponin elevation, electrocardiographic, or echocardiographic abnormalities[18]. One of the more intriguing mechanisms for systemic injury in severe COVID-19 patients stems from the significant systemic inflammatory response. Many reports have demonstrated severely elevated levels of inflammatory biomarkers and cytokines, including IL-6, CRP, TNF-a, IL-2R, and ferritin[26]. Higher levels of these biomarkers are associated with more severe COVID-19 manifestations, known as cytokine release syndrome or cytokine storm, and worse outcomes. Acute kidney injury is also very common and is manifested as deranged urea, creatinine and decreased urine output.

Radiological features

Radiological images play an important role in the diagnosis and providing guidance for treatment. Standard radiographic examination (X-ray) of the chest has a low sensitivity in identifying early lung changes and in the initial stages of the disease. At this stage, it can be completely negative. In the more advanced stages of infection, the

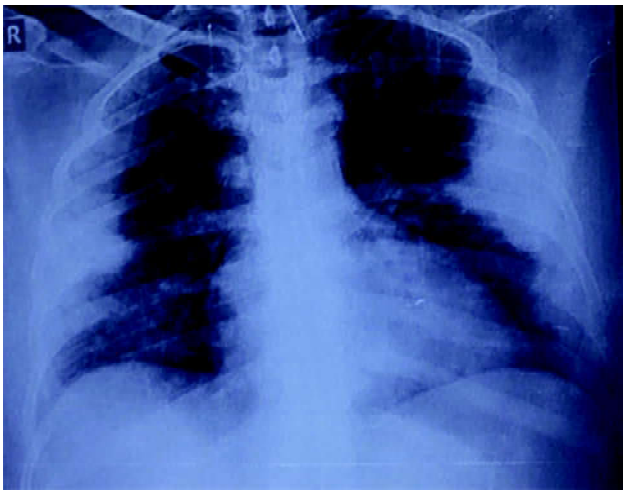


Fig. 4a: *Bilateral subpleural interstitial opacities.*

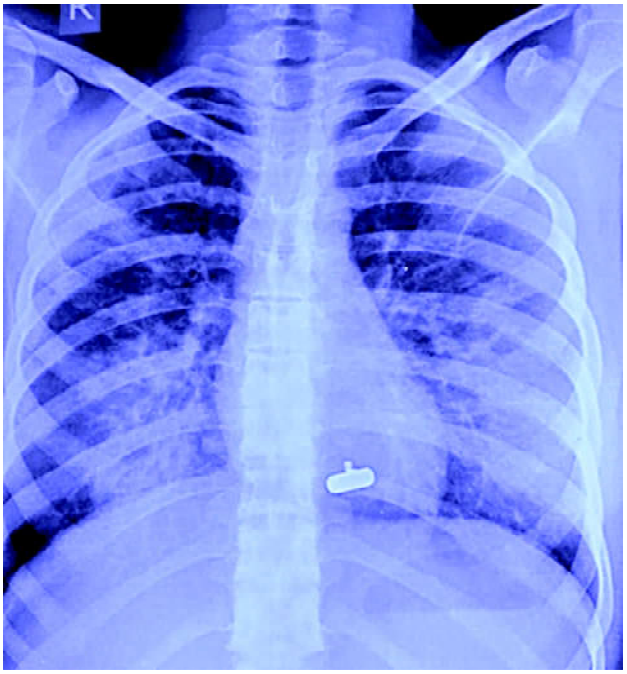


Fig. 4b: *Bilateral lower zone alveolar-interstitial infiltrates.*

Fig. 4 (a and b): *Some typical chest radiographs from confirmed COVID-19 cases.*

chest X-ray examination generally shows bilateral multifocal alveolar-interstitial opacities (Fig. 4a and 4b), which tend to confluence up to the complete opacity of the lung. Patients of varying severity presented significantly different lesions on chest CT imaging. Patients with mild disease manifested with unilateral and focal ground-glass opacities (GGOs) which gradually developed to bilateral or multilobular lesions. As the disease progressed further, GGOs evolved to consolidation lesions, presenting with mixed pattern or pure consolidation, with the latter being more common in critically ill patients admitted to ICU[27]. Consistent with the interstitial involvement in viral pneumonia, Zhao *et al* suggested that 48.5% of CT images manifested reticular patterns and 28.7% presented interlobular septal thickening[28]. Unlike influenza pneumonia, which usually exhibited unilateral GGOs and significant solid nodules, only 6% of COVID-19 patients had solid nodules. Moreover, other lesions included adjacent pleura thickening, vascular enlargement, bronchial wall thickening, traction bronchiectasis, air bronchogram, pericardial effusion, etc. During disease deterioration, increased number of or enlarged lesions could be observed in radiological imaging, and part of them even develop into a "white lung" with diffusely involved lung[29].

Broadly, COVID-19 pneumonitis has been divided into two primary phenotypes; L-type and H-type, although evidence is limited as of now[30].

COVID-19 pneumonia, type L

This group of patients presents with the following characteristics:-

- Low elastance : Nearly normal compliance.
- Low ventilation to perfusion (VA/Q) ratio: Hypoxaemia may be best explained by the loss of regulation of perfusion and by loss of vasoconstriction.
- Low lung weight. Only ground-glass densities are present on CT scan, primarily located subpleurally and along the lung fissures.
- Low lung recruitability. The amount of non-aerated tissue is very low.

COVID-19 pneumonia, type H (typical ARDS like picture)

- High elastance.
- High right-to-left shunt.
- High lung weight.

Lung ultrasound

Ultrasound approach can allow evaluating the evolution of the disease, from a focal interstitial pattern up to "white lung" with evidence often of subpleural consolidation. It should be performed within the first 24 hours in the suspect and every 24 to 48 hours and can be useful for patient follow-up, choice of the setting of mechanical ventilation and for indication of prone positioning. The main sonographic features are:-

- Pleural lines: Often thickened, irregular, and discontinuous until it almost appears continuous;

subpleural lesions can be seen as small patchy consolidations or nodules.

- B lines: They are often motionless, coalescent and can cascade and follow-up to the square of "white lung".
- Thickenings: They are most evident in the posterior and bilateral fields especially in the lower fields; the dynamic air bronchogram within the consolidation is a manifestation of disease evolution.
- Perilesional pleural effusion.

Clinical management

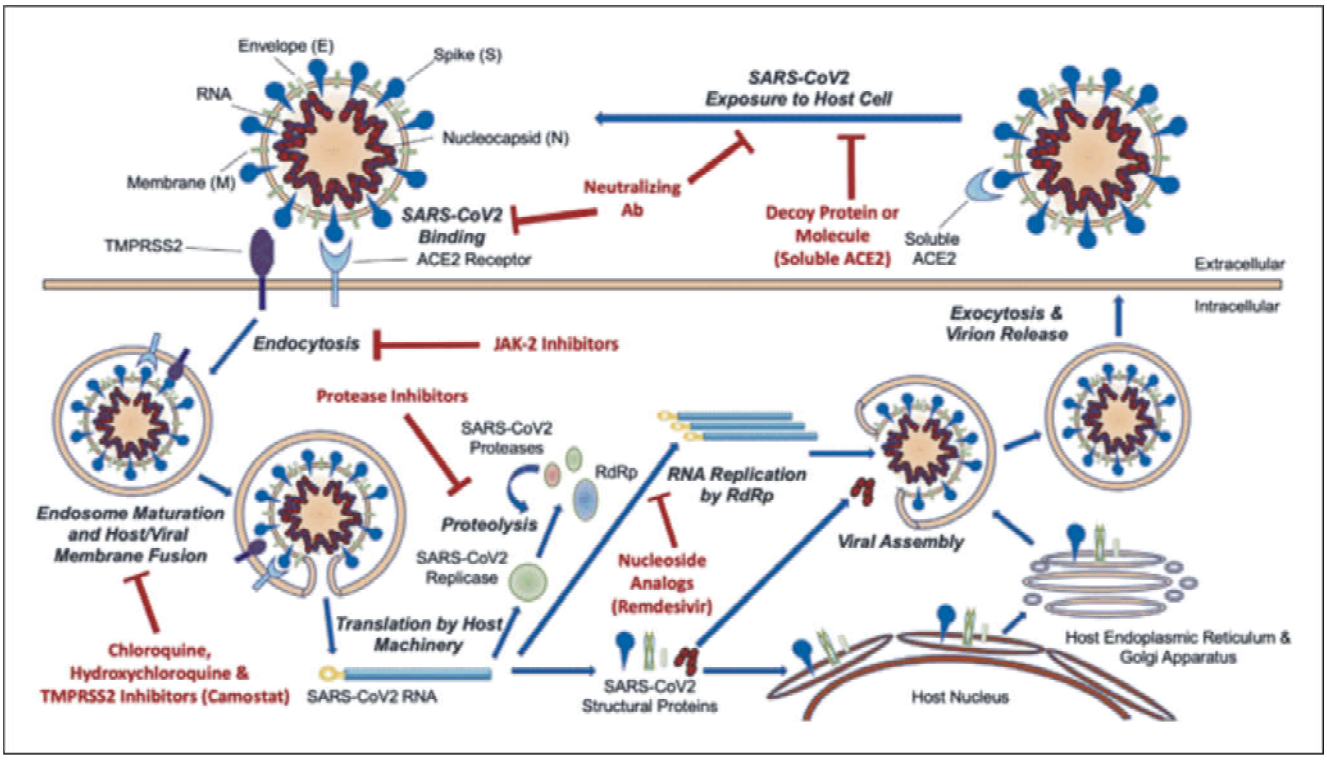
Infection prevention and control (IPC) measures

Preventive measures are the current strategy to limit the spread of cases because an epidemic will continue to propagate as long as R_0 is greater than 1. Control measures must focus on reducing the value to less than 1.

Preventive strategies are focussed on the isolation of patients and careful infection control, including appropriate measures to be adopted during the diagnosis and the provision of clinical care to an infected patient. For instance, droplet, contact and airborne precautions should be adopted during specimen collection, and sputum induction should be avoided.

The WHO and other organisations have issued the following general recommendations:-

- Avoid close contact with subjects suffering from acute respiratory infections.
- Wash your hands frequently, especially after contact with infected people or their environment.
- Avoid unprotected contact with farm or wild animals.
- People with symptoms of acute airway infection should keep their distance, cover coughs or sneezes with disposable tissues or clothes and wash their hands.



Severe Acute Respiratory Syndrome-CoronaVirus-2 (SARS-CoV-2) binds to the angiotensin-converting enzyme 2 (ACE2) receptor on the host cell membrane. Endocytosis is believed to be mediated, in part, by JAK-2. Membrane fusion occurs between the mature endosome and virion with facilitation by the transmembrane serine protease 2 (TMPRSS2) resulting in release of the SARS-CoV-2 RNA into the intracellular space. The RNA is translated by host machinery to produce the replicase and structural proteins. Host and SARS-CoV-2 proteases cleave the replicase into nonstructural proteins, including the RNA-dependent RNA polymerase (RdRp). RdRp mediates SARS-CoV-2 RNA replication and amplification. SARS-CoV-2 transmembrane proteins (spike [S], envelope [E], and membrane [M]) are shuttled via the endoplasmic reticulum and Golgi apparatus to the forming viral capsids. Viral assembly occurs with addition of the viral RNA and nucleocapsid (N) protein through association with the transmembrane viral proteins. Exocytosis results in release of the newly synthesised viral particle. Ab - antibody.

Fig. 5: *Putative SARS-CoV-2 life cycle and therapeutic targets.*

(Adapted from Atri et al. COVID-19 for the cardiologist. JACC: Basic to Translational Science 2020; 5 (5): 518-36).

- Strengthen – particularly in emergency medicine departments – the application of strict hygiene measures for the prevention and control of infections.
- Individuals that are immunocompromised should avoid public gatherings.

Healthcare workers caring for infected individuals should utilise contact and airborne precautions to include PPE such as N95 or FFP2/3 masks, eye protection, gowns, and gloves to prevent transmission of the pathogen.

Potential targeted or disease-modifying treatments in COVID-19

These is no specific antiviral treatment which has been proven to be effective for COVID-19. Combinations of over three antivirals are not suggested. Current treatment options are mainly based on previous experience showing clinical benefits in treating influenza, ebola, MERS, SARS, and other viral infections. The preceding review of the viral physiology of SARS-CoV-2 and the various potential mechanisms of injury to the host serve as the basis for considering specific targeted treatment and prevention (Fig. 5).

Antiviral therapy

Nucleoside analogs: inhibitors of viral genome replication (remdesivir, favipiravir)

The antiviral mechanism of nucleoside analogs is to interfere with RdRp (RNA dependent RNA polymerase) function and viral genome replication and amplification. The most widely applied agent in this class against SARS-CoV-2 has been remdesivir. Remdesivir functions as a chain terminator of RNA replication, initially designed for use against Ebola[31]. Addition of remdesivir to the growing RNA strand by RdRp, blocks the incorporation of additional nucleosides, thereby halting genome replication. The agent has been shown to have in vitro activity against SARS-CoV-2, leading to off-label and investigational use around the world[32]. Multiple randomised control trials are ongoing in China and the United States for moderate, severe, and critical COVID-19. Another nucleoside analog for the disruption of RdRp-dependent viral replication is favipiravir, which has investigational approval in several countries[33]. Additional agents that are under study include emtricitabine or tenofovir and ribavirin[33].

Protease inhibitors: inhibitors of nonstructural protein generation (lopinavir/ritonavir)

The antiviral mechanism of action of protease inhibitors is to block viral proteases that cleave the nonstructural proteins from the large, monomeric replicase. As the maturation of nonstructural proteins, such as RdRp, is necessary for viral reproduction, the pharmacologic impairment of the protease might be effective to stop viral replication. A randomised control trial of lopinavir-ritonavir, a combination protease inhibitor designed for human immunodeficiency virus treatment, in 199 patients with at least moderate COVID-19 did not significantly alter clinical improvement or viral clearance[34]. Other candidate protease inhibitors for SARS-CoV-2 include danoprevir, a drug originally intended for hepatitis C therapy[33].

Inhibitors of membrane fusion

For the viral genome to access the host cellular machinery for replication, a membrane fusion event must occur between the viral and endosomal membranes, which are non-covalently bound by the interaction between the S protein and ACE2. The exact mechanism of membrane fusion is not known but appears to be dependent on endosomal maturation and a membrane-bound host protease, TMPRSS2[35].

Chloroquine and hydroxychloroquine

Chloroquine (CQ) and hydroxychloroquine (HCQ) are thought to inhibit endosomal maturation, a process by which endosomes are translocated from the perimembrane regions of the cell to central hubs. CQ prevented viral replication of SARS-CoV-1 *in vitro*[36]. A follow-up study demonstrated comparable efficacy of HCQ, a less toxic derivative, and suggested that the mechanism of impaired endosomal maturation applied to SARS-CoV-2 infection *in vitro*[37]. Only poor quality, non-randomised, unblinded data exist assessing the benefit of HCQ in COVID-19. Although HCQ is being widely used, more data is needed to prove efficacy against SARS-CoV-2 in humans. Notably, CQ and HCQ prolong the QT_C interval and may induce arrhythmia; significant caution should be used in starting these agents in patients with a QT_C interval > 500 ms. Concomitant use of other QT_C prolonging agents is not recommended.

Camostat

Camostat is a protease inhibitor approved for the treatment of chronic pancreatitis. Camostat appears to inhibit TMPRSS2 in proteomic and *in vitro* studies[35]. A randomised, placebo-control trial is underway for this agent in COVID-19 in the US.

Neutralising antibodies/convalescent plasma and decoy proteins

Neutralising antibodies are designed to bind virions, preventing viral exposure or binding to host cells. Plasma

from patients who have recovered from SARS-CoV-2 may contain anti SARS-CoV-2 IgG antibodies. In a small, single-arm trial of convalescent plasma in COVID-19 patients with ARDS, all had clinical improvement, with 3 of 5 patients weaned off the ventilator[38]. Additional trials are ongoing to better define the safety and efficacy of this strategy.

Isolation of SARS-CoV-2 specific neutralising antibodies with clonal techniques is an appealing strategy to provide targeted therapy, potentially with lower risk of adverse events. Strategies currently under investigation include antibodies cloned from convalescent serum of individuals recovered from SARS-CoV-2 or SARS-CoV-1 and synthetic antibodies. It is unclear whether differences in the S proteins of SARS-CoV-1 and SARS-CoV-2 may limit the effectiveness of antibodies cloned from patients convalescent to SARS-CoV-1[39]. Synthetic antibodies represent an exciting, novel therapeutic avenue. One strategy being explored is to fuse ACE2 to fragment crystallisable region immunoglobulin G, with the hypothesis that this synthetic antibody would serve as a decoy receptor, preventing cellular binding of the virion[40]. Few studies are ongoing of decoy proteins that are designed to act as viral "sinks". There is preliminary success with this strategy using soluble human ACE2[41].

Anti-inflammatory therapy

Advanced stages of COVID-19 have been likened to cytokine storm syndromes with nonspecific widespread immune activation. Elevated levels of inflammatory biomarkers, such as IL-6 and hsCRP, identify patients at high risk of progressing to severe disease and death. Immunomodulatory and anti-inflammatory therapy have been used, despite limited data, in patients with evidence of hyperinflammation in an effort to curb pathologic immune activation.

Corticosteroids

Corticosteroids have been used in several, severe viral respiratory infections including influenza, SARS-CoV, and MERS-CoV with limited benefit and, in some instances, evidence of delayed viral clearance and increased rates of secondary infection and mortality. A retrospective analysis of 84 patients with ARDS secondary to SARS-CoV-2 observed an association with improved survival in patients who received solumedrol[42]. In the absence of robust evidence, major professional society guidelines do not recommend routine use of corticosteroids in treatment of COVID-19 but rather restricting its use to patients with other indications for steroids, such as refractory shock or advanced ARDS[43].

Interleukin-6 (IL-6) inhibitors

Elevation of IL-6 in patients with severe COVID-19 has prompted consideration of use of IL-6 inhibitors (tocilizumab, siltuximab) extrapolating from treatment of cytokine release syndrome[44]. Tociluzimab, a recombinant humanised monoclonal antibody, and siltuximab, a chimeric monoclonal antibody, both bind soluble and membrane bound IL-6 receptors resulting in inhibition of IL-6 mediated signaling. In one case series from China, 21 patients with severe or critical COVID-19 treated with tocilizumab experienced a salutary effect with resolution of fever, improved oxygenation, improvement in lung opacities on chest computed tomography, resolution of lymphopenia and a reduction in CRP levels within a few days of therapy in the absence of any significant reported adverse events[45].

Azithromycin

Azithromycin, a macrolide antibiotic, has long been touted for its anti-inflammatory effect and has been used as adjunctive therapy in treatment of community acquired pneumonia and chronic obstructive pulmonary disease exacerbations. A small nonrandomised study showed that combination azithromycin and HCQ was associated with more effective SARS-CoV-2 clearance in COVID-19 patients compared with either monotherapy with HCQ or standard of care; however, numerous limitations of this study render the data uninterpretable[46]. QT_C interval monitoring is important, especially when used in combination with HCQ.

Other anti-inflammatory therapies

JAK-2 inhibitors inhibit receptor mediated-endocytosis, leading to the hypothesis that it might prevent cellular entry of the SARS-CoV-2. Additionally, this class of agents have anti-inflammatory effects by inhibiting cytokine release. An agent in the class, baricitinib, is being studied in an open-label non-randomised pilot study in patients with COVID-19[47]. Currently, a 3-arm randomised control trial is being launched to compare anakinra monotherapy, emapalumab monotherapy, and standard of care. Anakinra is a recombinant monoclonal antibody that blocks IL-1 receptors. It has been used to treat autoimmune conditions including juvenile idiopathic arthritis as well as recurrent pericarditis. Emapalumab is a human anti interferon-gamma monoclonal antibody that has been approved for treatment of primary haemophagocytic lymphohistiocytosis, a disease reminiscent of the hyperinflammatory state seen in advanced COVID-19. Finally, colchicine, a microtubule polymerisation inhibitor and anti-inflammatory drug, is being tested in large randomised clinical trial of ambulatory COVID-19 patients.

Vaccine development

As the discovery of a safe and efficacious vaccine again

SARS-CoV-2 is clearly the aspiration for preventative strategies, intense efforts are ongoing employing numerous approaches with accelerated testing. It is believed that all 4 structural proteins (E, M, N, and S) may serve as antigens for neutralising antibody and $CD4^+$ $CD8^+$ T-cell responses. Encouragingly, administration of full length of the ACE2 receptor-binding domain of the S protein of SARS-CoV-1 induced highly potent neutralising antibodies that conveyed protective immunity in animal models. Potential delivery strategies include inactivated or attenuated virus, subunit vaccines, viral vectors, and DNA- or RNA-based vaccines[49].

Other supportive therapy

Anticoagulation

In clinical practice, nearly 20% of patients with COVID-19 are found to have abnormal coagulation function and almost all severely and critically ill patients presented coagulation disorders. Anticoagulation should be given with great caution in patients with DIC although microthrombosis has been observed in lung, liver, and other organs on autopsy of COVID-19 patients. Ishan Paranjpe and Valentin Fuster *et al*, analysed the association between in-hospital anticoagulation administration and mortality among patients hospitalised with COVID-19. Of the 2,773 hospitalised COVID-19 patients, 786 (28%) received systemic anticoagulation during their hospital stay. Patients who received anticoagulation were more likely to require mechanical ventilation. Longer duration of anticoagulation treatment was associated with a reduced mortality risk[48]. According to the researchers, anticoagulation may be associated with improved outcomes in COVID-19 patients, but the benefits should be weighed against the risk of bleeding. Also, heparins bind tightly to SARS-CoV-2 spike proteins and also downregulate IL-6, thus directly dampening the immune hyperactivation.

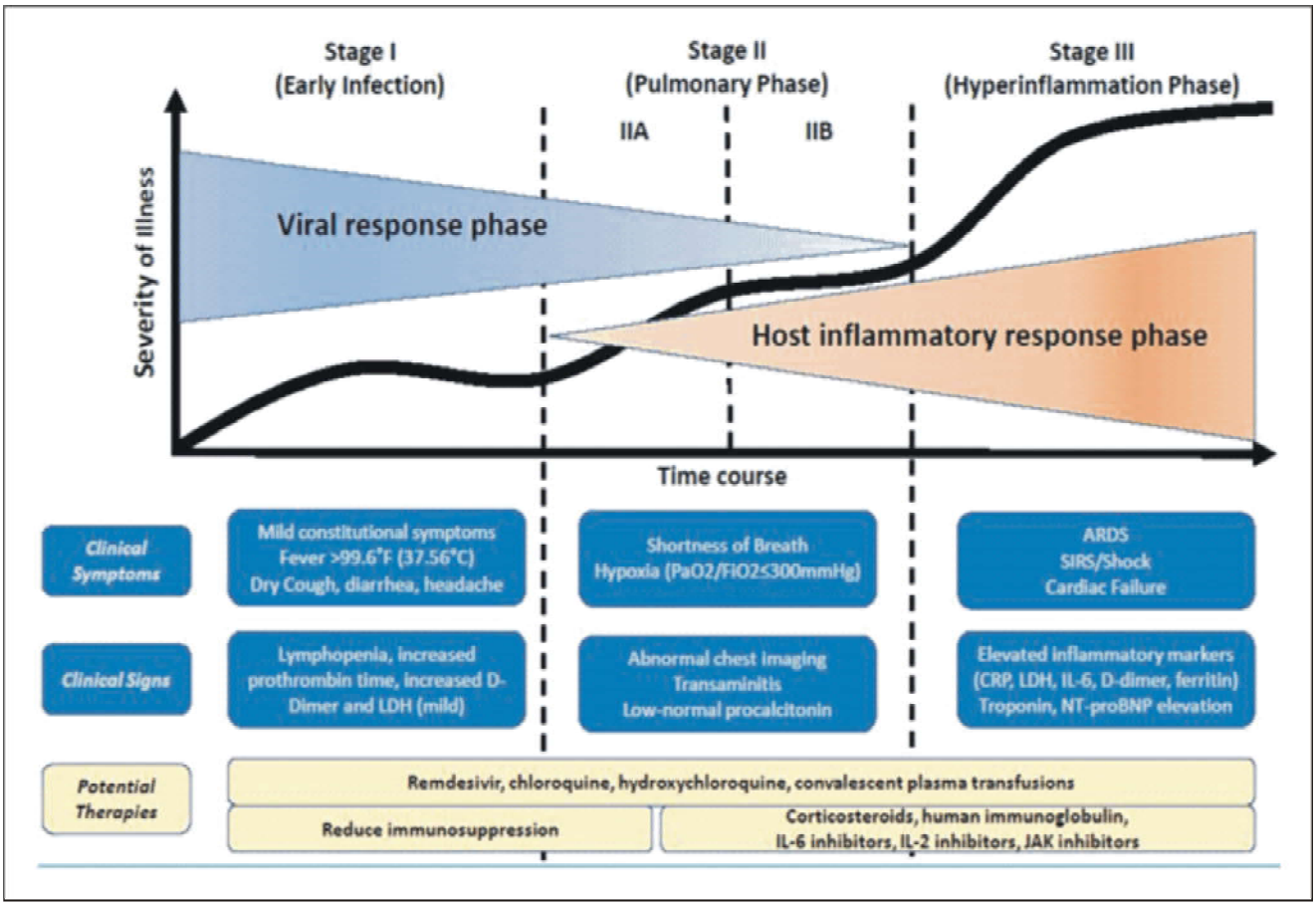


Fig. 6: *Classification of COVID-19 disease states and potential therapeutic targets. Legend: The figure shows three escalating phases of disease progression with COVID-19, with associated signs, symptoms, and potential phase-specific therapies. ARDS = Acute respiratory distress syndrome; CRP = C-reactive protein; IL = Interleukin; JAK = Janus kinase; LDH = Lactate dehydrogenase; SIRS = Systemic inflammatory response syndrome.*

(Adapted from Siddiqi HK et al. COVID-19 illness in native and immunosuppressed states: A clinical-therapeutic staging proposal. J Heart Lung Transplant, 2020).

Oxygen therapy and mechanical ventilation

For mild-to-moderate patients with hypoxaemia, nasal catheters and non-rebreather or venturi masks and even high-flow nasal cannula oxygen therapy (HFNC) are advised. While for severe and critical patients with respiratory distress, HFNC, non-invasive mechanical ventilation (NIV) with helmet mask or invasive mechanical ventilation, and even ECMO should be considered. Nebulisation therapy should be avoided in COVID-19 wards for risk of aerosol generation and spread.

HFNC (> 50 l/min) can provide accurate oxygen concentration and a certain positive airway pressure to promote alveolar expansion to improve oxygenation and respiratory distress. However, according to expert consensus on the use of HFNC for COVID-19, patients with cardiac arrest, weak spontaneous breathing, PaO_2/FiO_2 < 100 mmHg, $PaCo_2$ > 45 mmHg and pH < 7.25 and upper airway obstruction are contraindicated.

For severe patients with respiratory distress or hypoxaemia that cannot be alleviated after standard oxygen therapy, NIV can also be considered with close surveillance. It is important that appropriate fit masks or helmet masks should be used to mitigate aerosol spread.

Invasive ventilation should be done in case NIV fails to improve respiratory parameters within 1 - 2 hours trial. Endotracheal intubation should be performed by a trained and experienced provider using airborne precautions. Patients with ARDS, especially young individuals or those who are obese or pregnant, may de-saturate quickly during intubation. Pre-oxygenate with 100% FiO_2 for 5 minutes, via a face mask with a reservoir bag, bag-valve mask, HFNO, or NIV. Rapid sequence intubation is appropriate after an airway assessment that identifies no signs of difficult intubation. Implement mechanical ventilation using lower tidal volumes (4 - 8 ml/kg predicted body weight, PBW) and lower inspiratory pressures (plateau pressure < 30 cm of H_2O). Prone positioning and even ECMO might be required in refractory hypoxaemia even on invasive ventilation.

Antimicrobial therapy

Empiric antimicrobial therapy should be instituted in all severe COVID-19 patients within one hour of presentation, covering all usually encountered microbes as per the local ecological data of the microbiological flora. All relevant culture specimens especially paired blood culture samples should be obtained prior to first dose of antibiotic administration. De-escalation of therapy should be done as soon as the culture results are available.

Conclusion and future perspective

In this review, we have presented an overview of the epidemiological, aetiological, clinical, pathological, and imaging characteristics of COVID-19 and given a brief overview of the latest advancements in the treatment. As it is a new entity with a widely varying clinical disease spectrum, management poses a big challenge to all the treating clinicians. At the same time, therapeutic protocols need to be revised as per the rapidly evolving understanding of the disease. It is like building the ship while sailing. The treatment should be customised for every individual after assessing the clinical status and pathophysiologic phase of the disease spectrum (Fig. 6). The COVID-19 pandemic can cause short-term fiscal distress and longer-term damage to the global economic growth. A joint global cohesive effort is required in order to contain this pandemic. It is notable that in the present pandemic scenario, innovative artificial intelligence (AI) — powered surveillance, quick and strategic response actions — the trinity of testing-isolation-contact tracing, committed social distancing measures travel restrictions, self-isolation, implementation of personal and public hygiene, and extensive mobilisation of medical care facilities are helping the world mitigate through. For preventing future outbreaks of SARS-CoV-2 infection, high-volume cutting-edge investigations are warranted in understanding the COVID-19 pathology, CoV-2 origin, biology, structural data of potential surface antigens, and precise anti-CoV-2 antiviral therapies. Although the global economy is suffering at the hands of COVID-19, it is important to review the current action plans and suitably improvise the future action plans to avoid any potential recurrence.

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Need for Newer Antibiotics or Alternate Solution in ICU Management

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Introduction

The greatest threat to healthcare services is antibiotic resistance and evolution of multidrug resistant bacteria. Together they lead to infections, which cause extra burden on healthcare, thus leading to high morbidity, mortality, and expense. The estimated mortality due to sepsis from MDR is exponentially higher than the deaths caused by other infections.

Unfortunately, antibiotic-resistant pathogens have created a post-antibiotic era where new drugs are scarce and resistance develops faster. The twentieth century saw both – an era of development of newer antibiotics for human advantage, and at the same time leading to development of drug resistance. These have led to the never ending struggle to develop newer antibiotics for better cure and survival of humanity.

Further to this, a multi-factorial aetiology to sepsis leads to poorer outcomes and bigger challenge for critical care physicians. Developing newer antibiotics, which are economical, easier to administer, have a wide spectrum, and are least vulnerable to resistance is a greater challenge.

The last two decades have seen few antibacterial drugs being developed, which offer benefits over existing ones. It is unfortunate that out of these few drugs, five could reach the phase 3 clinical trials. Restriction of clinical use to few vulnerable diseases, short course of medical prescription, and limited medical fraternity prescribing it, makes antibiotics financially non profitable when compared to drugs used to treat non communicable diseases, i.e., hypertension, diabetes, etc. Financial loss to pharmaceutical firms becomes obvious and the race ends before it begins. A 2008 initiative named 10 x 20 Initiative was a challenge thrown by IDSA at USA and EU to develop ten new drugs over twenty years. Failure of this transatlantic initiative becomes quite apparent as no new drugs were developed over and above previous ones, except few with biosynthetic changes.

Recognition of metallo-beta-lactamases, extended spectrum beta lactamases (ESBLs), carbapenem-resistant Enteriobacteriaceae (CRE), *Klebsiella pneumonia* carbapenemases (KPCs), Vancomycin-resistant Enterococcus (VRE) and Methicillin-Resistant *Staphylococcus aureus* (MRSA) by microbiological laboratories needs to be much recognised and applauded in the ever-changing treatment of MDR infections.

Newer antibiotics

It is unfortunate that only two new classes of antibiotics were discovered over the last five decades. The last decade has seen even lesser numbers being brought into the market which is considerably lower than what was three decades age.

A dozen newer semi-synthetic salts are being tested and are in late clinical testing stage, but all appear to be modifications to pre-existing antibiotics. None from a new class has been on trial for the last decade. Their efficacy may get limited by the fact that many original salts showed resistance and their novo versions may just provide an extended window of time till further resistance is documented. Many strains of soil bacteria from different environments are already showing resistance to the new semi-synthetic antibiotics. This has been well documented with tigecycline which was introduced over a decade ago. In fact, resistance to many synthetic antimicrobials may already exist in nature. We all are aware that resistance is inevitable, and that primarily is due to the fact that organisms have been around for long and they know how to survive.

New antibiotics which have novel mechanisms of action against MDR organisms, with minimal side-effects, and are easier to administer (preferably by non intravenous route), and have specific effects on the microbiome, are the need of the hour.

Gram-positive organisms such as MRSA and VRE are stable or declining in frequency while Gram-negative ESBLs and CREs are increasing. It is important to remember and differentiate between carbapenemase-producing enterobacteriaceae (CPE) Gram-negative bacilli and carbapenem-resistant enterobacteriaceae (CRE) Gram-negative bacilli, the ones which have carbapenem resistance without producing a carbapenemase enzyme . A number of carbapenem-resistant Gram-negative bacilli are highly problematic and these are other than Enterobacteriaceae

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for, e.g., *Pseudomonas aeruginosa*, *Acinetobacter species* and *Stenotrophomonas maltophilia*. They are often implicated in infections within healthcare settings and survive within the milieu by using a combination of other resistance mechanisms. As the risk of transmission and dissemination is lower, it becomes important to identify them as coloniser versus source of infection to further isolate and/or initiate appropriate management.

Enterobacteriaceae family includes common pathogens such as *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae* and *Proteus species*. These are normal colonisers of the gut, but can lead to severe infections of the urinary tract, gastrointestinal tract, and the bloodstream. As human pathogens, they cause dissemination of infection, antimicrobial resistance, and cross-transmission of genes; this is further exaggerated by easy spread of cross-resistance between different species and strains within the Enterobacteriaceae family. Carbapenemase-producing Enterobacteriaceae (CPE) produce the enzyme carbapenemase, which inactivates all the common members of the carbapenem antimicrobial class. Other carbapenemase enzymes commonly identified are IMP, NDM, VIM, KPC, OXA-48 and this is an ever-expanding family. Compounding to the above it has been documented that they almost always have resistance to other important antibiotic classes, i.e., beta-lactams, beta-lactamase inhibitors, quinolones and aminoglycosides.

Newer antibiotics: The last two decades of the new millennia

Oxazolidinones

Linezolid, an oxazolidinone, was introduced more than two decades ago and inhibits bacterial protein synthesis at the initiation/elongation step. It has sensitivity against Gram-positive bacteria, especially methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE) and *Streptococcus pneumoniae* and *Mycobacterium tuberculosis*. Radezolid (RX-1741), Torezolid (TR-700), and a research molecule RWJ-416457 are under clinical trials.

Glycopeptides

Vancomycin, the first drug of this group has come a long way. Oritavancin, Telavancin, Dalbavancin are few of the new phenyl glycopeptides. They inhibit peptidoglycan biosynthesis by inhibiting transglycosylation and transpeptidation. They all have activity against vancomycin-intermediate isolates of *S. aureus* (VISA), vancomycin resistant staphylococci and *Enterococcus faecium* (VRE), MRSA. Oritavancin is not as potent against vancomycin intermediate *S. aureus* (VISA).

Ketolides

Elithromycin, a ketolide has Carbonyl group at C3 position in a fourteen-membered ring macrolide thus conferring sensitivity to macrolide resistant strains. Cethromycin and Telithromycin are the other few drugs made available and they all inhibit protein synthesis in *S. pneumoniae*.

Glycylcyclines

A tetracycline class of antibacterial drugs Tigecycline was approved in 2005, which shows efficacy against both non resistant and resistant isolates especially enterococci and streptococci. It also acts against carbapenamase producing *Acinetobacter* and enterobacteriaceae. PTK0796 an oral aminomethylcycline is under development.

Carbapenems

Carbapenems are β-lactam penicillins (penam) and cephalosporine (cephem). They differ from the penams by the replacement of carbon for sulphur at position 1 and unsaturation in the 5-membered ring. Doripenem, was approved in 2007 for urinary and intra-abdominal sepsis.

Non-fermentative MDR GNB especially *Pseudomonas, Acinetobacter spp*. and *Burkholderia cepacia* are highly susceptible to its antibacterial activity. Razupenem (PZ-601) is under trial for multi drug-resistant Gram-positive and Gram-negative (ESBL producers) bacteria.

Lipopeptides

Daptomycin is a cyclic lipopeptide, derived from *Streptomyces roseosporus*. This is the first drug in a new class of antimicrobials. Its unique mechanism of action of inserting a lipophilic tail into the cell membrane without entering the cytoplasm, makes it a promising drug for future research also. An adverse life-threatening complication of eosinophilic pneumonia has been reported in literature.

Cephalosporin

Ceftobiprole and ceftaroline are the newer cephalosporins. Ceftobiprole, binds strongly to PBP2a (or PBP2′) of MRSA and shows action against penicillin-resistant streptococci also. Being a broad spectrum antibiotic, it is effective against *P. aeruginosa* and *Enterococci* also.

Ceftaroline fosamil is a prodrug of ceftaroline, developed by modification of fourth generation cephalosporin cefozopran. Phosphatise enzyme-induced activation converts prodrug into active form once injected in blood.

Pleuromutilin

Retapamulin, the first approved drug in this new class is

used as a topical preparation for infections caused by *S. pyogenes* and *S. aureus* in the skin or soft tissue.

Dihydrofolate reductase inhibitors

Iclaprim, a synthetic diaminopyrimidine, selectively inhibits enzyme dihydrofolate reductase. It is quite similar to trimethoprim in action, but does not require to be combined with other sulphonamides. Though it has shown high synergistic activity with sulfamethoxazole and sulfadiazine as well, it is being used as single agent against Trimethoprim-resistant isolates.

Others

Nitazoxanide, a nitro-thiazolide, exhibits broad spectrum activity against anaerobic bacteria and against anaerobic intestinal parasites. Nitazoxanide is FDA approved for the treatment of *Giardia intestinalis* and *Cryptosporidium parvum, Clostridium difficile*. It has also demonstrated antiviral activity against rotavirus and hepatitis C.

NXL103 (XRP2868) is a mixture of modified forms of quinupristin/dalfopristin streptogramins making it more water-soluble and permitting oral administration.

Fidaxomicin (OPT-80) is a novel macrocycle antibiotic, which is non-absorbed systemically and has potency against anaerobes such as *C. difficile*.

Sulopenem is an orally active penem in current clinical development and is potent against multi-drug resistant pathogens including penicillin-resistant *S. pneumoniae* and ESBL producing Enterobactericeae.

Others under research

BAL30376	Combination of monobactam
BAL19764	Class C β-lactamase inhibitor
BAL29880	Clavulanic acid
NXL104	Serine β-lactamases
BLI-489	Bicyclic penem inhibitor,
JNJ-Q2	Fluoroquinolone type II topoisomerase inhibitors
Finafloxacin 8-cyano fluoroquinolone	
LED209 Quorum-sensing blockers	
PC190723	
Rx100472	
Fab I inhibitors	
Lipid II binding compounds	
Bacterial efflux pump inhibitors	
Bacterial 2 - component signal transduction inhibitors	

Developing next generation antimicrobials, alternate solutions and newer technology for the ICU: the way forward

Targeting bactericidal functions of bacteria, by inhibiting proteins and fat synthesis is one of the ways to counter bacteriostatic pathways of inhibition and drug resistance presently being encountered. For e.g., essential enoyl-ACP reductase FabI required for fatty acid biosynthesis is being researched for bactericidal effects. Multi-drug resistant pathogenic fungi can be similarly targeted by blocking nuclear receptor pathways required for multi-drug resistant efflux development. A new therapeutic approach is needed to counter the previous mechanisms of resistance.

Newer pathways being targeted

Bacterial proteins: Inhibiting beta-ketoacyl carrier protein synthase I/II enzyme required for the fatty acid biosynthesis.

Virulence factors: Virulence inhibitors targeting toxin function.

Inhibiting bacterial systems type II or III secretion

Gene regulation of gene expression and adhesion

Inhibition of the formation of pili by pilicides.

Modulating host response pathways: Toll like receptor activators and modulator for adaptive immune response.

Therapeutic bacteriophages: Small, acid soluble protein (SASPs) genes which bind and inactivate bacterial DNA.

Combination of antibiotics with bioenhancers: Bioenhancers agents are capable of increasing availability and efficacy of drug when co administered with another drug, but do not have any pharmacological activity themselves, e.g., cow urine distillate (CUD) combined with rifampicin increased the activity of drug manifold[1]. (*Escherichia coli* 5 - 7 times, Gram-positive bacteria 3 - 11 times).

Herbal drugs

Herbs with antibacterial potential

Common name	(Botanical name)	Spectrum of activity
Chakvad	(*Cassia tora*)	*S. Aureus*
Pot marigold	(*Calendula officinalis*)	*B. subtilis, P. aeruginosa*
Karela	(*Momordica charantia*)	*E. coli*
Peppermint	(Mentha piperita)	*E. coli*
St. John's wort	(*Hypericum perforatum*)	MRSA
Honey		*S. aureus, E. coli, S. faecalis, P. aeruginosa, P. mirabilis, Salmonella typhi*
Cow urine distillate		(CUD) *Klebsiella pneumonia, B. subtilis, P. aeruginosa, Salmonella typhi*

The rise of the superbugs and role of biotechnology

CRISPR

CRISPR (clustered regularly interspaced short palindromic repeats) is dependent on immune system of bacteria where-in a single protein for binding and cleavage is used for RNA to detect DNA followed by Cas enzyme for nucleic acid destruction[2]. A molecular tool devised on similar basis helps as an antimicrobial, killing bacteria and also immunising them against resistant plasmids. This selectively removes in a programmed manner the specific microorganisms.

Nanotechnology to combat resistant and MDR bacteria

Nanotechnology for the synthesis of newer and older antibiotics is new technological development, for both drug delivery and tackling antibiotic resistance. Nanometric size synthesis of antibiotics improves absorption, penetration, bioavailability, thus causing enhanced mucoadhesion and intracellular drug delivery with concentration[3]. A controlled release mechanism by encapsulated delivery system enhances the activity of adsorbed drugs. Metal specific nanoparticles, e.g., silver, has been used along with antibiotics for inhibition, alteration of cell wall synthesis and its lysis. Nano particle technology has a great potential as infectious pathogens can be targeted at inaccessible locations.

Polymeric nanoparticles and nanocrystals

Polymeric nanocapsules for antibiotics and drug nano crystals which are specific and stable components of delivery have been developed. Polylactide-co-glycolide (PLGA) along with encapsulated gentamicin sulfate/ zirconium is being used for drug delivery system. It is a revolutionary drug delivery system of the future.

Lipid nanoparticles (liposomes) containing rifabutin (RFB) for pulmonary tuberculosis and nanoceramics in orthopedic surgeries for local antibiotic administration have been developed and are being used[4]. Studies have documented formation on nanoparticle-pathogen complex in the microenvironment of release.

Metallic nanoparticles

Metallic nanoparticles or nanoparticulate metals, metal oxides, metal halides, and bimetallic materials have revealed antimicrobial activity especially when Ag, Au, Zn, Cu, Ti, and Mg have been used[5].

Nanocages

Hollow nanocages synthesized from metals proteins, polymers are being utililsed for antibiotic delivery especially in cases of MDR. Nanocages technology has led to improved adhesion, retention, and activity of antibiotics at the site of action. Gold nanocages, apoferritin-based nanocages, silica and silver naocages are being used for various therapies[6].

Bacteriophages

Bacteriophages-viruses targeting the bacterial cells – the natural predators of bacteria, have been the earliest discovery of science. With more than a thousand types known for nearly a century, their use in fighting antibacterial resistance has been advocated and researched over the last two decades. Their unique ability of specific receptor adhesion to bacteria and ability to kill them is the mainstay in combating and killing drug-resistant bacteria. Few clinical trials have been performed and accepted by FDA and EMA (European Medicines Agency).

Identification of specific bacteria involved in infection and its subsequent enveloping with the lytic bacteriophage is the pre-requisite for this therapy. Accumulation at high concentrations at host site is due to the bacteriophages site-specific exponential growth and this leads to bacterial death by cell wall lysis. Bacteriophage tailoring with new technology has improved upon:-

1. Penetrating capability into bacterial biofilms;
2. Polymicrobial phage typing;
3. Improving phage efficacy by making it more specific, stable, and highly lytic.

Microbiome manipulation

Ever-evolving mechanisms are being developed to control infections, and one such model is the microbiome. Currently, faecal transplants for *C. difficile* are the only approach to microbiome manipulation proven to work. Future microbiome manipulations could lead to decolonisation of MDR in gut.

Is it always the way forwards: Learning from the past, for strategies of the future

Preventing spread of resistance

1. Prevention, preparing, and planning to curtail infections in the hospital environment.

a) Patient screening on arrival from other healthcare facilities and identifying patients at risk.

b) Cleaning and disinfection of high-risk areas of the healthcare facility.

c) Microbiology laboratories to culture for infection spread and timely notification.

d) The five moments protocol of hand hygiene and strong implementation of it.

e) Patients and visitors education about hand hygiene.

2. Antimicrobial stewardship programme for appropriate use and prescription of antibiotics within healthcare facility.

   a) Monitor the use of antibiotics

   b) Audit system in place to identify and control inappropriate antibiotic use.

   c) Recent therapeutic guidelines should be followed.

   d) Monitoring antimicrobial resistance.

3. Screening and surveillance

   Strict screening and surveillance of patients who have had prolonged hospitalisation, undergone surgery in a facility outside the premises of present healthcare or overseas, multiple or recent exposures to antibiotics (e.g., cephalosporins, fluoroquinolones and carbapenems), post-ventilation or ET support, indwelling medical devices, post-organ or stem cell transplant patients.

4. Outbreak management

   Regular surveillance of data and notification or alert in healthcare facility of sudden increase of a particular infection should guide further management of the outbreak. All hospitals should have an outbreak management team with partners from all the facilities in the hospital.

5. Rotation of antibiotics

   Studies have shown that rotation of antibiotics decreased microbiologically documented infections significantly and a trend towards lower incidence of potentially antibiotic-resistant infections. The susceptibilities of potentially antibiotic-resistant bacteria to antibiotic regimens significantly increases. Increased antibiotic duration increases the incidence of colonization with MDR, especially nosocomial strains, and this was documented with facilities having higher rates of antibiotics prescription. The necessary time span to alter this bacterial ecology after antibiotic withdrawal or rotation is not known. Gram-positive infections are more difficult to treat with cyclic use as the number of effective antibiotics is limited.

Alternate source for new antibiotics

Penicillium notatum came from a mould in 1920, and since then soil-dwelling microorganisms are the source of antibiotics.

Genomic sequencing of bacteria and identification of their survival genes helps in the searchof an inhibitory chemical which subsequently is used to develop antibiotics. Isolating DNA directly from the soil and growing bacteria from lichens, seaweed, seawater, sea mud, fungi, helps in furthering the search of antibiotics with extended spectrum. Screening for antibiotic production in lab by this DNA sequencing strategy is called metagenomics.

Antimicrobial peptide called plectasin has been isolated from a fungus that acts against MRSA (presently under clinical trials), and this has been developed by genomic sequencing.

Preserving antibiotics for the future

British Columbia initiative "Do all bugs needs drug" targeted healthcare providers, children, teachers and seniors, and brought awareness about antibiotic misuse which led to 13% decrease in antibiotic prescription between 2005 - 2018. Cohesive interaction between medical associations, government and social groups can bring down antibiotic use and abuse by spreading awareness.

What we need to do as community contributors

- Promote appropriate antibiotic use.
- Share knowledge, skills, and training.
- Continue investing in research and surveillance.

Conclusion

Newer and innovative methods need to be developed for recognition and initiation of treatment for these infections. Antibiotic resistance has brought new challenges, but along with it came the opportunities to recognise and develop better ways to overcome them.

Inappropriate use of antibiotics needs to be curtailed. Defensive prescription and using broad spectrum antibiotics should be discouraged. Over-the-counter dispensing, self medication, and unwarranted indication have contributed in many ways to this resistance pattern. Overuse of antibiotics both in outpatient, and inpatients needs to be controlled

and guided by strict policies of hospital dispensing. Rampant misuse in developing countries and their use in veterinary practice have contributed to the continuing emergence of resistance and its spread. Rapid tests to diagnose infections will break the barriers to treat infections effectively and will alongside reduce unnecessary usage. Both of these will go a long way in implementing the guidelines.

These new, innovative technologies need to be mastered over a period of time before being put to therapeutic use. Till then we need to control and judiciously use the currently available antibiotics.

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How ART Guidelines are Changing over the Years

BB Rewari, Vipin Mediratta***

Introduction

Antiretroviral therapy (ART) is seen as a panacea for People Living with HIV (PLHIV) and has helped save millions of lives in addition to improving quality of life. In addition, this has saved many countries from catastrophic economic consequences of the disease.

Zidovudine, being used for some malignancies, was the first drug shown to be effective against HIV in 1985. Soon it was felt that the virus developed resistance quickly and drug becomes ineffective in less than a year with Zidovudine monotherapy. By 1995 many studies had demonstrated the clinical benefits of using a two-drug combination of Zidovudine or Stavudine in combination with Lamivudine. The year 1996 was a landmark in ART journey when results of using a triple drug combination using Protease Inhibitors were revealed at the International AIDS Society (IAS) conference in Vancouver. These drugs over the years have transformed lives of millions of people and have changed the outlook of HIV from that of a virtual death sentence to a chronic manageable condition. The Fig. 1 shows the development of various anti-retroviral (ARV) drugs over last three decades.

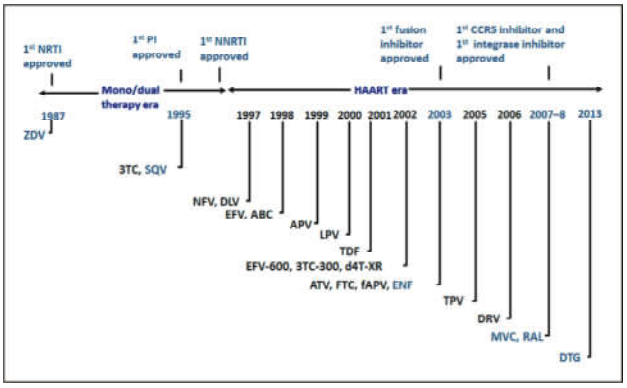

Fig. 1: *Evoluation of ARV therapy.*

Besides treating those with HIV, ARV drugs are also used for preventing mother-to-child transmission of HIV (PMTCT), for preventing acquiring HIV infection in case of accidental exposure to the virus (Post-Exposure Prophylaxis, PEP) and for preventing HIV infection in HIV negative individuals with substantial risk of being infected (Pre-Exposure Prophylaxis, PrEP).

Options available for ART

Highly Active Antiretroviral Therapy (HAART) or simply ART is a combination of three ARV drugs from different groups in a fixed-dose combination (FDC). The "one pill a day" therapy has potential for good adherence as ART is a lifelong therapy. Production of generic formulations of these drugs have helped reduced the costs from USD 10,000 to less than USD 80, thus making it affordable for most people. In addition, roll out of free ART programme in countries have helped increase coverage of ART resulting in individual patient benefits, as well as, prevention of transmission of HIV due to reduction in viral load. Presently available ARV drugs cannot cure HIV as the virus remains dormant in resting states in some cells like spleen, brain, bone marrow, etc. It starts replicating again if the ART is stopped. Hence, ART is a lifelong therapy.

The ARV drugs broadly act at various steps in the life cycle of the virus either by blocking enzymes (reverse transcriptase, protease, integrase) needed for replication or by blocking entry of HIV into CD4 cells (Fusion inhibitors) or by blocking maturation of virions and their budding out from CD4 cells. Based on the site of action, these drugs are broadly divided into six classes (Table I).

Table 1: Classes of ARV Drugs currently in use

Category	Drugs	
Nucleoside Reverse Transcriptase Inhibitors (NsRTI)	Zidovudine (AZT/ZDV)	Lamivudine (3TC)
	Abacavir (ABC)	Emtricitabine (FTC)
Nucleotide Reverse Transcriptase Inhibitors (NtRTI) Tenofovir (TDF)	Tenofovir (TDF)	
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI)	Nevirapine (NVP)	Efavirenz (EFV)
	Etravirine	
Protease Inhibitors (PI)	Ritonavir (RTV)	Lopinavir (LPV)
		Atazanavir (ATV)
	Tipranavir (TPV)	Darunavir (DRV)
Integrase Inhibitors	Raltegravir (RGV)	Dolutegravir (DTG)
CCR5 Entry Inhibitor	Maraviroc	

The combinations of antiretroviral drugs inhibit the replication of HIV leading to slowing of disease progression

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while reduced CD4 cell destruction leads to better immunity and fewer opportunistic infections. Over the years, the drugs have been evolving towards better efficacy, fewer toxicities, better pharmacokinetics, fewer drug-drug interactions and lesser chances of resistance. This has led to optimisation of ART and the WHO has released updated ART guidelines in July 2019.

When to start ART is no longer a question or discussion point

In the early days when HAART was just being introduced, it was considered that a 'hit hard, hit early' would be adopted. However, evidence that emerged in those years questioned the advantages of early HAART. Till about three years ago, treatment for HIV-infected person was based largely on the CD4 count levels and clinical stage of the infection. The CD4 count cut-off point for ART initiation was less than 200 cells/cmm in 2004 and later moved to less than 350 cells/cmm in 2010. The cut-off was advanced to less than 500 cells/cmm in 2013 while in 2016, the recommendation came to TREAT ALL, regardless of clinical stage or CD4 count. The Fig. 2 summarises the changes in CD4 cut-off for ART initiation over the years.

Fig. 2: *Evolution of CD4 cut-offs for ART initiation over time.*

The basis for these changes has been evolving evidence from various randomised clinical trials (RCT) and large observational cohorts which have revealed that with earlier ART initiation, there was a significant delay in progression to AIDS and reduction in incidence of TB. These studies are briefly summarized in Fig. 3.

Hence, the current recommendation (since 2016) is to initiate ART for all those who present with HIV infection regardless of CD 4 count or WHO clinical staging.

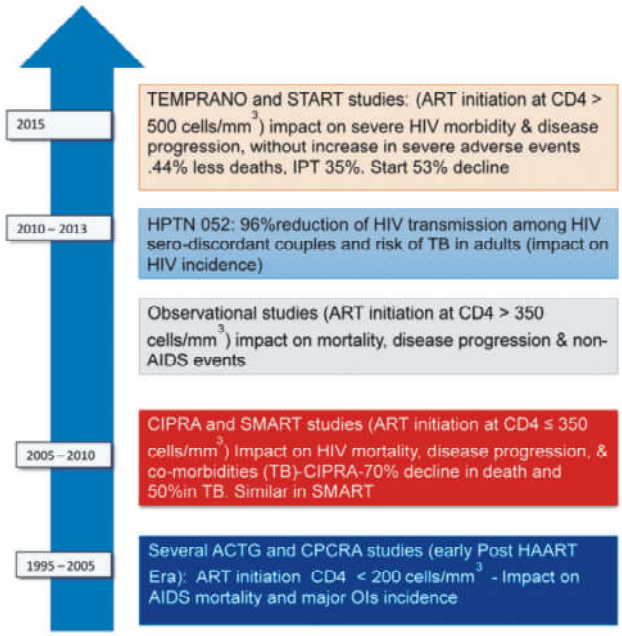


Fig. 3: *Overview and timelines of 'when to start ART' studies.*

WHO recommendation on which drugs to start in ART

As described earlier, ART comprises of using at least three drugs from two different groups of ARV drugs in a combination, preferably in single pill, to improve adherence to therapy. The most commonly used combination is using two drugs from NRTI and one from NNRTI. So far, most developing countries are currently following a combination of TENOFOVIR (TDF 300 mg) + LAMIVUDINE (3TC 300 mg) + EFAVIRENZ (EFV 600 mg) in a single pill, as standard of care. This regimen is widely available as a single, once-daily Fixed Dose Combination (FDC) tablet making it easy to prescribe and easy for patients to take, thereby facilitating treatment adherence. This regimen has the advantage of harmonisation of treatment for all adults, adolescents, and those with HIV-TB and HIV Hepatitis B co-infections, and is also safe in pregnancy.

What has changed in 2018/2019

In 2018 ART update, WHO recommended use of Dolutegravir (DTG) in the first-line ART based on evidence that with DTG: 1. viral suppression is faster than with EFV (Avg. 4 weeks for DTG vs 12 weeks for EFV), 2. DTG has fewer side-effects, 3. Fewer drug -drug interaction and 4. Patients on DTG have a higher threshold for developing resistance.

The SINGLE study compared the efficacy and safety of DTG as compared to current standard of care (Tenofovir plus

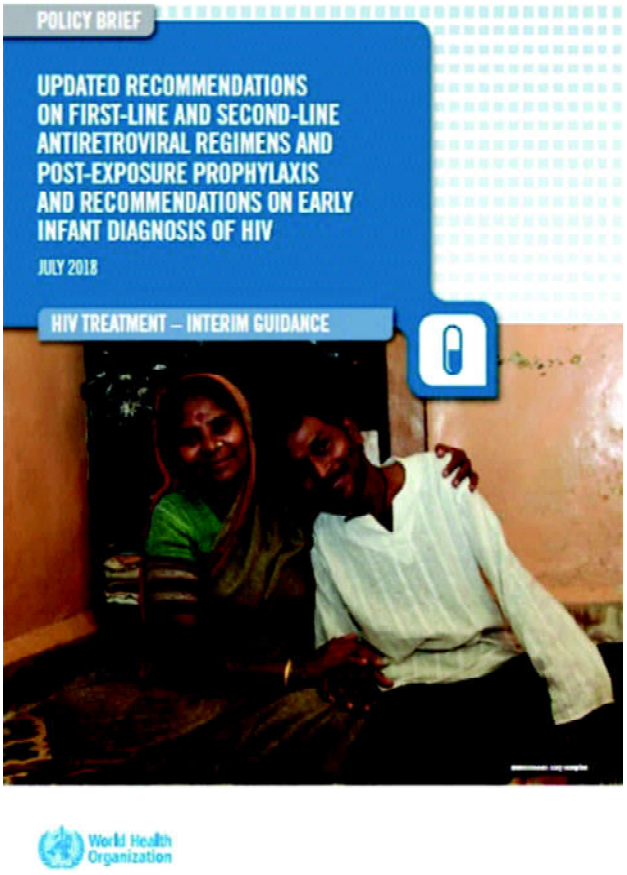
lamivudine plus efavirenz). A total of 833 participants who had an HIV-1 RNA level of > 1,000 copies/ml were chosen and randomly assigned to DTG-ABC-3TC group or EFV-TDF-FTC group. Primary end-point was the proportion of participants with an HIV-1 RNA level of < 50 copies per ml at week 48 and secondary end-points included the time to viral suppression, change from baseline in CD4+ T-cell count, safety, and viral resistance.

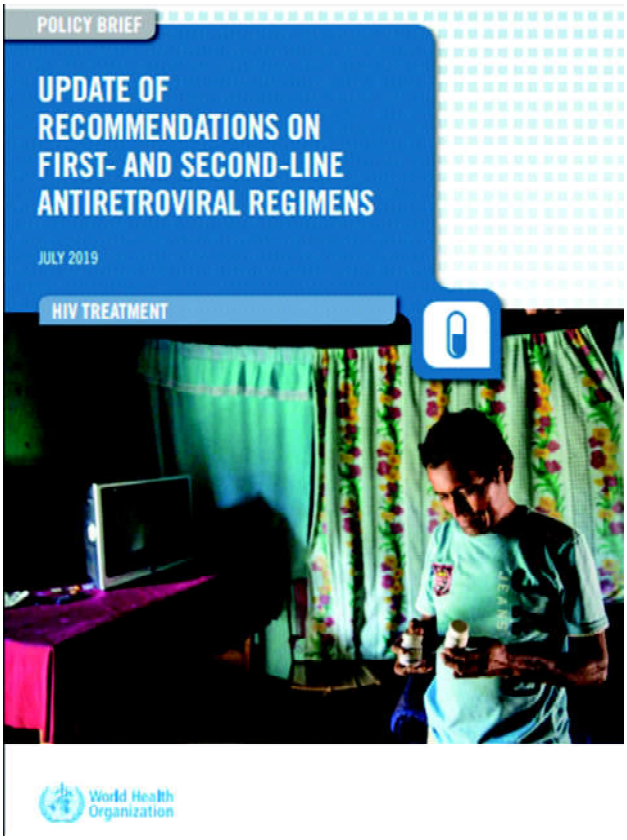
The key findings from study revealed that at week 48, the proportion of participants with an HIV-1 RNA level < 50 copies per ml was significantly higher in the DTG-ABC-3TC group than in the EFV-TDF-FTC group (88% vs 81%, P = 0.003). It was also seen that DTG-ABC-3TC group had a shorter median time to viral suppression than EFV-TDF-FTC group (28 vs 84 days, P < 0.001), as well as greater increases in CD4+ T-cell count (267 vs 208 per cubic ml, P < 0.001). The proportion of participants who discontinued therapy owing to adverse events was lower in the DTG-ABC-3TC group than in the EFV-TDF-FTC group (2% vs 10%).

The results from some other studies like FLAMINGO, SPRING2 and SAILING showed that:-

- DTG achieves viral suppression much faster than EFV (Avg. 4 weeks for DTG vs 12 weeks for EFV).
- There are very few discontinuations on DTG regimen due to drug toxicity (< 2%), less than with DRV/r and EFV.
- Main clinical adverse events seen are rash (2% vs 13%) and neuropsychiatric events (including dizziness). These were significantly more with common with EFV (5% vs 35%), while insomnia was reported more frequent in DTG (13% vs 7%) (SINGLE study).
- DTG has a strong resistance barrier. No known treatment-emergent resistance were seen across trials. This was a very significant finding as it is well known that EFV has a very week genetic barrier to resistance.

Accordingly, the WHO guidelines on what to start were updated in 2018 to include DTG as preferred first-line drug along with Tenofovir and lamivudine. However, an ongoing observational Tsepamo study in Botswana identified a signal of potential safety risk for developing neural tube defects among infants born to women who were taking DTG at conception. Interim analysis identified 4 neural tube defects out of 426 women taking DTG at the time of conception, for a rate of 0.9% (0.37% - 2.4%). So 2018 guidelines specified that women and adolescents of child bearing potential who want to become pregnant and have no effective contraception should not use DTG. An EFV-based regimen is a safe and effective first-line regimen and can





be used among women of childbearing potential during the period of potential risk for developing neural tube defects (NTDs). However, DTG has been found to be effective for pregnant women and is found in breast milk, resulting in significant plasma concentration in infants and thus a potential important tool to reduce the mother-to-child transmission of HIV infection.

As new evidences from Tsepamo study became available it showed that the risk NTDs associated with use of DTG at the time of conception is less than originally signaled. The updated prevalence in the study has declined from 0.94% to 0.30%. The difference remains statistically significant compared to EFV, but the overall risk remains low. The risk – benefit models suggest that the benefits of DTG for women of childbearing potential (WCP) newly initiating ART, are likely to outweigh the risks. DTG is also predicted to be more cost-effective, resulting in more disability-adjusted life-years averted at a lower cost than EFV.

The ART guidelines released by WHO in July 2019 recommend that FDC of Tenofovir, lamivudine and Dolutegravir (TLD) as the preferred first-line regimen for all adults including women and upgraded the recommendation from 'conditional' to 'strong'.

It also recommended to adopt a woman-centered approach to health care should be taken that consciously adopts the perspectives of women and their families and communities, with care provided in ways that respect women's autonomy in decision-making and provide information and options to enable women to make informed choices". The Table II and III below summarise the WHO 2019 ART guidelines.

Table II: WHO ART initiation guidelines (July 2019).

2019 WHO guidelines: Preferred and alternative1L regimens for adults and adolescents		
Perferred 1L regimen	**Alternative 1L regimen**	**Special 1L regimen**
TDF + 3TC (or FTC) + DTG[a]	TDF + 3TC + EFV 400 mg[b]	TDF + 3TC (or FTC) + EFV 600 mg[b]
		AZT + 3TC + EFV 600 mg[b]
		TDF + 3TC (or FTC) + PI/r
		TDF + 3TC (or FTC) + RAL
		TAF[c] + 3TC (or FTC) + DTG[a]
		ABC + 3TC + DTG[a]

Table III: WHO ART guidelines for those with failure to first-line ART (July 2019).

Population	First-line regimens	Preferred second-line reginens	Alternate second-line regimens
Adults (≥ 30 kg)	2 NRTIs* + DTG	2 NRTIs* + AVT/r + LPV/r	● 1 - 2 NRTIs* + DRV/r
	2 NRTIs* + EFV	2 NRTIs* + DTG	● 1 - 2 NRTIs* + DTG

Conclusion

ART has been evolving rapidly towards earlier initiation with more robust and less toxic regimen. The Fig. 4 below summariSes this evolution.

It will continue to evolve. Recently US FDA has approved a two-drug therapy using only dolutegravir and lamivudine and many new drugs are under trial including once a month injectable options. Simultaneously, research is ongoing for finding a cure for HIV. Vaccine trials have been partially successful but the best vaccine available is prevention and for those infected, early diagnosis and linkage to treatment remains crucial.

Topic	2002	2003	2006	2010	2013	2016	2018 - 2019
Earlier initiation When to start	CD4 ≤ 200	CD4 ≤ 200	CD4 ≤ 200 - Consider 350 - CD4 ≤ 350 for TB	CD4 ≤ 350 - Regardless CD4 for TB and HBV	CD4 ≤ 500 - Regardless CD4 for TB, HBV PW and SDC- CD4 ≤ 350 as priority	Towards treatment initiation at any CD4 cell count or clinical stage	Towards treatment initiation at any CD4 cell count or clinical stage
Simpler treatment 1st-Line ART	8 options - AZT preferred	4 options - AZT preferred	8 options - AZT or TDF preferred - d4T dose reduction	6 options and FDCs - AZT or TDF preferre - d4T phase out	1 preferred option and FDCs ● TDF and EFV preferred across all pops	Continue with FDC and phased introduction of new options (DTG, EFV_{400})	Two NRTI+ DTG as preferred first-line ART for all adults and women (with informed choice to women of child bearing age
Less toxic, more robust regimens 2nd-Line ART	Boosted and non-boosted PIs	Boosted PIs - IDV/r LPV/r, SQV/r	Boosted PI - ATV/r, DRV/r, FPV/r LPV/r, SQV/r	Boosted PI - Heat stable FDC: ATV/r, LPV/r	Boosted PIs ● Heat stable FDC: ATV/r, LPV/r	Add more heat stable PI options (DRV/r) and new strategies (NRTI sparing regimens)	Add more heat stable PI options (DRV/r) and new strategies (NRTI sparing regimens)
3rd-Line ART	None	None	None	DRV/r, RAL, ETV	DRV/r, RAL, ETV	Encourage HIV DR to guide	Encourage HIV DR to guide
Viral Load better and simpler monitoring	No	No (Desirable)	Yes (Tertiary centers)	Yes (Phase in approach)	Yes (preferred for monitoring, use of PoC, DBS)	Support for scale up of VL using all technologies	VL at 6 months, 12 months and then every 12 months

In India, ART is available free of cost through 530 government-run ART centres across the country, wherein 1.2 million PLHIV are currently receiving free ART. Yet, there are some who would prefer to access ART from the private sector. Private sector physicians must offer ART according to the treatment and related guidelines adopted in the country, to those who can afford it and also committed to treatment adherence and periodic follow-up. Being a lifelong therapy, adherence and affordability are the two key issues. Hence, it is important for clinicians in the private sector to carefully consider these factors before ART initiation. In situations where affordability and adherence are in doubt, clinicians may refer the PLHIV to government ART centre.

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CASE REPORT

JIACM 2020; 21(1-2): 71-73

Disseminated Kaposi's Sarcoma in HIV Infection with Fatal Consequences

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Abstract

We report a case of disseminated Kaposi's sarcoma (KS) in a HIV-infected patient of Nigerian origin. He presented with multiple painful voilaceous plaques and nodules over the right lower limb, trunk and back and, recurrent episodes of haemoptysis. He was managed with chemotherapy with paclitaxel. Due to the rarity of KS in India, especially disseminated disease, we wish to highlight the rapidly progressive course of disseminated KS.

Key words: Kaposi's sarcoma, KS, disseminated, haemoptysis, HIV.

Introduction:

Kaposi sarcoma (KS) is an angio-proliferative, vascular tumour that can involve multiple organs/sites: skin, mucous membranes, lymph nodes, gastrointestinal tract, respiratory system, heart, the testes, bone marrow, bone and skeletal muscle[1]. KS is linked with infection with Human Herpes virus (HHV-8), also known as KSHV[2]. KS has traditionally and historically been associated with AIDS and is an AIDS-defining malignancy. AIDS-related KS has a variable clinical course, ranging from mild disease detected as an incidental finding to a rapidly progressing cancer with significant morbidity and mortality. There are very few reports of KS from India probably due to the low prevalence of the HHV-8 infection – a reported prevalence of 4.7% from South India[3]. We report disseminated KS in a HIV-infected male patient who had a severe clinical course and outcome despite aggressive treatment.

Case history

A 38-year-old HIV-1-infected, homosexual male, of Nigerian descent, presented with multiple, painful, violaceous plaques and nodules over the right leg since 10 months. The plaques gradually appeared in the other limb, trunk and back, and later became lichenified and crusted. The patient complained of cough with expectoration and progressively increasing dyspnoea since 2 months. Over the past 1 month he also reported recurrent episodes of haemoptysis of significant quantity.

There was associated malaise, generalised weakness and significant weight loss. He was diagnosed with HIV infection in 2015 and was initiated on first-line ART (tenofovir/lamivudine/efavirenz) through the National Programme in India as he was incarcerated. On clinical examination, the patient was cachexic, had significant pallor, and the respiratory rate was 22 breaths/minute. There was no lymphadenopathy and oral cavity examination was normal. On cutaneous examination, there were multiple, confluent, painful, crusted nodules present over the right leg extending up to the thigh and fresh erupting well-defined, non-scaly, dusky, violaceous, tender papules and nodules of 1.5 x 2 cm size all over the back Fig. 1. Respiratory examination revealed right infra-scapular coarse crackles with reduced breath sounds at the base. Rest of the physical examination was unremarkable. His blood oxygen saturation by pulse oximetry was 82%.

Upon investigations, there was pancytopenia (haemoglobin

Fig. 1: *Clinical photograph depicting confluent crusted nodules over leg.*

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- 6.2 g/dl, TLC - 1,900 cells/mm^3, platelet count - 95,000/mm^3). His baseline CD4 count (at the time of HIV diagnosis) was 578 cells/mm^3 and the current CD4 count was undetectable. The HIV viral load was 1,22,000 copies/ml. The VDRL, HBsAg, anti-HCV IgG were all non reactive.

In view of haemoptysis, a contrast enhanced CT of the chest was done. It revealed a heterogenously enhancing soft-tissue mass lesion with spiculated margins in the left upper lobe with areas of consolidation in the right middle lobe, nodular opacities in bilateral lung parenchyma in peri-bronchovascular distribution with mediastinal lymphadenopathy and bilateral pleural effusion (right > left) Fig. 2.

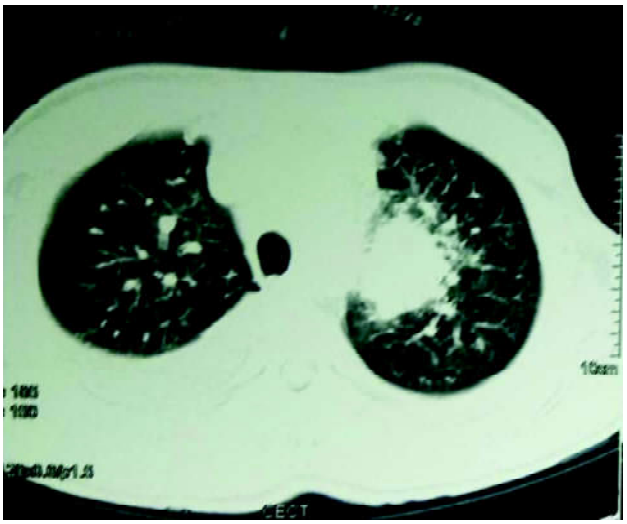

Fig. 2: *CECT chest showing heterogeneously enhancing soft-tissue mass lesion with speculated margins in the upper lobe of left lung.*

A punch biopsy done from the skin lesions on the back and leg showed spindle-cell proliferation with slit-like congested capillaries dissecting between collagen bundles throughout the dermis, present individually as well as in groups with extravasation of erythrocytes – suggestive of KS (Fig. 3). Pleural fluid was grossly haemorrhagic and analysis showed total count – 440 cells, differential cell count – 18% polymorphs, 45% lymphocytes, and 37% malignant cells. The pleural fluid glucose was109 mg/dl and protein 3.2 gm/dl.

Due to persistent hypoxia and poor general condition, the bronchoscopy was not performed.

A final diagnosis of disseminated Kaposi sarcoma was made – involving skin, lungs and pleura-stage (T1I1S1 ACTG staging- overall poor risk).

Patient was switched to second-line ART regimen (raltegravir and lopinavir/ritonavir) for ART failure. As patient had disseminated severe KS, systemic chemotherapy was started with paclitaxel 100 mg/m^2. The patient showed marginal improvement symptomatically with 2nd-line ART and 2 cycles of chemotherapy. However, on day 23 of his admission, he developed massive haemoptysis and succumbed to his illness.

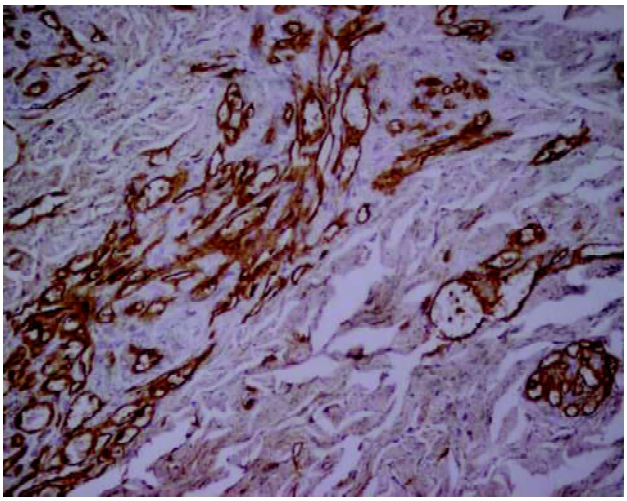

Fig. 3: *Histopathology: IHC (Immunohistochemistry) (200 x) showing CD 34 positive endothelial cells in KS.*

Discussion

Although KS can involve virtually any site in the body, cutaneous disease is most common and is the usual initial presentation. The most frequent sites of non-cutaneous disease are the oral cavity, gastrointestinal tract, and respiratory system. However, visceral involvement as the initial manifestation of KS is relatively uncommon[4]. Pulmonary involvement is the most life-threatening form of KS. In 80 - 90% of cases, pulmonary involvement with KS occurs in conjunction with more extensive mucocutaneous disease[5]. Unusually, pulmonary involvement can be the initial manifestation of KS and occurs in the absence of mucocutaneous disease in 15 per cent of patients[6]. Parenchymal lung involvement is usually manifest clinically by dyspnoea, hypoxaemia, and dry cough developing over a few weeks . Haemoptysis, fever, fatigue, and occasionally respiratory failure can also occur.

The most commonly utilised staging system for AIDS-related KS is ACTG system which considers 3 factors: extent of the tumour (T), status of the immune system (I), as measured by the number of CD4 cells and extent of systemic illness (S) within the body .This system divides patients into good or poor risk prognostic categories, taking into account both the KS and HIV infection. Patients with poor risk KS having extensive cutaneous lesions, oral or visceral disease, CD4 count < 100 cells/mm^3, systemic diseases and opportunistic infections have worst prognosis. This patient had poor risk KS disease. Management of KS includes early initiation of

ART, surgery, radiotherapy, cryotherapy, intralesional chemotherapy for skin lesions. Systemic chemotherapy is indicated for disseminated KS. Pegylated liposomal doxorubicin is recommended as the first-line regimen in the absence of a cardiac contraindication. Other available options include a single-agent taxane, oral aetoposide, vinblastine, vinorelbine, or gemcitabine. No one regimen can be recommended over any other. The decision must be individualised, taking into consideration the patient's age, accompanying co-morbidity, and clinician and patient preference. Our patient had poor ejection fraction on 2-D echocardiography and was hence given paclitaxel.

Even in the age of advanced, universal, and early HIV treatment, disseminated KS continues to be a life-threatening disease with high mortality rate though the prevalence and aggressiveness of KS has decreased with early administration of ART. In HIV-infected patients with atypical pneumonia, KS should be high on the list of differentials so that prompt diagnosis can be made for timely initiation of chemotherapy.

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CASE REPORT

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A Rare Case of Weil's Disease with Empyema Thorax

*Sonu Suman**

Abstract

Leptospirosis is a zoonotic disease caused by Leptospira interrogans, common in tropical countries during monsoon. Here we report a case of a rare form of leptospirosis with multiorgan failure called Weil's disease. This patient was having empyema thorax as a pulmonary component of Weil's disease.

Introduction

Leptospirosis is a zoonotic disease caused by pathogenic spirochetes of the genus Leptospira. It was first isolated in Japan by Inada and co-workers in 1915, nearly 30 years after Weil described the clinical disease in 1886.

Human infection by pathogenic *Leptospira* may present variable clinical manifestations ranging from subclinical infection with undifferentiated febrile illness to jaundice, renal failure, and potentially lethal pulmonary disease[1]. Leptospirosis is typically an anicteric illness, but a fulminant disease icterohaemorrhagic form (Weil´s Disease) can be found in 5 - 10% of all patients. Fatalities typically arise from renal, cardiac, or respiratory failure[2]. Most of the cases present with a febrile illness of sudden onset. Fever, chills, headache, severe myalgia, conjunctival suffusion, anorexia, nausea, vomiting, and prostration usually characterise acute leptospirosis.

Pulmonary involvement occurs in 20 to 70% of patients; the severe pulmonary manifestation is rare. This case is highly pertinent to the medical field as leptospirosis is an ever-growing problem and atypical pulmonary-related complication is an emerging manifestation of it. Therefore, early recognition and intervention is required to reduce the morbidity or mortality.

Case report

A 23-year-old male military recruit from a village of Maharashtra (India) presented with complaints of fever for 05 days, which was continuous, high grade, and associated with chills and rigors. He also had headache with repeated episodes of nonprojectile vomiting and diffuse pain in abdomen. There was generalised body ache.

His blood pressure was 100/70 mm of Hg and there was tachycardia (130/min) with tachypnoea (34/min). He was febrile (102.5° F). There was a conjunctival suffusion without purulent discharge (Fig. 1). He was having muscle tenderness most notable in the lumbar area. Hepatosplenomegaly was present and chest examination revealed decreased air entry in the right hemi-thorax .

Initial investigations revealed deranged hepatic functions (bilirubin - 5.4 mg/dl, aspartate aminotransferase (AST) - 40 IU/L, alanine aminotransferase (ALT) - 23 IU/L, and deranged renal function (creatinine - 1.7 mg/dl and S urea - 111 mg-dl). Haemogram revealed Hb 12.8 gm/dl and total leukocyte count - 20,900/dl with 86% polymorphs. USG abdomen showed mild hepatosplenomegaly. Coagulation profile was normal. The urine and blood culture were negative for bacterial growth. Serology for HIV, dengue, salmonella, malaria parasite, chickungunya

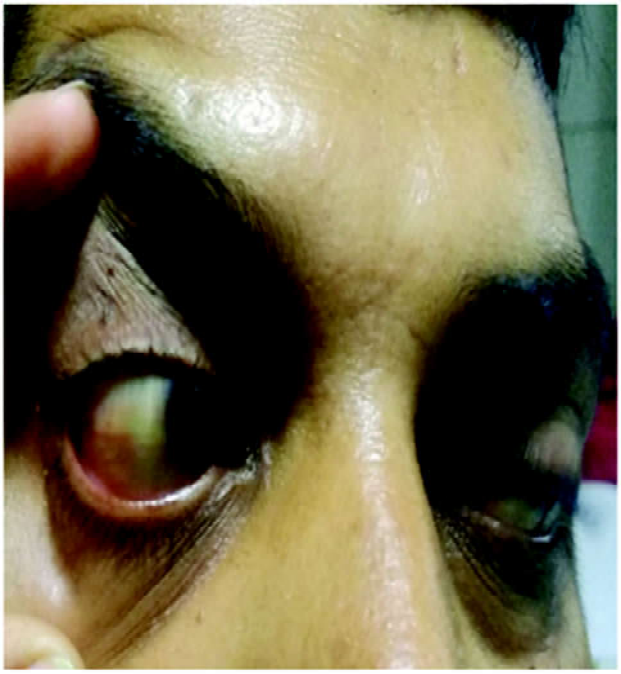

Fig. 1: *Conjunctival suffusion.*

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and hepatotrophic viruses was negative. The chest X-ray revealed a homogenous opacity in the right lower zone with concave inward margin (Fig. 2). Thick pus was aspirated on thoracocentesis. No acid-fast bacilli were detected in the sputum samples.

Leptospirosis was clinically suspected, which was further confirmed by the positive serum IgM-ELISA.

Patient was managed with antibiotic therapy and thoracotomy tube drainage. After two weeks of hospitalisation, the patient was asymptomatic and was discharged with bilirubin 1.3 mg/dl, aspartate aminotransferase (AST) - 36 IU/L, alanine aminotransferase (ALT) - 19 IU/L, and creatinine - 0.8 mg/dl and S urea - 27 mg/dl and total leukocyte count - 8,600/dl with 54% neutrophil.

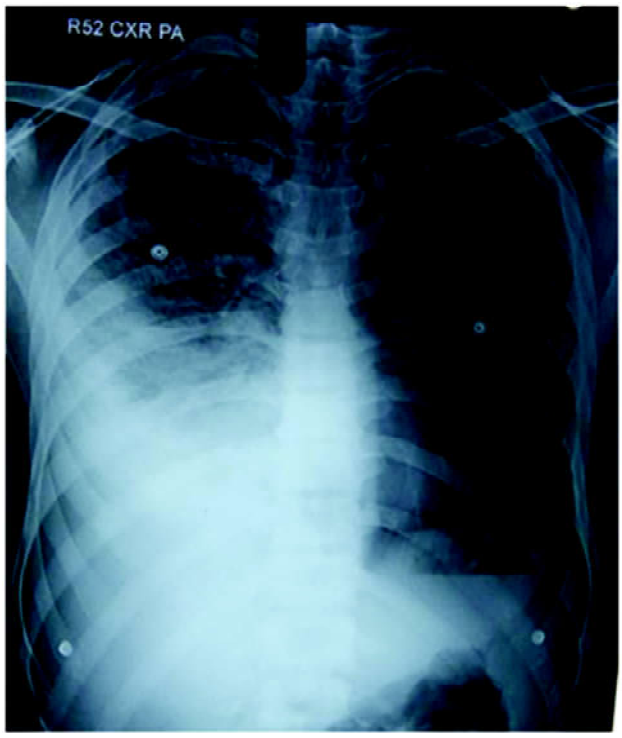

Fig. 2:

Discussion

Leptospirosis is the most widespread zoonosis in the world. Tropical countries and low socio-economic conditions with poor sanitation have particularly been identified as favourable for disease transmission. Human leptospiral infections result primarily from direct or indirect exposure to the urine of infected animals. Rats are the most common reservoir in India.

Leptospirosis is caused by the bacteria that belongs to the genus *Leptospira interrogans* which is pathogenic for humans. The genus can be separated into more than 200 serovars belonging to 23 serogroups. The median global incidence of endemic human leptospirosis, excluding cases due to outbreaks, is five cases/1,00,000 population, but in some areas the incidence is as high as 975 cases/1,00,000. The mean annual global incidence of epidemic leptospirosis, as reported in outbreak reports, is 14 cases/ 1,00,000 population. The main occupational groups at risk are farm workers, field agricultural workers, plumbers, sewer workers, sanitation workers, and military troops.

A retrospective study reported that in patients with leptospirosis, the common clinical features included fever (100%), headache (75%), myalgia (55%), arthralgia (45%), and vomiting (39%).

The severe form of leptospirosis is called Weil's disease. it is usually characterised by jaundice and renal dysfunction, can be fatal in up to 5 - 15% of cases.

Hepatic derangement does not seem to be due to hepatocellular damage, but seems to be more related to the cholestasis of sepsis. Renal insufficiency is due to acute tubular necrosis. Marked elevation of bilirubin with mild elevated transaminase are the characteristic feature of Weil's disease[3] associated with early acute onset renal failure in the form of deranged renal function.

The true incidence of pulmonary involvement in leptospirosis is unclear, but may range from 20% to 70%[4-6]. Pulmonary abnormality is due to exposure of circulating toxin produced by the pathogen at distant sites such as liver[1].

The present case was suspected for leptospirosis on clinical presentation, was and confirmed with laboratory findings. Fever with gastro-intestinal symptoms, nonpurulent conjunctival suffusion, and muscle pain with tenderness, are helpful in detecting the disease. Other pointers to leptospirosis in this present patient were deranged hepatic and renal function, along with pulmonary manifestations (Weil's disease). Patient was having marked elevation of bilirubin with mild elevated transaminase and acute onset renal failure. Our patient had classic Weil's disease with characteristic jaundice and kidney dysfunction.

Icteric leptospirosis has been differentiated from other fulminant viral hepatitis such as hepatitis A and E. The important differentiating features are the presence of renal failure very early, neutrophilic leucocytosis and continuation of fever even on appearance of jaundice which usually disappears in viral hepatitis.

The lungs are involved in leptospirosis in 20 to 70% of cases in different series and the frequency of such involvement has been on the rise and is becoming the main cause of death from the disease. Mortality rates for

severe lung involvement may be as high as 50%[7]. Pulmonary lesion is primarily haemorrhagic. Focal or diffuse areas containing alveoli filled with erythrocytes characterise the pulmonary involvement observed in leptospirosis.

To the best of my knowledge, leptospirosis complicated with empyema thorax has not been reported in India till date. Even lung abscess being one of the rarest manifestations of leptospirosis has been reported from other part of world in literature[8].

Conclusion

A common disease like leptospirosis can present with a rare complication as empyema thorax. High index of suspicion is required for early diagnosis and treatment to prove it non-fatal We wish to emphasise that leptospirosis should be considered as a differential diagnosis in tropical countries when a patient presents with multiorgan failure or fever of > 3 days duration.

Referrance

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CASE REPORT

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Imaging of an Intrahepatic Portosystemic Venous Shunt with an Associated Aneurysm: A Rare Entity

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Abstract

Background: Intrahepatic portal venous shunts are rare hepatic vascular communications between branches of portal veins and systemic veins. Early diagnosis is important because the condition can lead to hepatic encephalopathy and hypoglycaemia. Radiologists studying patients with liver disorders should be aware of this vascular anomaly and should also recognise that many occur in asymptomatic patients without liver disease and as such do not require treatment. In patients without any hepatic aetiology or a history of trauma, it is presumed to be spontaneous or congenital in origin.

Objective: The aim of our study is to describe the imaging findings in incidentally discovered asymptomatic intrahepatic portal venous shunts.

Key words: CT, intrahepatic portal venous shunts, liver, shunts, aneurysm.

Introduction

An intrahepatic portosystemic venous shunt is defined as communication between an intrahepatic portal vein and a systemic vein, including the hepatic and peri-hepatic veins, via an anomalous intrahepatic venous channel. Intrahepatic shunts between portal and systemic veins can be acquired (liver parenchymal diseases, post-traumatic, leaking of a portal vein aneurysm) or congenital[1]. Intrahepatic portosystemic shunts was first reported by Doehner *et al*[2] and later illustrated by Raskin *et al* in 1964[3]. The circumstances surrounding the discovery of an intrahepatic portal venous shunt in a patient without cirrhosis are variable. A few patients may present with hepatic encephalopathy due to high-output shunting. In this situation, hepatic dysfunction prompts an imaging examination and, thus, discovery of the shunt. In a series in Japan, of noncirrhotic patients with portal systemic encephalopathy, 36.2% of 47 patients presenting with encephalopathy had intrahepatic portosystemic shunts[4].

Intrahepatic portal venous shunts between a portal vein and a hepatic vein are much less common than those to perihepatic veins or the inferior *vena cava*. A 2003 report of angiographic findings suggests that only fifty patients have been reported in the English-language literature and that most of these cases (76%) were not associated with cirrhosis[5].

With the increased use of imaging studies, these lesions are likely to be increasingly encountered. We report the imaging features of incidentally discovered asymptomatic intrahepatic portal venous shunts in a 50-year-old female patient.

Case report

A 50-year-old female presented to the OPD with a short history of painful micturition with no relevant past history. On physical examination, vitals were normal with SpO_2 of 98% . Patient's blood pressure was 110/86 mmHg. Routine biochemical examination was unremarkable while urine culture showed many pus cells. Urea levels were raised (102 mg/dl). Serum ammonia levels were performed which were normal. There was no history of any kind of liver biopsy or any interventional procedure done.

Ultrasound of the abdomen showed normal size and echo-texture of the liver along with a large anechoic cystic lesion Color Doppler showed pulsatile flow within the veins adjacent to the right hepatic vein. The lesion showed venous flow in the color Doppler (Fig. 2). No e/o splenomegaly or ascites seen. Left kidney was echogenic and bulky.

Triple phase CT was performed. Patient received IV 150 ml of iodinated contrast material (iohexol; 300 mg I/ml). Contrast material was administered at a rate of 2 - 4 ml/s. Left kidney was found to be bulky and measured approx. 11.7 x 6.3 mm and showed reduced parenchymal enhancement (Fig. 1a). There was an incidental finding of focal collection of vessels in the anteroinferior segment of right lobe of liver (segment V) measuring approx. 38 x 34 mm showing enhancement in the venous phase with density equal to that of the blood vessels. The right hepatic

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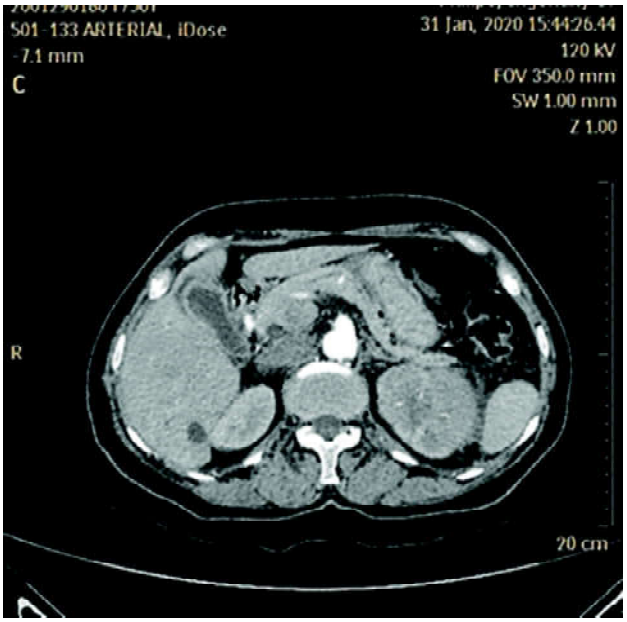

Fig. 1a: *Axial post-contrast CT (arterial phase) image shows a small hepatic cyst in segment VI of liver with a non enhancing area in segment V.*

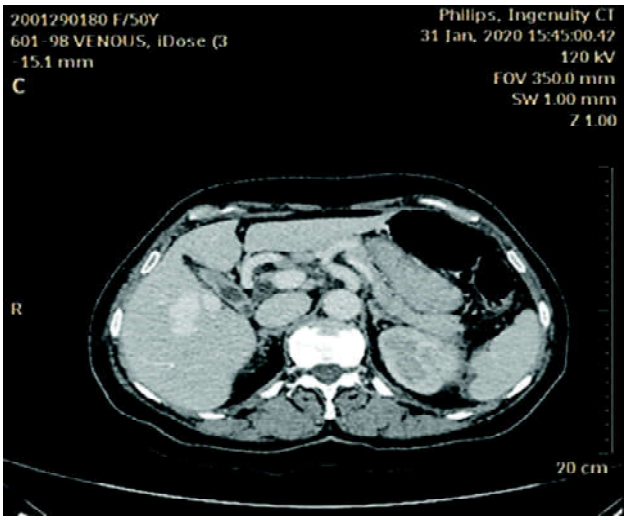

Fig. 1b: *Axial post-contrast CT (venous phase) demonstrating focal conglomerate vessels in segment V s/o intrahepatic portosystemic venous shunt between right portal vein and right hepatic vein.*

vein was dilated and measured approx 13 mm in calibre. Both anterior and posterior branches of the right portal vein were prominent with abnormal communication between the right portal vein branches and the right hepatic vein with resultant aneurysmal dilated vessels in segment V s/o porto-systemic venous shunt. Left branch of the portal vein was not dilated. No enhancement of the lesion was seen in the arterial phase. No other abnormal arteriovenous or venovenous shunt was seen. A small hepatic cyst measuring approx 11 mm was seen in segment VI. IHBR were not dilated. Final diagnosis of intrahepatic portosystemic venous

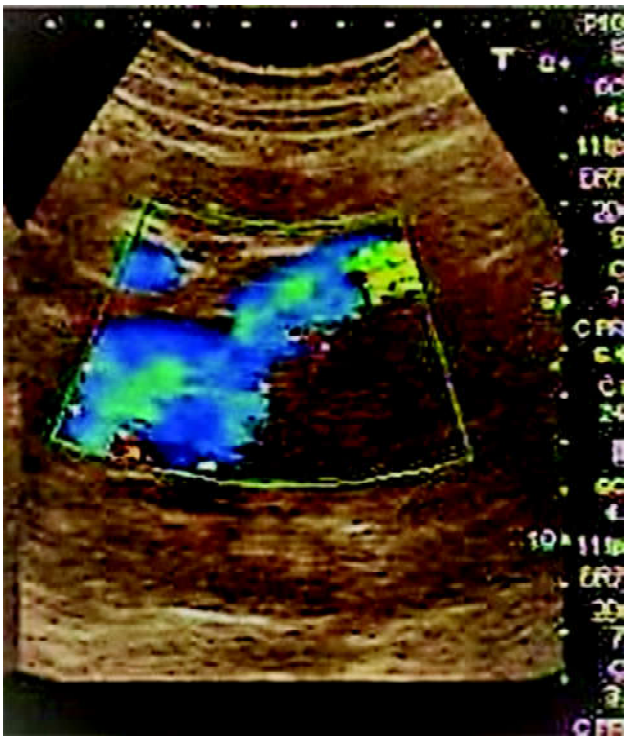

Fig. 2: *USG colour Doppler image showing venous flow in dilated cystic lesion adjacent to right hepatic vein showing venous flow on colour Doppler.*

shunt with aneurysmally dilated vessels (Type III Park's classification) was made.

Discussion

Portal-to-systemic venous communications are mostly seen on imaging studies in patients with portal hypertension from liver cirrhosis. These communications are largely extrahepatic and are commonly via the coronary vein, oesophageal varices, or retroperitoneal collaterals. Intrahepatic or transhepatic portosystemic communication refers to communication between the intrahepatic portal vein and a systemic vein[6]. They are much less frequent than extrahepatic shunts. Intrahepatic portal venous shunts were stratified by the system described by Park *et al*[7]. Type I is a single large tubular vessel of constant diameter that joins the right portal vein to the inferior *vena cava*; type II is a peripheral shunt in which solitary or numerous communications are found between peripheral branches of portal and hepatic veins in one hepatic segment; type III is an aneurysmal connection between the peripheral portal and hepatic veins; and type IV is multiple, diffuse communications between peripheral portal and hepatic veins in both lobes of the liver.

The origin of these shunts is the matter of differing views. When a 'portal vein-hepatic vein' communication is seen in

a patient without liver disease or a history of trauma, it is considered to be spontaneous or congenital in origin[8]. The basis of these shunts lies in the abnormality during the 4th week of intrauterine life in the development of vitelline veins and omphalomesentric system and the sinus venosus due to local absence of formation of sinusoids. Others speculate sudden rupture of a portal vein aneurysm into the hepatic vein is the cause[8]. During development, the right umbilical vein involutes and the left umbilical vein forms a direct communication with the ductus venosus (right hepatocardiac channel), bypassing the sinusoidal plexus of the liver[9]. Blood therefore flows from the placenta through the umbilical vein, ductus venosus, into the right hepatocardiac channel (later part of the inferior vena cava). After birth, the left umbilical vein forms the ligamentum teres and the sinus venosus forms the ligamentum venosum. Both the ligamentum teres and the ligamentum venosum are contiguous to the left hepatic lobe. Possibly these shunts represent persistent developmental communications[10].

Various embolising agents are used to occlude these shunts in symptomatic patients[5]. However in asymptomatic patients, no intervention is required as in our case[11].

Conclusion

The importance of this case was not only knowing the rarity of this pathology, but also highlighting the efficiency of imaging modalities like ultrasound and CT in detecting the condition. Cyst-like lesions in the liver should be evaluated with colour Doppler ultrasonography for flow characteristics and should be differentiated with triple phase CT.

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CASE REPORT

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Combined Diagnosis of Systemic Lupus Erythematosus (SLE) and Tuberculosis (TB) in a Young Woman

Akanksha Singh, Jyotsana Prasad**, Subodh Kumar Mahto*, Nehal Aggarwal***, AK Malhotra*****

Abstract

Systemic lupus erythematosus (SLE) and tuberculosis present with a myriad of clinical manifestations and thus can mimic each other. The non-specific symptoms like unexplained fever, joint pains, lymphadenopathy, fatiguability, and serositis can be present in both diseases – thus can lead to misdiagnosis. We report a case of a 23-year-old woman who presented with fever, joint pains, recurrent oral ulcers and rash over face. The patient was evaluated and was diagnosed to have both SLE (lupus nephritis) and tubercular lymphadenitis.

Key words: Systemic lupus erythematosus, tuberculosis, extrapulmonary tuberculosis (EPTB).

Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease. Tuberculosis (TB) remains one of the commonest infectious diseases globally with an estimated 10.0 million (range, 9.0 - 11.1 million) people diagnosed with TB in 2018[1]. Tuberculosis (TB) is a common infection among patients with SLE. Leading causes for high incidence of TB infection are immunosuppressive therapy and immune disturbances of lupus itself. We report a case of a young woman, who was diagnosed with SLE (lupus nephritis with secondary vasculitis) and TB (tuberculous lymphadenitis) simultaneously, with no prior history of any immunosuppressive therapy.

Case report

A 23-year-old woman presented with low-grade, continuous fever with joints pain and recurrent oral ulcers since 2 months and also rash over face since 1 month. Small and large joints of upper limbs and lower limbs were involved and the distribution of pain was symmetrical bilaterally. There was history of morning stiffness, and pain was inflammatory in nature. There was no history of smoking, alcohol consumption, or prolonged use of steroids or any other drug. The patient's pulse rate and blood pressure was 86/min and 126/82 mm Hg respectively. Pallor was present. Painless oral ulcers were present over the tongue and buccal mucosa. Maculopapular rash was present over the face involving the forehead, base of nose, and malar area (Fig. 1). Papular eruptions were present over the extensor surfaces of forearms (Fig. 2). Blackish discoloration of skin was present over the tip of the left ring finger (Fig. 3). Soft-to-firm, non-tender, non-matted, mobile cervical lymph nodes were present at level Ib, II, III, V on right side. Rest of the general physical and systemic examination was within normal limits.

Laboratory tests revealed haemoglobin of 7.3 gm% and total leukocyte count of 4,300/mm^3 with normal differential count and platelet count. The erythrocyte sedimentation rate was 42 mm/1st hour. Peripheral smear showed normocytic,

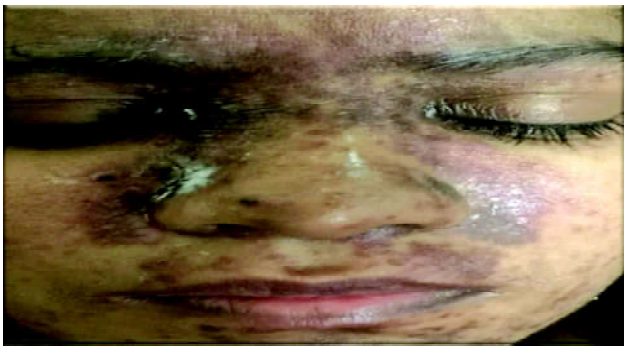

Fig. 1: *Maculo – papular rash present over face involving the forehead, base of nose, and malar area.*

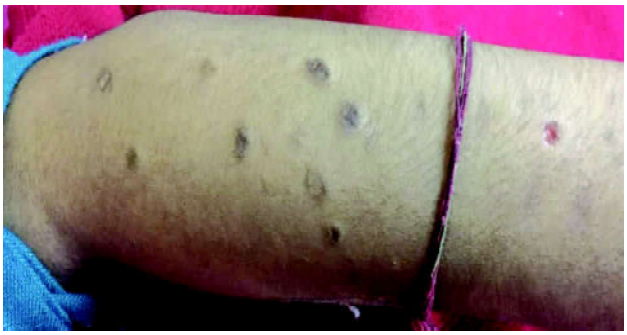

Fig. 2: *Papular eruptions present over the extensor sarface of forearm.*

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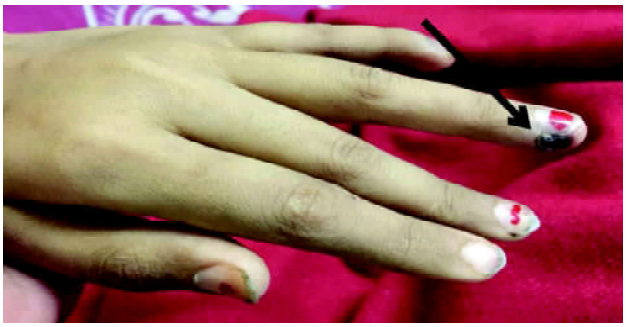

Fig. 3: *Blackish discolouration of skin present over tip of left ring finger.*

normochromic anaemia. Renal function tests were all within normal limits. Albumin/globulin ratio was reversed (2.8/4.5 gm/dl). Urine examination showed 6 - 8 RBCs, proteinuria (3+) with a 24-hr urinary protein of 1.6 gms/day. Urine for dysmorphic RBC was negative. HBsAg, anti-HCV and HIV were all negative. Coomb's test (Direct and indirect) was negative. Both Anti-Neutrophil Antibody level (ANA) and anti-ds DNA were positive. ANA (homogeneous pattern) in a titre of 1:360 by indirect immunofluorescence was positive. Complement levels, i.e., C3 (32 mg/dl) and C4 (5.20 mg/dl) were low. Fine needle aspiration cytology (FNAC) of cervical lymph nodes showed degenerated lymphoid cells, few fibrofatty fragments and necrosis in the background, with positive Ziehl Neelsen stain for acid-fast bacilli (AFB). Lymph node biopsy showed necrotising lymphadenitis (Fig. 4). Renal biopsy was done which showed lupus nephritis with moderate activity (class III A/C) (Fig. 5). Finally, the diagnosis of SLE with class III lupus nephritis with secondary vasculitis with tuberculous cervical lymphadenitis was made. Thus, patient was having TB with concomitant organ-threatening lupus. After consulting the Department of Rheumatology, it was decided to withhold immunosuppressive therapy. The patient was given pulse steroid (inj. methylprednisolone pulse therapy for 3 days) followed by oral steroids. She was started on a full course anti tubercular treatment (ATT), angiotensin converting enzyme (ACE) inhibitors, hydroxychloroquine and statins. The patient became afebrile and rashes over her face and forearm improved. She was thereafter discharged on oral steroids and ATT. It was planned to give her immunosuppressive therapy after completion of the full course of ATT.

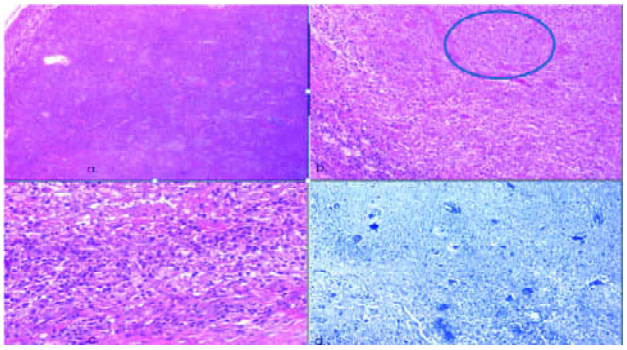

Fig. 4: *Lymph node biopsy showing necrotizing lymphadenitis (caseating necrosis has been encircled).*

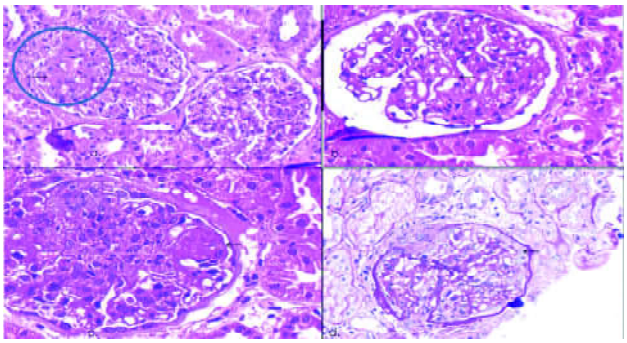

Fig. 5: *Renal biopsy showing Lupus Nephritis with moderate activity (class III A/C) (wire loop sesions are encircled).*

Discussion

SLE is characterised by genetically determined loss of self-tolerance and cellular activation dependent on non-genetic factors, such as environmental, hormonal, and infectious. Activation of T-lymphocytes by γ-interferon stimulates the sequence of progressive and persistent expansion of apoptosis-resistant polyclonal B-lymphocytes, which produce auto-antibodies characteristic of the disease[3]. Uncontrolled hyperactivity of the immune system actually makes SLE patients immunocompromised. Impaired cellular and humoral immune functions in SLE patients have been associated with predisposition to TB. Besides multiple immune abnormalities, immunosuppressive therapy given for treatment of lupus also leads to increased susceptibility to TB[4-6]. High doses of corticosteroids are a major risk factor.

Several global studies have documented a definite increase in the incidence of TB in patients with SLE[7]. A Spanish study reported a six-fold higher incidence of TB in the SLE group as compared to the general population[8]. Similarly, a study from Hong Kong reported a 5- to 15-fold higher risk of TB in the SLE group as compared to the general population[9].

In SLE patients, extra-pulmonary tuberculosis (EPTB) is more common than pulmonary TB[10]. TB in patients with SLE imparts a challenge to the clinical acumen especially in the setting of higher number of cases of EPTB. Presentation of EPTB is a constellation of non-specific symptoms like unexplained fever, joint pains, lymphadenopathy, fatiguability, and serositis, which are also seen in patients with SLE, making them mimickers of each other[11]. Moreover, some of the diagnostic laboratory investigations can be positive in both diseases. For instance, patients with TB are found to have positivity for rheumatoid factor and anti-nuclear antibodies, the latter of which are characteristically seen in lupus. Elevated ADA levels can be seen in conditions like para-infective effusions, empyema, malignancy, and autoimmune diseases

like RA and SLE. Pettersson *et al*[12], found that the mean ADA levels are significantly higher in patients with TB than in patients with SLE. Determination of isoforms of ADA activity is helpful in differentiating these conditions. Predominant ADA2 activity is seen in TB and predominant ADA1 activity is seen in empyema and para-infective effusions[13]. In another study, it was noted that the serum ADA levels are elevated in SLE and the isoform was ADA2, similar to that seen in TB[14]. Therefore, diagnosis of EPTB in lupus patients often requires tissue and body fluid analysis thus prolonging the time in reaching a definitive diagnosis. In our patient, we did a lymph node biopsy and renal biopsy which led to the simultaneous diagnosis of TB lymphadenitis with lupus nephritis.

It is also important to be aware of the impact of tuberculous infection in a SLE patient. There is growing evidence, which supports the crucial role of infections in the induction and exacerbation of SLE. Several mechanisms have been suggested by which microbes may trigger autoimmune reactions. Firstly, microbial antigens may get associated with self-antigens to form immunogenic strains and bypass the T-cell tolerance. Secondly, certain bacterial and viral products are non-specific polyclonal B-cell mitogens and may induce the formation of autoantibodies. Thirdly, infection may induce the suppression of T-cell functions[15]. Available literature links mycobacterial infections with humoral autoimmunity.

The treatment of TB in patients with SLE is same as for other patients with this disease. This regimen usually includes a combination therapy with isoniazid, rifampicin, ethambutol and pyrazinamide for 2 months followed by at least 4 months of isoniazid and rifampicin[16]. Also, before starting immunosuppressants and biologics, tuberculosis needs to be ruled-out. Patients should have risk assessment, physical examination, and chest radiograph. Tuberculin skin test only has sensitivity of 70%. Interferon-gamma Release Assays (IGRA) screening is recommended. IGRA are one of the recent innovations for the identification of latent tuberculous infection. These assays measure the release of interferon-gamma from sensitised T lymphocytes after stimulation with antigens from *Mycobacterium tuberculosis*. The IGRAs are performed in two ways, i.e., Quantiferon gold and T-SPOT TB. Screening tests decrease the reactivation of TB by 80%. Patients with latent MTB should delay biologic initiation until 1 month of latent TB therapy has been administered. They should receive a full course, i.e., 9 months ATT. Patients with active MTB should have a complete course of anti- tuberculosis therapy before starting a biologic (anti-TNF alpha agent)[17].

Lastly, most of the cases reported in literature demonstrated diagnosis of tuberculosis in already diagnosed Lupus patients[4]. These patients were usually on immunosuppressive therapies. Whereas, in our case, the diagnosis of TB and SLE was made simultaneously, with no prior history of any immunosuppressive therapy in the patient.

Conclusion

Our case highlights the fact that TB and SLE can mimic each other. This usually leads to delay in diagnosis and initiation of treatment. Also, extra-pulmonary TB is more common in SLE, thus a high suspicion is needed by the physician to diagnose these diseases.

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CASE REPORT

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Teneligliptin-induced Allergic Rhinopharyngitis

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Introduction

Teneligliptin – a novel DPP IV inhibitor is evolving as a drug of choice for managing both drug naïve and as an add-on therapy for previously diagnosed diabetics on other oral hypoglycaemic agents, this is in part due to low cost of therapy and a favourable adverse effects profile of the drug. Teneligliptin has dual (both renal and hepatic) mode of excretion, long biologic half-life (26.9 hours) and requires no dose modification in hepatic and renally compromised patients. There have been anecdotal incidences of increased allergic events pertaining to the respiratory tract and skin with the usage of various DPP IV inhibitors. This case report highlights one such case that we encountered where teneligliptin exposure in a known diabetic, on glimepiride therapy precipitated allergic symptoms of upper respiratory tract.

Case history

A 45-year-old diabetic female came to the OPD for the management of uncontrolled hyperglycaemia. She was on glimepiride 2 mg and metformin 500 mg daily. Her blood sugar fasting was 136 mg/dl and post-prandial was 210 mg/dl, her HbA1c was 7.8. She was further advised to take teneligliptin 20 mg 1 OD for glycaemic control but the next day she came with complaints of running nose/ breathlessness/nasal stuffiness/cough/severe burning sensation in throat 2 hours after ingestion of teneligliptin tablet. She was advised to stop the drug immediately and for symptomatic treatment she was advised oral antihistaminic, cough suppressant, and saline nasal drops on which her symptoms decreased in the next 24 hours. After 15 days she was again prescribed tablet teneligliptin by some other physician for hyperglycaemia, followed by recurrence of similar symptoms. She visited our OPD and she was asked to stop teneligliptin and was advised the same symptomatic treatment as advised before. Her symptoms again responded well to it. This case brought into our notice this rare side-effect of teneligliptin.

Discussion

Teneligliptin is a third generation DPP-4 inhibitor approved for treatment of type 2 diabetes. It is currently available in Japan, South Korea, Argentina, and India. It is under pre-registration in Indonesia and under phase I trials in the US and phase II trials in Denmark, Germany, Hungary, Lithuania, Poland, Romania, and the UK[1]. Teneligliptin offers a pharmacodynamic advantage with unique "J-shaped anchor-lock domain" which signifies for its potent and long duration of action. It also offers a pharmacokinetic advantage with a long half-life of 26.9 hours and a convenient once-daily administration as an oral unit dosage form. It has a dual mode of elimination via renal and hepatic routes which sheds the burden of its clearance and can be a preferred choice for the treatment of patients with renal and mild-to-moderate hepatic impairment[2]. DPP IV inhibitors like sitagliptin and vildagliptin have been associated with stuffy and runny nose and sore throat – nasopharyngitis[3]. Aetiogenesis of such symptoms has been attributed to accumulation of substances such as substance P, eotaxin, and neuropeptide Y, etc., in the upper respiratory tract mucosa[4]. The effects of substance P are blunted by angiotensin converting enzyme (ACE), neutral endopeptidase, and DDP-4. Notably, angioedema in patients on ACE inhibitors is accompanied by low concentration of circulating DPP-4[5]. During ACE inhibition, DPP-IV inactivates substance P. Studies in rodent models suggest that substance P contributes to the pathogenesis of ACE inhibitor-associated angioedema. Thus certain studies suggest that genetic deficiency or pharmacological inhibition of DPP-IV predisposes to ACE inhibitor-associated angioedema by decreasing the degradation of substance P. In fact it has been reported that overall there was no association between vildagliptin use and angioedema in the pooled analysis; however, concomitant use of vildagliptin and ACE inhibitor was associated with a 9-fold increased risk of angioedema[6].

The symptoms in our case appeared after introduction of teneligliptin in an otherwise asymptomatic patient and waned off promptly after discontinuation of the same on to reappear after reintroduction. The patient's symptoms also responded to antihistaminic suggesting mucosal hyper-reactivity of allergic origin. Although literature is replete with case reports of other DPP IV inhibitors causing allergic adverse effects involving upper respiratory tract and skin

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but teneligliptin per se has not been incriminated with such symptoms, a literature search in PUBMED with keywords 'teneligliptin', 'respiratory allergy', led to 'zero' search results. This case reports also highlights the dose limiting nature of such adverse effects.

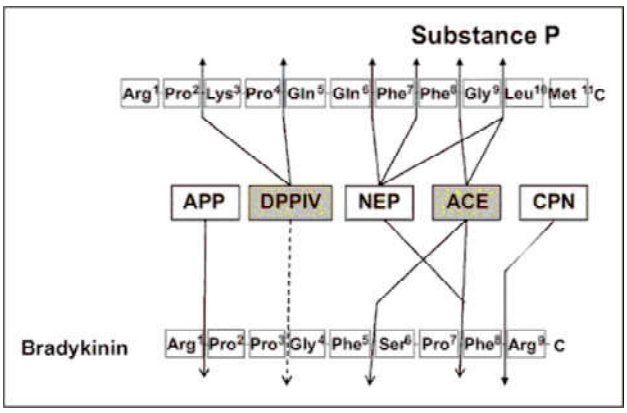

Fig. 1: *Schematic diagram showing the role of angiotension-converting enzyme (ACE) and dipeptidyl peptidase-IV (DPP-IV) in the degradation of bradykinin and substance P. Studies in rodents suggest that DPP-IV is the primary enzyme responsible for the inactivation of substance P when ACE is inhibited. The dotted line indicates that bradykinin is already inactivated by aminopeptidase P (APP) before it is degraded further by DPP-IV. CPN indicate carboxypeptidase N; NEP, neutral endopeptidase.*

On applying the Naranjo ADR scale in our case, a score of 6 was obtained which falls under the probable ADR category. Apart from allergic rhinopharyngitis, other serious adverse drug reactions such as urticaria, laryngeal oedema, angioedema, or asthma[7] have not been associated with DPP IV inhibitors. However, when used concomitantly with ACE inhibitors then the incidence of ACE inhibitor-associated angioedema was increased 9-folds[6]. It has been found that DPP IV inhibitors can be safely used in patients with asthma and it does not affect the control of asthma[7] and as such there is no report which would suggest that DPP4 inhibitors worsens any pre-existing allergies. Thus, it may be safely prescribed to patients with pre-existing asthma or allergies. As far as allergic rhinopharyngitis is concerned, an appropriate management would be withdrawal of the incriminating drug and concomitant use of an antihistaminic.

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CASE REPORT

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Acute Onset Blindness in a Tubercular Meningitis Patient on Antitubercular Treatment: A Rare Case

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Abstract

Ethambutol is a widely used antitubercular drug but has been known to cause optic neuritis, more specifically retrobulbar neuritis causing blurred vision, decreased visual acuity, central scotomas and loss of red-green colour vision[1,2,3]. This type of visual defect is termed as toxic optic neuropathy caused by ethambutol. Ethambutol, however, causes this side-effect 2 - 8 months after being started[4,5,6]. We present a case of a rare side-effect of complete but reversible blindness noted within 4 days of starting antituberculosis treatment with ethambutol in standard dosage.

Key words: Antitubercular treatment, ethambutol toxicity, occular ethambutol toxicity.

Introduction

Tuberculosis is widely prevalent in the Indian subcontinent and manifests as pulmonary and extra-pulmonary forms. Ethambutol is used as one of the first-line antitubercular therapy. However, ethambutol is associated with serious complication of toxic optic neuropathy which is generally seen 2 - 8 months after starting it.

Hereby we present a rare case report of a young female suffering from tubercular meningitis who presented to us within 4 days of starting antitubercular therapy with sudden onset, painless, complete loss of vision in both eyes.

Case report

A 23-year-old female presented to a private hospital with complaints of fever, headache for 15 days, and altered sensorium since 7 days. Therefore she was suspected of meningitis and on subsequent evaluation her CSF examination was done (CSF cells 4 - 5/mm^3 all mononuclear; CSF proteins 73 mg/dl; CSF sugar 40 mg/dl; CSF ADA-7; CSF CBNAAT- Mtb detected without resistance), suggestive of tubercular meningitis. Non contrast MRI spine was also done there and showed D10-11 discitis with erosion of end plates with small right-sided psoas abscess (Fig. 2). She was started on all four 1st-line antitubercular medication.

She presented in our hospital in emergency with complaints of blurring of vision on the 3rd day and complete loss of vision on the 4th day after starting fixed-dose antitubercular therapy without any other symptoms of focal nerological deficit. On clinical examination, she was completely blind with no light perception in either eye; her bilateral pupils were dilated and light reflexes (both direct and consensual) were absent with preservation of accomodation reflexes (other cranial nerve examinations were normal).

She was evaluated further and subjected to contrast MRI-brain which showed multiple tuberculomas with mild hydrocephalus not involving the optic nerve or tract with

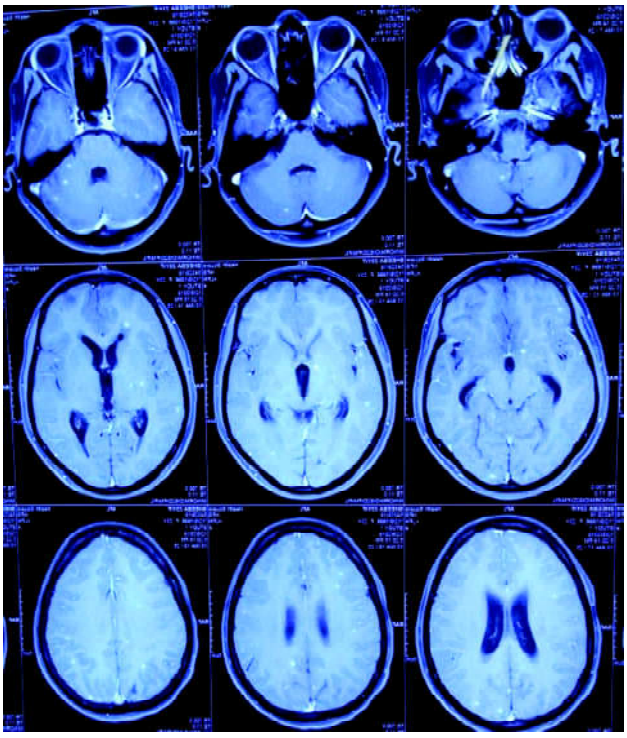

Fig. 1: *Multiple tuberculomas in bilateral cerebral and cerebellar hemispheres.*

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no evidence of infarct or abcess (Fig. 1). Ophthalmic examination was done which revealed normal bilateral fundus, and visual evoked potentials (VEP) showed p values of 105 and108 (Fig. 3) and macular Optical coherence tomography (OCT) suggestive of CMT 224 um and 190 um.

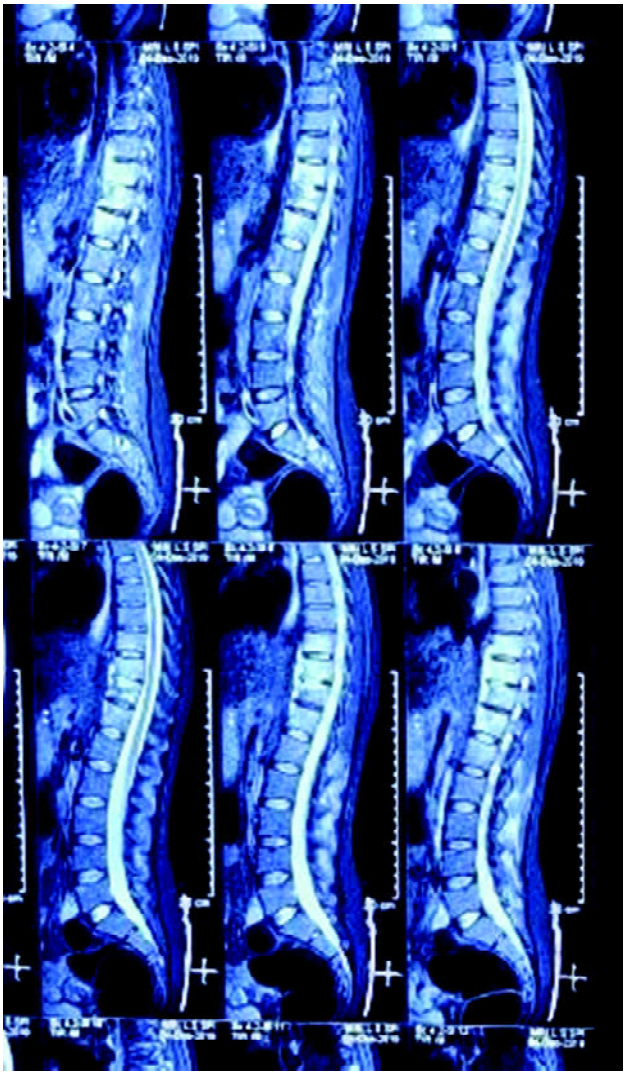

Fig. 2: *D10-11 discitis with erosion of end-plates.*

On evidence of this, ethambutol-induced optic neuropathy was suspected, and ethambutol was withdrawn. Further, the patient was managed symptomatically along with other 1st-line group of ATT.

On withdrawal of ethambutol, her vision improved gradually with projection of rays to 6/60 by the 10th day[10,11].

Discussion

Tuberculosis is a widespread disease in India and a major killer among infectious diseases. Various antitubercular drugs have been used which encompasses isoniazid, rifampin, pyrazinamide, and ethambutol as 'first-line'. These drugs have been attributed to various adverse effects during the treatment short course.

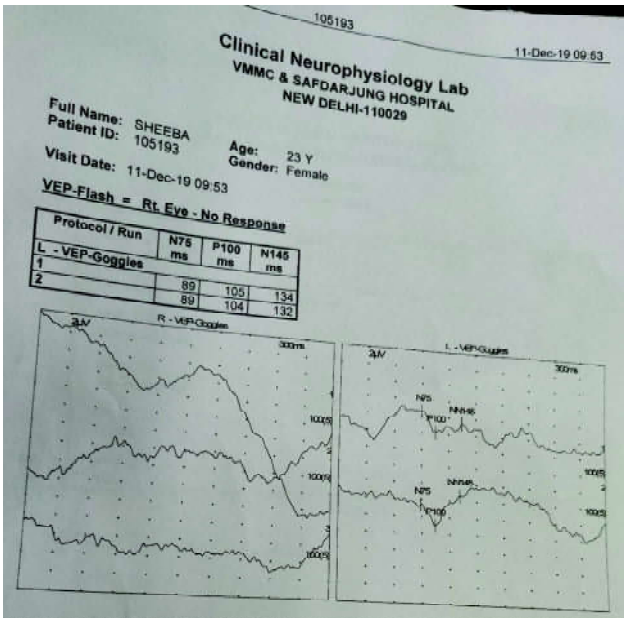

Fig. 3: *Visual evoked potential showing increase p wave latentcies.*

Ethambutol is a bacteriostatic agent active against slow growing mycobacteria. It acts on the bacterial cell wall by inhibiting the formation of mycolyl-arabinogalactan-peptidoglycan complex and increasing the permeability of the cell wall[7,8].

Ocular toxicity of ethambutol manifests as optic neuritis (retro-bulbar). The sign and symptoms manifest as visual field defects, red-green colour blindness. Unlike other more commonly known visual toxicity agents (e.g., hydroxychloroquine), where long durations of therapy are required for toxicity, ethambutol optic neuritis may begin rapidly between 1 month and 36 months after beginning the therapy. In general, however, most patients experience visual symptoms within the first 9 months of treatment. In more than 60% of patients, physical examination reveals bilateral, painless, and typically symmetric loss of visual acuity as well as abnormal colour vision. Colour vision loss is typically of indistinguishing green and red, though blue-yellow colour changes may also occur. Initially, the optic nerve is normal, but eventually optic disc pallor develops. If optic atrophy is present at the onset, it is generally considered to be a poor prognostic sign. Visual field testing most often reveals central or ceco-central scotoma, though bitemporal breakout of the visual field defect with optic chiasma involvement has also been reported.

This reaction is proportional to the dose of ethambutol and is observed in 15% of patients receiving 50 mg/kg/day, in 5 - 6% of patients receiving 25 mg/kg/day and in < 1% of patients receiving daily doses of 15 mg/kg[4,5,9]. In one study, 13 patients developed optic neuritis between 1 and 6 (mean = 2.9) months after receiving ethambutol at a dose ranging from 13 to 20 mg/kg/day (mean = 17 mg/kg/day) for pulmonary tuberculosis or of the lymph nodes. However, in our case, the patient developed severe ocular toxicity with a daily dose of 15 mg/kg and that too within 4 days of starting the drug. The possibility of such toxicity according to literature is < 1%[4,5,19]. A rare case report of idiosyncratic reaction with ethambutol has been described by Karnik *et al*[13]. Rapid development of optic neuritis in our patients could possibly be due to idiosyncratic reaction to the drug.

Factors which may predispose to toxicity include altered renal function. Furthermore, history of ethanol and tobacco consumption may predispose to ocular toxicity[6,14]. In our case, the patient had no history of ethanol and tobacco consumption, and renal functions were normal.

The exact mechanism of this ocular neurotoxic effect has not been identified. Animal studies have demonstrated ethambutol toxicity in the retinal ganglion neurons of rodents. One of the principal theories for its toxicity has been the zinc-chelating effect of ethambutol and its metabolite[15,16,17]. Postulated biochemical pathways that mediate the toxic damage include downstream effector caspase-3 and caspase-6,815 and an excitotoxic pathway[18].

Karnik *et al*, in their article reported rapidly progressive deterioration of vision after only 3 days of treatment with ethambutol[13]. In conclusion, ethambutol could cause an optic neuritis after even a few doses. The mechanism of injury is probably different from the common optic neuritis secondary to ethambutol. Early detection of these cases and withdrawal of ethambutol along with initiation of hydroxycobalamin may be associated with good prognosis in such cases[13].

In many studies, treatment of sudden severe acute toxicity caused by ethambutol includes withdrawal of the drugs. It is recommended to stop isoniazid also in severe cases, as the drug itself has been implicated in probable ocular toxicity. Isoniazid should also be stopped if less severe optic neuritis does not improve within 6 weeks after stopping ethambutol[6,19].

Conclusion

Anti-tubercular drugs like ethambutol can cause potentially dangerous adverse effects. Measures to ensure a high level of awareness of these potential adverse effects appear to be the best current preventive method. Although rare, ethambutol induced acute vision loss is an alarming complication, which needs timely withdrawal of anti-tubercular drugs (both isoniazid and ethambutol in severe cases), and initiation of hydroxycobalamin.

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CASE REPORT

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Anti-convulsant Hypersensitivity Syndrome – A Rare Life Threatening Adverse Effect of a Commonly Prescribed Drug

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Abstract

Anti-convulsant hypersensitivity syndrome is a delayed adverse drug reaction associated with the use of aromatic anti-convulsant drugs. It has been most commonly reported with the use of phenytoin, carbamazepine, and phenobarbital. Although its occurrence is rare, it is a serious adverse event often resulting in hospitalisation and even death. The clinical manifestations of anti-convulsant hypersensitivity syndrome include a triad of symptoms consisting of skin rashes, fever, and evidence of systemic organ involvement. Diagnosis is most frequently based on the recognition of this triad of symptoms and clinical judegment. The exact mechanism remains to be determined but is thought to have at least three components: deficiency or abnormality of the epoxide hydroxylase enzyme that detoxifies the metabolites of aromatic amine anticonvulsants, associated reactivation of herpes-type viruses, and ethnic predisposition with certain human leukocyte antigen subtypes. Management of anti-convulsant hypersensitivity syndrome primarily includes discontinuation of the associated anti-convulsant drug. Systemic corticosteroids are usually required for full recovery. An important issue regarding anti-convulsant hypersensitivity syndrome is the cross-sensitivity among aromatic anti-convulsant drugs, which has been reported to be 40 - 80%. This means that patients with a history of anticonvulsant hypersensitivity syndrome should avoid further use of any aromatic anti-convulsant drug.

Key words: Anti-convulsant, arene oxide, aromatic ring.

Case report

A 24-year-old male was admitted with complaints of fever, generalised pruritic rash all over the body, and swelling of both lips – all of 2 days duration. He had a history of head injury following a road traffic accident a month ago and had developed seizures. He was prescribed tab phenytoin 100 mg bd for the same. The patient took tab phenytoin regularly at the prescribed dose for 32 days, following which he developed fever, rash, and lip swelling for which he was admitted at our hospital.

On examination, he was conscious, oriented. Pulse rate of 102/minute, blood pressure - 110/80 mm of Hg, respiratory rate - 26/minute, oral temperature - 103° F. He was icteric, had tender cervical, axillary, and inguinal lymph nodes. The patient had periorbital oedema and marked labial oedema. He had a diffuse erythematous maculopapular rash all over the body. Examination of gastrointestinal, cardiovascular, respiratory, and nervous systems were within normal limits.

Investigations (day 1 of admission):

Complete blood count	
Total count	19,100 cells/mm^3
Differential count	Polymorphs - 69, lymphocytes - 6, eosinophils - 15
Erythocyte sedimentation rate	78 mm at 1 hour
Haemoglobin	11.8 g%
Platelets	1.90 lakhs
Red blood cell count	4.08 million/mm^3
Haematocrit	35

Renal function tests	
Glucose	77 mg/dl
Urea	52 mg/dl
Creatinine	1.8 mg/dl
Sodium	136 mmol/l
Potassium	5.0 mmol/l

Liver function tests	
Total bilirubin	15.7 mg/dl
Direct bilirubin	6.0 mg/dl
Alanine transaminase	515 IU/l
Aspartate transaminase	210 IU/l
Serum alkaline phosphatase	245 IU/l
Albumin	4.0 gm/dl
Total protein	6.4 gm/dl

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Peripheral smear – normocytic, normochromic red blood cells, leucocytosis with eosinophilia, atypical lymphocytes noted, platelets adequate.

Urine routine – No abnormalities detected

24 hour urine proteinuria – 200 mg protein/day

Absolute eosinophil count – 1,600 cell/mm^3

Ultrasound abdomen – Normal study

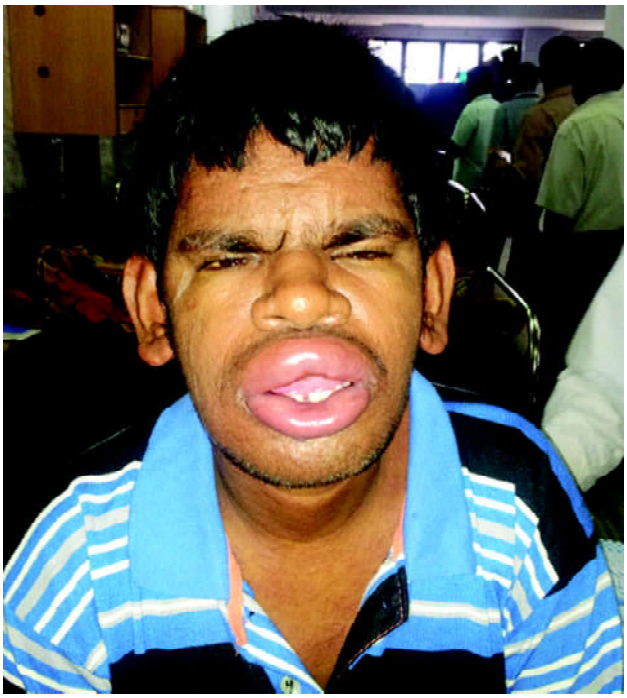
In view of the classical triad of rashes, fever, and organ damage occurring in the 5th week after starting phenytoin, a diagnosis of anti-convulsant hypersensitivity syndrome secondary to phenytoin with acute kidney injury and drug-induced liver disease was made. Tab phenytoin was stopped and the patient was treated with inj dexamethasone 4 mg IV bd for 3 days followed by tab prednisolone 60 mg OD and tapered off over 6 weeks. For the pruritic rash, topical calamine lotion was applied. Patient was put on tab valproate 200 mg BD for seizure control. Tab paracetamol 500 mg was given to control fever. Serial monitoring of blood investigations was done.

Complete blood count	**Day 3**	**Day 7**	**Day 12 (at discharge)**
Total count	18,800 cells/mm^3	13,400 cells/mm^3	8,900 cells/mm^3
Differential count	Polymorphs - 47, Lymphocytes - 36, Eosinophils - 17	Polymorphs-70, Lymphocytes - 20, Eosinophils - 10	Polymorphs-90, Lymphocytes - 8, Eosinophils - 2
Erythocyte sedimentation rate (ESR)	40 mm at 1 hour	28 mm at 1 hour	35 mm at 1 hour
Haemoglobin	11.6 g, %	10.9 g, %	11.0 g, %
Platelets	2.90 lakhs	1.66 lakhs	1.60 lakhs
Red blood cell count	4.24 million/mm^3	3.70 million/mm^3	3.60 million/mm^3
Haematocrit	37	434	33
Renal function tests	**Day 3**	**Day 7**	**Day 12 (at discharge)**
Glucose	111 mg/dl	127 mg/dl	98 mg/dl
Urea	60 mg/dl	40 mg/dl	28 mg/dl
Creatinine	1.7 mg/dl	1.0 mg/dl	0.6 mg/dl
Sodium	132 mmol/l	135 mmol/l	140 mmol/l
Potassium	3.7 mmol/l	3.8 mmol/l	4.9 mmol/l
Liver function tests	**Day 3**	**Day 7**	**Day 12 (at discharge)**
Total bilirubin	10.3 mg/dl	8.7 mg/dl	8.5 mg/dl
Direct bilirubin	5.7 mg/dl	4.2 mg/dl	3.8.0 mg/dl
Alanine transaminase	439 IU/L	218 IU/L	98 IU/L
Aspartate transaminase	208 IU/L	112 IU/L	103 IU/L
Serum alkaline phosphatase	212 IU/L	227 IU/L	280 IU/L
albumin	4.0 gm/dl	3.4 gm/dl	3.9 gm/dl
Total protein	6.2 gm/dl	6.2 gm/dl	6.9 gm/dl

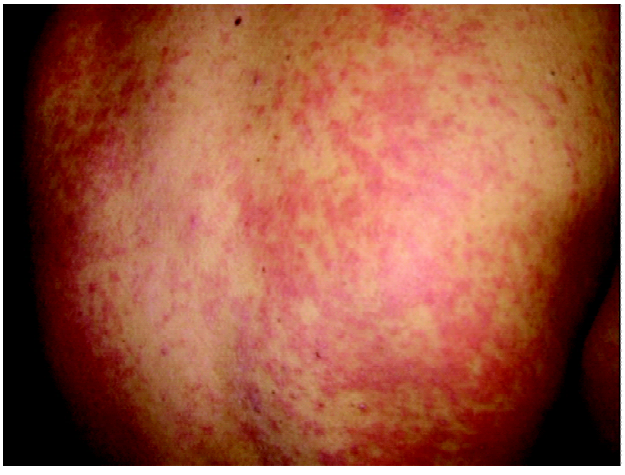
Skin biopsy showed superficial and deep dermal perivascular lymphocytic dermatitis with abundant eosinophils.

Blood culture, Widal, IgM Dengue, peripheral smear for malarial parasite, HbsAg, anti HCV, IgM anti HAV, IgM anti HEV were negative.

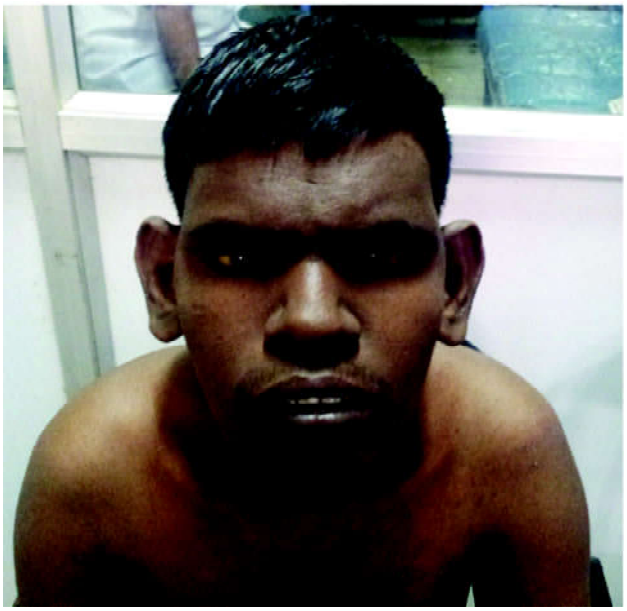
The patient's facial and labial oedema settled in 3 days; fever subsided in 5 days; patient was discharged 12 days after admission with advice to avoid tab phenytoin henceforth in future. He was prescribed tab prednisolone 30 mg OD to be tapered over weekly visits.



Day One of admission: Labial oedema.



Day 2: Erythematous maculopapular rash present over trunk.



On day of discharge (12th day of admission).

Discussion

We present this case report of a patient with characteristic features of the anticonvulsant hypersensitivity syndrome (PHS), who developed multi-system organ failure after treatment with phenytoin. In addition to the clinical picture, the time of onset of symptoms, and the absence of a septic focus, the probable response to corticosteroid therapy is compatible with the diagnosis of anti-convulsant hypersensitivity syndrome.

Anti-convulsant hypersensitivity syndrome is a rare adverse effect which typically develops within 3 weeks to three months after initiation of treatment with anti-convulsants. There is no age or sex predilection. However, the black population appears to be at increased risk for developing this syndrome. First-order relatives of patients who have experienced this reaction have also been reported to have an increased risk.

The exact incidence is unknown; however, it is estimated to occur in 2.3 - 4.5 per 10,000 patients on phenytoin, 1 - 4 per 10,000 patients on carbamazepine, and 2 - 6 per 10,000 patients on phenobarbitone. The exact mechanism of anti-convulsant hypersensitivity syndrome is not known. However, several observations suggests that it is a result of a Gell and Coombs delayed type IV hypersensitivity reaction. Aromatic anti-convulsants may act directly as antigen or indirectly as a hapten to trigger antibody production. In some patients, circulatory IgG antibodies to phenytoin have been detected. It has also been suggested that some individuals may lack the enzyme epoxide hydrolase which is needed to detoxify arene oxides. These oxides, which are very highly reactive and potentially cytotoxic, are formed as a result of oxidative metabolism of the aromatic chain. Phenobarbital and carbamazapine share the same metabolic pathway as phenytoin and consequently cross-sensitivity to these drugs is found in most patients. Studies have also shown reactivation of human herpes virus - 5, 6 and 7 to play a role. It is also thought that HLA- B1502 may also play a role.

The clinical presentation of anti-convulsant hypersensitivity syndrome varies; however, the most frequent findings are fever, skin rashes, and lymphadenopathy. A generalised macular papular eruption with follicles and pustules on the face and upper trunk is characteristic. However, generalised erythroderma, patchy erythema, and less commonly, erythema multiforme and toxic epidermolysis have been reported. Hepatitis occurs in about 75% of the patients, and is characterised by hepatomegaly and a marked increase in serum aminotransferase values. Severe hepatitis is associated with a prolonged hospital stay and a mortality of up to 50%. Additional findings that have been reported in some cases include interstitial nephritis, myopathy, Coomb's negative haemolytic anaemia, and interstitial pulmonary infiltrates. Rhabdomyolysis and acute renal failure have also been seen. Other complications which may be seen include interstitial pneumonitis, hypersensitive myocarditis, encephalitis or aseptic meningitis. Laboratory evaluation usually reveals leukocytosis with eosinophilia and atypical lymphocytosis, and a mild Coomb-negative haemolytic anaemia.

Summary of the clinical findings seen in anti-convulsant hypersensitivity syndrome.

Clinical features	Incidence (%)
Fever*	90 - 100
Rash*	87 - 90
Lymphadenopathy*	70
Hepatitis*	50 - 60
Haematological abnormalities*	23 - 50
Periorbital, orofacial oedema*	25
Myalgia, arthralgia	20
Acute kidney injury*	11
Pharyngitis	10
Pulmonary manifestations	9

**Clinical features present in our patient.*

There is no definite criteria for the diagnosis of anti-convulsant hypersensitivity syndrome. The characteristic triad of fever, rash and visceral organ involvement which occurs between 2 weeks to 8 weeks after starting the

offending drug is useful in making the diagnosis.

There is no specific therapy for anti-convulsant hypersensitivity syndrome other than immediate discontinuation of the offending anti-convulsant and supportive care. Systemic corticosteroids are required in most cases. Most case reports suggest a positive response to steroids when initiated early in the course of the disease. Of practical importance is the fact that re-exposure to the drug, or exposure to phenobarbital or carbamazepine, will result in reactivation of the syndrome with a potentially fatal outcome. If further use of an anti-convulsant drug is necessary, all aromatic anti-convulsant drugs should be avoided. Valproic acid appears safe, as do the benzodiazepines. Alternatively, one of the other nonaromatic anti-convulsant drugs may be used: ethosuximide, gabapentin, levetiracetam, tiagabine, and topiramate.

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CASE REPORT

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Amoebic Liver Abscess and Inferior Vena Cava Thrombosis – A Rare Case Report

Ram Babu, Priyanka Singh***

Abstract

Amoebic liver abscess is the most common extra-intestinal manifestation of infection with Entamoeba histolytica. It is a common disease especially in endemic areas, but it is a rare cause of inferior vena cava thrombosis, with only a few cases appearing in literature. Imaging techniques, serological tests, image-guided interventional procedures, and appropriate therapeutic regimens have significantly reduced mortality, yet the disease is associated with many complications and can be fatal if untreated. We describe one such case of inferior vena cava (IVC) thrombosis which presented as a rare complication of liver abscess. The case responded well to radiological intervention and pharmacological treatment including anti-thrombotic medication.

Key words: Amoebic liver abscess, complication, inferior vena cava thrombosis.

Introduction

Amoebic liver abscess is a collection of pus in the liver in response to the intestinal parasite *Entamoeba histolytica*. This parasite causes amebiasis, an intestinal infection that is also called as amoebic dysentery. Once infection occurs, the parasite may get carried by the blood stream from the intestine to liver. This infection occurs worldwide. Amoebiasis is the second leading cause of death from parasitic disease worldwide. It can be diagnosed easily by ultrasound and amoebic serology, but CT scan of abdomen is the best tool to diagnose its complications. Complications include rupture of liver abscess into adjacent pleural, pericardial, peritoneal cavities, and rarely into gastrointestinal tract. Vascular complications in the form of portal vein, hepatic vein and inferior vena cava thrombosis is also known to occur rarely.

Case report

A 36-year-old male, known case of hypertension, presented with history of fever with chills from the past 8 - 10 days along with history of breathlessness and pain in abdomen from the past two days. On examination, the patient was conscious but with a toxic look, mild icterus was present, blood pressure was 120/70 mmHg, pulse rate was 128 per minute with normal volume, respiratory rate was 28 per minute, SpO2 92% on room air, and bilateral air entry diminished in chest with a two fingers tender, palpable liver. So we summarised this case of pyrexia, breathlessness, icterus with hepatomegaly with the differential diagnosis of pneumonia with septicaemia, malaria fever, liver abscess.

The haematological investigations revealed a haemoglobin of 12.7 gm%, TLC - 15,360/cumm, platelets - 1.34 lacs/cumm, total bilirubin - 4.3 mg/dl, direct bilirubin - 3.8 mg/dl and indirect - 0.5 mg/dl, SGOT - 83 IU/L, SGPT - 73 IU/L, ALP - 387 U/L, total protein - 5.8 gm/dl, albumin - 2.8 gm/dl, globulin - 3.0 gm/dl, serum sodium - 139 meq/l, serum potassium - 4.0 meq/l, blood urea - 23 mg/dl, serum creatinine - 0.9 mg/dl, RBS - 118 mg/dl, Typhi dot IgM negative, PS for malaria and MP serology-negative, serum procalcitonin - 4.10, serum lipase - 12 iu/l, PT with INR - 1.25, APPTc - 28.6, APPTt - 31.6, amoebic serology - 1.754 (positive), anti HAV - negative, anti-HEV - negative, anti HCV - negative, HbsAg - negative, Elisa for dengue IgM - negative, HIV 1 and 2 - negative, rapid test for leptospira IgM - negative, blood and urine culture - sterile. Arterial blood gas analysis showed a pH - 7.381, pCO2 - 25.8 mmHg, pO2 - 67 mmHg, BE - 10 mmol/l, HCO3 - 15.3 mmol/l sO2 - 93% suggestive of compensatory metabolic acidosis. Chest X-ray showed mild raised right-sided diaphragm with bilateral haze in both lower zones. Abdomen ultrasound suggestive of a large liver abscess (10.8 x 7.5 x 10.2 cm) with suprahepatic inferior vena cava thrombus (2.8 x 1.4 cm). 2D echocardiography showed no RWMA with an ejection fraction of 65% and no vegetations on cardiac valves. We performed USG guided pigtail insertion and drainage of abscess with 120 cc of anchovy pus, which was sent for amoebic serology. Patient was started on injection monocef 2 gm twice daily, injection metrogyl 750 mg thrice daily, inj fragmin 5,000 units subcutaneous twice daily, and injection albumin 20% OD. Nebulisation and incentive spirometry was advised along with oxygen supplementation via nasal

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prongs in propped-up position. The patient started showing dramatic improvement, but chest X-ray still showed left-sided plural effusion. Hence, for further evaluation CECT chest and abdomen was advised which revealed hepatomegaly with partially liquefied abscess with pigtail in situ, moderate right pleural and mild left pleural effusion with minimal ascites and non visualised right hepatic vein ? thrombosed and a small thrombus in the IVC. Patient was discharged in stable condition on tablet levoflox 750 mg OD, tablet metrogyl 800 mg TID for 10 days , tablet ceftum 500 mg BID, cap superia DSR before breakfast and tab warfarin 5 mg per day and was advised to monitor PT with INR weekly and keep INR in the range of 2.5 to 3 for 6 months. Patient improved dramatically, pigtail catheter was removed after few days and all the medications were stopped after 14 days. Warfarin was stopped and the patient was shifted to tablet afogatran 110 mg BID. He was discharged in a stable condition.

Discussion

Amoebic liver abscess is the most common extra-intestinal manifestation of infection with *Entamoeba histolytica*. ALA develops in less than 1% of patients infested with *E. histolytica*, but still represents a large number of patients, especially in endemic areas. It is a rare cause of IVC thrombosis with only few cases reported in literature. The diagnosis of amoebic liver abscess relies on the identification of a space-occupying lesion of the liver and positive amoebic serology. Ultrasound abdomen is the preferred and easy choice to diagnose, but CT scan is ideal to detect liver abscess, particularly smaller lesions and associated complications. The rate of various complications was reported to be 10.3% including rupture in the pleural, pericardial and peritoneal cavity, rupture into bile ducts and vascular thrombosis. Though thrombosis of hepatic vena cava is rare, referred to as obliterative hepatocavopathy, is described mostly in autopsy studies. However, a recent case report described this complication prospectively but the exact pathophysiology of IVC thrombosis in amoebic liver abscess is uncertain. Proposed mechanisms include external mechanical compression, thrombotic state associated with inflammatory process of amoebiasis and an adjacent spread of inflammation. In our case, we suspected that the inflammatory process in the wall of the amoebic abscess spread and caused injury to the IVC wall, leading to inflammation followed by thrombosis. Hepatic abscess in the close proximity to the IVC or hepatic veins should be investigated using CT or Doppler ultrasonography. Coagulation profile should be assessed in order to rule-out any pre-existing thrombogenic state. The management of amoebic liver abscess with IVC thrombosis mainly includes anti amoebic, antibiotics and drainage of abscess but in few cases, anticoagulation therapy may be needed to achieve complete resolution. The management of complicated amoebic liver abscess is operative. Extension of thrombus up to the right atrium mandates aggressive management with thrombectomy to reduce chances of pulmonary embolism.

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Indian Association of Clinical Medicine

Headquarters: P.G. Department of Medicine, S.N. Medical College, Mahatma Gandhi Road, Agra - 282 002, U.P.

IACM MEMBERSHIP / FELLOWSHIP FORM

No. ..... Date .....

The Honorary General Secretary,
Indian Association of Clinical Medicine (IACM)

Photograph

We hereby propose the admission of

Name (in full): .....
Qualifications: .....
(Branch of Medicine for P.G. Degree)
University: .....
Year of obtaining the first Postgraduate Qualification: .....
Address: .....
.....
..... Pin Code: .....
Phone (with STD code): ..... E-mail: .....

as an Associate Life Member/Life Member/Fellow of the Indian Association of Clinical Medicine.

To the best of our knowledge and belief, the above particulars are correct and we consider him/her a fit and proper person to be admitted as Associate Life Member/Member/Fellow of the 'Association'.

A D.D. No. ..... Dated ..... drawn on .....
..... for Rs. ..... is enclosed herewith.

Signature ..... (Proposer)
Name: .....
Fellowship/Membership No.: .....

Signature ..... (Seconder)
Name: .....
Fellowship/Membership No.: .....

Subject to approval of the Governing Body, I agree to become Associate Life Member/Member/Fellow, and if admitted, to abide by the Rules and Regulations of the 'Association'.

.....
(Signature of the Candidate)

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Correspondence Address:
Dr. TP Singh, Hony. Gen. Secretary, IACM, P.G. Department of Medicine, Sarojini Naidu Medical College, Mahatma Gandhi Road, Agra-282 002, U.P.