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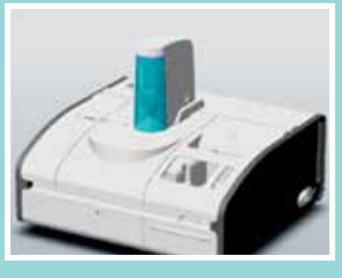

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Dr KK Aggarwal: A Life to be Celebrated

Dr KK Aggarwal, Group Editor-in-Chief, IJCP Group of Publications, breathed his last on May 17, 2021.

The committed doctor that he was, Dr KK Aggarwal devoted his entire life to the welfare of the public and to create awareness about numerous health issues. Even during the COVID-19 pandemic, he made constant efforts to educate the masses, including doctors, about the disease. He reached out to over 100 million people through his numerous videos and educational programs and helped save countless lives.

Dr KK Aggarwal wanted his life to be celebrated and not mourned. His spirit of spreading positivity, especially in dire circumstances must keep him alive in each one of us.

Let us remember him for his work and indomitable spirit and strive to carry forward his legacy.

DR KK AGGARWAL

5TH SEPTEMBER 1958 - 17TH MAY 2021

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Toothbrush Grips for Special Children

MILIND WASNIK*, ARUN SAJJANAR†, MIRANDA GEORGE‡, DURGA BHATTAD#, HARSHITA SHUKLA#

ABSTRACT

The American Academy of Pediatric Dentistry (AAPD) recognizes that the essential part of the specialty of pediatric dentistry includes providing both primary and comprehensive preventive and therapeutic oral healthcare to individuals with special healthcare needs (SHCN). Providing healthcare for individuals with special needs requires specialized knowledge which is acquired by additional training, as well as increased awareness and attention, adaptation and accommodative measures beyond what are considered routine. This article discusses about various toothbrush grips and design for children with special healthcare needs.

Keywords: Pediatric dentistry, special child, toothbrush, toothbrush grips, toothbrush design

The American Academy of Pediatric Dentistry (AAPD) recognizes that the essential part of the practice of pediatric dentistry includes primary and comprehensive preventive as well as therapeutic oral healthcare to those with special healthcare needs (SHCN). The AAPD defines SHCN as a physical, developmental, mental, sensory, behavioral, cognitive or emotional impairment or a limiting condition needing medical management, healthcare intervention and/or specialized services or programs. It may be congenital, developmental or may be acquired through disease, trauma or an environmental cause and may result in limitations in carrying out the daily activities of self-maintenance or may cause considerable limitations in a key life activity.

Providing healthcare for those with special needs demands specialized knowledge which is acquired by additional training, and enhanced awareness and attention, adaptation and accommodative measures beyond the routine ones. Increased risk for oral diseases is present in individuals with SHCN throughout their lifetime. Oral diseases can have a direct and destructive impact on the health and quality of life of those with certain systemic health problems or conditions. Patients with mental, developmental or physical disabilities who do not have the ability to understand, assume responsibility for, or cooperate with preventive oral health practices are susceptible as well. Oral health is an inseparable part of general health and well-being. The word handicapped was first recorded in the late 19th century in the sense referring to a person's mental or physical disabilities. It has been used in reference to mental disability, expressions such as having learning difficulties or learning-disabled.

Tooth brushing is the most practical and effective means of achieving and maintaining adequate oral hygiene. Dental plaque, which is the cause of various dental and periodontal problems, must be removed effectively. Good dentifrices and only tooth-brushing methods will not help to remove the dental plaque. Therefore, for effective oral hygiene, it is necessary to know the duration and proper toothbrush grip. Brushing is the most basic method to maintain good oral hygiene. However, even for adults, inconclusive or insufficient brushing can cause gum inflammation that ultimately leads to tooth decay. One of the factors which affect the quality of life is oral health that not only has impact on physical health, but can affect the effective functioning, social relationships, interpersonal relationships, self-esteem and mental health.

The effect of brushing depends on three factors:

- Method of brushing

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- Frequency and duration of brushing
- Toothbrush design.

The first two factors show the brushing behavior of a person which is ultimately learned by experience, while the third factor shows the improvement of technology by influence of physical and mechanical properties of the bristles of brush, size, shape and form of the head of toothbrush and its handle.

TOOTHBRUSH DESIGNS AND TOOTHBRUSH GRIPS

Various studies looking into preventive dental strategies, including those by Kimmelman et al and Mathur et al, have focused on toothbrush designs along with their ability to meet the needs of children. Other studies have focused on the duration of tooth brushing. Tooth brushing, in association with the removal of interdental plaque once per day is an adequate measure to prevent the development of dental caries and gingivitis. Use of the correct toothbrush and following the method advised largely determine the effectiveness of tooth brushing. However, in spite of the increased research focus on methods of tooth brushing and its duration, there has been little focus on the different ways in which people hold their toothbrushes while brushing their teeth.

Beals et al outlined the ways in which people grip their toothbrushes during normal tooth brushing and mentioned five main grips. They were:

- Power grip
- Distal oblique grip
- Precision grip
- Oblique grip
- Spoon grip.

The power grip and the distal oblique grip make use of the palm, while the other three grips involve the fingers to grip the toothbrush.

The physical disabilities presented by many individuals, with or without accompanying mental retardation, contribute to the difficulties in maintaining adequate oral hygiene. The proper choice of a toothbrush for individuals with disabilities is frequently the same as for the general population. Usually the preferred choice of toothbrush is with soft nylon bristle, rounded end, multi-tufted with a long strong neck. Generally, brushes with longer handles help in reaching the posterior teeth. An extra soft bristle brush is sometimes indicated for those with sensitive periodontal conditions or severe abrasion to the enamel. The size of the oral cavity and the person's ability to open guide the size of the brush head.

In patients with poor motor coordination, grip problems or extreme spasticity, adaptation of toothbrushes by changing the size and shape of the handle will facilitate sufficient grasping. The use of adaptive aids is rewarding for the self brusher who has limited motion or restricted hand dexterity. These adaptive aids can be bought or easily made from items available in a local pharmacy or hardware store. Some examples are mentioned below:

- Attaching the brush to the person's hand using wide elastic bands or Velcro fasteners.
- For individuals with limited grasp, the brush handle can be enlarged using a sponge, rubber ball or a bicycle handle grip.
- For individuals who are unable to raise their hand or arm, the length of the brush can be increased with ruler, tongue depressor or long wooden spoon.

Some handicapped patients are able to brush their own teeth and can frequently do so with encouragement and support from dental personnel and the use of special toothbrushes. A manual brush with an enlarged handle, elastic cuff or small strap attached to the brush or a long-handled holder for patients who cannot raise their arms or do not have hands, permits the patient to brush. The elastic cuff is generally fitted around the hand and holds the toothbrush in the patient's palm. Patients who are unable to reach their mouths for brushing can attach the brush in a stationary upright position by using a clamp. The National Foundation of Dentistry for the Handicapped is developing a preventive program to promote tooth brushing to the beat of music. In case of tetraplegics, a brush wheel, which can be used in between the teeth and moved through the dentition without using the hands, might be helpful. Mentally retarded patients can often brush using a soft toothbrush with the plastic handle bent for better grasping. A three-headed toothbrush or a powered toothbrush assisted by a caregiver can be useful.

POWERED TOOTHBRUSHES

Powered toothbrushes were first advertised in Harper's Weekly in February 1886, but only became a factor in the US market place beginning in the 1960s. With the commercial success of this product, battery-powered products were introduced having the advantage of being portable and available at a lower cost. Most common problems related with these battery-powered products included short working times and mechanical breakdowns. The eagerness for the powered toothbrush

declined and was recommended mainly for the handicapped.

The second-generation powered toothbrush possessed a uniquely rotating head and had long-life/rechargeable batteries. Increased efficacy in comparison with manual toothbrushes was demonstrated in various studies. Third-generation sonic-powered toothbrushes have now been developed that have been shown to remove more plaque compared with manual toothbrushes. Two primary types of head designs are used: the rotating, oscillating type that has a small, round molar-crown-size brush head and three oscillating brushes with either vibrating or rotational sonic movements.

Plaque removal by these brushes appears equally efficient and periodontal therapeutic effects have been shown in pockets of 5 mm. Powered toothbrushes have been introduced which are battery-powered or disposable. In developed countries, the fraction of sale of powered toothbrush products has increased considerably in recent years. Epidemiological studies suggest that there has been a rise in gingival abrasion and recession which has been tied to the increased use of oscillating powered toothbrushes. Sonic toothbrushes, on the other hand, have been shown to do little harm to the gingiva. Additionally, sonic brushes of this type can be used up to 6 or 12 months as the bristles do not splay. The heads of most mechanical or powered toothbrushes are smaller in comparison with the manual toothbrushes and are usually removable to enable replacements. The head follows three patterns when the motor starts: 1) reciprocating, a back-and-forth movement; 2) arcuate, an up-and-down movement; and 3) elliptical, combined reciprocating and arcuate motions. Powered toothbrushes have been found to be superior to manual toothbrushes in plaque removal and gingivitis efficacy.

CONCLUSION

In spite of the fact that a good grip affords greater dexterity when brushing the teeth, a good grip alone is not adequate for maintaining optimal oral health. The most efficient way to reduce plaque on the teeth is combining an appropriate technique for tooth brushing with an appropriate toothbrush grip.

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■■■■

WHO Urges Affluent Nations to Delay Vaccinating the Young, Donate to COVAX Initiative

The Chief of the WHO urged affluent countries to delay vaccinating the younger population against COVID-19 and donate vaccine doses to the COVAX vaccine solidarity scheme.

WHO Head, Tedros Adhanom Ghebreyesus, again cautioned against vaccine nationalism, as low-income nations at present are receiving a mere 0.3% of the supply. He stated that vaccine supply in low and lower-middle income countries has not been enough to even vaccinate the health and care workers. He further said, "I understand why some countries want to vaccinate their children and adolescents, but right now I urge them to reconsider and to instead donate vaccines to COVAX." (*UN*)

Sputnik Light may be India's First Single-Dose Vaccine

Russia's Sputnik Light vaccine could be the first one-dose vaccine to be used in India and Dr Reddy's will hold discussions with the government and the regulator in the month of June regarding an immediate launch, stated the company.

Deepak Sapra, CEO of Dr Reddy's, said that they were working closely with their Russian partner and the Gamaleya Institute. Sputnik Light has been approved in Russia and has shown an efficacy of 79.4%.

At present, the two-dose Sputnik V vaccine will be rolled out at 35 centers across the country. The first batch of Sputnik vaccines has been imported from Russia and the imported vaccine is priced at ₹ 995.40 in India, said Dr Reddy's Laboratories. The price will be reduced once the vaccine is manufactured in India… (*NDTV*)

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Sudden Blindness in Children Passing Roundworm Per Oral

AVINASH SHANKAR*, SHUBHAM†, AMRESH SHANKAR‡, ANURADHA SHANKAR#

ABSTRACT

Background: *Ascaris lumbricoides* infestation is the most prevalent parasitic infection among the children in tropical and developing countries but the incidence of sudden blindness after passing the worm per oral is undocumented. The lag period depends on the prodromes. Investigations reveal mere raised eosinophilic count and decreased hemoglobin with normal CT scan and CSF examination. **Materials:** Ten cases of sudden blindness investigated and treated at various centers without any positive response attending our center after 30-45 days of incidence from January 2018 to March 2019, were selected. **Methods:** Selected patients' parents were interrogated for the course of disease, treatment taken and their response. Patients were clinically examined, investigated for basic bioparameters, vision and were treated with the prescribed regime-containing pyridoxine, methylcobalamin, nicotinamide, pantothenic acid and herbal neurovitalizer composite. **Results:** All patients had progressive vision gain and attained complete vision after 6 months therapy without any adversity and residual effect or any alteration in hepatorenal profile. **Conclusion:** Sudden blindness in children after passing roundworm or with history of roundworm must be suspected for photoreceptor blockade by roundworm toxin and be treated with pyridoxine and herbal neurovitalizer to assure complete recovery.

Keywords: *Ascaris lumbricoides*, CT scan, cerebrospinal fluid, photoreceptor, neurovitalizer, recovery

Prevalence of intestinal worm infection has been found to be nearly 49.35% and *Ascaris lumbricoides* as the most common parasitic infection (46.85%) in an Indian study. Soil-transmitted helminth infections form the most important group of intestinal worms affecting 2 billion people worldwide causing considerable morbidity.

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A. lumbricoides remain the most prevalent parasitic infection despite therapeutic response to albendazole and mebendazole, but eradication is difficult due to recurrent infection.

Considering the changing effect of worm infestation, the Government of India (GoI) has launched a program to combat worm infestation, i.e., National deworming day for children of age group 1-19 years biannually.

As per the World Health Organization (WHO), >836 million children are at risk of parasitic manifestation worldwide and 214 million children are of age group 1-14 years. In addition, evidence of disproportionate worm infestation and self-drug use resulting in resistance to available deworming agent and presently a combination of parasitocide i.e., albendazole and ivermectin, is in consideration. As these agents only act on adult worm, not on cyst or ova, its recurrent dose must be prescribed as on 45th day every ovum develops to active adult roundworm.

MATERIALS AND METHODS

Materials

Ten children attending the Center for Critical Care with complaints of sudden blindness after passing

roundworm per oral having treated at various hospitals without any positive response and advised brain surgery were included in the study. Ophthalmological examination and CT brain showed no evident pathology except blood showing high eosinophilic count. Table 1 summarizes the clinical presentation of the study patients.

Methods

All the patients presenting with sudden blindness and associated history of passing roundworm per oral and treated at various hospitals without any vision improvement in spite of medication and no pathology detected on various investigations like CT brain, retinal examination and various hematological examinations, were interrogated, examined thoroughly and investigated for basic hematological, hepatic and renal profile.

All the selected patients were administered the following irrespective of age and presentation:

- Intravenous (IV) mannitol 10% with glycerine and 10% in therapeutic dose.
- Injection methylcobalamin, nicotinamide, pyridoxine and pantothenic acid with betamethasone, 1 mL IV every 4th day very slow.
- Syrup Herbal neuroenergizer 2.5-5 mL every 8 hours.
- Susp albendazole 400 mg *plus* ivermectin 3 mg at bedtime for 5 days.
- Bland and simple high carbohydrate diet.

Herbal neurovitalizer constitutes:

Each 5 mL–

- *Acorus calamus* 100 mg
- *Herpestis monnieria* 100 mg
- *Convolvulus pluricaulis* 100 mg
- *Nardostachys jatamansi* 100 mg
- *Cassia angustifolia* 100 mg

Patients' parents were instructed to daily ascertain visual response by finger counting or light reflex, and were also suggested to mark any adversity or new emerging manifestation and report immediately.

Patients were routinely examined every week to ascertain response to the therapy and safety profile. At the end of therapy, patients were examined by ophthalmologist for vision and visual acuity.

OBSERVATION AND RESULTS

Selected patients were in the age group 6-14 years (Table 2) and among them, 4 were male and 6 female (Fig. 1). They approached for medical care within the lag

Table 1. Clinical Presentation of Study Patients

Patient	Age/Sex	Clinical presentation	Lag period
A	10/F	History of passing roundworm per oral, loose motions, vomiting, fever, loss of vision both sides	3 days
B	9/M	Loose motions, vomiting, pain in abdomen, itching over the body, loss of vision both sides, passage of roundworm per oral	2 days
C	12/M	Vomiting, pain in abdomen, fever urticarial rash over the extremity, passage of roundworm per oral, loss of vision both sides	4 days
D	6/M	Vomiting, loose motions, involuntary body movement, urticarial rash, passing roundworm per oral, sudden blindness	2 days
E	13/F	Loose motions, urticarial rash, fever, shivering, nausea, pain in abdomen, passage of roundworm per oral, sudden blindness	3 days
F	12/F	Loose motions of white color, dark urine, intense itching with rash, fever, vomit of roundworm, abdominal pain, loss of vision	5 days
G	8/F	Agonizing pain in abdomen, loose motion, vomiting, urticarial rash, passage of roundworm per oral, loss of vision	4 days
H	8/M	Nausea, vomiting, urticarial rash, passage of roundworm per oral, loss of vision	5 days
I	6/F	Vomiting, loss of appetite, urticarial rash, passage of roundworm, loss of vision	4 days
J	14/F	Fever, pain in abdomen, vomiting, headache, urticarial rash, passage of roundworm both from mouth and stool	1 day

period of 3-5 days at appropriate center. Investigations included CT scan, ophthalmological examination to assess vision and retina status, which were within normal limits in all cases, except for raised eosinophilic count. Common presentation of the patients included sudden loss of vision, passage of roundworm per oral and lag period of blindness and passage of worm was 24-72 hours (Table 3).

Patients were treated with many neurotropics and topical eye drops without any positive response.

Majority of the patients attended our center after 30-45 days of the onset of blindness. Patients presenting with associated central nervous system (CNS) manifestation like involuntary movement and headache had very short lag period of 1 or 2 days.

At our center, hematological examination show raised eosinophil count with other normal parameters, i.e., hepatic and renal.

All patients showed visual improvement by 8th day of therapy and complete visual recovery by 6th month of therapy without any visual debility. Optometry confirmed the vision in all patients as 6/6 in both eyes (Tables 4 & 5 and Fig. 2).

Table 2. Distribution of Patients

Age group (years)	Number of patients		
	Male	Female	Total
6-8	2	2	4
8-10	1	1	2
10-12	-	-	-
12-14	1	3	4

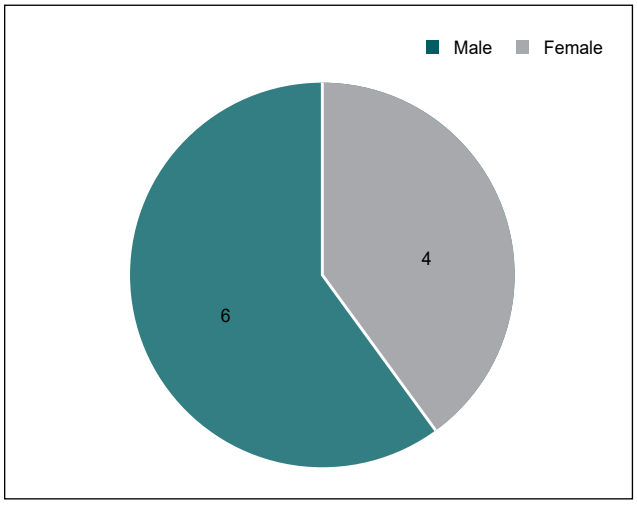

Figure 1. Pie diagram showing sex-wise composition of the patients.

Table 3. Presentation of the Patients

Sudden blindness
Passing worm per oral
Nausea and vomiting
Fever
Lag period of onset of blindness and passing the worm per oral: 24-72 hours
Blurring of vision
Sign of avitaminosis/xerosis/Bitot's spot

Table 4. Bioparameter Status at Various Stages

Basic bioparameters	Number of patients		
	A	B	C
Hematological			
Absolute eosinophil count			
<200/cc	-	-	8
200-300/cc	3	4	2
300-400/cc	6	6	0
400-500/cc	1	0	0
TLC			
<6000/cc	1	0	0
6000-7000/cc	8	10	10
>7000/cc	1	0	0
Hemoglobin percent			
<10 gm%	5	3	0
>10 gm%	5	7	10
Diabetic profile			
Blood sugar			
Fasting			
<100 mg%	9	10	10
>100 mg%	1	0	0
Postprandial			
<150 mg%	10	10	10
>150 mg%	0	0	0
Hepatic profile			
SGOT			
<30 IU	7	8	10
>30 IU	3	2	0
SGPT			
<30 IU	7	8	10
>30 IU	3	2	0

Table 4. Bioparameter Status at Various Stages

Basic bioparameters	Number of patients		
	A	B	C
Alkaline phosphatase			
<140 mg%	10	10	10
>140 mg%	0	0	0
Renal profile			
Blood urea			
<26 mg%	10	10	10
>26 mg%	0	0	0
Serum creatinine			
<1.5 mg%	10	10	10
>1.5 mg%	0	0	0
CT scan			
Altered	None	None	None
Unaltered	10	10	10
Vision			
Status of eye	Normal	Normal	Normal
PL			
Absent	10	10	0
Present	0	0	10
PR			
Absent	2	0	0
Present	8	10	10
Vision	Absent	Absent	Normal

A = At first center of treatment; B = At our center on admission; C = On completion of treatment.

Table 5. Outcome of the Study

Particulars	Number of patients
Perception of light	10
Finger counting	10
Blurred vision	None
Clear near vision	10
Clear distant vision	10
Completely normal vision	10
Safety profile	
Hematological	Improved in all
Hepatic profile	Normal in all
Renal profile	Normal in all

No adversity or sequel was noted in any case or any evidence of post-therapy withdrawal effect, i.e., decline in vision or visual acuity or any CNS manifestation.

DISCUSSION

Roundworm infestation is very common but manifestations like blindness after passing the worm per oral is very uncommon or remains unmarked. In addition, variable lag period of onset of blindness and worm passage, suggests its dependence on prodromes. Those who had CNS prodromes like headache and involuntary movement had earlier onset.

Patients' presentation on passing worm per oral suggests worm irritation leading to release of a polypeptide ASCARON which stimulates the intestinal mucosal nerve endings, resulting in nausea, vomiting and loose motions.

Absorption of toxin in blood causes anaphylactic reaction resulting in fever and urticarial rash while access to CSF results in neurosuppression due to inhibition of neurotransmitter GABA as a result of inhibition of co-enzyme pyridoxal phosphatase by the toxin.

Sudden blindness occurs as neuroconduction suppression results in blockade of neurotransmission from photoreceptors of retinal fovea (Fig. 3).

Figure 4 depicts the pattern of vision improvement in the patients. No change in bioparameters was observed in any case and eosinophil count came to normal.

All patients recovered of blindness having progressive vision gain from perception of light to normal vision in 6 months' duration with the treatment. It is attributed to:

- IV mannitol 10% with glycerine and 10% relieved neural edema.
- Supplementation of pyridoxine as injection of methylcobalamin, pyridoxine, nicotinamide and pantothenic acid competitively inhibits polypeptide and activates pyridoxal phosphatase and ensures increased neurotransmitter GABA. Methylcobalamin and pantothenic acid promote neuroconduction.
- Herbal composite constituents ensure neuro-vitalization and photoreceptor activation.
- Administration of albendazole *plus* ivermectin ensures worm eradication.
- Nutritious diet supports recovery.

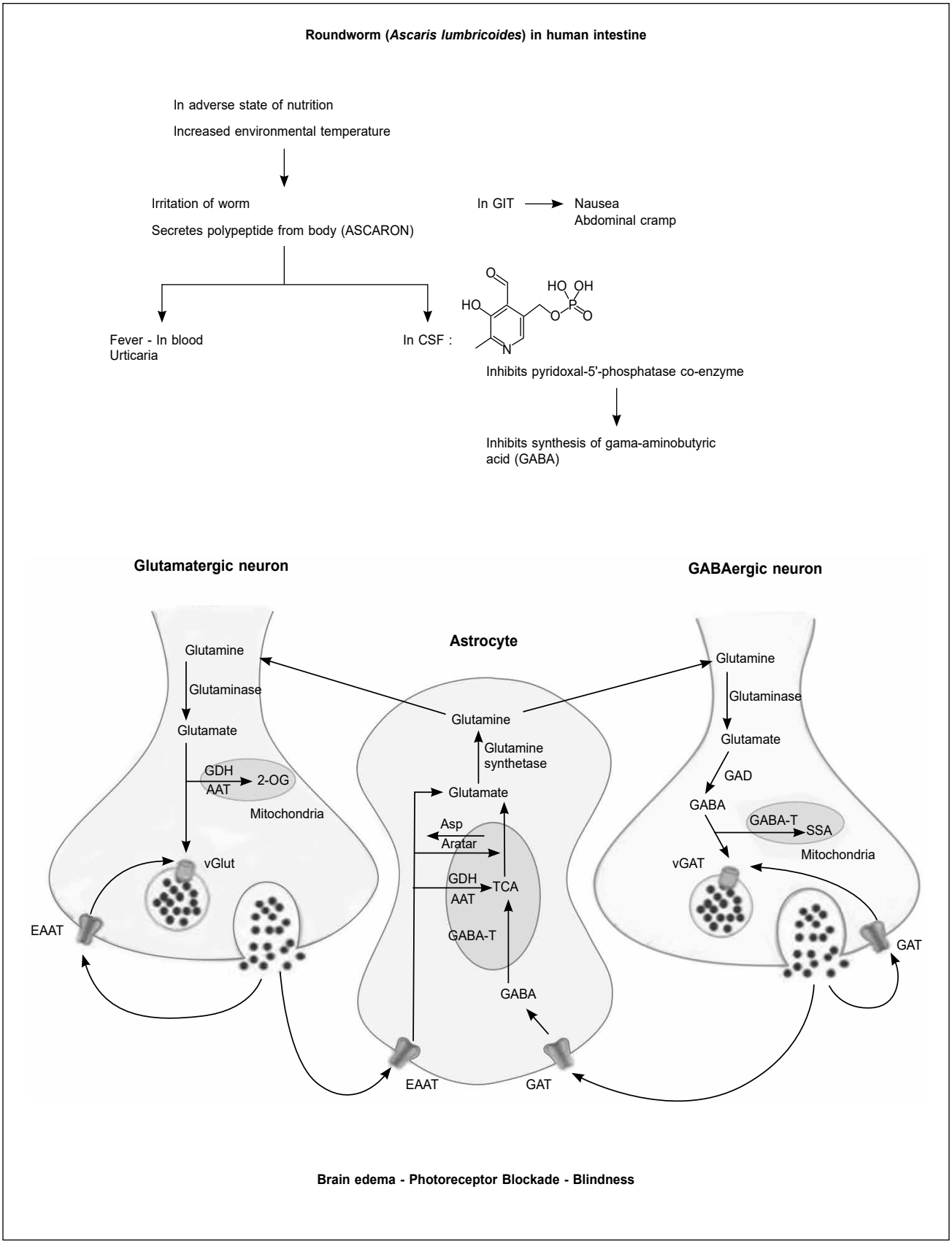

Figure 2. Roundworm kinetics in intestine.

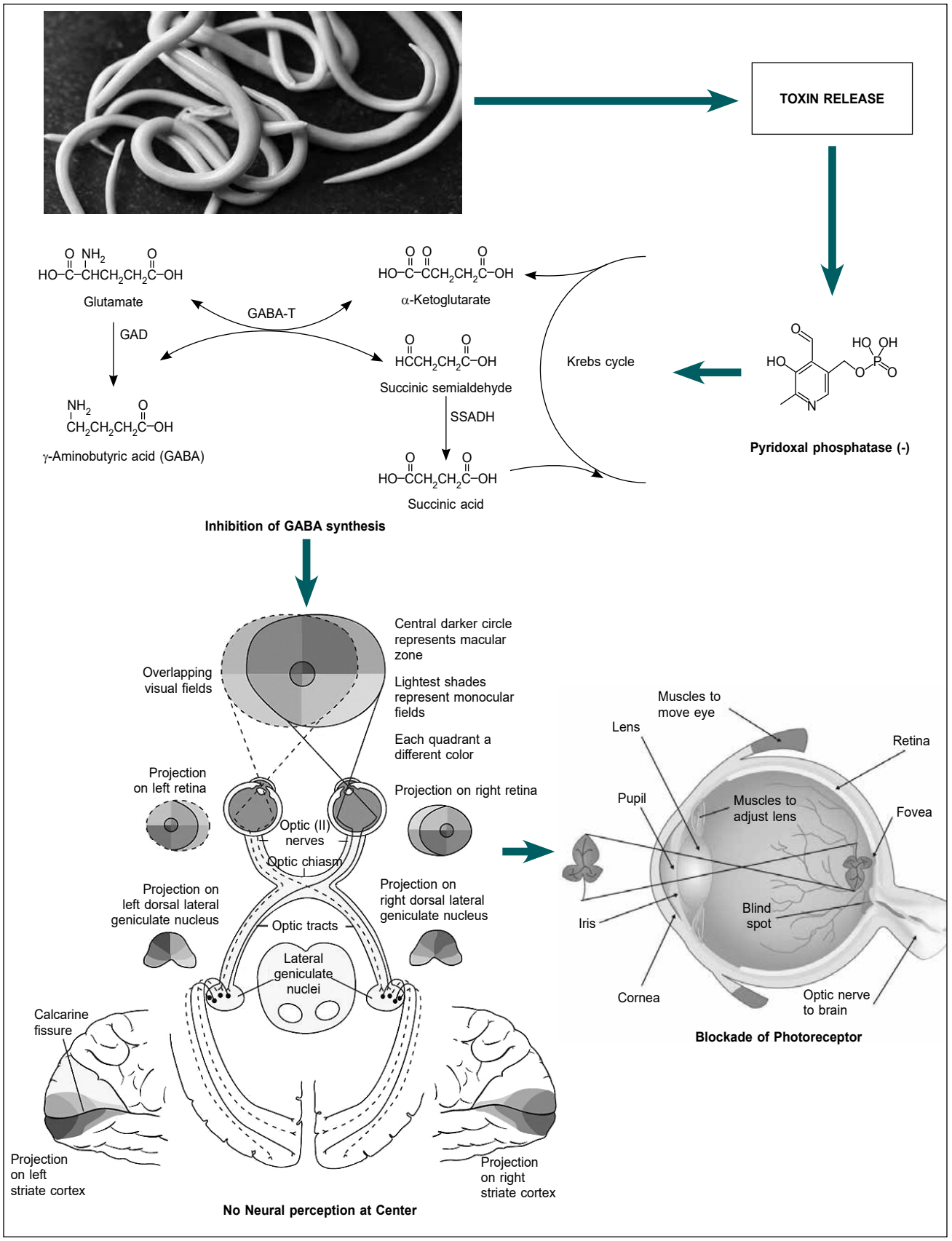

Figure 3. Schematic presentation of pathogenesis of sudden blindness.

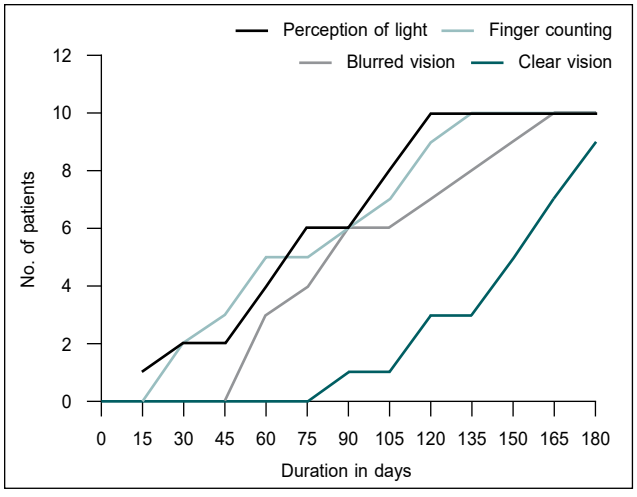

Figure 4. Pattern of vision improvement.

CONCLUSION

Sudden blindness after passing roundworm must be duly taken care of, suspecting Ascaris toxin as a factor. Treatment will ensure cure and safety from undue expenses, especially in tropical countries where roundworm infestation is very common. Herbal composite and pyridoxine supplementation proves a boon for cure.

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■■■■

Fully Vaccinated People can Avoid Wearing a Mask in Most Places, Says US CDC

The US CDC has advised that individuals who are fully vaccinated do not have to wear masks outdoors and can avoid wearing them indoors in most places.

The CDC is hopeful that the guidance will encourage more Americans to get vaccinated. The agency further stated that fully immunized individuals do not have to physically distance in most places. CDC Director Rochelle Walensky stated that the new guidance comes after a steep fall in cases, expansion of vaccines to younger individuals as well as vaccine efficacy against coronavirus variants.

President Joe Biden emerged at the White House for remarks without wearing a mask. "I think it's a great milestone, a great day," he said… (*Reuters*)

Gap Between Two Doses of Covishield Increased to 12-16 Weeks

The Union Health Ministry has increased the time interval between the two doses of Covishield vaccine to 12-16 weeks from 6 to 8 weeks, after recommendation of an expert panel.

The National Technical Advisory Group on Immunisation (NTAGI) has recommended that the time interval between Covishield doses should be increased; however, no changes were suggested in the dosage interval for Covaxin doses. The government has said that the decision has been taken following real-life evidence, particularly from the UK.

The government panel had also suggested that pregnant women may be given the choice to receive any COVID-19 vaccine and lactating women can be vaccinated any time following delivery… (*ET Healthworld – Timesofindia.com*)

Among Asymptomatic People, 2% may Carry 90% of Community's Viral Load: Study

According to a new study, about 2% of asymptomatic college students were noted to carry 90% of COVID-19 viral load levels on a Colorado campus in 2020. The viral loads in these students were found to be as high as those observed in hospitalized patients.

Senior study author Sara Sawyer, PhD, Professor of Virology at the University of Colorado Boulder said that walking around a college campus could be as dangerous as walking through a COVID hospital ward; these viral super carriers will be found equally in both settings. The study strengthens the evidence that viral load is not too tightly correlated with symptoms… (*Medscape*)

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Chronic Calculous Cholecystitis: Reasons to Consider Advanced Laparoscopic Surgery

JUWAIRIAH ABDUR RAHEEM*, SURESH CHANDRA ANNU†

ABSTRACT

Background: Laparoscopic cholecystectomy (LC) has been a basic laparoscopic procedure performed mostly by a general surgeon without a multidisciplinary team (MDT) setup. In cases of chronic calculous cholecystitis (CCC), surgeons are faced with greater challenges. **Objective:** To critically evaluate the parameters which are likely to be associated with increased morbidity in patients undergoing LC for CCC. **Material and methods:** Information on patients aged more than 15 years who underwent elective LC for gallbladder stone disease from February 2016 to December 2019 was collected and those diagnosed as CCC were analyzed in detail. **Results:** Chronic calculous cholecystitis was seen in 37.32% of all cases diagnosed as gallbladder stone disease and 6.17% cases were associated with complications. **Conclusion:** Cases of CCC undergoing elective LC are best managed under MDT and need to be placed under advanced laparoscopic surgery.

Keywords: Chronic calculous cholecystitis, gallstone complications, laparoscopic cholecystectomy, laparoscopic cholecystectomy complications

Chronic calculous cholecystitis (CCC) is one of the commonest benign disease of the biliary system, and usually when diagnosed, is associated with other complications which make the management, especially surgery by laparoscopic cholecystectomy (LC) difficult, in turn increasing the chances of morbidity and mortality. Due to the large period of uncomplicated symptomatic phase, patients seek medical care in the late stages of the disease leading to complications, one of the commonest being CCC. Once this particular complication develops, the disease course becomes more challenging.

Around 90% cases of chronic cholecystitis are associated with cholelithiasis. The pain in the upper right abdomen gradually increases in intensity, becomes habituated to painkillers and risks analgesic nephropathy. On ultrasound, the damage to the walls of the gallbladder is seen as thickening and scarring. CCC can lead to a number of serious complications like cholangitis, obstructive jaundice, biliary pancreatitis, perforation of gallbladder, Mirizzi's syndrome, papillary stenosis, emphysematous cholecystitis, gangrenous gallbladder and can also be associated with gallbladder cancer. An expected mortality of 4% is observed in patients of calculous cholecystitis.

We intend to critically evaluate the parameters which are likely to be associated with increased morbidity in patients undergoing LC for CCC. As the patients approach the outpatient department in the late stages of disease, they are usually diagnosed as complicated CCC. This requires the patient to be subjected to additional special/invasive investigations like magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP) and intraoperative cholangiography (IOC). The chances of conversion from laparoscopic to open cholecystectomy in a complicated case of CCC is also higher.

MATERIAL AND METHODS

The study was retrospectively carried out in the Dept. of Gastroenterology and General Surgery, after receiving approval from the Institutional Review Board (IRB): Deccan College of Medical Sciences, Hyderabad. A total of 217 LC were performed for gallstone disease between February 2016 and December 2019.

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Inclusion Criteria

Individuals more than 15 years of age who underwent elective LC for CCC, defined based on clinical, imaging and bio-chemical criteria.

Exclusion Criteria

- All open cholecystectomies.
- LCs done for uncomplicated cholelithiasis and acute cholecystitis.
- Age under 15 years.
- Unfit for LC/general anesthesia or categorized as American Society of Anesthesiologists (ASA) Grade IV.

Parameters Studied

Patient's demographic factors, past medical history, clinical presentation, laboratory investigations, imaging studies, intraoperative and postoperative complications, and duration of hospital stay were assessed. Ultrasound abdomen was done for all the patients in postoperative period as a departmental protocol before being discharged.

All the cases studied were under minimal access surgical division of Dept. of General Surgery. Out of 217 patients who underwent LC for gallbladder disease, the case sheets of 81 patients who satisfied the inclusion criteria were collected from the Medical Records Department (MRD) and studied thoroughly. The patients were under follow-up for a minimum of 7 months and a maximum of 1 year. Hand written mails were sent to patients residing in regions of poor network facilities, to get updates on their health status. The data was recorded in an excel sheet and results were studied and analyzed.

RESULTS

Chronic calculous cholecystitis was seen mostly in females (75.3%) with overall mean age of occurrence being 42.7 years. Modified BG Prasad method was used to categorize patients into their socioeconomic status (Table 1).

Majority presented with biliary colic with right upper quadrant tenderness in 73 patients (90.1%), fever in 1 patient and 1 patient had jaundice. Routine laboratory investigations revealed normal liver function in majority of the patients (79%). Pancreatic enzymes were within normal limits. Ultrasonography in all subjects revealed gallbladder stones and gallbladder wall thickening of more than 3 mm (Table 2). Patients with common bile duct (CBD) dilatation were subjected to MRCP (Fig. 1) and those showing bile duct stones underwent ERCP and stenting.

Table 1. Demographic Data of Patients

Characteristics	Value	Count	Percentage (%)
Age	<40	30	37
	>40	51	62.9
Gender	Male	20	24.6
	Female	61	75.3
Socioeconomic status	Class V	57	70.3
	Class IV	23	28.3
	Class III	1	1.2

Table 2. Clinical Data and Imaging Results

Data		Count	Percentage (%)
Clinical features	Biliary colic	81	100
	Tenderness	73	90.1
	Nausea, vomiting	23	28.3
	Fever	1	1.2
	Jaundice	1	1.2
Liver function	Normal	64	79
	Borderline abnormal	16	19.7
	Abnormal	1	1.2
Ultrasonography	GB wall thickening	81	100
	CBD dilatation	2	2.4
	Bile duct stone	1	1.2
	IHBRD	2	2.4
	Pancreatitis	2	2.4
MRCP	Dilated CBD	2	2.4
	CBD stones	1	1.2
ERCP	CBD dilatation	3	3.7
	Sludge	1	1.2
	CBD stones	2	2.4
ASA Grading	Grade I	23	28.3
	Grade II	55	67.9
	Grade III	3	3.7

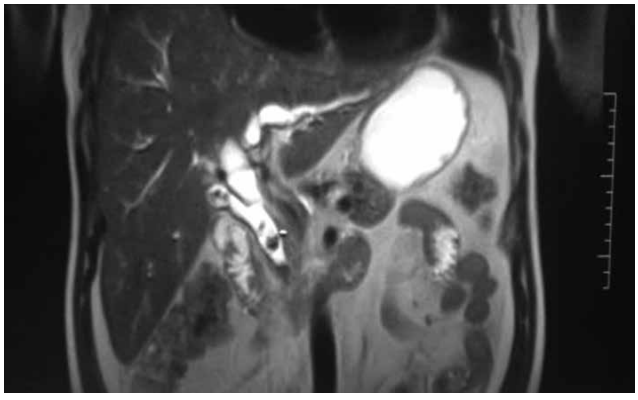

Figure 1. MRCP showing stone in CBD.

Table 3. Intra- and Postoperative Results

Findings		Count	Percentage (%)
Intraoperative	GB adhesions	81	100
	Thickened GB	81	100
	Distended GB	14	17.2
	Inflamed GB	25	30.8
	Bleeding	49	60.4
	Mirizzi's syndrome	1	1.2
	IOC	1	1.2
Postoperative	Cholelithiasis	81	100
	Chronic cholecystitis	81	100
	Biliary pancreatitis	3	3.7
	Emphysematous GB	1	1.2
	CBD stones	2	2.4
	Biliary peritonitis	2	2.4
	Mirizzi's syndrome	1	1.2
	Biliary stricture	1	1.2

Various intraoperative findings were observed (Table 3). Gallbladder adhesions and thickening were seen in all cases of CCC. The omento gallbladder adhesions were universally present in all. Among the entero gallbladder adhesions, prepyloric adhesions were seen in 36 cases (44.4%), transverse colon adhesions in 20 cases (24.6%) and both type of adhesions seen in 25 cases (30.8%). Forty-one patients (50.6%) were discharged on the same day of the surgery and 19 patients (23.4%) were discharged the next day. Twenty-one patients had a longer hospital stay, i.e., more than 2 days.

There were 5 cases of morbidity and 1 postoperative mortality. Morbidity included 4 cases of conversion due to various reasons and 1 surgical site infection (SSI). The final diagnosis was made after operative findings and histopathological examination. CCC was confirmed in all the study cases along with few other complicated findings.

DISCUSSION

Patients of chronic cholecystitis usually present months or years after the onset of symptoms. Due to late presentation, the patients are usually diagnosed in the complicated stage. Chronic cholecystitis mostly succeeds cholelithiasis, well have shown in our study, in which all patients diagnosed with chronic cholecystitis, showed gallbladder stones on imaging and also intra-operatively. As the incidence of gallstone increases with age, there is increased risk of development of chronic cholecystitis. The associated complications and conversion rates were also increased beyond 35 years of age. As observed, majority of LCs for CCC were done in females. Various studies have shown the occurrence of gallstone disease to be increased in higher socioeconomic status, older and multiparous females. The present study revealed that majority of the patients belonged to lower socioeconomic status unlike the western world. In India, the Northern region is considered endemic for the prevalence of gallbladder stone, but our hospital area could be one of the few pockets in southern India endemic to gallbladder stones. Some of the reasons for increased incidence of cholelithiasis could be dietary factors, lifestyle and genetics, as there were few individuals who had a family history of cholelithiasis. Fever is rare in cases of chronic cholecystitis, but 1 patient did present with fever which was due to acute on chronic cholecystitis. Patients of CCC associated with CBD stones, were subjected to ERCP for stones retrieval, balloon trawl followed by temporary stenting and LC (Fig. 2).

Bleeding was the most common complication and was termed major when LC had to be converted, requiring additional surgical procedure or blood transfusions. Most bleeds were controllable by energy source, gallbladder fundal pressure, gauge packing. Bleeding was seen mainly during frozen or inflamed Calot's dissection and during adhesiolysis. Calot and hilar bleeds were severe and difficult to control. Noninvasive management was done by blood transfusions, vitamin K administration or fresh frozen plasma (FFP), whereas invasive management required conversion or admission in intensive care unit (ICU). Interventional radiology

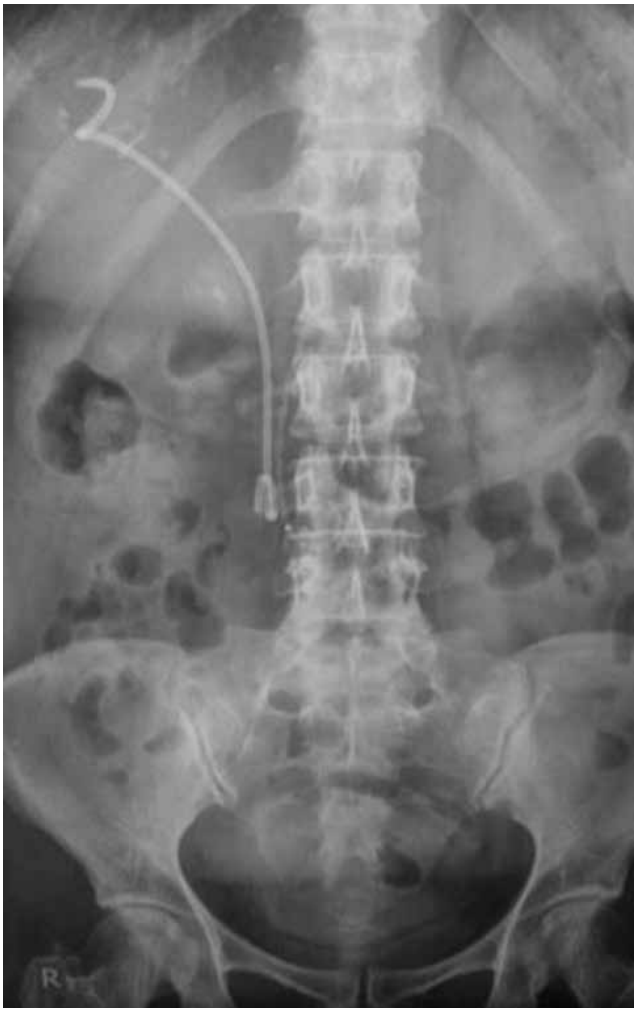

Figure 2. Post-ERCP bile duct stent on plain X-ray abdomen proceeded for LC.

has been included under both invasive and noninvasive management. The incidence of bleeding recorded in cases of LC has been reported to be 10%. In CCC, we observed 10 cases (12.3%) of significant bleeding (more than 200 mL), which had to be managed by noninvasive measures and 1 case that had to be converted.

Out of 81 LCs that were performed for CCC, 75 cases (92.59%) were safely operated. There were 5 cases of morbidity and 1 case of in-hospital mortality (Table 4).

A male patient who presented with jaundice, showing normal MRCP, further underwent IOC, which revealed a distal block, obstructing the free flow of contrast, with dilated CBD and mild intrahepatic biliary radical dilatation (IHBRD; Fig. 3). The case was converted and immediate Roux-en-Y hepaticojejunostomy done.

Another male patient with normal liver function test (LFT) levels, belonging to ASA Grade III developed excessive intraoperative bleeding due to portal hypertension and had to be converted and packed for 24-48 hours for stabilization in ICU, followed by second look laparotomy. Ultrasonography could not reveal chronic liver disease pathology preoperatively as the patient had micronodular cirrhosis.

A female patient with normal lab and imaging studies, had to be converted to manage Mirizzi's syndrome type II which was diagnosed intraoperatively by IOC for primary bile duct repair but had postoperative bile leak approximately 100-150 mL/day and tube cholangiogram revealed biliary stricture, which was managed by delayed Roux-en-Y hepaticojejunostomy after 8 weeks (Figs. 4-6).

Table 4. Complications and Its Management

	Complication	Management	Clavien-Dindo classification
Immediate/Intraoperative (24-48 hours after surgery)	Extensive bleeding due to portal cavernoma	Conversion and packing for 48 hours for ICU stabilization followed by second look surgery	Grade IV
	IOC revealed dilated CBD with distal biliary stricture	Converted for immediate Roux-en-Y hepaticojejunostomy	Grade III
	Bile peritonitis	Resuscitated but succumbed	Grade V
Delayed (>1 month after surgery)	Post-surgical site infection/sinus	Sinus exploration and sequestrectomy of rib	Grade III
	Bile duct leak	Delayed bile duct repair by Roux-en-Y hepaticojejunostomy	Grade III
	Mirizzi's syndrome Bile leak, 100-150 mL/24hr and biliary stricture	Converted and delayed Roux-en-Y hepaticojejunostomy	Grade III

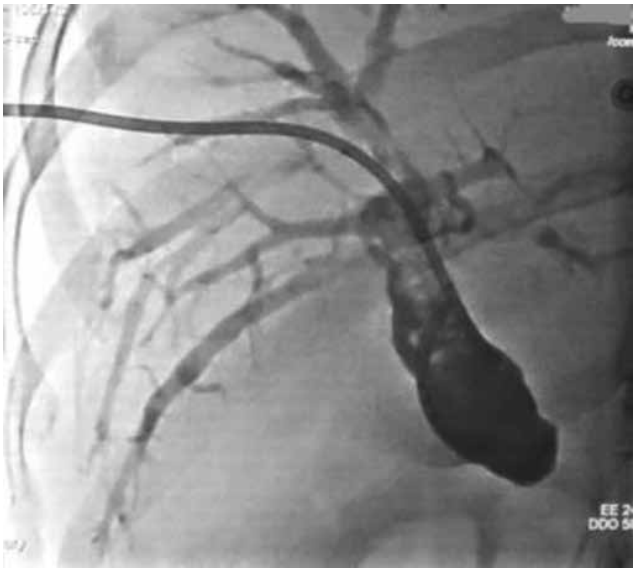

Figure 3. IOC revealing distal block.

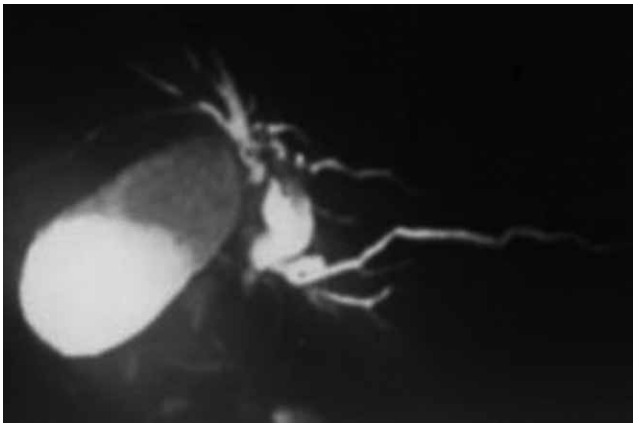

Figure 4. MRCP showing Mirizzi's syndrome type 1.

Another case of morbidity was a male patient, intraoperatively having dense gallbladder adhesions with bleeding and 2 months postoperatively developed epigastric port surgical site infection (SSI) as sinus due to osteomyelitis of the right 9th rib, as revealed by CT sinogram; required sinus exploration and sequestrectomy (Fig. 7).

The difficulties encountered in cases of CCC undergoing LC include conversion, intraoperative bleeding, injury to bile duct leading to bile leak and biliary peritonitis. As observed, bleeding can be due to patient related factors like anatomical anomalies, portal hypertension, comorbidities or due to CCC disease related factors such as dense adhesions, frozen Calot's, cholangitis and Mirizzi's syndrome. Incidence of bile duct injury by LC is recorded to be more than 3%, and the value noted in cases of CCC is 5%. Cases of bile duct injury were converted and bile duct repair done, as bile duct

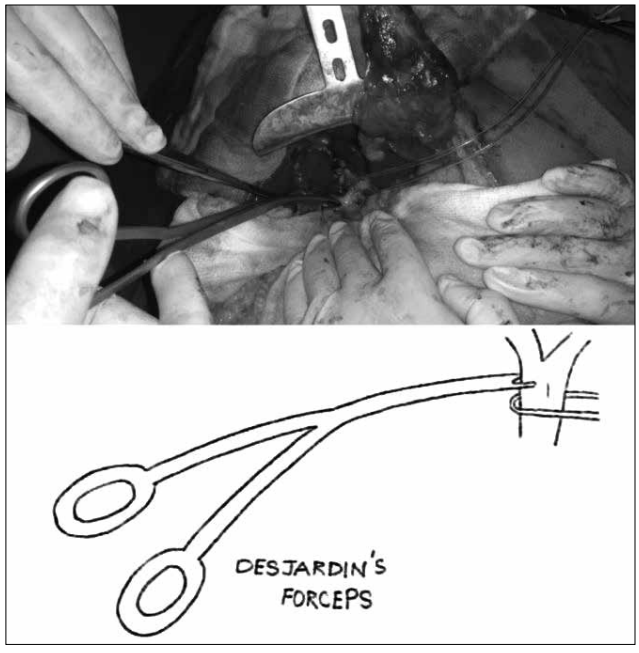

Figure 5. CBD exploration.

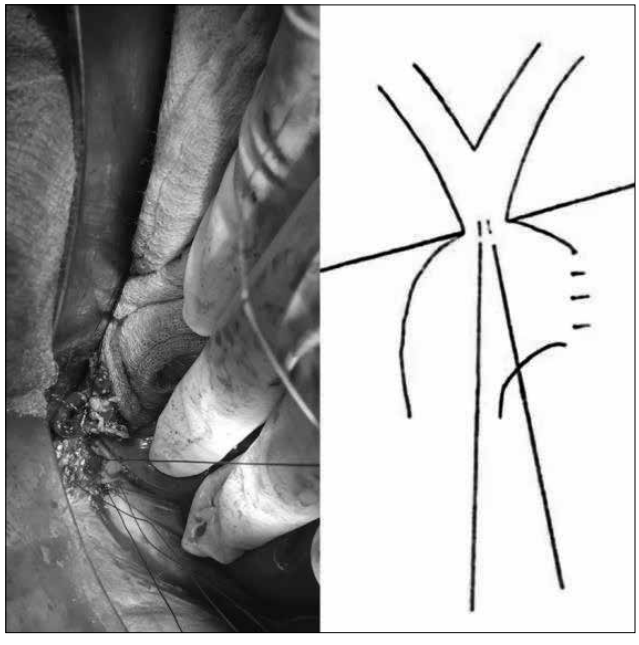

Figure 6. CBD repair by Roux-en-Y hepaticojejunostomy.

injuries are reported to cause difficult reconstruction, prolonged hospitalization and high risk of long-term complications with rate of mortality being 2.4%. Hence, intensive measures should be taken for the prevention and early management of bile duct injuries. The conversion of LC to an open procedure is considered to be multifactorial, and could be due to intraoperative bleeding, bile duct injury and Mirizzi's syndrome. Most patients were discharged within 2 days and those associated with complications had a prolonged duration

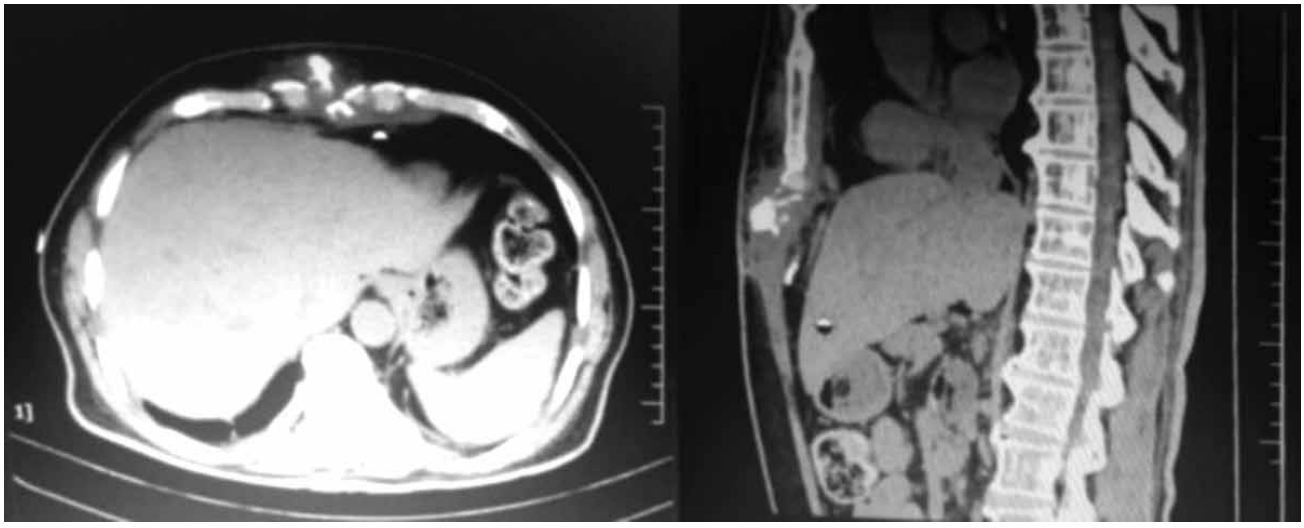

Figure 7. CT sinogram of SSI revealing sinus tract originating from underlying rib osteomyelitis.

of stay (2-3 weeks). Mortality was seen in one female patient who after an uneventful LC, developed bile peritonitis, as revealed by intra-abdominal collections on bedside ultrasonography done 4-5 hours of LC and succumbed before planned for urgent exploration.

Though the cases of CCC are observed more in females, morbidity recorded is higher in males, as also revealed in present study (1 female and 4 male). Men with cholecystitis need rapid surgical intervention to prevent and reduce complications of disease, as they are more prone to the development of complications.

Adhesions, significant bleeding and bile leak are not encountered in an uncomplicated gallbladder disease and hence treated by basic LC. We recommend advanced laparoscopic surgery that requires skills and extensive training, to be carried out in cases of chronic CCC, to reduce morbidity and:

- To achieve homeostasis (arresting intraoperative bleeds)
- To do adhesiolysis for dense adhesions
- For use of energy sources (bipolar, harmonic, ligasure, endoclips and endo-suturing)
- Expertise
- IOC (if required).

CONCLUSION

The patient safety in CCC can be increased by the presence of a multidisciplinary team (MDT). MDT comprises of physician, surgeons (general, gastro and hepato-pancreatico-biliary [HPB]), gastroenterologist, interventional radiologist, pathologist, microbiologist, biochemist, critical care specialists/intensivists, nephrologist, cardiologist and pulmonologists. Laparoscopic cholecystectomy for CCC should be considered as advanced laparoscopic surgery managed within a MDT setup as:

- Intraoperative and postoperative complications seen in CCC undergoing LC have their own specific characteristics.
- Bleeding is the major complication observed in CCC and requires surgical expertise and energy sources for its management. Adequate blood and blood products and informed consent for conversion is required in all patients of CCC.
- Bile duct injury in cases of CCC needs rescue procedures like IOC, intraoperative or early or delayed bile duct repair by Roux-en-Y hepaticojejunostomy, if local HPB surgery expertise is available or referred to higher center with drain *in situ*.
- Mirizzi's syndrome type II and beyond is best repaired by open Roux-en-Y-hepaticojejunostomy.
- There is a tendency to have resistant port site infections (SSI deep) in CCC.

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Single AstraZeneca COVID-19 Vaccine Dose Leads to 80% Lower Death Risk: Study

Data from the AstraZeneca COVID-19 vaccine rollout suggests that one dose of the vaccine leads to 80% lesser risk of death from the disease, stated Public Health England.

It further stated that protection against death provided by the Pfizer-BioNTech vaccine increases from about 80% after one dose to 97% after two doses, according to a new analysis. The study assessed new symptomatic cases of COVID-19 from December through April and individuals who died within 28 days of their positive test by vaccination status. Those who had one dose of AstraZeneca vaccine were 55% protected against death, while there was 44% protection after a single dose of Pfizer vaccine, in comparison with unvaccinated people. A PHE statement said, "Combined with the protection vaccines offer against becoming a case in the first place, this is equivalent to approximately 80% protection against mortality in individuals vaccinated with a single dose of either vaccine." (*ET Healthworld – Reuters*)

Neurologic Complications in Hospitalized COVID-19 Patients Common

According to a new global study, 8 in 10 patients hospitalized with COVID-19 develop neurologic complications. Additionally, these patients have greater odds of dying in hospital compared to their counterparts who do not have neurologic complications.

The Global Consortium Study of Neurologic Dysfunction in COVID-19 (GCS-NeuroCOVID) noted that around 82% of hospitalized COVID-19 patients had neurologic manifestations and a 6 times greater mortality risk. Of the 3,744 patients hospitalized with COVID-19, 82% were found to develop neurological manifestations, with the most common self-reported neurologic symptoms being headache (37%) and anosmia (loss of smell) or ageusia (loss of taste) (26%). Furthermore, the most common neurologic signs and/or syndromes included acute encephalopathy (49%), coma (17%) and stroke (6%). Meningitis and/or encephalitis were found to be rare (0.5%)… (M*edscape*)

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Seasonal Variation of Predominant Bacterial Growth in Sputum of Patients with AECOPD

SUMIT KHATRI*, SANJAY BHARTI†, KRISHNA GOPAL SINGH‡, KSHITIZ CHOURASIYA*

ABSTRACT

Both viruses and bacteria, either independently or in combination, have been implicated in exacerbations of chronic obstructive pulmonary disease. This study was conducted in a total of 100 patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) and showed most bacterial exacerbations occurred in summer and monsoon season and they were lesser in post-monsoon and winter.

Keywords: Acute exacerbation of chronic obstructive pulmonary disease, Global Initiative for Obstructive Lung Disease

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) contribute significantly to morbidity and mortality. Pathogen infection-related inflammation is a major cause of AECOPD. Bacteria-causing AECOPD vary between geographical areas and with time period also. Studies conducted in various countries showed the predominance of *Streptococcus pneumoniae*, followed by *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus* and other Gram-negative bacteria whilst those in India showed predominance either of *S. pneumoniae* or Gram-negative bacteria, e.g., *Pseudomonas aeruginosa*, Klebsiella and *Escherichia coli*. This study was conducted to see the variation with seasons in predominant bacterial growth.

MATERIAL AND METHODS

This was an observational (prospective, cross-sectional) study with a sample size of 100. The study was conducted at Pt BD Sharma Post Graduate Institute of Medical Sciences (PGIMS), Rohtak over a period of 1 year. All patients aged 40 years and above, presenting to Pulmonary Medicine ward, and fulfilling the AECOPD diagnostic criteria according to Global Initiative for Obstructive Lung Disease (GOLD) 2017 were evaluated by medical interview and physical examination.

Seasons of sputum sample collection were classified according to Indian Meteorological Department: Winter - *January to February*, Pre-Monsoon (Summer) - *March to May*, Monsoon - *June to September*, Post-Monsoon - *October to December*. Patients were requested to keep 2-3 mL of sputum after coughing, as far as possible, prior to starting antibiotics and corticosteroids. The sample was subjected to Gram's stain and bacterial culture and sensitivity. A sputum sample was considered adequate when <10 epithelial cells and >25 leukocytes (pus cells) were present per low magnification field. Gram's stain, culture and antibiotic sensitivity were done according to standard protocol.

All the data analysis was done using SPSS (Statistical Package for the Social Sciences) version 20. Student *t*-test and one way ANOVA was used for quantitative data, whereas Chi-square test was used for categorical data. Level of significance was assessed at 5%.

RESULTS

Two-thirds of the samples were collected in summer (36%) and monsoon (31%) and the rest were collected in post-monsoon (13%) and winter (20%) seasons. Overall, bacterial growth was present in 36% of sputum samples (Table 1).

Table 2 shows that higher growth was seen in summer and monsoon compared to winter and post-monsoon period. Bacterial growth was present in 43.3% of

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Table 1. Baseline Parameters of Patients

Parameters			No. of patients	Percentage (%)	Statistical test used
General characteristics	Age	41-50	6	6	Frequency distribution
		51-60	24	24	
		61-70	48	48	
		71-80	21	21	
		>80	1	1	
	Gender	Male	89	89	
		Female	11	11	
Sputum characteristics	Season of sputum collection	Summer	36	36	
		Monsoon	31	31	
		Post-Monsoon	13	13	
		Winter	20	20	
	Growth present	No. of patients	36	36	
	Sterile	No. of patients	64	64	

Table 2. Sputum Bacterial Growth and Seasons

	Summer and Monsoon	Post-Monsoon and Winter	Total	P value
No. of sputum samples analyzed	67	33	100	
No. of sputum samples with bacterial growth	29 (43.3%)	7 (21.2%)	36	0.031

Table 3. Sputum Samples and Bacterial Spectrum

Bacteria	No. of samples	Percentage of samples in which bacterial growth present
Citrobacter	2	5.5
S. aureus	3	8.4
E. coli	7	19.5
Klebsiella species	10	27.8
P. aeruginosa	14	38.8
Total	**36**	**36 (100)**

samples collected in summer and monsoon and 21.2% of samples collected in post-monsoon and winter.

Table 3 shows the predominant bacteria isolated were *P. aeruginosa* (14%), followed by Klebsiella species (10%), *E. coli* (7%) and Citrobacter (2%). The only Gram-positive bacterium, *S. aureus*, was grown in 3% of patients.

Figure 1 shows in summer, the most frequently isolated organism was *P. aeruginosa* and in monsoon, it was Klebsiella species, although *P. aeruginosa* was also grown in a good number of samples in monsoon. In post-monsoon, the growth of *P. aeruginosa* was higher than other bacteria. No predominance of any bacteria was seen in winter.

DISCUSSION

The purpose of our study was to observe the bacterial profile in various seasons.

In the present study, bacterial growth was present in 36% of sputum samples. This was significantly lower than that reported by Papi et al and Groenewegen et al, who found bacterial growth in 50-55% in AECOPD.

According to a systemic review by Uzun and colleagues, bacteria as the cause of AECOPD is reported from 30% to 55%. Prior use of antibiotics by patients

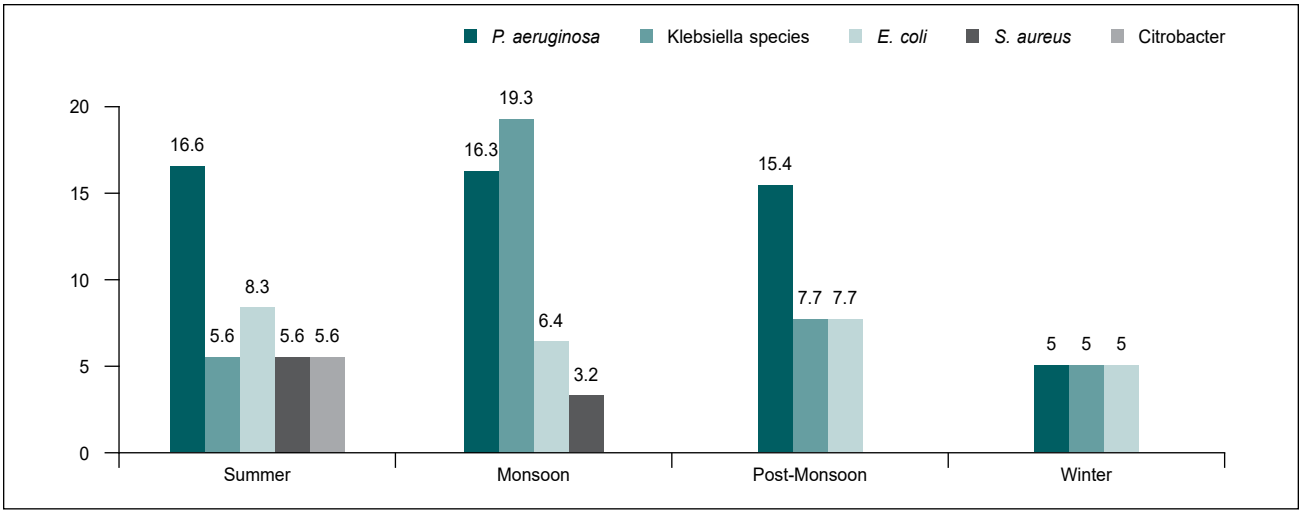

Figure 1. Sputum bacterial spectrum according to season.

within the past 3 months could be one of the causes of culture negativity. According to Chawla et al, sputum samples collected at times other than morning may not have bacterial growth. In our hospital-based study, patients were admitted any time during day or night and antibiotic treatment was given without any delay in such patients, sometimes before sputum collection. Collection of morning sputum sample was also not possible every time.

Furthermore, the classical microbial culture techniques using standard conditions can culture only 30% of bacteria. This may explain lower bacterial culture growth of 36% in our study.

Various cities have reported different hospital admission rates with seasons. In London, most of the exacerbations occurred in cold season, November-February. Whereas in New Delhi, there was no statistically significant difference in admissions per month in winter - November to February v/s summer - March to October.

In our study, admissions with AECOPD were more in summer (36%) and monsoon (31%) than in winter (20%) and post-monsoon (13%). Majority of the bacteria were isolated in summer and monsoon (43.3%) as compared to post-monsoon and winter (21.2%).

The low bacterial isolation in post-monsoon and winter could be because of higher viral exacerbations of COPD and/or allergic cause of AECOPD. Previous studies suggested that cold and humid environment might favor the occurrence of viral infections. Viruses may have important interactions with cold temperature. Allergens may also cause acute exacerbations of COPD.

CONCLUSION

This study concluded that maximum bacterial growth was seen in summer and monsoon season, and the dominant pathogen was *P. aeruginosa*. In post-monsoon and winter season, bacterial infections were less.

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Expert Panel Recommends Covaxin for Phase 2/3 Trials on 2- to 18-year Olds

An expert panel has recommended Bharat Biotech's COVID-19 vaccine – Covaxin - for phase II/III clinical trials on individuals aged 2-18 years, reported official sources.

The trial is set to be conducted among 525 subjects at several sites, including AIIMS Delhi, AIIMS Patna and Meditrina Institute of Medical Sciences, Nagpur. The Subject Expert Committee (SEC) on COVID-19 of the CDSCO contemplated Bharat Biotech's application to seek approval for phase II/III clinical trials to determine the safety, reactogenicity and immunogenicity of Covaxin in children aged 2-18 years. Following consideration, the committee recommended the proposed trials in that age group, with the condition that the company must submit the interim safety data of phase II clinical trial along with Data and Safety Monitoring Board (DSMBs) recommendations to the CDSCO prior to starting the phase III of the study… (*ET Healthworld – PTI*)

Vaccines Effective Against B.1.617 Variant of COVID-19, Says WHO

The WHO has said that the vaccines, therapeutics and diagnostics are effective against the B.1.617 variant of COVID-19.

WHO Representative to India, Dr Roderico H Ofrin, said that on the basis of what is known thus far as per discussions with global experts, vaccines, therapeutics and diagnostics continue to be effective against B.1.617 variant, which has been classified as a variant of concern. The B.1.617 of the coronavirus is the fourth variant that has been classified as one of global concern that calls for more tracking and evaluation. The three others strains include the ones that were first identified in the United Kingdom, South Africa and Brazil… (*NDTV – ANI*)

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Vaginal Estrogen Therapy in Postmenopausal Overactive Bladder

MANIDIP PAL*, T DEB†

ABSTRACT

Objective: To assess the efficacy of vaginal estrogen therapy in postmenopausal overactive bladder (OAB). **Study design:** It is an OPD (outpatient department) based prospective study. Postmenopausal women attending gynecology OPD with complaint of OAB were enrolled for the study. Women fulfilling the criteria for the study were given estradiol 2 mg vaginal tablet everyday for 2 weeks, then weekly twice for 10 weeks. Patients were assessed by 3-day bladder diary, Patient Global Impression scale, before and after the therapy. **Results:** Ninety-three patients completed the study. Increased frequency of micturition was cured in 92.5% cases; urgency and urge incontinence was cured in 74.2% cases. Patient's subjective feeling of improvement scale revealed only 12.9% women felt either no change or little better; rest all were happy. **Conclusion:** Local estrogen therapy in postmenopausal women with OAB resulted in a good outcome.

Keywords: Overactive bladder, estrogen, vaginal

Menopause causes different types of morbidity in women's lives – urinary incontinence is one of them. Postmenopausal women many a times complain of frequency, urgency, urge incontinence (overactive bladder or OAB). While evaluating them, ruling out infectious etiology (urinary tract infection) is very important. Next to infection, hypoestrogenism is thought to be the major etiological factor. The present study evaluates the efficacy of local estrogen in treating postmenopausal OAB.

MATERIAL AND METHODS

The study was conducted in the Dept. of Obstetrics and Gynecology, College of Medicine and JNM Hospital, Kalyani, Nadia, West Bengal. It was an OPD (outpatient department) based prospective study. Postmenopausal women attending gynecology OPD with complaint of OAB were enrolled for the study.

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Inclusion criteria were – 1) Patient should be at least 1 year postmenopausal; 2) increased frequency of micturition and nocturia (normal voiding habits ≤8 episodes/day and ≤2 episodes/night)[1]; 3) urgency of urination ± urge incontinence. Exclusion criteria were – 1) Undiagnosed vaginal bleeding; 2) endometrial hyperplasia, and other estrogen-dependent disease, especially malignancy; 3) hypertension (blood pressure systolic >160 mmHg, diastolic >100 mmHg); 4) previous thromboembolic episodes; 5) liver disease; 6) estrogen therapy within last 6 months.

Informed consent was obtained from all patients. All patients underwent a detailed history and clinical examination including breast, per abdominal, per vaginal examination, blood pressure measurement, etc. Complete blood count, liver and renal function tests, coagulation profile, Pap smear, pelvic ultrasonography were done for all the cases. Mid-stream urine culture and sensitivity was done routinely before starting estrogen therapy. If infection was present, it was cured with respective sensitive antibiotic. After that also, if OAB symptoms persisted then only vaginal estrogen therapy was started. Urodynamic study could not be done as there is no such facility in our setup. Patients were asked to maintain a 3-day bladder diary before starting therapy and also at the end of the therapy at 12 weeks. Estradiol vaginal tablet 2 mg was inserted in the posterior fornix every night for first 2 weeks; followed by weekly twice for 10 weeks. Total 12 weeks

therapy was given. The effect of treatment on patients' perception of urgency was evaluated by asking each patient to complete a three-point urgency perception scale at baseline and 12 weeks following treatment.

Patients described their experience when they felt the desire to urinate. The response options included: 1) Unable to hold urine; 2) Usually able to hold urine until I reach the toilet if I go immediately and 3) Usually able to finish my work before going to the toilet.[2] Patient's feelings were also assessed by Patient Global Impression (PGI) scale.[3] At the starting of the study, PGI of Severity (PGI-S) scale measured the severity of the disease. The woman was asked to check the one number that best described how her urinary tract condition was now − 1) Normal, 2) mild, 3) moderate, and 4) severe. It is a scale which measures the patient's subjective feeling about the severity of her condition. Result of the treatment is assessed by PGI of Improvement (PGI-I) scale at 12 weeks. This scale measures the patient's feeling of her OAB condition after the treatment – whether improved or not. Again she was asked to check the one number that best described how her urinary tract condition was now, compared with how it was before she began taking medication in this study – 1) Very much better; 2) much better; 3) a little better; 4) no change; 5) a little worse; 6) much worse and 7) very much worse.

RESULT

Hundred women were enrolled for the study. Four were unfit for estrogen therapy after investigations. Three were lost to follow-up. Total 93 women completed the trial. At the beginning of the study, increased

Table 1. Frequency of Micturition, Nocturia and Nocturnal Enuresis Before and After Therapy

Frequency of micturition	No.	%	Nocturia	No.	%
At starting			**At starting**		
9-15 times	38	39.6	3-4 times	13	13.5
16-20 times	43	44.8	5-6 times	4	4.2
>20 times	15	15.6	**Total**	**17**	**17.7**
Total	**96**		**After 12 weeks of therapy**		
After 12 weeks of therapy			3-4 times	2	11.8 (2/17)
≤8 times	86	92.5	**Nocturnal enuresis**		
9-15 times	7	7.5	At starting	5	5.2
Total	**93**		After 12 weeks of therapy	0	0

Table 2. Urgency and Urge Incontinence

	No.	%
At starting		
I am usually not able to hold urine	84	87.5
I am usually able to hold urine until I reach the toilet if I go immediately	12	12.5
I am usually able to finish my work before going to the toilet	0	0
Total	**96**	**100**
After 12 weeks of therapy		
I am usually not able to hold urine	23	24.7
I am usually able to hold urine until I reach the toilet if I go immediately	1	1.1
I am usually able to finish my work before going to the toilet	69	74.2
Total	**93**	**100**

Table 3. Patient Global Impression Scale

	No.	%
Patient Global Impression of Severity (PGI-S) scale (at the beginning)		
Normal	0	
Mild	19	19.8
Moderate	56	58.3
Severe	21	21.9
Total	**96**	**100**
Patient Global Impression of Improvement (PGI-I) scale (after 12 weeks of therapy)		
Very much better	69	74.2
Much better	12	12.9
A little better	7	7.5
No change	5	5.4
A little worse		
Much worse		
Very much worse		
Total	**93**	**100**

frequency of micturition >20 times was present in 15.6% cases, nocturia in 17.7% cases and nocturnal enuresis in 5.2% cases. Eighty-four (87.5%) patients had urge incontinence. Patient's subjective feeling revealed that 21.9% had severe problem.

At the end of 12 weeks of vaginal estrogen therapy, 92.5% women had no more increased frequency of micturition. There was no case of nocturnal enuresis. Urgency and urge incontinence was cured in 74.2% cases. Patient's subjective feeling of improvement scale revealed only 12.9% women felt either no change or little better; rest all were happy (Tables 1-3).

DISCUSSION

Local estrogen therapy in postmenopausal women resulted in a good outcome in relation to their improvement in OAB problem.

Hypoestrogenism affects the sensory threshold of the urinary tract, and this reduces the volume and time needed to change the first sensation to void into the feeling of imminent micturition, and in some subjects causes involuntary detrusor contraction.[4] This could be the reason why estrogen therapy helped in reducing the OAB symptoms in postmenopausal women.

Various studies have demonstrated that estrogen replacement can improve, or even cure, urinary stress and urge incontinence. High-dose estrogen can decrease the total number of voids in a 24-hour span, including nocturnal voids.[5] Cochrane database review 2009 also revealed that estrogen therapy can cure or improve urinary incontinence in women, especially urge incontinence.[6]

In evaluation of estradiol absorption from vaginal tablets in postmenopausal women, it was found that absorption of the drug is not so high to cause systemic side effect. Over 12 weeks of therapy also, absorption patterns remained consistent, and there were no accumulations of circulating E2.[7]

Cardozo et al[8] had performed a systematic review of the effects of estrogen therapy on symptoms suggestive of OAB in postmenopausal women. Eleven randomized trials were identified where total of 430 subjects were included. Estrogen (estriol, estradiol, conjugated estrogens or combination of estradiol and estriol) systemic or local vs. placebo was reviewed. Overall, all of the outcome variables, which included diurnal and nocturnal frequency, urgency, number of incontinence episodes, first sensation to void, and bladder capacity,

were significantly improved in patients given active treatment compared with those taking placebo. When the authors analyzed data separately for systemic and local therapies; however, they found that only numbers of incontinence episodes and first sensation to void were significantly improved in patients taking systemic treatment, whereas local treatments had beneficial effects on all outcomes. Based on these findings, it was concluded that estrogen therapy may be effective in relieving the symptoms suggestive of OAB, but local administration may be the most effective route of administration.

In light of available evidence, it seems preferable to use vaginal estrogens rather than systemic for the management of menopause-related bladder problems.[9]

In our study, though 100 patients were initially recruited, 93 could complete the whole course. Other studies on effect of vaginal estrogen on urinary incontinence in postmenopausal women had sample sizes of 40 (Enzelsberger et al,[10] used estriol cream 1 mg/day, 3 mg/day), 59 (Nelken et al,[11] estradiol vaginal ring vs. oral oxybutynin), 110 (Cardozo et al,[12] used 17-beta estradiol tablet) cases.

CONCLUSION

The bladder and its surrounding structures are rich in estrogen receptors and there are demonstrable physiological and anatomical changes that occur around and immediately after menopause. The prevalence of many bladder symptoms, such as frequency, urgency and incontinence (OAB) does seem to increase around menopause. Hence estrogen therapy, especially vaginal therapy which has less systemic side effects than oral form, appears to be helpful in managing such situation.

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Study on Correlation Between MELD Score and Hematological Abnormalities in Predicting Prognosis in Patients with Chronic Liver Disease

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ABSTRACT

Abnormalities in hematological indices are frequently encountered in cirrhosis of liver. Multiple causes contribute to the occurrence of hematological abnormalities. Recent studies suggest that the presence of hematological cytopenias is associated with a poor prognosis in cirrhosis. This study was conducted on 43 patients with chronic liver disease to assess the hematological abnormalities. We found 37 (90%) patients had hemoglobin <12 g/dL. Macrocytic anemia was the predominant type, followed by normocytic normochromic and microcytic type. Twenty-four patients had platelets <1.5 lakh/dL; 28 patients had prolonged prothrombin time (PT) and international normalized ratio (INR). Twelve patients showed peripheral smear picture suggestive of pancytopenia. We observed patients with anemia had model of end-stage liver disease (MELD) score above 15% compared to patients without anemia. We also observed patients with MELD score above 20% had mean platelets of 1.5 lakh/dL compared to lower score. Thirty-eight patients had splenomegaly. We also observed that mean platelet count in patients with hepatic encephalopathy was low and they also had prolonged PT.

Keywords: Anemia, cirrhosis, hematological spectrum in cirrhosis

The liver is the largest organ in the body and amongst the most complex organs that has a wide range of functions. It has a major role to play in the metabolism of carbohydrates, proteins and lipids, inactivation of various toxins, metabolism of drugs, hormones, synthesis of plasma proteins and maintenance of immunity. The liver has a significant role in maintenance of blood homeostasis - from being a primary site of hematopoiesis in fetal life to maintenance of hematological parameters in postnatal life. It stores iron, folic acid and vitamin B12, and secretes clotting factors and inhibitors. Therefore, a range of hematological abnormalities are encountered in association with liver diseases.[1]

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Decompensated chronic parenchymal liver disease is one of the most common diseases encountered in day-to-day practice. Because of chronic disease many hematological abnormalities are present in these patients. The hematological abnormalities in a chronic disease add morbidity to the primary pathology and increase the mortality. Hence, it becomes necessary to investigate the hematological abnormalities and hemostatic abnormalities to decrease the comorbidity. Abnormalities in hematological parameters are commonly seen in patients with cirrhosis. Abnormal hematological indices (HIs) in cirrhosis have a multifactorial pathogenesis that includes sequestration due to portal hypertension, altered bone marrow stimulating factors, bone marrow suppression due to viruses, toxins or excess alcohol consumption, etc.[2-4]

Abnormalities in HIs are associated with an increased risk of complications such as bleeding and infection.

Various studies on patients with varying stages of cirrhosis have shown a prevalence of hematological abnormalities ranging from 6% to 77%.[4-6]

In an analysis of homogenous patients with compensated Child-Pugh Class A/B cirrhosis, 84% were found to have abnormalities in the HIs, defined as a platelet count of

≤150 × 10^9/L, white blood cell (WBC) count of ≤400 × 10^9/L or hemoglobin level ≤135 g/L for men and 115 g/L for women. Thirty-two percent of these patients had a combination of cytopenias.[7] Thrombocytopenia was the most common single abnormality and thrombocytopenia and leukopenia was the most common combined abnormality.[8]

The study was conducted at RajaRajeswari Medical College and Hospital, Bangalore. The study was conducted to assess the hematological abnormalities and derangements and the nature of hematological abnormalities mainly to reduce the morbidity. Broadly the hematological abnormalities are viewed under abnormalities in red blood cells (RBCs), WBCs, platelets and coagulation profile.

MATERIAL AND METHODS

This study was conducted at RajaRajeswari Medical College and Hospital, Bangalore. Institutional Ethical Committee clearance was obtained before the study. Informed consent was obtained from all patients who met with inclusion criteria.

Inclusion Criteria

- Patients above 18 years.
- Patients presenting with signs and symptoms of chronic liver disease.
- Patients with ultrasound evidence of chronic liver disease with portal hypertension.

Exclusion Criteria

- Patients with underlying malignancy or known primary hepatocellular carcinoma.
- Patients with primary coagulation disorder or primary abnormalities of hemostatic function.
- Patients with acute hepatic failure.
- Patients with pre-existing anemia due to other causes.
- Patients suffering from end-stage medical diseases like chronic obstructive pulmonary disease, coronary artery disease, cardiac failure, chronic kidney disease.

All patients who met with inclusion criteria were evaluated with detail history and clinical examination. Blood sample was taken for assessment of liver function tests, complete hemogram, coagulation profile, peripheral blood smear, renal function tests and ultrasound abdomen and baseline upper gastrointestinal (GI) endoscopy were done for all patients. Results were analyzed with statistics.

RESULTS

We conducted the study on 43 patients with clinical and sonological diagnosis of chronic liver disease with various etiologies. In all, data were available for 41 patients. Hematological parameters, including anemia, leukocyte count, prothrombin time (PT) and platelet count were assessed in the subjects and were categorized under the different groups of model of end-stage liver disease (MELD) score. The relationship of these variables with MELD score was studied and statistical analysis was done.

This was an observational noninterventional correlational clinical study. Maximum number of patients was in 41-50 years and 30-40 years of age groups. Only 6 patients were above 50 years. Eighty-eight percent of patients were males and 12% were female. Alcohol consumption (38 patients) was common etiology for all these patients and 3 patients had cirrhosis of cryptogenic origin. Fifty percent of patients had history of alcohol consumption for more than 10 years. Ascites, jaundice, generalized weakness and edema of limbs were common symptoms at admission.

Nine patients had bleeding manifestations and 37 patients had hemoglobin <12 g/dL (Table 1). Macrocytic anemia was predominant type. Thirteen patients had leukopenia, 8 patients had leukocytosis and 20 patients had normal leukocyte count. Thrombocytopenia was observed in 24 patients. Twenty-eight patients had prolonged PT and international normalized ratio (INR) (Table 2). Elevated total bilirubin was observed in 16 patients; 36 patients had serum albumin <3 g. Enlarged spleen of more than 10 cm was observed in 38 patients (Table 3). We also observed peripheral smear suggestive of pancytopenia in 12 patients. We found 16 patients with upper GI evidence of varices. Most of patients with platelets <1.5 lakhs/dL had findings of upper GI bleed, but only 2 patients with platelets above 1.5 lakh had upper GI bleed. There was significant drop in hemoglobin and in platelets in patients with MELD score above 20%. Mean corpuscular volume (MCV) was prolonged in patients with MELD score above 20%. This finding was statistically significant. In our study, only 2 patients had MELD score <9%. Most other patients had score above 20% and about 7 patients had very high score (Table 4).

We also found there was increase in PT in patients who had MELD score above 15%. Mean duration of alcohol consumption was also >15 years in patients with MELD score above 20%. There was significant rise in MELD score with fall in hemoglobin. Mean platelet count

Table 1. Clinical Investigations

Variables	No. of patients (n = 41)	Percentage (%)
MCV		
<80	3	7.3
80-95	15	36.6
>95	23	56.1
Hemoglobin (g/dL)		
<10	25	61.0
10-12	12	29.3
12-14	2	4.9
>14	2	4.9
PS		
Macrocytic	23	56.1
Microcytic	7	17.1
Normocytic	11	26.8
Total count		
<4000	13	31.7
4000-11000	20	48.8
>11000	8	19.5
Platelets		
<0.50	2	4.9
0.50-1.50	22	53.7
>1.50	17	41.5
ESR		
<35	11	26.8
35-60	26	63.4
>60	4	9.8

MCV = Mean corpuscular volume; PS = Peripheral smear; ESR = Erythrocyte sedimentation rate.

Table 2. Coagulation Profile

	No. of patients (n = 41)	Percentage (%)
PT, INR		
<20	13	31.7
20-40	27	65.9
>40	1	2.4
Raised INR		
<3 sec	0	0.0
3-5 sec	22	53.7
>5 sec	19	46.3

PT = Prothrombin time; INR = International normalized ratio.

Table 3. Spleen Size in Patients Studied

	No. of patients (n = 41)	Percentage (%)
No	1	2.4
<10	2	4.9
10-15	34	82.9
>15	4	9.8

Table 4. MELD Score Distribution of Patients Studied

MELD	No. of patients	Percentage (%)
1-9%	2	4.9
10-19%	11	26.8
20-29%	21	51.2
30-39%	7	17.1
Total	**41**	**100.0**

was <1.5 lakhs/dL in patients with MELD score above 15%. We observed low mean serum albumin and total protein among patients with high MELD score; this observation was statistically significant (Table 5). Only 2 patients had MELD score <10%. Rest all patients had high score. MELD score above 30% was observed in 7 patients. We observed Child-Pugh score of category B in 19 patients and category C was seen in 7 patients. Most of the patients with high MELD score presented with jaundice, ascites and edema. Few patients had bleeding symptoms. There was significant correlation between high MELD score and hepatic encephalopathy in our patients.

DISCUSSION

The vital functions of many organs in the body depend directly or indirectly on the liver. The hematopoietic system is an exception. Beginning early in fetal life, it exerts a profound influence on the formation and maintenance of blood. It acts as a hematopoietic organ and after birth it plays an active and important role in the production of many elements necessary for homeostasis and hematopoiesis. Indirectly, when the liver is damaged by either acute or chronic disease, the effect

Table 5. Comparison of Clinical Variables According to MELD Score of Patients Studied

Variables	MELD				P value
	1-9%	10-19%	20-29%	30-39%	
Age (years)	47.00 ± 0.00	52.00 ± 14.30	48.90 ± 12.43	45.29 ± 10.64	0.731
Duration	15.00 ± 0.00	18.36 ± 10.22	14.19 ± 10.25	9.14 ± 8.01	0.294
MCV	87.00 ± 0.00	95.09 ± 3.86	94.33 ± 12.34	93.71 ± 13.73	0.808
Hemoglobin (g/dL)	12.50 ± 0.00	10.23 ± 1.91	9.32 ± 2.30	10.74 ± 2.96	0.187
Total count	5700.00 ± 424.26	7514.55 ± 5256.15	6200.00 ± 3932.43	10500.00 ± 6318.49	0.222
Platelets	2.63 ± 0.33	1.72 ± 0.95	1.52 ± 0.87	1.59 ± 1.07	0.440
ESR	42.50 ± 17.68	48.64 ± 13.42	46.09 ± 14.49	48.43 ± 16.83	0.948
PT INR	16.00 ± 0.00	21.36 ± 3.61	23.65 ± 6.00	28.43 ± 27.45	0.521
INR	1.11 ± 0.01	1.69 ± 0.48	1.95 ± 0.57	2.51 ± 2.52	0.348
Total bilirubin	1.40 ± 0.00	2.95 ± 1.75	6.06 ± 4.37	17.23 ± 14.96	0.001**
OT	23.00 ± 0.00	57.18 ± 19.43	79.48 ± 55.37	117.71 ± 55.73	0.034**
PT	13.00 ± 0.00	21.55 ± 6.85	31.81 ± 19.65	66.00 ± 46.35	0.002**
Total protein	8.20 ± 0.00	6.36 ± 0.84	6.15 ± 0.74	6.03 ± 0.85	0.008**
Albumin	3.90 ± 0.00	2.24 ± 0.54	2.25 ± 0.41	2.49 ± 0.82	0.001**
Sodium (mEq/L)	133.00 ± 7.07	135.73 ± 4.52	131.81 ± 3.54	127.57 ± 1.51	0.001**
Potassium	4.60 ± 0.00	4.27 ± 0.45	4.05 ± 0.52	3.81 ± 0.54	0.142

**Statistically significant.

on these functions may be catastrophic. Liver plays a major role in carbohydrate, lipid and protein metabolism. Its role in hematological manifestations is also important. Loss of liver function can manifest as subtle metabolic abnormalities and derangements in hematological parameters, which can ultimately culminate in grave complications. Liver plays a major role in maintaining the hematological parameters and maintain the homeostasis. Liver stores iron, vitamin B12 and folic acid, which are necessary for normal hematopoiesis. Liver also secretes the clotting factors and inhibitors, and keeps the homeostasis in equilibrium. Chronic liver disease is usually accompanied by hypersplenism. Diminished erythrocyte survival is frequent. Dietary deficiencies, alcoholism, bleeding and difficulties in hepatic synthesis of proteins used in blood formation or coagulation add to the complexity of the problem.

In our study, we found anemia and thrombocytopenia as two major hematological abnormalities. And presence of these abnormalities can affect prognosis of patients which was observed by elevated MELD score. And thus, these abnormalities can contribute to patient's mortality. We also observed significant relation between prolonged PT and increase in MELD and Child-Pugh score. Once again, presence of thrombocytopenia and prolonged PT can contribute to development of hepatic encephalopathy and adverse prognosis. We observed most of the patients with thrombocytopenia and prolonged PT had evidence of upper GI bleed, which could lead to the development of hepatic encephalopathy and anemia.[9,10] Hence, identification and treatment of all abnormal HIs are a vital part of the management of patients with chronic liver disease. Similar results were observed is previous studies by Selvamani et al. Among the 100 patients, 52 patients had normochromic and normocytic anemia, 30 patients had microcytic anemia and 16 patients had macrocytosis. Two had dimorphic anemia and thrombocytopenia was found in 46 patients.[9] Rajkumar Solomon et al, in their study, found 50% of the patients had thrombocytopenia (<1 lakh). Out of the 13 patients who had an upper GI bleed, 3 patients had

normal platelet counts and the remaining had counts <1 lakh. They also found that most of the patients with thrombocytopenia had prolonged PT.[1]

CONCLUSION

Apart from serum protein, albumin, which reflects synthetic function of liver, alteration in hematological parameters are telltale signs of chronicity of liver disease. Efforts can be made to normalize the hematological parameters, so that we can reduce the mortality and morbidity of these patients effectively.

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UK Allows Hugging Close Family and Friends as it Eases Lockdown

People in the United Kingdom will now be able to hug close family and friends and meet indoors at pubs, restaurants and cinemas from next week, as the lockdown rules are eased further.

Hugging will be a personal choice as people are allowed to meet indoors in a group of six or as two households, staring May 17. However, social distancing rules will continue to remain in place for shops, pubs, restaurants and offices.

Infection rates in the UK are at their lowest since September, according to Prime Minister's office, while deaths and hospitalizations are at their lowest since July. UK chief medical officers also brought down the COVID-19 alert level from four to three, suggesting that the epidemic is in general circulation while transmission is not high or rising exponentially… (*NDTV – Bloomberg*)

New Monoclonal Antibody Drug Helps COVID Patients Breathe on Their Own

As a new monoclonal antibody drug was added to treatments for hospitalized COVID-19 patients who were still breathing on their own, the drug - lenzilumab – led to significant improvement in their likelihood of not requiring invasive mechanical ventilation, report researchers.

There were 540 patients in the randomized trial who were being given different standard treatments. Half of them were also given lenzilumab through three intravenous infusions. Researchers noted that patients receiving lenzilumab had 54% better chance of surviving without requiring mechanical ventilation. In patients receiving steroids and remdesivir, the addition of lenzilumab led to improved survival without the need for mechanical ventilation by 92%. The findings were posted on *medRxiv* ahead of peer review… (*Reuters*)

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Scrub Typhus and Guillain-Barre Syndrome: A Rare Association

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ABSTRACT

Scrub typhus, also called bush typhus, is a zoonotic disease caused by *Orientia tsutsugamushi*, a Gram-negative bacterium. Its presentation ranges from nonspecific febrile illness to a much severe form of disease like cardiovascular, renal, hepatic and neurological involvement. Guillain-Barre syndrome (GBS) is one of the rare presentations following scrub typhus infection. Hence, we are reporting a case of a 65-year-old male, farmer by occupation, presenting to us with GBS following scrub typhus infection. Thus, GBS should always be considered if a patient of acute febrile illness during infection or during recovery phase develops progressive areflexic paralysis.

Keywords: Bush typhus, Guillain-Barre syndrome, *Orientia tsutsugamushi*, scrub typhus

Scrub typhus is a zoonotic disease, also called bush typhus or tsutsugamushi disease. It is caused by a Gram-negative intracellular bacterium, *Orientia tsutsugamushi* which belongs to family *Rickettsiae*. It is transmitted through the bite of mites' larvae (chiggers), which belongs to the family *Trombiculidae*.[1] Although the disease has a worldwide distribution, most of the cases are reported from the so called "tsutsugamushi triangle", which is a wide area bounded by Pakistan, India and Nepal in the West, Siberia, Japan, China and Korea in the North and Indonesia, Philippines, Australia and the Pacific islands in the South. There are an estimated 1 million new scrub typhus infections each year and over 1 billion people around the world are at risk. Scrub typhus disease ranges from mild nonspecific febrile illness to a much severe form of disease such as cardiovascular, renal, hepatic and neurological involvement. The neurological complications of scrub typhus include aseptic meningitis, meningoencephalitis, seizures, delirium, hearing loss, cerebellitis, myelitis.[2,3] Guillain-Barre syndrome (GBS) may be one of the rare presentations seen following scrub typhus infection and have been rarely reported worldwide.[4-6] Hence, we are reporting a case of GBS following scrub typhus infection.

CASE REPORT

A 65-year-old male, farmer by occupation, presented to us with complaints of fever and cough for last 10 days, pain in both lower limbs for last 5 days, weakness in both lower limbs for the last 4 days, which rapidly progressed to involve both upper limbs within a day. There was no history of numbness, paresthesias, cranial nerve and bladder and bowel involvement. On general physical examination, patient was found conscious, poorly nourished, anemic, mild pedal edema without eschar mark on the body. Neurological examination revealed hypotonia in all four limbs, power 3/5 in both lower limbs, whereas 4/5 in both upper limbs. Deep tendon reflexes were absent in both upper and lower limbs, plantar response was found mute bilaterally. Sensory system and cerebellar system examination was normal and there were no signs of meningeal irritation.

On the basis of history and clinical examination, we made our provisional diagnosis of acute febrile illness with acute onset rapidly progressive pure motor ascending areflexic quadriparesis, probably GBS.

For confirmation of the above diagnosis, the patient was thoroughly investigated and the following results were found: complete blood count (hemoglobin [Hb] - 9.8 g/dL, total leukocyte count [TLC] - 11,700/mm^3,

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platelet count - 3,09,000/mm^3), blood urea - 63 mg/dL, serum creatinine - 0.75 mg/dL and liver function tests (serum glutamic-oxaloacetic transaminase [SGOT] - 143 U/L, serum glutamic-pyruvic transaminase [SGPT] - 103 U/L, alkalikne phosphatase [ALP] - 138 U/L). Malaria parasite quantitative Buffy coat test (MPQBC), Dengue rapid test, Venereal Disease Research Laboratory (VDRL), hepatitis B surface antigen (HBsAg), anti-HCV (hepatitis C virus), human immunodeficiency virus (HIV), immunological profile, chest X-ray and ECG were found normal. Scrub typhus immunoglobulin (IgM) antibody test was positive (IgM capture enzyme-linked immunosorbent assay [ELISA] test).

Patient underwent lumbar puncture and cerebrospinal fluid (CSF) was examined which revealed albuminocytological dissociation (protein - 102 mg/dL, cell count - 0 cells/mm^3). Nerve conduction study was done in median, ulnar, peroneal, tibial and sural nerves and revealed prolonged distal latency with reduced amplitude and normal conduction velocity suggestive of both demyelinating and axonal neuropathy.

Patient was treated for scrub typhus as well as GBS in form of capsule doxycycline 100 mg PO twice a day for 7 days along with intravenous immunoglobulin (IVIg) 2 g/kg body weight in divided doses for 5 days. Patient started improving after 1 week; his fever subsided and his motor power in upper as well as lower limbs improved significantly (5/5 in both upper limbs and 4/5 in both lower limbs). Hence, patient was discharged and advised follow-up in medical OPD.

DISCUSSION

Scrub typhus is a well-known mite-borne disease distributed throughout the world, but predominantly seen in Asia Pacific regions. Patients usually present with fever, headache, malaise, suffused face, lymphadenopathy, hepatosplenomegaly and eschar. There are a wide range of neurological manifestations reported with scrub typhus which includes delirium, myelitis, cerebral hemorrhage, hearing loss, 6th and 7th nerve palsy, trigeminal neuralgia, opsoclonus, transient parkinsonism, myoclonus, acute disseminated encephalomyelitis and GBS.[7,8] The pathological findings in central nervous system (CNS) in scrub typhus include mononuclear cell exudates in leptomeninges and presence of typhus nodules that are distributed throughout brain substance.[9] A study showed that CNS was involved at least slightly in almost all patients of scrub typhus; however, focal neurological deficit occurs rarely.[10] Kim et al[3] had described 6th and 7th nerve palsy with scrub typhus infection.

GBS is one of the rarest neurological presentations following scrub typhus fever seen in adults. It is an acute fulminating polyradiculoneuropathy, possibly autoimmune, post-infectious or post-vaccination in nature. It is characterized by rapidly progressive areflexic motor paralysis with or without sensory involvement and without bowel and bladder involvement. Common variants of GBS are acute inflammatory demyelinating polyneuropathy, acute motor axonal neuropathy, acute motor sensory axonal neuropathy and Miller-Fisher syndrome. The common infectious agents which can cause GBS are *Campylobacter jejuni*, cytomegalovirus, Epstein-Barr virus, HIV, influenza and mycoplasma.

The exact mechanism of GBS is unknown but it might possibly occur as a result of cell-mediated immunological response to non-self antigen that misdirects to host nerve tissue via a resemblance of epitope mechanism, called molecular mimicry. *O. tsutsugamushi* antibody or antigens presented on infected cells are suspected to activate mimicry on myelin cells or peripheral nerve axons, which elicits immune reactions similar to autoimmune diseases.

Diagnosis of GBS is mainly based on clinical and laboratory findings. The following is the criteria for diagnosis of GBS (Asbury criteria):[11]

Required

- Progressive weakness
- Areflexia
- Duration <4 weeks
- Exclude other causes (vasculitis, toxins, porphyria).

Supportive

- Symmetrical weakness
- Mild sensory involvement
- Cranial nerve involvement
- Absence of fever
- Typical CSF finding (albumin-cytological dissociation)
- Nerve conduction study suggestive of demyelination.

CONCLUSION

Guillain-Barre syndrome is a rare neurological complication of scrub typhus. It should always be considered if a patient of acute febrile illness during infection or during recovery phase develops progressive areflexic paralysis. The patient should be diagnosed and treated as early as possible to reduce morbidity and

mortality. Thus, our case report calls attention to physicians for the possibility of GBS in association with scrub typhus.

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COVID Severity Starts in Normal BMI Range, Particularly in Young

The risk of severe outcomes with COVID-19 tends to increase with excess weight in a linear manner starting in the normal body mass index (BMI) ranges, and the effect seems to be independent of obesity-related diseases such as diabetes and stronger among younger individuals and Blacks, suggests new research.

The authors noted that even a small rise in BMI above 23 kg/m² is a risk factor for adverse outcomes after COVID-19 infection. The prospective, community-based study, assessed data on around 7 million individuals registered in the UK QResearch database from January 24 through April 30, 2020. Patients had a mean BMI of 27 kg/m². A total of 13,503 patients (0.20%) were admitted to the hospital, with 1,601 (0.02%) admitted to an ICU and 5,479 (0.08%) died after testing positive. The findings are published in the *Lancet Diabetes Endocrinology*… (*Medscape*)

FDA Authorized Pfizer-BioNTech Vaccine for Emergency Use in Adolescents

The US FDA expanded the EUA for the Pfizer-BioNTech COVID-19 vaccine to include adolescents 12-15 years of age. The EUA originally issued on December 11, 2020 for administration of the vaccine in individuals 16 years of age and older was amended by the agency. The FDA ascertained that the vaccine developed by Pfizer and BioNTech met the criteria for amendment of the EUA, and the known and potential benefits of the vaccine in people 12 years of age and above outweigh the known and potential risks, thus supporting the use of the vaccine in this population group… (*FDA*)

WHO Classifies Virus Strain in India as 'Variant of Concern'

Health experts have declared the coronavirus mutation in India as a "variant of concern".

The WHO in Geneva stated that the B.1.617 variant circulating in India is more contagious and might also have increased resistance to vaccine protections. WHO's COVID-19 lead, Maria Van Kerkove, said that they have classified this as a variant of concern at the global level.

Meanwhile, the virus has been surging in several countries. However, rapid vaccination programs have enabled some of the affluent nations to start moving towards normality… (*ET Healthworld – AFP*)

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Indian Journal of Clinical Practice, Vol. 32, No. 1, June 2021

A Rare Case of Secondary Abdominal Pregnancy with Placental Implantation Between Leaves of Broad Ligament

SEEMA DWIVEDI*, NEENA GUPTA†, GN DWIVEDI‡, SHEFALI PANDE#

ABSTRACT

Abdominal pregnancy is a relatively uncommon condition with an incidence of 1 in 10,000 live births while the incidence of advanced abdominal pregnancy is about 1 in 25,000 births. The overall maternal mortality rate associated with abdominal pregnancy is high. It usually occurs after tubal abortion or rupture. Continuation of pregnancy is very rare without manifestation of hemoperitoneum. We report a case of secondary abdominal pregnancy following rupture of cornual pregnancy.

Keywords: Abdominal pregnancy, tubal pregnancy

Abdominal pregnancy is a relatively uncommon condition. The incidence of abdominal pregnancy is 1 in 10,000 live births and the incidence of advanced abdominal pregnancy is approximately 1 in 25,000 births. The overall mortality rate associated with abdominal pregnancy is 0.5-8.0%. Delay in diagnosis is mainly due to difficulties in clinical assessment caused by variance in presentation. It usually occurs after tubal abortion or rupture. Very rarely, it occurs following rupture of rudimentary horn. Continuation of pregnancy is very rare without manifestation of hemoperitoneum.

Abdominal pregnancy has been characterized as implantation in the peritoneal cavity, exclusive of tubal, ovarian or intraligamentary pregnancy. This rare obstetric complication has a high maternal mortality and even higher perinatal mortality. It can be primary or secondary, with secondary abdominal pregnancy being the most common type. Studdiford defined three criteria for diagnosing primary peritoneal pregnancies: 1) normal fallopian tubes and ovaries; 2) no evidence of uteroperitoneal fistula and 3) a pregnancy that is exclusively related to the peritoneal surface and is early enough to rule out the possibility of secondary implantation after a primary nidation in the tube.

Secondary abdominal pregnancy is a condition where the embryo grows in the abdominal cavity after its expulsion from the fallopian tube or another site of its primary development.

Secondary abdominal pregnancy often occurs after early rupture of a tubal ectopic pregnancy into the peritoneal cavity.

Risk factors for abdominal pregnancy and ectopic pregnancy are same. As soon as abdominal pregnancy is identified, immediate laparotomy with removal of the fetus is recommended. This is a life-threatening condition, therefore, expectant management involves a risk of sudden life-threatening intra-abdominal bleeding and poor fetal prognosis.

We report a case of secondary abdominal pregnancy following rupture of cornual pregnancy.

CASE REPORT

A 32-year-old lady, third gravida with 2 live issues presented with 8 months pregnancy with intrauterine death, ascites and poor general condition.

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During her antenatal period, patient complained of pain abdomen at 2 months of gestational age, for which she consulted some general practitioner and sonography was advised.

Her ultrasonography (USG) report showed 8 weeks live gestation; fetal pole, fetal cardiac activity and fetal movements were seen. Mild free fluid was present in pelvis. Inflamed bowel loops were present.

After this, patient continued to have dull aching pain in the abdomen throughout her pregnancy, with acute exacerbations off and on.

She gave history of acute pain abdomen, for which she again consulted some general practitioner and repeat USG was done. USG report showed single live fetus of 23 weeks with regular cardiac activity and placenta in right lateral position, Grade 1. Moderate amount of free fluid was present in peritoneal cavity.

Then she experienced a third episode of exacerbation of pain abdomen. Patient presented in emergency with history of severe pain abdomen, two episodes of vomiting and abdominal distention for 1 day. Her USG report showed a single dead fetus of 31 weeks in breech presentation and maternal ascites with a few septations.

Obstetric history: Her previous two deliveries were term vaginal deliveries at home, 8 and 4 years back, respectively.

On examination, patient was dyspneic and unable to lie down due to pain abdomen. Her pulse rate was 120/min, blood pressure (BP) was 110/70 mmHg with respiratory rate of 30/min. Her temperature was 98.4°F and pallor was +++ with no edema.

On per abdominal examination, uterus was 34 weeks size. Tenderness was present in epigastrium and right lumbar area, fetal parts could not be assessed and fetal heart sounds could not be heard.

On per speculum examination, no bleeding was seen. On per vaginal examination, os was closed and cervix was found to be firm, tubular and posteriorly placed.

Here, patient was admitted in emergency and after routine investigations, induction of labor was started with prostaglandin E2 (PGE2) gel and misoprost 50 ug per vaginally 4-hourly, which was unsuccessful. After 24 hours of induction, patient was taken up for lower segment cesarean section (LSCS).

On opening the abdomen, about 3.5 liters of hemoperitoneum was found. Dead macerated fetus of approximate 30 weeks gestational age was found in abdominal cavity (Fig. 1). Whole of the placenta was adherent and going into leaves of the broad ligament on

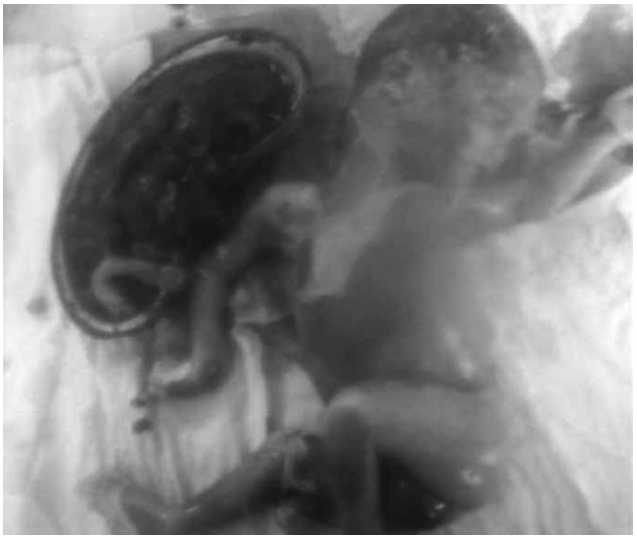

Figure 1. Dead fetus along with placenta.

right side with right cornual defect with healed margins and no active bleed from that side. Bladder was badly adherent to anterior surface of uterus. Placenta was found implanted between the leaves of broad ligament, bleeding was present from placental site. Decision for hysterectomy was taken and hysterectomy was done.

DISCUSSION

The patient probably had a cornual pregnancy which ruptured around 8 weeks, when she experienced pain abdomen. Due to rupture, free fluid was present in pelvis and bowel loops were inflamed. After the rupture, placenta got implanted between the two leaves of broad ligament, while the fetus continued to grow intra-abdominally in an intact amniotic sac.

Abdominal pregnancy is a rare obstetric complication that is associated with high maternal and perinatal mortality. Ultrasound, magnetic resonance imaging (MRI), computed tomography (CT) scan and laparotomy have a role in helping differentiate primary from secondary abdominal pregnancy.

Early rupture of tubal ectopic pregnancy usually precedes a secondary abdominal pregnancy. Therefore, a suggestive history is often available. There may be spotting or irregular bleeding with abdominal pain, nausea, vomiting, flatulence, constipation, diarrhea and abdominal pain. Common complications include fetal malpresentation, extreme anterior displacement of the cervix, failure of spontaneous onset of labor and failure of artificial induction of labor. Small fetal parts may be palpable through the vaginal fornices and detected outside the uterus.

As in this case, despite repeated USG, diagnosis was not made. Therefore, we should have a constant suspicion in our mind while dealing with such cases. Nearly 50% of diagnoses can be missed on ultrasound, but MRI and CT are both excellent diagnostic tools to diagnose secondary abdominal pregnancy.

Adequate preoperative evaluation with appropriate diagnostic techniques can help with a timely diagnosis, and preoperative treatment such as methotrexate administration to limit blood loss at surgery can help with maximal placental removal. The placenta continues to grow throughout the pregnancy, therefore, methotrexate administration is advised at all gestational ages.

CONCLUSION

This is a rare case of secondary abdominal pregnancy with placental implantation between the leaves of broad ligament. Ultrasound can miss 50% of the diagnoses, as was seen in our patient. A high index of suspicion is needed in such cases.

Preoperative systemic methotrexate followed by laparotomy to remove the fetus and placenta can potentially limit the blood loss, and appears to be a rational approach in a patient who has an abdominal pregnancy with placental implantation to the abdominal viscera and blood vessels. If the placenta is attached to vital organs, it should be left behind during surgery. Early diagnosis is the key to reduce associated maternal morbidity and mortality.

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Dr Reddy's may Distribute Sputnik Light

Dr Reddy's Labs will distribute in India the single-dose COVID-19 vaccine, Sputnik Light, approved for use by Russia.

The company already has a distribution deal with Russian Direct Investment Fund (RDIF) for Sputnik V. A source said that Sputnik Light will also be distributed by Dr Reddy's Laboratories in India, following necessary approvals. The single-shot vaccine has a 79.4% efficacy 28 days after administration, compared to 92% efficacy shown by the two-dose Sputnik V. The vaccine will be priced below $10 per dose, stated RDIF. (*ET Healthworld – TNN*)

Canada Authorized Pfizer COVID-19 Vaccine for 12- to 15-year Olds

Canada authorized the use of Pfizer COVID-19 vaccine for children aged 12-15 years.

It became the first country to do so for this age group. The country's health ministry made the decision on the basis of data from phase III clinical trials conducted on children in this age group. It was determined that the vaccine is safe and effective in this age group. The country has already authorized the use of Pfizer vaccine in individuals above 16 years of age. (*BBC*)

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About Sameer Malik Heart Care Foundation Fund

"Sameer Malik Heart Care Foundation Fund" it is an initiative of the Heart Care Foundation of India created with an objective to cater to the heart care needs of people.

Objectives

- Assist heart patients belonging to economically weaker sections of the society in getting affordable and quality treatment.
- Raise awareness about the fundamental right of individuals to medical treatment irrespective of their religion or economical background.
- Sensitize the central and state government about the need for a National Cardiovascular Disease Control Program.
- Encourage and involve key stakeholders such as other NGOs, private institutions and individual to help reduce the number of deaths due to heart disease in the country.
- To promote heart care research in India.
- To promote and train hands-only CPR.

Activities of the Fund

Financial Assistance

Financial assistance is given to eligible non emergent heart patients. Apart from its own resources, the fund raises money through donations, aid from individuals, organizations, professional bodies, associations and other philanthropic organizations, etc.

After the sanction of grant, the fund members facilitate the patient in getting his/her heart intervention done at state of art heart hospitals in Delhi NCR like Medanta – The Medicity, National Heart Institute, All India Institute of Medical Sciences (AIIMS), RML Hospital, GB Pant Hospital, Jaipur Golden Hospital, etc. The money is transferred directly to the concerned hospital where surgery is to be done.

Drug Subsidy

The HCFI Fund has tied up with Helpline Pharmacy in Delhi to facilitate patients with medicines at highly discounted rates (up to 50%) post surgery.

The HCFI Fund has also tied up for providing up to 50% discount on imaging (CT, MR, CT angiography, etc.)

Who is Eligible?

All heart patients who need pacemakers, valve replacement, bypass surgery, surgery for congenital heart diseases, etc. are eligible to apply for assistance from the Fund. The Application form can be downloaded from the website of the Fund. http://heartcarefoundationfund.heartcarefoundation.org and submitted in the HCFI Fund office.

Important Notes

- The patient must be a citizen of India with valid Voter ID Card/ Aadhaar Card/Driving License.
- The patient must be needy and underprivileged, to be assessed by Fund Committee.
- The HCFI Fund reserves the right to accept/reject any application for financial assistance without assigning any reasons thereof.
- The review of applications may take 4-6 weeks.
- All applications are judged on merit by a Medical Advisory Board who meet every Tuesday and decide on the acceptance/rejection of applications.
- The HCFI Fund is not responsible for failure of treatment/death of patient during or after the treatment has been rendered to the patient at designated hospitals.
- The HCFI Fund reserves the right to advise/direct the beneficiary to the designated hospital for the treatment.
- The financial assistance granted will be given directly to the treating hospital/medical center.
- The HCFI Fund has the right to print/publish/webcast/web post details of the patient including photos, and other details. (Under taking needs to be given to the HCFI Fund to publish the medical details so that more people can be benefitted).
- The HCFI Fund does not provide assistance for any emergent heart interventions.

Check List of Documents to be Submitted with Application Form

- Passport size photo of the patient and the family
- A copy of medical records
- Identity proof with proof of residence
- Income proof (preferably given by SDM)
- BPL Card (If Card holder)
- Details of financial assistance taken/applied from other sources (Prime Minister's Relief Fund, National Illness Assistance Fund Ministry of Health Govt of India, Rotary Relief Fund, Delhi Arogya Kosh, Delhi Arogya Nidhi), etc., if anyone.

Free Diagnostic Facility

The Fund has installed the latest State-of-the-Art 3 D Color Doppler EPIQ 7C Philips at E – 219, Greater Kailash, Part 1, New Delhi.
This machine is used to screen children and adult patients for any heart disease.

Free Education and Employment Facility

HCFI has tied up with a leading educational institution and an export house in Delhi NCR to adopt and to provide free education and employment opportunities to needy heart patients post surgery. Girls and women will be preferred.

Laboratory Subsidy

HCFI has also tied up with leading laboratories in Delhi to give up to 50% discounts on all pathological lab tests.

Help Us to Save Lives

The Foundation seeks support, donations and contributions from individuals, organizations and establishments both private and governmental in its endeavor to reduce the number of deaths due to heart disease in the country. All donations made towards the Heart Care Foundation Fund are exempted from tax under Section 80 G of the IT Act (1961) within India. The Fund is also eligible for overseas donations under FCRA Registration (Reg. No 231650979). The objectives and activities of the trust are charitable within the meaning of 2 (15) of the IT Act 1961.

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About Heart Care Foundation of India

Heart Care Foundation of India was founded in 1986 as a National Charitable Trust with the basic objective of creating awareness about all aspects of health for people from all walks of life incorporating all pathies using low-cost infotainment modules under one roof.

HCFI is the only NGO in the country on whose community-based health awareness events, the Government of India has released two commemorative national stamps (Rs 1 in 1991 on Run For The Heart and Rs 6.50 in 1993 on Heart Care Festival- First Perfect Health Mela). In February 2012, Government of Rajasthan also released one Cancellation stamp for organizing the first mega health camp at Ajmer.

Objectives

- Preventive Health Care Education
- Perfect Health Mela
- Providing Financial Support for Heart Care Interventions
- Reversal of Sudden Cardiac Death Through CPR-10 Training Workshops
- Research in Heart Care

Heart Care Foundation Blood Donation Camps

The Heart Care Foundation organizes regular blood donation camps. The blood collected is used for patients undergoing heart surgeries in various institutions across Delhi.

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This Fund is dedicated to the memory of **Sameer Malik** who was an unfortunate victim of sudden cardiac death at a young age.

- HCFI has associated with Shree Cement Ltd. for newspaper and outdoor publicity campaign
- HCFI also provides Free ambulance services for adopted heart patients
- HCFI has also tied up with Manav Ashray to provide free/highly subsidized accommodation to heart patients & their families visiting Delhi for treatment.

http://heartcarefoundationfund.heartcarefoundation.org

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Pregnancy with Eisenmenger Syndrome: A Challenge to Obstetrician

KIRAN PANDEY*, S PANDE†

ABSTRACT

Eisenmenger syndrome is defined as the development of pulmonary hypertension in response to a left-to-right cardiac shunt with consequent bidirectional or reversal (right-to-left) of shunt flow. Maternal mortality in the presence of Eisenmenger syndrome is reported to be 30-50%. If the patient continues her pregnancy against advice, a well-coordinated multidisciplinary team approach is advocated. Here, we report a case of pregnancy with Eisenmenger syndrome and its successful outcome.

Keywords: Pregnancy, Eisenmenger syndrome, maternal mortality

Congenital heart disease patients are reaching reproductive age due to improved healthcare facilities and more of them are conceiving. Eisenmenger syndrome involves pulmonary hypertension with a reversed or bidirectional shunt at the atrial, ventricular or aortopulmonary level.

Eisenmerger syndrome in pregnancy is usually associated with high mortality rates of around 30-50%.

Such patients are advised against pregnancy or to interrupt pregnancy before 10th gestational week, but if they continue pregnancy against advice, a well-organized multi-specialist care is required.

Here, we report a successful pregnancy in a woman with Eisenmenger syndrome.

CASE REPORT

A 30-year-old woman, $G_3P_1A_1$, gestational age (GA) 36 weeks, presented to our setting with chief complaints of pain abdomen for 6 hours and breathlessness (dyspnea on less than ordinary activity and orthopnea) for 3 days. She had marked limitation of physical activity (New York Heart Association [NYHA] Class III).

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Obstetric history: Previous lower segment cesarean section (LSCS) 4 years back (Indication – cephalopelvic disproportion [CPD]), miscarriage in first trimester 3 years back.

Past history: She had no history of dyspnea previously. She had a previous uneventful cesarean section. Her symptoms were much worse in this pregnancy.

Recently diagnosed with pulmonary arterial hypertension (PAH) and atrial septal defect (ASD).

Echocardiography revealed moderate-sized ASD, severe PAH, moderate pulmonary regurgitation (PR) and tricuspid regurgitation (TR).

Routine antenatal investigations were within normal limits.

General examination: Blood pressure (BP) - 124/80 mmHg, pulse rate - 92/min, Pallor +, edema -, cyanosis ++.

Systemic examination: *CVS:* S1 normal, S2 single-narrow split, pulmonary ejection systolic murmur, enlarged right heart.

P/A: Uterus 36 weeks size, longitudinal, cephalic, moderate contractions, FHS + tachycardia, scar tenderness present.

As per cardiological review, she was treated with propped up position and oxygen inhalation. Injection ampicillin 2 g and injection gentamicin 80 mg were given as infective endocarditis prophylaxis.

Decision for emergency LSCS was taken. Her cesarean section was performed. A healthy baby of weight 2.9 kg was born. Her bilateral tubal ligation was performed.

Intraoperative and postoperative period was uneventful. Continuation of same cardiac treatment was done. Patient was discharged on 8th post-op day in a good condition with a healthy baby.

DISCUSSION

The hemodynamic changes occurring in pregnancy are not well-tolerated among women with Eisenmenger syndrome.

Most women with Eisenmenger syndrome have a delicately balanced state and this balance must not be disrupted. In women with Eisenmenger syndrome and a low cardiac output state, the right ventricle is compromised, which may fail to meet the demands of increasing blood volume and cardiac output in pregnancy.

A fixed pulmonary vascular resistance and failure to increase pulmonary blood flow may not be able to hold an increase in cardiac output. A compromised cardiovascular system may not be able to tolerate massive fluctuations in blood volume, pre- and postpartum. The decrease in peripheral vascular resistance during pregnancy can amplify right-to-left shunting, and aggravate maternal hypoxemia and cyanosis.

Pregnancy is a cause of significant mortality in women with Eisenmenger syndrome. A systematic review of published studies from 1978 to 1996 examined maternal mortality rates in women with Eisenmenger syndrome and demonstrated mortality rates of 56%.

The degree of maternal hypoxemia is a key predictor of fetal outcome. Pre-pregnant arterial oxygen saturation of 85% or less is tied to live birth rate as low as 12%, while saturation of 90% or more is associated with a 92% live birth rate.

This can be explained by an increase in spontaneous abortions, risk of premature delivery of around 30-50% and low birth weights.

Maternal mortality, in association with Eisenmenger syndrome, has been reported to be as high as 30-50%. Gleicher et al reported a 34% mortality associated with vaginal delivery and a 75% mortality associated with cesarean section.

Mortality is high if pregnancy is continued. Therefore, abortion is the treatment of choice for women ho have Eisenmenger syndrome. For patients who wish to continue gestation, hospitalization in the second trimester is highly recommended.

Intrauterine growth restriction is observed in 30% of pregnancies on account of maternal hypoxemia. Furthermore, premature labor is encountered in around 50-60% of cases and the high perinatal mortality rate of around 28% is often attributed to prematurity. In a study conducted among women with Eisenmenger syndrome, 47% delivered at term, 33% delivered between 32 and 36 weeks, and 20% delivered prior to 31 weeks of gestation.

Continuous administration of oxygen, anticoagulation and pulmonary vasodilator is disputed. While there is a scarcity of controlled trials, a Brazilian series of 13 pregnancies revealed that there was improved maternal mortality (23%) with oxygen therapy, heparin before delivery and warfarin after 48 hours. About 60% of infants were live births, mostly premature.

There seems to be no evidence to support the choice of vaginal or cesarean delivery based on cardiac reasons. However, vaginal delivery is tied to a lower average blood loss at the cost of escalated maternal effort.

Mortality among patients with Eisenmenger syndrome who concieve remains high. All patients should receive appropriate advice regarding contraception. If a patient becomes pregnant, clinicians must offer therapeutic termination of pregnancy. However, if pregnancy is continued against medical advice, treatment strategies mentioned above may help, with prolonged hospital care, pre- and postpartum.

CONCLUSION

Although pregnancy should be discouraged in women with Eisenmenger syndrome, it can be successful with careful monitoring and a well-coordinated multi-specialist care, as elucidated in this case.

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■■■■

Sotrovimab, the Latest Addition to the Anti-COVID-19 Armamentarium

Sotrovimab, a monoclonal antibody, has been accorded EUA by the US FDA for use in patients aged 12 years and older with lab-confirmed mild-to-moderate COVID-19 who are at risk of progression to severe disease characterized by hospitalization or even death.

Sotrovimab is a monoclonal antibody that is specifically directed against the spike protein of SARS-CoV-2. It prevents virus entry into the cells by preventing the virus from attaching to the cells.

As per the FDA, sotrovimab is not authorized for use in the following patients because of apprehension that it may worsen clinical outcomes in them. These include patients:

- Who are hospitalized due to COVID-19
- Who require oxygen therapy due to COVID-19
- Who require an increase in baseline oxygen flow rate due to COVID-19 (in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity).

Dose and administration: Single dose (500 mg) intravenously.

Side effects: Anaphylaxis, infusion-related reactions, rash, diarrhea.

The evidence for the beneficial role of sotrovimab comes from an interim analysis from a phase 1/2/3 randomized, double-blind, placebo-controlled clinical trial. Five hundred eighty-three nonhospitalized adult patients with mild-to-moderate COVID-19 were randomized to receive either sotrovimab or placebo. Treatment with sotrovimab reduced severe outcomes by 85%. Hospitalization or death occurred in 21 (7%) patients who received placebo compared to 3 (1%) patients treated with sotrovimab.

Sotrovimab was also found to exhibit neutralizing activity against viral variants in experimental studies, including activity against the variants detected in the UK, South Africa, Brazil, California and India.

A fact sheet on sotrovimab is available on the FDA website.

The FDA had earlier granted EUAs to two combination products of monoclonal antibodies for emergency use.

- Bamlanivimab 700 mg + etesevimab 1400 mg
- Casirivimab 1200 mg + imdevimab 1200 mg.

(*Source: US FDA, May 26, 2021*)

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COVID-19 Presented with Bilateral Lower Limb Deep Vein Thrombosis: A Rare Case Report

ARCHANA GOKHROO*, PUNEET PATEL†, MEGH OBERAY†, RAMIT SINGH PALA†, MANOJ MAHERA†

ABSTRACT

Novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a public health emergency of international concern. In this report, we present a case of a 50-year-old man who presented with mild fever, dry cough and shortness of breath. With suspicion of COVID-19 atypical pneumonia, nasopharyngeal and oropharyngeal swabs were taken and reverse transcription polymerase chain reaction (RT-PCR) was done and found positive. On day 3rd of admission, he complained of left lower limb swelling, pain, warmth and tenderness which was progressively increasing and also appeared in right lower limb in next 2 days. He had no risk factors for deep vein thrombosis. Bilateral lower limb venous color Doppler ultrasound revealed dilatation and thrombosis in the left external iliac vein, left common femoral vein up to left popliteal vein and its distal branches & left great saphenous vein and in the right external iliac vein, right common femoral vein up to right saphenofemoral junction, with bilateral saphenofemoral junctions incompetence. Anticoagulation therapy was given along with COVID-19 management and patient improved gradually. Currently, there is minimal data available highlighting bilateral deep vein thrombosis in patients infected with COVID-19. This case aims to arouse the healthcare providers for awareness of deep vein thrombosis in COVID-19 case.

Keywords: COVID-19, deep vein thrombosis, pulmonary thromboembolism, SARS-CoV-2

On December 31, 2019, it was informed to the World Health Organization (WHO) that a cluster of cases of pneumonia of unknown cause has been detected in Wuhan City, China. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which caused the pneumonia soon became widespread globally, leading to a pandemic, which has been associated with substantial morbidity and mortality. Novel coronavirus disease 2019 (COVID-19) has spread to more than 200 countries, and the death toll remains very high. Healthcare providers continue to see new and frightening displays of its pathogenicity. Symptoms are similar to the common cold, with most notable symptoms of COVID-19 being fever and dyspnea.[1,2] The disease is highly contagious, and the WHO's weekly epidemiological update on 16 May 2021 reported a total number of confirmed cases 162,184,263 and 3,364,446 confirmed deaths.[3] The SARS-CoV-2 enters host cells through the binding of spike glycoprotein to the angiotensin-converting enzyme 2 (ACE2),[4] sialic acid receptor, transmembrane protease serine 2 (TMPRSS2) and extracellular slow cell matrix metalloproteinase (CD147). This condition, which causes endothelial dysfunction, is exacerbated by hypoxia and causes thrombosis by increasing blood viscosity as well as the signaling pathway associated with the hypoxia transcription factor. We present here a case involving a 50-year-old male patient with COVID-19 who developed bilateral deep vein thrombosis (DVT).

CASE REPORT

A 50-year-old male admitted to suspected COVID-19 intensive care unit (ICU) in RNT Medical College, Udaipur, Rajasthan with history of mild fever, dry cough and shortness of breath for 5-6 days. He had no comorbidity like diabetes mellitus, hypertension, coronary artery disease, stroke, chronic obstructive lung disease, asthma, hyperlipidemia, cancer or any other history of surgery, trauma, paralysis, paresis or recent cast, bedridden and insect bite in recent past. His vital signs included a temperature of 99°F, pulse

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rate of 120/min, blood pressure of 100/60 mmHg, respiratory rate of 30/min and oxygen saturation of 60% on room air. Therefore, he was put on noninvasive ventilation.

On physical examination, crepitation was present in both the lung fields, more on left side than right side. No obvious abnormalities were found on the rest of the examination. An electrocardiogram (ECG) showed sinus tachycardia with no acute ST-T segment changes. A chest X-ray posteroanterior view showed multifocal and bilateral ground glass opacities in both lung fields. Laboratory data showed elevated white blood count of 21 × 10^3/mm^3 (with 87.9% granulocytes and 8.1% lymphocytes), hemoglobin of 13.2 g/dL, hematocrit at 40.6% and platelet count of 303 × 10^3/mm^3. The biochemistry reports were within the normal range except for aspartate aminotransferase - 47 U/L (normal range = 15-37 U/L), alkaline phosphatase - 129 U/L (normal range = 46-116 U/L), total protein - 6.0 g/dL (normal range = 6.4-8.2 g/dL), serum albumin - 2.1 g/dL (normal range = 3.4-5.0 g/dL) and also elevated C-reactive protein (CRP) level - 246.77 mg/L (normal range = <5.0 mg/L), lactate dehydrogenase - 962.27 U/L (normal range = <200 U/L), serum ferritin - 373.20 ng/mL (normal range = 22.00-322.00 ng/mL) and D-dimer - 4,983 ng/mL (normal range = <500 ng/mL). His interleukin (IL)-6 level was 4.93 pg/mL (normal value = 0.0-6.4 pg/mL) and prothrombin time-international normalized ratio (PT-INR) value 23 seconds/1.94, respectively. Because of patient presentation, chest X-ray finding and lymphopenia, COVID-19 reverse transcription polymerase chain reaction (RT-PCR) test of nasopharyngeal and oropharyngeal swabs was sent and found positive. The patient received antiviral treatment including remdesivir injection with low molecular weight heparin, steroids, antibiotics and supportive treatment according to the Ministry of Health and Family Welfare (MoHFW) and Indian Council of Medical Research (ICMR) Updated Clinical Management Protocol for COVID-19.[5] On day 3rd of admission, he complained of left lower limb swelling, pain, warmth and tenderness which was progressively increasing and also appeared in right lower limb in next 2 days.

On physical examination, the pain and tenderness were present in both lower limbs and on dorsiflexion of the foot with the leg extended, pain presented in calf of the leg (Homan's sign positive) (Fig. 1). Bilateral lower limb venous color Doppler ultrasound revealed dilatation and thrombosis in the left external iliac vein and left common femoral vein up to left popliteal vein and its distal branches and left great saphenous vein and dilatation and thrombosis in the right external iliac vein and right common femoral vein up to right saphenofemoral junction and bilateral saphenofemoral junctions incompetence (Fig. 2).

Other tests including antinuclear antibody, anti-double stranded DNA, rheumatoid factor test, anti-cardiolipin antibodies, factor V Leiden and protein C, protein S tests were normal. Since the patient was hemodynamically stable, tissue plasminogen activator (TPA) administration was not considered. His symptoms significantly improved with anticoagulation. The hypercoagulable panel did not show any other active risk factor for thrombotic conditions. After a week, COVID-19 RT-PCR of nasopharyngeal and oropharyngeal swabs was negative. The swelling and tenderness reduced gradually first in right lower limb and then slowly from left lower limb. The patient was discharged with continuous anticoagulation treatment (warfarin 3 mg daily) and advised to follow-up after 7 days with PT-INR reports (PT-INR value on day of discharge was 23.3 seconds/1.94, respectively).

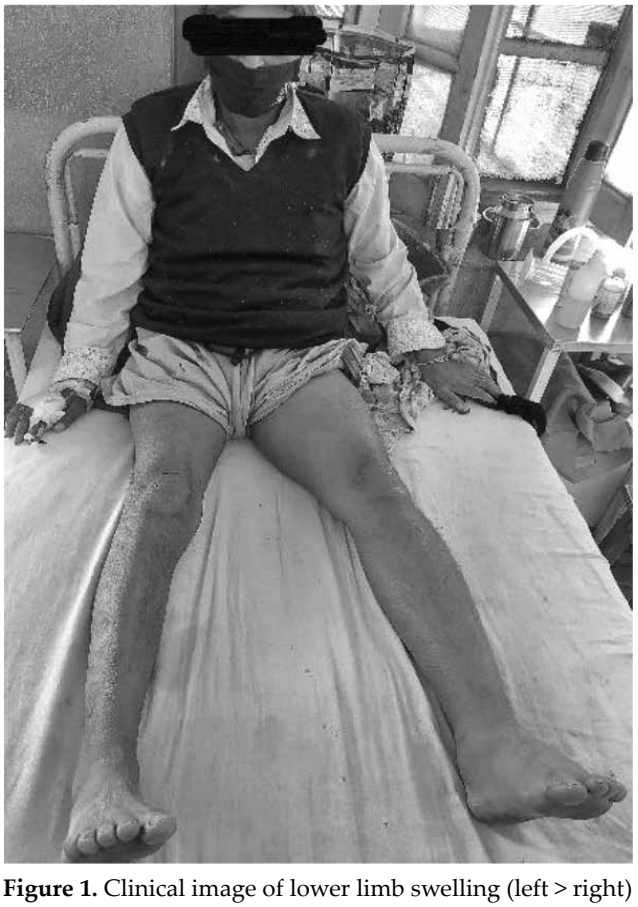

Figure 1. Clinical image of lower limb swelling (left > right) due to deep vein thrombosis.

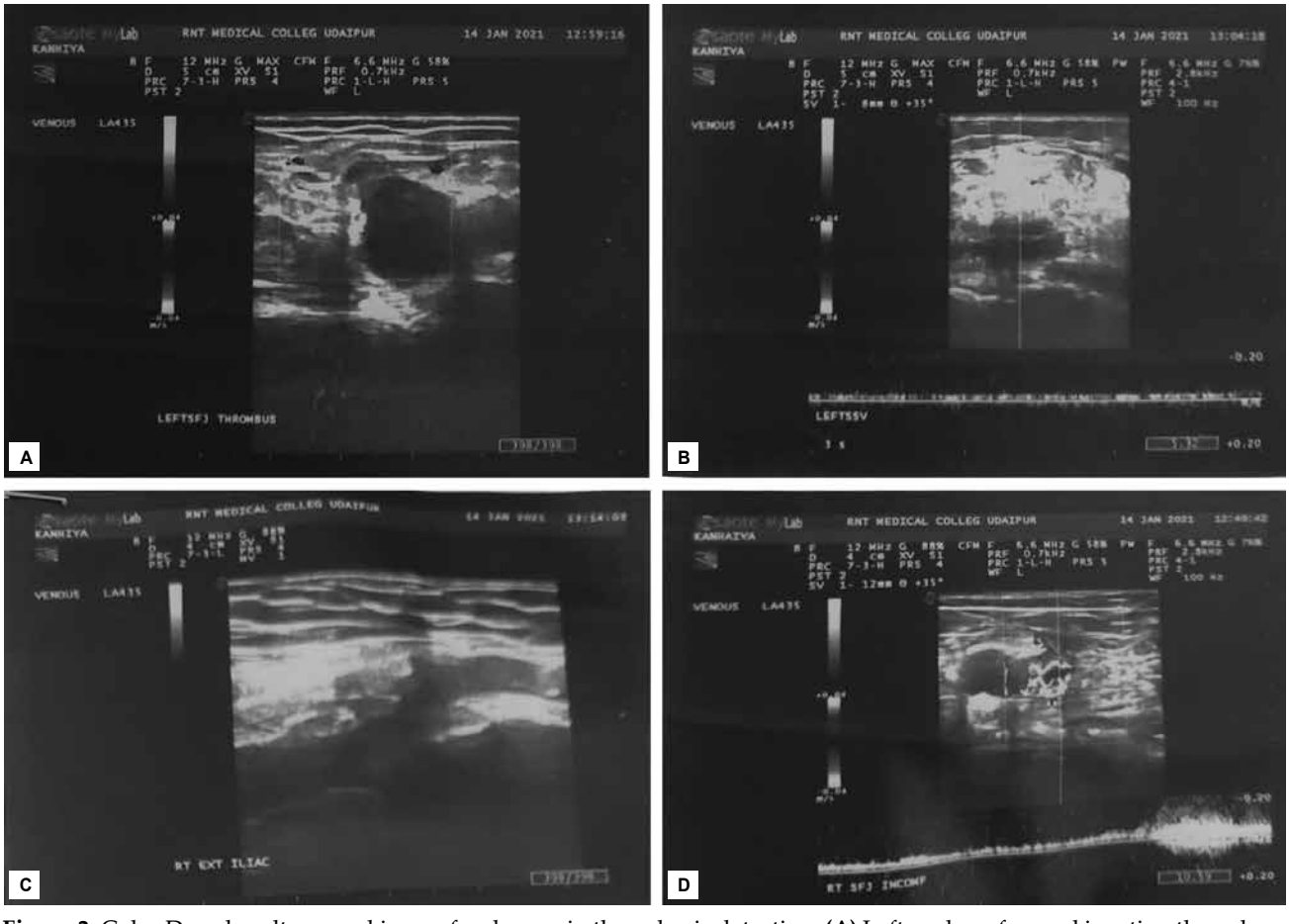

Figure 2. Color Doppler ultrasound image for deep vein thrombosis detection, **(A)** Left saphenofemoral junction thrombus, **(B)** Left short saphenous vein, **(C)** Right external iliac vein thrombus and **(D)** Right saphenofemoral junction incompetence.

DISCUSSION

The COVID-19 pandemic started in December 2019 when a cluster of patients presented with pneumonia of unknown etiology that was associated with a seafood market in Wuhan, China.[6] The source of this condition was identified as a novel coronavirus, which was later named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease caused by this virus was named as coronavirus disease 2019 (COVID-19). Coronaviruses are enveloped ribonucleic acid (RNA) viruses found among animals such as pigs, bats, camels and cats. As humans acquire these viruses, they commonly result in mild-to-moderate upper respiratory diseases. Three of the coronaviruses are now known to cause severe, and fatal disease in humans, which include severe acute respiratory syndrome (SARS) coronavirus, Middle East respiratory syndrome (MERS) coronavirus and SARS-CoV-2.[7]

Emerging evidence, though limited, has shown venous thromboembolism as a complication of COVID-19.[8] The possible mechanism may be that coronavirus attacks the human body through the enzyme ACE2, which is distributed over blood vessels and various organs.[9] The virus then causes cytokine storm, which can increase blood clotting problems and damage. Finally, the blood clots of deep vein thrombosis can be caused by anything that prevents blood from circulating or clotting normally, such as injury to a vein, surgery, certain medications and limited movement but the exact cause of deep vein thrombosis caused by COVID-19 is still unknown.

Viral infections can cause an imbalance between pro- and anticoagulant states during the course of the disease and it is often associated with the disruption of the vascular endothelium.[10] Several pathways involving the coagulation cascade, including raised von Willebrand factor, can lead to the development of fibrin clots. These clots breakdown, resulting in the elevation of D-dimer levels and fibrin degradation product levels. Both of these are tied to poor prognosis in COVID-19 patients, including the need for ICU admission, and

death. The activation of systemic coagulation, associated with the immobility due to bed rest heightens the risk of venous thromboembolism.

Klok et al and Middeldorp et al[8,11] advise against prophylactic treatment-dose anticoagulation in patients with COVID-19 admitted to the hospital and advocate the use of a lower threshold for diagnostic tests to assess thrombotic complications including deep vein thrombosis and pulmonary embolism. More research is required to understand if pre-emptive and prolonged treatment dose anticoagulation results in a favorable clinical outcome in patients with COVID-19 infection.

CONCLUSION

As COVID-19 continues to lead to significant mortality, more data is emerging that is exposing its perplexing pathogenicity. Meanwhile, the presentation of venous thromboembolism in patients with COVID-19 remains an unusual finding. It is imperative for healthcare providers to be mindful of this unique association to make necessary diagnostic evaluations and provide appropriate treatment for the patients.

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CDC Website Stresses Coronavirus Spreads in the Air

The US CDC has updated its explanations on the transmission of coronavirus, emphasizing that inhalation is one of the key ways in which the virus is spread and has now placed less emphasis on the risk of contracting it from surfaces.

The changes to the CDC website conform to a shift in the agency's advice to emphasize that the virus spreads through air.

CDC said on its updated website, "COVID-19 spreads when an infected person breathes out droplets and very small particles that contain the virus. These droplets and particles can be breathed in by other people or land on their eyes, noses or mouth. In some circumstances, they may contaminate surfaces they touch. People who are closer than 6 feet from the infected person are most likely to get infected." (*CNN*)

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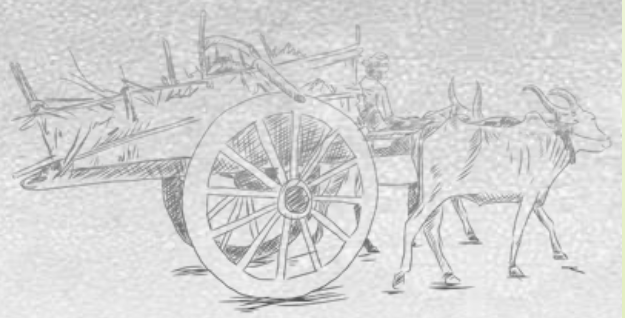

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Indian Journal of Clinical Practice, Vol. 32, No. 1, June 2021

Aggressive Angiomyxoma of Vulva: A Rare Case of Soft Tissue Tumor

SHREYASI KARMAKAR*, NALINI ARORA†, BIBHAS SAHA DALAL‡, NADEEM HOSSAIN#

ABSTRACT

Aggressive angiomyxoma is a rare mesenchymal tumor occurring commonly in females in reproductive age. It has a propensity of local recurrence. We describe a case of a 75-year-old post hysterectomy woman presenting with a large pedunculated mass in clitoris and vulva.

Keywords: Aggressive angiomyxoma, smooth muscle tumor, recurrence

Aggressive angiomyxoma is a rare, slow growing, morphologically distinctive, myxoid neoplasm involving mainly the genital, perineal and pelvic region of women, predominantly in reproductive age. The peak incidence is in the fourth decade of life. In male, it is recognized in inguinal region, along the spermatic cord, scrotum or pelvic cavity. It is six times more common in females than in males.[1] The commonest site reported is vulva in women. Local recurrence rate is about 30%.[2] Its incidence and prevalence in the community is unknown due to its rarity. The World Health Organization (WHO) defines aggressive angiomyxoma as a "tumor of uncertain differentiation".

The objective of this article is to report a case of a patient with aggressive angiomyxoma of clitoris, to analyze the histological and immunohistochemical findings as well as to discuss the therapeutic possibilities.

CASE REPORT

A 75-year-old post hysterectomy woman, with uncontrolled diabetes, presented in Gyne OPD on June 2017 with rapidly growing mass in the clitoral region for 6 months. On clinical examination, a soft polypoidal, nontender mass of 12 × 10 cm size was noted in lower part of mons pubis and clitoris with smooth surface (Fig. 1). It was free from underlying bone. The inguinal lymph nodes were not enlarged. Vault and vagina were healthy and no pelvic mass was noted.

Preoperative investigations, whole abdomen and pelvic ultrasonography were normal but blood sugar level was high. Excision of the mass was performed in July 2017 after proper glycemic control. Her postoperative period was uneventful.

The tumor was sharply marginated, with no adherence or infiltration into surrounding soft tissues noted. Cut section showed solid, gelatinous, glistening surface with intralesional hemorrhages (Fig. 2).

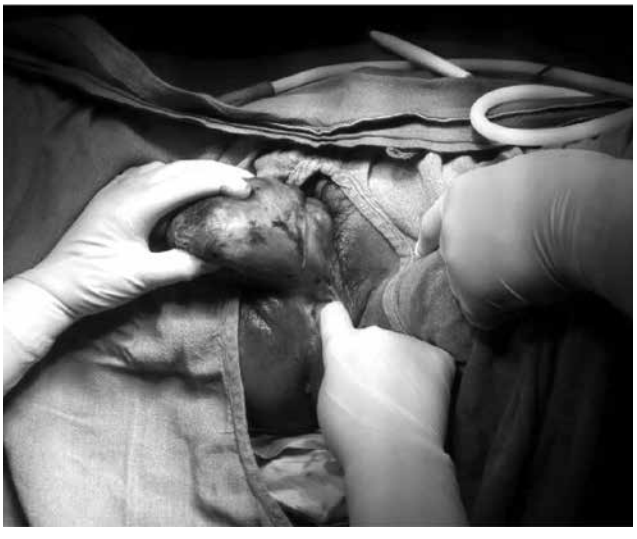

Figure 1. A large mass arising from the mons pubis and clitoris.

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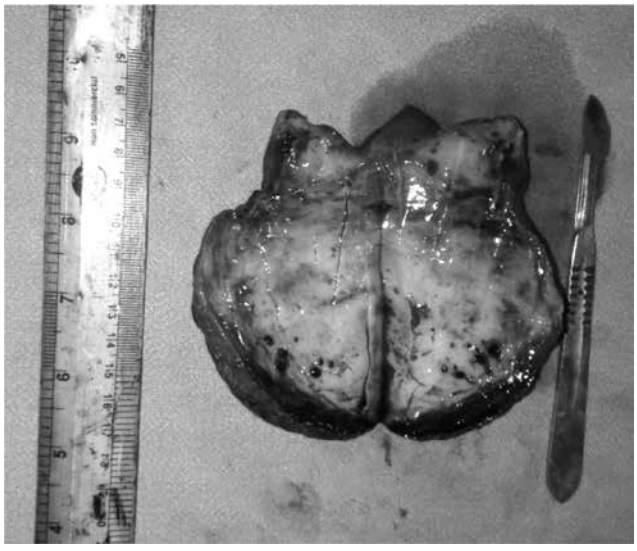

Figure 2. Solid mass showing intralesional hemorrhage.

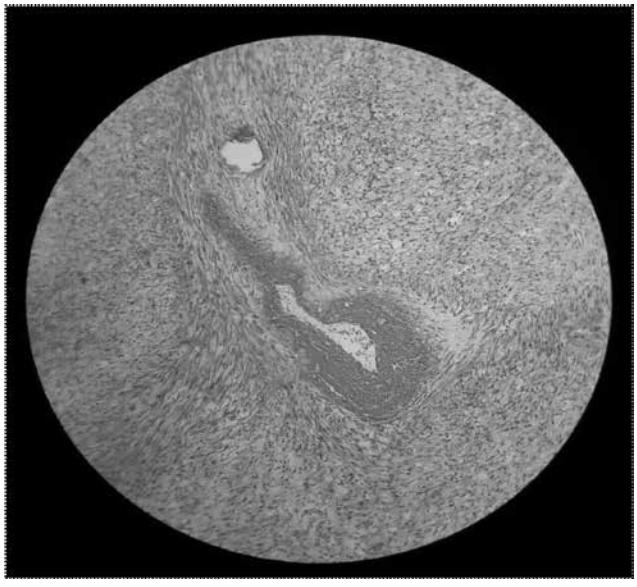

Figure 3. Histopathology showing small spindle and stellate cells and myxoid stroma with multiple thick-walled blood vessels.

Histopathology showed small spindle and stellate cells, mild atypia with rare mitosis and myxoid stroma with multiple thick-walled blood vessels, suggestive of aggressive angiomyxoma of vulva (Fig. 3).

Immunohistochemical staining of the tumor was positive for - estrogen receptor, desmin, CD34 and vimentin with negative result for S-100 and cytokeratin, which was indicative of angiomyxoma of female genital tract.

The patient was followed up for 3½ years in our OPD. No evidence of local recurrence was noted. Figure 4 shows vulva after excision of mass and reconstruction.

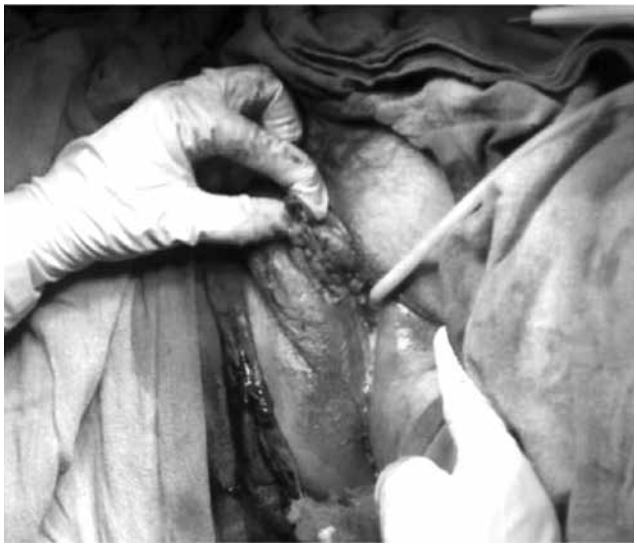

Figure 4. Vulva after excision of mass and reconstruction.

DISCUSSION

Smooth muscle tumors of specialized genital stromal cell origin include:

- Angiomyofibroblastoma
- Cellular angiofibroma
- Aggressive angiomyxoma.

The term aggressive angiomyxoma was coined by Steeper and Rosai, first in 1983. The adjective 'aggressive' emphasizes the neoplastic character of the blood vessels, its locally infiltrative nature and high risk of local recurrence, not indicating a malignant potential of the lesion.[4]

In our case, the woman was 75 years old, postmenopausal (surgical), and the mass was rapidly growing. As she was diabetic, the provisional diagnosis was more in favor of infective origin. Differential diagnosis includes Bartholin cyst/abscess, periurethral cyst, hernia of levator or leiomyofibroma, labial cyst, Gartner duct cyst. Most of the cases are diagnosed on histology after surgical excision.

Gross features: Soft, partly circumscribed or polypoidal in nature – cross-section shows glistening, homogeneous and gelatinous appearance; may have infiltration into the surrounding soft tissues.

Microscopic features: Tumor is composed of widely scattered spindled to stellate-shaped cells with ill-defined cytoplasm and variably sized, thin or thick-walled vascular channels in a collagen rich myxoid stroma. Histologically, aggressive angiomyxoma can be differentiated from angiomyofibroblastoma. Aggressive

angiomyxoma has thick-walled vasculature but angiomyofibroblastoma shows numerous thin-walled vasculature often with perivascular hyalinization.

Immunohistochemistry: It shows positive reaction for desmin, actin, CD34 and estrogen/progesterone receptors, whereas S-100 protein and cytokeratins are not expressed by the neoplastic cells.

All the above-mentioned features were compatible with our case.

Lee et al reported a similar case of aggressive angiomyxoma in the right labia majora in 2014. It was excised locally and did not show any evidence of recurrence in 7 years of continuous follow-up.[5]

Review of literature shows out of 55 individual cases, 16 had recurrence and 3 had distant metastasis. Local recurrence is common but distant is rare. Time of recurrence varies from 2 months to 15 years.

In view of high risk of local recurrence, wide local excision with tumor free margins was initially thought to be the treatment of choice. Re-excision, if the initial surgery was deemed incomplete, was also advocated.

There is one instance where lymphadenectomy was performed as a part of primary surgery as it was misdiagnosed as recurrent urethral rhabdomyosarcoma and final histopathology revealed aggressive angiomyxoma.[6]

Most of these tumors are estrogen and progesterone receptor positive and are likely to be hormone dependant, as rapid growth has been observed during pregnancy. Hormonal manipulation is thus thought to be a viable treatment option. Several beneficial results with gonadotropin-releasing hormone (GnRH) agonist have been described in primary treatment of small tumors, as adjuvant therapy for residual tumor and even treatment in recurrence.[7-9]

Fine et al achieved complete resolution of recurrent aggressive angiomyxoma with GnRH agonist in a female patient who refused to undergo a second surgery.[10] However, long-term use of these drugs is associated with side effects, like postmenopausal symptoms and bone loss. Moreover, the optimal duration of therapy is also unknown. Preoperative shrinking of tumors using GnRH agonist might increase chances of complete excision and minimize the radicality of surgical procedure. Radiation therapy and chemotherapy are less appropriate options owing to the tumor's low mitotic activity.[5]

Angiographic embolization is an option to shrink the tumor preoperatively and thus increase the chances of complete removal. But the possibility of blood supply from multiple sources rather than a singular feeding vessel would reduce the success of such procedure.[11]

CONCLUSION

High index of clinical suspicion is needed for diagnosis. Aggressive angiomyxoma should be differentiated from other myxoid neoplasms like angiomyofibroblastoma or cellular angiofibroma by histopathology, immunohistochemistry and genetic findings. Wide margin local excision of tumor is the gold standard of treatment. Strict periodic follow-up is needed for prevention and early detection of local recurrence.

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Cocktail Inferno – Multiple Sclerosis with Type 2 Diabetes Mellitus in a Patient with Lepromatous Leprosy

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ABSTRACT

Co-occurrence of multiple sclerosis with type 2 diabetes mellitus with lepromatous leprosy is rare. We hereby report a case of multiple sclerosis with type 2 diabetes mellitus with lepromatous leprosy in a middle-aged female. She was clinically diagnosed as having multiple sclerosis with type 2 diabetes mellitus and presented with fever, ENL and neuritis. Her MRI reports were normal but she had a positive slit-skin smear and skin biopsy as lepromatous leprosy. Proceeding with this diagnosis, she was treated with baclofen for spastic bladder, antibiotics for urinary tract infection, oral hypoglycemic agents and oral steroids with multibacillary treatment for leprosy with type 2 reactions. She responded well and currently is being followed-up.

Keywords: Multiple sclerosis, leprosy, diabetes mellitus, demyelinating neuropathy

Multiple sclerosis is a disorder with heterogeneous clinical and pathologic features reflecting various pathways to tissue injury.[1] Inflammation, demyelination and axonal degeneration are the key pathologic mechanisms, which lead to clinical manifestations.[2,3] However, the cause of multiple sclerosis remains unknown.[4,5] The most widely accepted theory suggests that it begins as an inflammatory immune-mediated disorder characterized by autoreactive lymphocytes.[1,6] Later, the disease is dominated by microglial activation and chronic neurodegeneration.[2]

Leprosy (Hansen's disease) is an infectious disease caused by *Mycobacterium leprae* that involves the skin and peripheral nerves. Early diagnosis and a full course of treatment are critical for preventing lifelong neuropathy and disability.[7] Although the infection is highly responsive to treatment, leprosy became an important global health concern due to deformities and disabilities of the eyes, hands and feet secondary to neuropathy which are often irreversible and require lifelong care and rehabilitation. Therefore, early diagnosis and management are necessary to minimize the likelihood of these disabilities.[8]

Type 2 diabetes mellitus is characterized by hyperglycemia, insulin resistance and relative impairment in insulin secretion. It is a common disorder with a prevalence that rises markedly with increasing degrees of obesity.[9]

The prevalence of type 2 diabetes has risen alarmingly in the past decade,[10] in large part linked to the trends in obesity and sedentary lifestyle.[11]

CASE REPORT

A 55-year-old female was brought by her relatives to the skin department. She had flexor spasms, difficulty in walking, spastic bladder with an indwelling catheter since last 4 years and was diagnosed to have multiple sclerosis. She had multiple admissions for fever and urinary tract infection and was on oral hypoglycemic agents on regular basis. She presented with fever, multiple red-colored raised lesions (Erythema nodosum leprosum or ENL) all over the body (Fig. 1), with weakness, tingling and numbness over both upper and lower limbs. ENL were also present over her face

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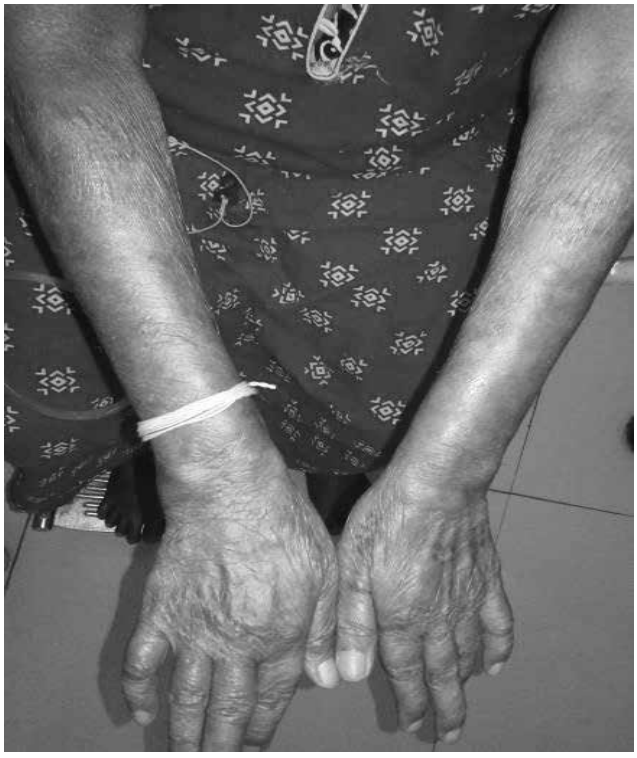

Figure 1. Multiple red-colored raised lesions (ENL) over body.

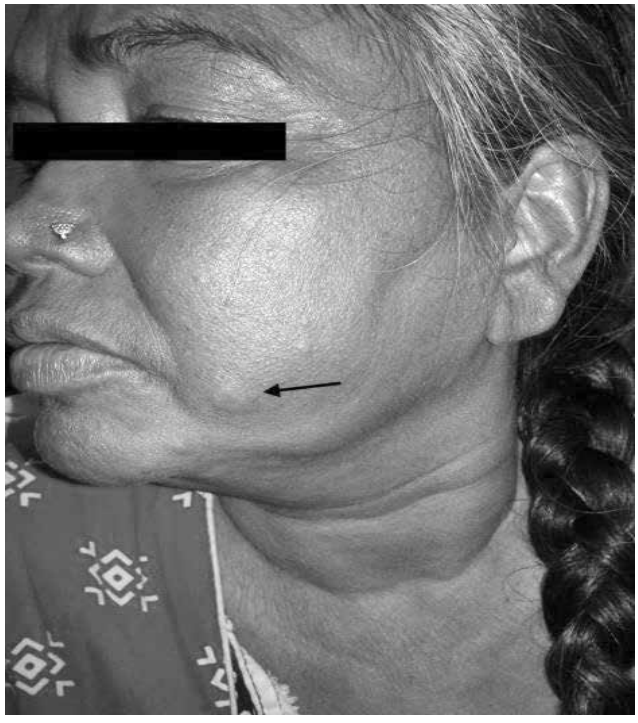

Figure 2. ENL present over face adjacent to angle of mouth (*arrow*).

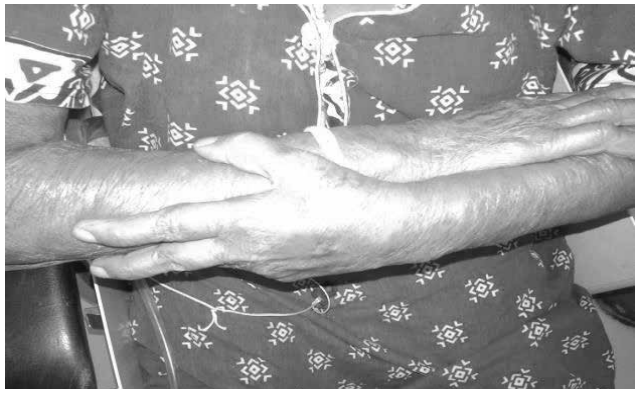

Figure 3. Xerosis and icthyosis visible over bilateral upper limbs.

adjacent to the angle of mouth (Fig. 2). Xerosis and ichthyosis characteristic of leprosy was visible over bilateral upper limbs (Fig. 3). There was no history of photosensitivity or any drug intake or application of any local irritant prior to the initial lesion.

Her detailed central nervous system evaluation revealed upper motor neuron type of paraparesis, sensorimotor with proximal as well as distal muscle involvement with urge incontinence suggestive of spastic type of neurogenic bladder. Her mental functions were intact with no cranial nerve involvement. Cardiovascular system, respiratory system and per abdominal evaluation was within normal limits.

Her routine blood biochemistry was normal except for low hemoglobin levels (5.9%), raised white blood cell (WBC) counts (15,800) and raised random blood sugar (RBS) levels (157 mg/dL). Urine analysis revealed urinary tract infection for which she was treated with antibiotics. Bladder care was given. She was treated with baclofen. Skin examination revealed positive slit-skin smear for acid-fast bacilli with bacteriological index of 3.5 and skin biopsy consistent with lepromatous leprosy. She was put on oral steroids for type 2 lepra reaction and multibacillary anti-leprosy treatment for leprosy. Appropriate oral hypoglycemic agents were continued as she was reluctant with insulin administration. Brain imaging was normal. She responded well and her flexor spasms decreased. A psychiatric consultation was sought for her depression due to chronic illness and was started on antidepressants.

DISCUSSION

Dominant or recessive genetic mutations give rise to a number of inherited neuropathies. The basic pathology happens to be in the Schwann cells, the myelinating unit of the neuron leading to defective myelination, alteration of the axonal cytoskeleton and disruption of the axonal transport.[12] Genes involved in the axonal transport are the chief site of mutation in the majority

of inherited neuropathies leading to the atrophy of the axons and directly correlate with the clinical features in the inherited neuropathies.[12]

Diabetes mellitus is characterized by a number of sensorimotor and mixed neuropathies. The pathologic hallmark of neuropathies occurring in long-term diabetics involves the advanced glycation end products, persistent oxidative stress, polyol pathway flux and protein kinase C activation, ultimately contributing to microvascular disease and nerve dysfunction.[13]

Common symptoms of multiple sclerosis include sensory abnormalities including pain, motor symptoms due to involvement of the pyramidal tracts, visual disturbances, ataxia and Lhermitte sign. The pattern of abnormalities can vary from subtle limb weakness or sensory symptoms like Uhthoff phenomenon to more severe sensorimotor noncompressive myelopathies like acute transverse myelitis. Retrobulbar neuritis and optic neuritis have been the common causes of transient visual disturbances in multiple sclerosis. The onset is often polysymptomatic. Neuropathy is an early feature in Hansen's disease, as earliest diagnostic lesions are characterized by hypoesthesia.[14] Though early sensory loss is a common finding in leprosy, in some cases, patients can present with pain, which is often late in the course of the disease.[15,16]

In the tuberculoid spectrum of the Ridley-Jopling classification, neuropathy occurs in the proximity of the skin lesions, as against neuropathy in lepromatous disease, which is more generalized. Common nerves include the ulnar, median nerves (claw hand), the common peroneal nerve (foot drop), the posterior tibial nerve (claw toes and plantar insensitivity), the facial nerve (lagophthalmos), the radial cutaneous nerve, and the great auricular nerve. Subclinical neuropathy is found more commonly, as against it was previously believed in leprosy.

These results may have implications for the design of ErbB2 RTK-based therapies for both leprosy nerve damage and other demyelinating neurodegenerative diseases.[17]

Here we report this case as to the best of our knowledge, leprosy with multiple sclerosis has not been reported in literature.

CONCLUSION

Multiple sclerosis, Hansen's disease and diabetes mellitus are multisystem diseases with distinct etiologies affecting the sensory as well as motor nerve fibers. It is considerably rare to find a demyelinating, infectious and autoimmune disease of the nerves to co-exist in the same patient. All these conditions can be managed simultaneously and successfully.

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Post-Dengue Guillain-Barre Syndrome: A Rare Association

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ABSTRACT

Dengue fever is a vector-borne disease, transmitted by female mosquito *Aedes aegypti*. The common symptoms may be in the form of high-grade fever, headache, periorbital pain, myalgia, arthralgia, fatigue, nausea, vomiting and skin rashes in mild cases to renal, hepatic, hemorrhagic tendencies, shock and neurological involvement in severe cases. Incidences of neurological symptoms varied from 0.5% to 21% in recent years. Guillain-Barre syndrome (GBS) may be one of the rare presentations following dengue viral infection with only 20 cases of GBS reported worldwide and most of the cases being in pediatric age group, whereas very few cases have been reported in adults. Hence, we are reporting a case of a 24-year-old male presenting with GBS, which occurred during recovery phase of dengue fever.

Keywords: Dengue fever, *Aedes aegypti*, Guillain-Barre syndrome

Dengue fever is a common vector-borne disease, transmitted by female mosquito *Aedes aegypti*. It is also called break-bone fever, caused by dengue virus which is an RNA virus, and belongs to Flaviviridae family, genus Flavivirus. There are 5 serotypes of dengue virus (DEN1, DEN2, DEN3, DEN4 and DEN5). Fifth serotype was announced in 2013.[1] Dengue fever has worldwide distribution but is predominantly seen in tropical and subtropical countries, like India. The World Health Organization (WHO) estimates an annual incidence of approximately 50 million infections, with approximately 5,00,000 people with dengue hemorrhagic fever. For the past 10 years, incidences of dengue fever are constantly increasing in India and from 1998 to 2009, 82,320 cases (6.32 per million population) were reported, which increased to 2,13,601 cases (34.8 per million population) from 2010 to 2017.

Dengue fever may present with variable symptoms which usually begin 4-6 days after infection and last for up to 10 days. These symptoms may be in the form of high-grade fever, headache, periorbital pain, myalgia, arthralgia, fatigue, nausea, vomiting and skin rashes (3-5 days after onset of fever) in mild cases to renal, hepatic, hemorrhagic tendencies, shock and neurological involvement in severe cases.

Incidences of neurological symptoms varied from 0.5% to 21% in recent years.[2,3] These may be in the form of encephalitis, meningoencephalitis, stroke, cerebellar syndromes, transverse myelitis and Guillain-Barre syndrome (GBS).

GBS may be one of the rare presentations following dengue viral infection and only 20 cases of GBS have been reported worldwide with most of the cases being in pediatric age group, and very few cases reported in adults.[4,5] Hence, we are reporting a case of GBS which occurred during recovery phase of dengue fever.

CASE REPORT

A 24-year-old male patient was admitted in medical ward with history of fever, headache, body ache, nausea, vomiting and retro-orbital pain for last 2 days. He was examined and found to have mild throat congestion without hepatosplenomegaly, chest was clear and there were no signs of meningeal irritation. For above febrile illness, patient was investigated and was found to have mild leukopenia (3,200/mm^3) with thrombocytopenia (48,000/mm^3). Malaria Parasite Quantitative Buffy Coat Test (MPQBC) and Scrub typhus serology was negative but Dengue serology

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(NS1 antigen) was found positive. Patient responded well with symptomatic therapy and hence was discharged after 5 days of admission. He remained asymptomatic for 2 days after discharge and then suddenly developed weakness of both the lower limbs, which progressed rapidly to involve both upper limbs over a period of 6-10 hours to the extent that he was not able to move the limbs and get up from lying down posture. He was readmitted in our ward and was further investigated, which revealed that he had history of paresthesia and numbness in both extremities without cranial nerve and bladder-bowel involvement. Patient was examined thoroughly and was found to have normal vital signs. Neurological examination revealed normal mental function and cranial nerves. Motor system examination revealed hypotonia in all 4 limbs, power 1/5 in both lower limbs, whereas 2/5 in both upper limbs. Deep tendon reflexes (DTR) were absent in both upper and lower limbs, plantars were found flexor bilaterally. Sensory system and other neurological examination including signs of meningeal irritation were found normal.

On the basis of history and clinical examination, we made our provisional diagnosis of post-Dengue GBS.

For confirmation of the above diagnosis, patient was investigated extensively which revealed that complete blood count (platelet 1.5 lacs/mm^3), renal function test, human immunodeficiency virus (HIV), hepatitis B and hepatitis C, immunological profile, chest X-ray, ECG, USG abdomen were normal, whereas liver function tests were slightly deranged (AST-60 IU/L and ALT-194 IU/L) and Dengue NS1 was negative, whereas IgM Dengue was found positive.

Patient underwent lumbar puncture and cerebrospinal fluid (CSF) was examined, which revealed albumino-cytological dissociation (protein-82 mg/dL, cell count-2 cells/mm^3 only lymphocytes). Nerve conduction study was done in median, ulnar, peroneal and sural nerves and revealed reduced compound muscle action potential (CMAP) amplitude with delayed F wave latency and prolonged R median suggestive of both demyelinating and axonal neuropathy.

Patient was treated with intravenous immunoglobulin (IVIg) for 5 days and started improving in form of power in both upper and lower limbs significantly (4/5 in both upper limbs and 3/5 in both lower limbs), hence was discharged and advised to follow-up in the outpatient clinic.

DISCUSSION

Dengue fever is one of the leading causes of mortality and morbidity in tropical and subtropical regions of the world. Dengue fever may present with variable clinical presentation which may be in the form of mild febrile illness to dengue shock syndrome, dengue hemorrhagic fever and neurological complications.

Neurological manifestations in dengue fever are rare. Verma et al described neurological complications in dengue patients and noted that they have been categorized into three groups on the basis of possible pathological mechanisms:[6]

- Neurotropic complications such as encephalitis, myelitis and myositis
- Systemic complications such as hypokalemic periodic paralysis
- Post-infectious immune-mediated complications such as GBS, opsoclonus-myoclonus syndrome.

GBS is one of the rarest neurological presentations following dengue fever seen in adults. It is an acute fulminating polyradiculoneuropathy possibly auto-immune, post-infectious or post-vaccination in nature; males are predominantly involved. It is characterized by rapidly progressive areflexic motor paralysis with or without sensory involvement and without bowel-bladder involvement. Common variants of GBS are acute inflammatory demyelinating polyneuropathy, acute motor axonal neuropathy and acute motor sensory axonal neuropathy and Miller-Fisher syndrome.

Approximately 70% of cases of GBS occur 1-3 weeks after an acute infectious process. The common infectious agents which can cause GBS are *Campylobacter jejuni*, cytomegalovirus (CMV), Epstein-Barr virus, HIV, influenza and mycoplasma. The rare causes may be Zika and dengue viral infection.

The exact mechanism is unknown but possibly it may be due to cell-mediated immunological response to non-self antigen that misdirects to host nerve tissue through a resemblance of epitope mechanism (molecular mimicry).[7,8] Dengue virus would initiate this immunological event, leading to the disease. Myelin or axons could be the target of this immune response.

Diagnosis of GBS is mainly based on clinical and laboratory findings.

The following is the criteria for diagnosis of GBS (Asbury criteria):[9]

Required

- Progressive weakness
- Areflexia
- Duration <4 weeks
- Exclude other causes (vasculitis, toxins, porphyria).

Supportive

- Symmetrical weakness
- Mild sensory involvement
- Cranial nerve involvement
- Absence of fever
- Typical CSF finding (albumin-cytological dissociation)
- Nerve conduction study suggestive of demyelination.

GBS can be treated by IVIg (2 g/kg body weight divided in 5 daily doses) or plasmapheresis, as they are equally effective for typical GBS. Glucocorticoids have not been found to be effective in the treatment of GBS.

CONCLUSION

GBS is a rare neurological complication of dengue infection which is generally underestimated. It should always be considered if a patient of dengue fever during the infection or in recovery phase develops progressive areflexic paralysis. The patient should be diagnosed and treated as early as possible to reduce morbidity and mortality. Thus, our case report calls attention to physicians for the possibility of GBS in association with dengue fever.

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■■■■

COVID-19 Confinement Likely Tied to Myopia in Kids

The COVID-19 pandemic may have escalated the prevalence of myopia as young children are confined indoors, report researchers.

Spending more time indoors focused on computer screens seems to have most affected the eyesight of the youngest school children, reported Xuehan Qian, of Tianjin Medical University Eye Hospital in Tianjin, China.

Researchers noted time spent indoors and the duration and intensity of near work as potential risk factors for myopia. The quality of light under these conditions seems to affect the way the eye develops, especially in children, stated Jeffrey Cooper, professor emeritus at the State University of New York, College of Optometry in New York City.

The findings from the research were presented at the virtual Association for Research in Vision and Ophthalmology (ARVO) 2021 annual meeting, and have been published in *JAMA Ophthalmology*… (*Medscape*)

Medicolegal Insights

Can the Consent be Taken a Few Days Before the Procedure?

Recall of informed consent is not affected by the timing of obtaining informed consent before any procedure.

Evidence: Sixty patients scheduled for colonoscopy or esophagogastroduodenoscopy were enrolled in a prospective, randomized study. Each patient received informed consent 24-72 hours or immediately before the procedure, and follow-up occurred 1-3 days post procedure. There was no statistically significant difference in recall of informed consent or the individual elements of informed consent (indication, risks, benefits, alternatives) between the two groups. The study concluded that recall of informed consent is similar whether consent is obtained immediately or several days before endoscopic procedures.

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What are the Duties of a Doctor in Respect of Signing Professional Certificates, Reports and Other Documents?

Regulation 7.7 elaborates on the issue of signing professional certificates, reports and other documents.

It states as follows: "Registered medical practitioners are in certain cases bound by law to give, or may from time to time be called upon or requested to give certificates, notification, reports and other documents of similar character signed by them in their professional capacity for subsequent use in the courts or for administrative purposes, etc. Such documents, among others, include the ones given at Appendix 4.

Any registered practitioner who is shown to have signed or given under his name and authority any such certificate, notification, report or document of a similar character which is untrue, misleading or improper, is liable to have his name deleted from the Register."

Can Deviation from Medical Practice be Termed Medical Negligence?

In Jacob Mathew v. State of Punjab SC/0457/2005:(2005) 6 SCC 1, the Supreme Court of India has observed: "Deviation from normal practice is not necessarily evidence of negligence. To establish liability on that basis, it must be shown:

- that there is a usual and normal practice
- that the defendant has not adopted it and
- that the course adopted is no professional man of ordinary knowledge skill would have taken had he been acting with ordinary care."

What are the Violations in Advertising in Indian Penal Code?

Sec. 292(2) (d) of Indian Penal Code, 1860, makes it a punishable offence to publish, distribute, sell, hire or circulate any obscene advertisement.

Section 292 in The Indian Penal Code

[260][292. Sale, etc., of obscene books, etc.—[261]]

(1) For the purposes of Sub-section (2), a book, pamphlet, paper, writing, drawing, painting, representation, figure or any other object, shall be deemed to be obscene if it is lascivious or appeals to the prurient interest or if its effect, or (where it comprises two or more distinct items) the effect of any one of its items, is, if taken as a whole, such as to tend to deprave and corrupt person, who are likely, having regard to all relevant circumstances, to read, see or hear the matter contained or embodied in it.

[262][(2)] Whoever—

(a) sells, lets to hire, distributes, publicly exhibits or in any manner puts into circulation, or for purposes of sale, hire, distribution, public exhibition or circulation, makes, produces or has in his possession any obscene book, pamphlet paper, drawing, painting, representation or figure or any other obscene object whatsoever, or

(b) imports, exports or conveys any obscene object for any of the purposes aforesaid, or knowing or having reason to believe that such object will be sold, let to hire, distributed or publicly exhibited or in any manner put into circulation, or

(c) takes part in or receives profits from any business in the course of which he knows or has reason to believe that any such obscene objects are for any of the purposes aforesaid, made, produced, purchased, kept, imported, exported, conveyed, publicly exhibited or in any manner put into circulation, or

(d) advertises or makes known by any means whatsoever that any person is engaged or is ready to engage in any act which is an offence under this section, or that any such obscene object can be procured from or through any person, or

(e) offers or attempts to do any act which is an offence under this section, shall be punished [263][on first conviction with imprisonment of either description for a term which may extend to 2 years, and with fine which may extend to two thousand rupees, and, in the event of a second or subsequent conviction, with imprisonment of either description for a term which may extend to 5 years, and also with fine which may extend to five thousand rupees].

Can a Patient Seek Redressal for Grievances Regarding Treatment Received?

Yes, patient who is the sufferer from the negligent act of the doctors can seek remedy under various laws:

1. **Compensatory action -** Complaint against doctors, staff or hospital whether private or government hospitals who committed negligence seeking monetary compensation before:
   i. Civil Court under law of Torts or Law of Contract,
   ii. High Court under the Constitutional Law, or
   iii. Consumer Courts under Consumer Protection Act.
2. **Punitive action -** Criminal complaint under Indian Penal Code against the doctor.
3. **Disciplinary action -** Complaint seeking disciplinary action against the medical practitioner or the hospitals as the case may be, before statutory bodies governing the medical practitioners such as Medical Council of India or State Medical Council.
4. **Recommendatory action -** Complaint before the National/State Human Rights Commission seeking compensation.

Does a Decision Taken in Good Faith Amount to Negligence?

A decision taken in good faith is not a crime. Defenses are available to the doctors under Indian Penal Code (IPC) sections 88, 92 and 93.

- **Section 88.** Act not unintended to cause death, done by consent in good faith for person's benefit: Nothing, which is not intended to cause death, is an offence by reason of any harm which it may cause, or be intended by the doer to cause, or be known by the doer to be likely to cause, to any person for whose benefit it is done in good faith, and who has given a consent, whether express or implied, to suffer that harm, or to take the risk of that harm.

  The illustration along with this section is: "A, a surgeon, knowing that a particular operation is likely to cause the death of Z, who suffers under a painful complaint, but not intending to cause Z's death and intending in good faith, Z's benefit, performs that operation on Z, with Z's consent. A has committed no offence."
- **Section 92.** Act done in good faith for benefit of a person without consent: Nothing is an offence by reason of any harm which it may cause to a person for whose benefit it is done in good faith, even without that person's consent, if the circumstances are such that it is impossible for that person to signify consent, or if that person is incapable of giving consent, and has no guardian or other person in lawful charge of him from whom it is possible to obtain consent in time for the thing to be done with benefit.

  The illustration along with this section is: Z is thrown from his horse, and is insensible. A, a surgeon, finds that Z requires to be trepanned. A, not intending Z's death, but in good faith, for Z's benefit, performs the trepan before Z recovers his power of judging for himself. A has committed no offence. A, a surgeon, sees a child suffer an accident which is likely to prove fatal unless an operation be immediately performed. There is no time to apply to the child's guardian. A, performs the operation in spite of the entreaties of the child, intending, in good faith, the child's benefit. A committed no offence.
- **Section 93.** Communication made in good faith. No communication made in good faith is an offence by reason of any harm to the person to whom it is made, if it is made for the benefit of that person. Illustration A, a surgeon, in good faith, communicates to a patient his opinion that he cannot live. The patient dies in consequence of the shock. A has committed no offence, though he knew it to be likely that the communication might cause the patient's death.

A Specialist Gives an Opinion to a Physician on Phone Regarding a Patient (not seen by him). Is he/she Liable for any Mishap?

No legal liability will fall upon the doctor for giving an opinion on phone for cases not seen by him as there is

no contract between him and the patient. For negligence to be proved there has to be a duty, breach of that duty and resultant damage. In this case, there will no breach of duty. But, if the specialist has charged a fee for his opinion from the patient (patient can sue) or from the physician (patient and doctor both can sue), then he/she is liable. If the fee has been paid by the referring physician, it will be deemed to be paid by the patient.

Is There a Difference Between Active Euthanasia and Passive Euthanasia?

Yes. Active euthanasia and passive euthanasia differ from each other.

Active euthanasia means where death is caused by the administration of a lethal injection or drugs. Active euthanasia also includes physician-assisted suicide, where the injection or drugs are supplied by the physician, but the act of administration is undertaken by the patient himself. Active euthanasia is not permissible in most countries. The jurisdictions in which it is permissible are Canada, the Netherlands, Switzerland and the States of Colorado, Vermont, Montana, California, Oregon and Washington DC in the United States of America.

Passive euthanasia is when medical practitioners do not provide life-sustaining treatment (i.e., treatment necessary to keep a patient alive) or remove patients from life-sustaining treatment. This could include disconnecting life support machines or feeding tubes or not carrying out life-saving operations or providing life extending drugs. In such cases, the omission by the medical practitioner is not treated as the cause of death; instead, the patient is understood to have died because of his underlying condition.

In the matter titled as **"Common Cause versus Union of India, 2018 (5) SCC 1" the Hon'ble Constitution Bench of 4 Judges of the Supreme Court of India,** has held that:

"(v) There is an inherent difference between active euthanasia and passive euthanasia as the former entails a positive affirmative act, while the latter relates to withdrawal of life support measures or withholding of medical treatment meant for artificially prolonging life.

(vi) In active euthanasia, a specific overt act is done to end the patient's life whereas in passive euthanasia, something is not done which is necessary for preserving a patients life. It is due to this difference that most of the countries across the world have legalized passive euthanasia either by legislation or by judicial interpretation with certain conditions and safeguards."

Can a Patient Seek Redressal for Grievances Regarding Treatment Received?

Yes. The National Board for Accreditation of Healthcare (NABH) Patient Charter has provisions for this.

5. Right to redress

- Patient has the right to justice by lodging a complaint through an authority dedicated for this purpose by the health care provider organization or with government health authorities.
- The patient has the right to a fair and prompt hearing of his/her concern.
- The patient in addition has the right to appeal to a higher authority in the health care provider organization and insist in writing on the outcome of the complaint.

The Patient was not Getting Cured. Can this be Termed as Medical Negligence?

No doctor can give 100% guarantee about the treatment or surgery. The only assurance which a doctor can give or can be understood to have given by implication is that he is possessed of the requisite skill in that branch of profession which he is practicing and while undertaking the performance of the task entrusted to him he would be exercising his skill with reasonable competence.

The Hon'ble Apex Court in various judgments has duly held that no guarantee is given by any doctor or surgeon that the patient would be cured.

- In the matter titled as **"P. B. Desai versus State of Maharashtra, AIR 2014 SC 795,"** the Hon'ble Apex Court has held that:

  "39. It is not necessary for us to divulge this theoretical approach to the doctor-patient relationship, as that may be based on model foundation. Fact remains that when a physician agrees to attend a patient, there is an unwritten contract between the two. The patient entrusts himself to the doctor and that doctor agrees to do his best, at all times, for the patient. Such doctor-patient contract is almost always an implied contract, except when written informed consent is obtained. While a doctor cannot be forced to treat any person, he/she has certain responsibilities for those whom he/she accepts as patients. Some of these responsibilities may be recapitulated, in brief:

  (a) to continue to treat, except under certain circumstances when doctor can abandon his patient;

  (b) to take reasonable care of his patient;

  (c) to exhibit reasonable skill: The degree of skill a doctor undertakes is the average degree of skill

possessed by his professional brethren of the same standing as himself. The best form of treatment may differ when different choices are available. There is an implied contract between the doctor and patient where the patient is told, in effect, "Medicine is not an exact science. I shall use my experience and best judgment and you take the risk that I may be wrong. I guarantee nothing."

(d) Not to undertake any procedure beyond his control: This depends on his qualifications, special training and experience. The doctor must always ensure that he is reasonably skilled before undertaking any special procedure/treating a complicated case.

(e) Professional secrets: A doctor is under a moral and legal obligation not to divulge the information/ knowledge which he comes to learn in confidence from his patient and such a communication is privileged communication."

- In the matter **"Malay Kumar Ganguly vs. Sukumar Mukherjee & Ors. AIR 2010 SC 1162,"** the Hon'ble Supreme Court of India has held that:

"INDIVIDUAL LIABILITY OF THE DOCTORS There cannot be, however, by any doubt or dispute that for establishing medical negligence or deficiency in service, the courts would determine the following:

(i) No guarantee is given by any doctor or surgeon that the patient would be cured.

(ii) The doctor, however, must undertake a fair, reasonable and competent degree of skill, which may not be the highest skill.

(iii) Adoption of one of the modes of treatment, if there are many, and treating the patient with due care and caution would not constitute any negligence.

(iv) Failure to act in accordance with the standard, reasonable, competent medical means at the time would not constitute a negligence. However, a medical practitioner must exercise the reasonable degree of care and skill and knowledge which he possesses. Failure to use due skill in diagnosis with the result that wrong treatment is given would be negligence.

(v) In a complicated case, the court would be slow in contributing negligence on the part of the doctor, if he is performing his duties to the best of his ability. Bearing in mind the aforementioned principles, the individual liability of the doctors and hospital must be judged."

- In the landmark judgment of **"Jacob Mathew Petitioner v. State of Punjab & Anr. 2005 (3) CPR 70 (SC),"** the Hon'ble Supreme Court has held that:

"Para 28: No sensible professional would intentionally commit an act or omission which would result in loss or injury to the patient as the professional reputation of the person is at stake. A single failure may cost him dear in his career. Even in civil jurisdiction, the rule of res ipsa loquitur is not of universal application and has to be applied with extreme care and caution to the cases of professional negligence and in particular that of the doctors. Else it would be counterproductive. Simply because a patient has not favorably responded to a treatment given by a physician or a surgery has failed, the doctor cannot be held liable per se by applying the doctrine of res ipsa loquitur."

- In the matter titled as **"Martin F. D'Souza versus Mohd. Ishfaq, 2009(3) SCC 1,"** the Hon'ble Supreme Court has held that:

"Para 124: "It must be remembered that sometimes despite their best efforts the treatment of a doctor fails. For instance, sometimes despite the best effort of a surgeon, the patient dies. That does not mean that the doctor or the surgeon must be held to be guilty of medical negligence, unless there is some strong evidence to suggest that he is."

- In the matter titled as **"Lok Nayak Hospital versus Prema, RFA No. 56/2006,"** the Hon'ble High Court of Delhi vide judgment dated 06.08.2018 has held that:

"8. Firstly, it is to be noted that the only allegation of negligence alleged by the respondent/plaintiff against the appellant/defendant is that the tubectomy/ sterilization operation failed. ***Since medically there is never a 100% chance of success in sterilization operations, the mere fact that the operation was not successful, that by itself cannot be a reason to hold the appellant/defendant and its doctors guilty of negligence.*** *This aspect is no longer res integra and is so held by a Division Bench of this Court in the case of Smt. Madhubala Vs. Govt. of NCT of Delhi, 118 (2005) DLT 515 (DB)."*

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HCFI Dr KK Aggarwal Research Fund

Minutes of Virtual Meeting of CMAAO NMAs on "Hospital-based COVID-19 Therapies"

8th May, 2021 (Saturday, 9.30 am-10.30 am)

Participants: Member NMAs: Dr KK Aggarwal, President-CMAAO; Dr Yeh Woei Chong, Singapore Chair-CMAAO; Dr Alvin Yee-Shing Chan, Hong Kong, Treasurer-CMAAO; Dr Angelique Coetzee, President-South African Medical Association; Dr Debora Cavalcanti, Brazil; Dr Marthanda Pillai, India, Member-World Medical Council; Dr Marie Uzawa Urabe, Japan Medical Association; Dr Md Jamaluddin Chowdhury, Bangladesh Medical Association; Dr Qaiser Sajjad, Secretary General-Pakistan Medical Association; Dr Akhtar Husain, South African Medical Association; Dr Prakash

Invitees: Dr Monica Vasudev, Allergist Immunologist, Advocate-Aurora Health, WI, USA; Dr S Sharma, Editor-IJCP Group, Dr Meenakshi Soni Bamalwa

Key points from the discussion

- Mild disease means fever, malaise, cough, upper respiratory infection (URI) in the absence of dyspnea. Presence of dyspnea means moderate or severe disease.
- Severe disease is characterized by hypoxia (SpO_2 90%) and the need for oxygenation or ventilator support.
- Management recommendations are rapidly evolving. Local protocols and guidance should be followed.
- Monitoring: Complete blood count (CBC) with differential, complete metabolic panel, creatine kinase, C-reactive protein (CRP), ferritin, procalcitonin, prothrombin time (PT), D-dimer, interleukin (IL)-6 (marker of cytokine storm), lactate dehydrogenase (LDH), troponin, electrocardiogram (EKG), chest X-ray, computed tomography (CT) scan and sputum culture sensitivity (to look for secondary infection).
- Oxygen target is 92-96%; if the patient retains CO_2 then the target is 88-92%. The target is >92-95% in pregnant patients and >94% during resuscitation and >90% once stable for children.
- A nasal cannula, Venturi or nonrebreather mask can be used. High-flow nasal cannula oxygen can be used if no relief. Noninvasive ventilation (BiPAP) and endotracheal intubation (strict airborne protection precautions), if needed.
- Avoid fans and nebulized therapy due to the risk of aerosolization.
- Low-flow devices: Nasal cannula (first step for mild hypoxia), shovel mask, simple face mask, non-rebreather mask (good next step for hypoxia).
- High-flow devices: High-flow nasal cannula (risk of aerosolization), Venturi mask (good next choice for hypoxia).
- Prone positioning with moderate-to-severe acute respiratory distress syndrome (ARDS); avoid in patients with pacemaker, facial trauma.
- Dexamethasone: Moderate-to-severe patients; 6 mg daily × 10 days or until discharge (hydrocortisone 150 mg, methylprednisolone 32 mg, prednisone 40 mg).
- Thrombosis is a major feature of coronavirus disease 2019 (COVID-19). Up to 30% COVID-19 patients develop thrombosis (arterial and venous). Microthrombosis is the key mediator of COVID-19–related morbidity and mortality and organ dysfunction. Hence, D-dimer is measured.
- Approved therapies: Dexamethasone, remdesivir, monoclonal antibodies, baricitinib, tocilizumab.
- Therapies undergoing trials: Convalescent plasma, inhaled interferon, full-dose anticoagulation, colchicine, ASA, vitamin D, ivermectin, molnupiravir, bevacizumab.
- Therapies with no benefit: Hydroxychloroquine, lopinavir + ritonavir.
- Remdesivir: RNA-dependent RNA polymerase (RdRp) inhibitor; RdRp is essential for replication of the virus. Dose: 200 mg on Day 1, 100 mg daily from Day 2 administered only via IV infusion × 5 days (can be used for additional 5 days). It is recommended for use in patients in early stages of severe disease. It should not be used in patients on chloroquine or hydroxychloroquine.
- Baricitinib: Oral JAK inhibitor used to treat rheumatoid arthritis. Dose: 4 mg once daily × 14 days of total treatment or until hospital discharge, whichever is first.

- Clinical trials have shown that baricitinib + remdesivir was superior to remdesivir alone in reducing recovery time and hastening improvement in clinical status in hospitalized COVID-19 patients, especially those on high-flow oxygen (*NEJM*).
- Tocilizumab: IL-6 receptor antagonist. Dose: 8 mg/kg IV as a single dose (max 800 mg) in combination with steroids within 14 days of onset. The Infectious Diseases Society of America (IDSA) recommends that tocilizumab should be used in addition to standard care and should be used early in hospitalized severe/critical patients in ICU and raised inflammatory marker. Avoid if other bacterial/viral/fungal infection is suspected, thrombocytopenia (<50,000), AST/ALT >5 upper limits of normal, latent tuberculosis (TB), history of diverticulitis or bowel perforation and pregnancy.
- Monoclonal antibodies (bamlanivimab-etesevimab) have been given emergency use authorization in the US for nonhospitalized adults (≥65 years or who have certain chronic medical conditions) and pediatric patients (≥12 years weighing at least 40 kg). Not recommended for hospitalized patients or those who require oxygen therapy. It should be given as early as possible after a positive test and within 10 days of symptom onset and administered together as a single IV infusion.
- Favipiravir: Antiviral, in mild-to-moderate infection, 1800 mg orally twice daily on 1st day followed by 800 mg orally twice daily up to maximum of 14 days. Used extensively across the world, including India.
- Convalescent plasma gives passive immunity. It is perhaps beneficial if used earlier in the disease; no benefit in severe disease.
- Hydroxychloroquine/chloroquine: Lack of benefit in hospitalized patients, toxicity (QTc prolongation, arrhythmia), emergency use authorization (EUA) revoked in the US in June 2020.
- Lopinavir-ritonavir: Trials have failed to show efficacy; no benefit in hospitalized adult patients with severe COVID-19 beyond standard care (*NEJM*).
- Ivermectin: US Food and Drug Administration (FDA) has not approved ivermectin for use in treating or preventing COVID-19.

Co-infection and Superinfection with SARS-CoV-2 and Other Pathogens

Co-infections and superinfections with other pathogens in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have often been reported. However, there is no clarity on the frequency of co-infection and superinfections by other pathogens and associated clinical outcomes among patients having SARS-CoV-2 infection.

While co-infection has been defined as the recovery of other respiratory pathogens in SARS-CoV-2 infected patients at the time of diagnosis of SARS-CoV-2 infection, superinfection has been defined as recovery of other respiratory pathogens during treatment of SARS-CoV-2 infection.

A meta-analysis has been published recently in *PLOS One* which noted that 19% of patients with COVID-19 had co-infection with other pathogens, while 24% patients with COVID-19 had a superinfection. The meta-analysis included 118 studies, of which around half were retrospective cohort studies, 35% case series and 9% prospective cohort studies.

Sixty-seven of the studies (57%) reported on co-infections, 44 (37%) reported on superinfections and 7 (6%) reported on both co-infections and superinfections in COVID-19 patients.

- The pooled prevalence of co-infection was 19% (95% confidence interval [CI] 14-25; I^2 = 98%), with the highest prevalence seen in non-ICU patients (29%). The pooled prevalence of superinfection was 24%, with the highest being in ICU patients (41%).
- Bacterial superinfections had a prevalence of 20%, which was followed by viral co-infections at 10%, bacterial co-infections at 8% and fungal superinfections at 8%. Viral superinfections and fungal co-infections had a prevalence of 4% each.
- Among patients with co-infections, the most common causative bacteria included *Klebsiella pneumoniae*, *Streptococcus pneumoniae* and *Staphylococcus aureus*. The most common viruses in patients with co-infections included influenza type A, influenza type B and respiratory syncytial virus. Aspergillus was the most commonly identified fungus among patients with a co-infection.
- In patients with superinfections, the most frequent bacteria included Acinetobacter spp., Pseudomonas and *Escherichia coli*, while the most frequently detected virus was Rhinovirus. Candida spp. was the most frequently identified fungus.
- The mortality risk was higher among patients with a co-infection or superinfection compared to those with only SARS-CoV-2 infection (odds ratio [OR] 3.31).

The data presented in the meta-analysis has significant implications. The authors emphasize that protocols for respiratory virus diagnostic testing must consider the fact that co-infection with SARS-CoV-2 is common. Management approach must also involve co-infection evaluation in order to provide adequate treatment for SARS-CoV-2 as well as the co-infection.

Source: *Musuuza JS, Watson L, Parmasad V, et al. Prevalence and outcomes of co-infection and superinfection with SARS-CoV-2 and other pathogens: A systematic review and meta-analysis. PLoS One. 2021;16(5):e0251170.*

HCFI Round Table Expert Zoom Meeting on "Preparing for the Third Wave in India"

8th May, 2021 (11 am-12 pm)

Participants: Dr Suneela Garg, Dr Mahesh Verma, Dr Ashok Gupta, Dr Alex Thomas, Dr Girdhar Gyani, Dr Anita Chakravarti, Dr Jayakrishnan Alapet, Dr DR Rai, Mrs Upasana Arora, Dr KK Kalra, Dr Anil Kumar, Ms Ira Gupta, Dr S Sharma

Consensus Statement of HCFI Expert Round Table

- The second wave in India is very aggressive vis-a-vis the first wave. The number of daily cases crossed 4 lakh and daily deaths more than 4,000. Ninety percent of cases and deaths in south Asia region are contributed by India (at the time of meeting).
- Now children are also being affected. About 40% cases are being reported from rural areas.
- There is still lot of ignorance about the disease especially in rural areas. Complacency set in when cases declined in February. The virus mutated fast to its advantage. Only 2.6% population has been vaccinated so far (at the time of meeting).
- There is a huge demand and supply gap in view of the sheer large number of the cases. Health system seems to have collapsed.
- We have not learnt from the previous wave. The third wave is inevitable given the current situation – COVID-inappropriate behavior and reduced vaccination pace, virus mutations, rural areas (which are vulnerable pockets), immune evasive variants.
- Total 16.5 Cr vaccine doses have been administered (at the time of meeting). This number is still very low, given the huge population that needs to be vaccinated to achieve herd immunity.
- Some states like Punjab, Jammu & Kashmir, Assam, Himachal Pradesh, Puducherry, Meghalaya, Tripura, Nagaland and Arunachal Pradesh are showing an increasing trend, which is a cause for worry.
- The time of occurrence of the third wave is still speculated; it could be wider and deadlier, will it affect the young healthy individuals third wave and children more, remains to be seen. There is adaptive pressure on the virus in order to survive. Will the virus evolve further? Will it be as transmissible as now or more?
- The third wave is typically smaller, but multiple parameters together can be exponential.
- Potential factors influencing the third wave: proportion of vaccinated persons, prevention of super spreader events and crowds, early detection of new variants. Asymptomatic and infected persons may lose immunity in 6-8 months.
- Possible prevention and mitigation measures: Prepare incrementally and implement what has been learnt from the second wave. Community awareness needs to be increased. Other measures include aggressive vaccination, microplanning (communication and surveillance strategy), oxygen generation plants at healthcare facilities, rapid genome sequencing of virus, continued collaboration, budget and funding and political will.
- Three pillars to disrupt the chain: Best behavior; quick vaccination; isolation, testing, tracking, treatment and containment.
- Never lose sight of the current wave.
- Whenever there is lockdown, the immunization program should not suffer.
- There should be strict punishments for noncompliance to lockdown guidelines, especially in vegetable markets, etc.; paramilitary and military forces can be involved to implement this.
- Not wearing mask should be made a criminal offense.
- The third wave is more likely to affect children; if this happens, arrangements will have to be made for parents to stay with the child in the hospital. Another concern is lack of vaccination for children. We need quick clinical trials for children. Canada has authorized Pfizer vaccine for children aged 12 years and above. We need to have standard protocols for management of children and start preparing pediatric ICUs and NICU beds. Pediatric formulations of different medications will be needed. Sample collection will be a challenge with children.
- Challenge is huge: Supply chain management, infrastructure.
- There should be an inventory for everything such as oxygen, drugs, ICUs.

- Vaccinate as fast as possible.
- Waste management guidelines for COVID facilities and home management have to be strictly enforced.
- Expand telemedicine and teleconsultation services. Teaching videos should be developed as manuals for pediatric patients.
- Lack of adequate number of healthcare workforce is going to be a bigger problem in the future. Plan and identify now ways to increase healthcare workforce including doctors and nurses.
- All hospitals should increase their bed strength and equipments (such as oxygen supplies, ventilators).
- Community involvement and their participation are very important.
- There is an urgent need to discuss strategies to upgrade and strengthen primary healthcare.
- An integrative approach should be adopted; there should be only one source of authentic information.
- We need to act now and not just plan.

Round Table - HCFI Expert Group on Environment Zoom Meeting: Record of Discussions and Recommendations on "Environmental Compliances during COVID-19 Pandemic"

16th May, 2021 (12 noon-1 pm)

Participants: Dr KK Aggarwal, Dr Anil Kumar, Dr Ajay Deshpande, Dr SK Tyagi, Dr SK Gupta, Dr Dipankar Saha, Dr M Dwarkanath, Mr P Khandelwal, Mr RS Tyagi, Mr Vivek Kumar, Mr Vikas Singhal, Mr SA Verma, Mr Aishwarya Mukherjee, Mr Varun Singh, Mr Neeraj Tyagi, Mr Kamal Sharma, Ms Ira Gupta, Dr S Sharma

Key points from the discussions

- Environmental compliances by the industries during the pandemic are very poor because of various reasons such as lockdown/curfew imposed, inadequate manpower, etc.
- Last year during the Nation-wide lockdown, we actually experienced what is wholesome and pristine air. But we have not learnt any lesson and we did not set any target for the maintenance of wholesomeness of environmental components (air and water quality) irrespective of the situation and circumstances.
- This year the pandemic was unprecedented and unpredicted which is affecting human health. Environmental health and human health are interdependent. We have failed to educate the people about this and not learnt lessons from the past.
- Sewage Treatment Plants (STPs)/Effluent Treatment Plants (ETPs), Air Pollution Control Devices (APCDs) are not properly operated and monitored during the pandemic. Other important issues that have been affected are solid waste management, biomedical waste management (collection of discarded PPE kit/masks from hospitals and COVID care centers), etc. The entire composition and quantification of biomedical waste has changed in this pandemic. Waste generation has increased and we do not have the capacity to handle the biomedical waste. Mixing of biomedical waste with municipal waste is a big problem. Though, staff engaged in municipal solid waste management/biomedical waste management doing remarkable work has rightly been called frontline warriors as they are collecting and disposing the waste in such critical times.
- There is a robust system for grant of Environmental Clearances, Consents and Authorizations. But these documents which were earlier limited to one page are now almost 10 pages long and include several conditions (around 60). There are multiple Regulatory Authorities. We should be aware of the challenges of implementing these conditions, many of which are qualitative. The conditions should be measureable, monitorable and quantifiable to reflect into actual enforcement of compliance.
- The pandemic has thrown up several challenges, especially for environmental compliances, during the COVID times. There have been many disasters in the industries because of leniency in compliances and poor safety standards such as the gas leak at the polymer chemical plant in Visakhapatnam (Andhra Pradesh), boiler blasts in Tamil Nadu and Gujarat. Environmental compliance continues to be a big issue even today and may be much more in the future.
- Industries are facing many challenges such as reduced staff because of which they cannot function properly, e.g., poor functioning of Air Pollution Control Devices, ETPs, STPs, poor housekeeping, especially getting third party contractors who do the sampling and monitoring of the environmental parameters in the industries. There are limitations of delivery of proper and efficient services at remote locations as it is difficult to travel during the pandemic. A loss of market demand has also been seen because of which many activities have been curtailed. As they are not able to perform in full capacity therefore they are not able to comply with the environmental regulations.

- Indian environmental standards are merely pollution control standards and not environmental or ecological restoration standards. Besides, our environmental standards are load-based standards and not cluster-based standards especially for the industries. However, most of the operations and pollution control in industries have become automated. If industries are functional, pollution control systems must be operated. Relaxation can be considered in white and green category industries, but only to a certain extent – sewage treatment; if more than 25 KLD, it needs to be treated; if less than 25 KLD, relaxation can be given during the pandemic. For red and orange category industries, the regular operation of pollution control systems should be insisted upon. Green and white industries can be considered for giving relaxation.
- Therefore, some flexibility may be considered in enforcement in the present context particularly with regards to monitoring and reporting. But all reports must be kept for potential legal defense with due diligence. However, industry should not relax any safety standards. Extension of Consent to Establish (CTE), Consent to Operate (CTO) may be granted. The validity of CTE and CTO has been extended up to October/November by some Pollution Control Boards and Committees.
- Economic slowdown is a concern, but economic revival can run parallel to environmental revival. Therefore, environmental compliances should continue to be followed. However, most of the environmental regulations are very stringent and difficult to adhere to. There should be a dialogue between the industry and the experts.
- For example, in DMRC, the environmental compliance is a part of the construction tender document. COVID requirements have also been added now. The problem they are facing is that most of the labor has gone back to their native villages and so productivity/output has gone down. Working capital has also gone down for the contractors. Inadequate availability of raw material is another issue. Physical visits for monitoring have reduced. Construction activities at sites are being monitored via CCTVs and video conferencing to fulfil the environmental conditions laid down in the contract. COVID compliances (thermal scan, double mask, etc.) are also being monitored via CCTVs.
- There is no emergency management plan, for example, if there is fire. Roads should be kept empty and not be a parking place for fire vehicles to move quickly. The general public is also unaware of what is an emergency management system.
- Authorities have to be visionaries; technologies will bring convenience, they will not bring comfort. We have to assess how each new technology/activity is going to adversely affect the environment. For this, we have to either expand the scope of environmental compliances or completely stop that particular activity.

Recommendations

- Laws for environmental compliances are integral to industrial activities and should be followed regardless of the pandemic situation.
- Extension of validity of Environmental Clearance (EC), Consent to Establish (CTE), Consent to Operate (CTO) and Authorization may be granted.
- No relaxation should be given as far as compliance to environmental regulations and standards is concerned. Relaxing the standards even during the pandemic will only result in an ecological boomerang.
- Integrated action by Industries, Regulatory Authorities and application of technologies in monitoring will lead to proper environmental compliances.

Consider Now COVID-19 also as a Likely Cause of Acute-onset Neuropsychiatric Symptoms in Children

COVID-19 is known to have protean manifestations. But, even almost 1½ year later since the pandemic was first recognized, the virus continues to unravel itself every day to reveal some new aspects of the disease.

A small case series from Italy has suggested that children who present with pediatric acute-onset neuropsychiatric syndrome (PANS) may have COVID-19 as the underlying cause. The case series published in *The Lancet Child and Adolescent Health* has described the cases of two adolescent boys, who developed PANS 2 weeks after testing positive for COVID-19 with a nasopharyngeal swab test.

- The first patient, a 12-year-old boy, presented with sudden onset of psychiatric disturbances. He had no such personal or family history of either neuropsychiatric disturbances or any movement disorders. Two weeks after the positive test, he suddenly became fearful of catching infections and touching handles and developed the urge to repeatedly wash his hands along with anorexia. Examination revealed severe emotional lability and

facial motor tics. His tests were negative for Group A streptococci and antibasal ganglia antibodies, including full autoimmune panel. Electroencephalogram (EEG), electrocardiogram (ECG) and brain magnetic resonance imaging (MRI) showed no abnormal findings. The Children's Yale-Brown Obsessive-Compulsive Scale score was 22 indicating moderate-severe obsessive-compulsive disorder (OCD). At follow-up after 2 months, he continued to have the desire to wash his hands along with selective eating and motor tics. However, he tested negative for COVID-19.

- The second patient, a 13-year-old boy, developed a sudden compulsive disorder. He used only a tablespoon during his meals and before sleeping, he began to arrange his shoes in a particular manner. No such symptoms in the past were reported. Two weeks prior to hospitalization, the boy had symptoms of fever, cough, gastrointestinal (GI) disturbances and skin rash. He tested positive for COVID-19. On examination, he had a facial motor tic, guttural vocal tics, hyperactivity, aggressiveness, irritability, inattentiveness and lack of appetite. Like the first patient, he too tested negative for Group A streptococci antibodies, full autoimmune panel and viral serology, including normal EEG, ECG and brain MRI. However, the basal ganglia antibodies titer was 1:100. Also, the Children's Yale-Brown Obsessive-Compulsive Scale score was 28, indicating severe OCD. No improvement was seen at 1 month follow-up.

PANS is a disorder that affects children and adolescents and its features include sudden development of neuropsychiatric symptoms such as OCD along with severe lack of appetite or motor dysfunction. An infectious or autoimmune mechanism seems to be in play in its etiology. A pediatric autoimmune neuropsychiatric disorder may also occur following streptococcal infection (PANDAS). The two cases reported tested negative for antistreptolysin O (ASO) titer and anti-DNAse B.

Based on their findings, the authors of the study said that since a temporal association between the sudden onset of symptoms and the diagnosis of COVID-19 was observed, it is likely that PANS may have been caused by the SARS-CoV-2 virus. Hence, they suggest that COVID-19 should be considered in the differential diagnosis of PANS.

Source: Pavone P, Ceccarelli M, Marino S, et al. SARS-CoV-2 related paediatric acute-onset neuropsychiatric syndrome. Lancet Child Adolesc Health. 2021;5(6):e19-e21.

Minutes of Virtual Meeting of CMAAO NMAs on "COVID-19 Variants & Country Updates"

22nd May, 2021 (Saturday, 9.30 am-10.30 am)

Participants: Member NMAs: Dr YehWoei Chong, Singapore Chair-CMAAO; Dr Marthanda Pillai, India, Member-World Medical Council; Dr Debora Cavalcanti, Brazil; Dr Marie Uzawa Urabe, Japan Medical Association; Dr Md Jamaluddin Chowdhury, Bangladesh Medical Association; Dr Salma Kundi, President-Pakistan Medical Association; Dr Qaiser Sajjad, Secretary General-Pakistan Medical Association; Dr Akhtar Husain, South African Medical Association; Dr Tony Bartone, Australia; Dr Shiv Prasad Shrestha, Nepal Medical Association

Invitee: Dr Russell D'Souza, Australia UNESCO Chair in Bioethics; Dr Monica Vasudev, USA; Mr Vivek Kumar; Dr S Sharma, Editor-IJCP Group; Dr Meenakshi Soni Bamalwa

Key points from the discussion

#1: COVID variants

Dr Monica Vasudev, Allergist Immunologist, Advocate Aurora Health, WI, USA

- The SARS-CoV-2 genome is made of about 30,000 letters (A, T, C and G) of RNA. The RNA produces four structural proteins: S (spike), E (envelope), M (membrane) and N (nucleocapsid). The S, E and M proteins form the viral envelope, while the N protein has the RNA. The virus attaches to the human cells by the spike protein.
- Viruses mutate at a much higher rate. They also replicate very rapidly in a very short period of time. Hence, mutants invariably develop.
- Mutants may be inferior to the original virus, i.e., the mutations make the virus less able to replicate or spread from one host to another. Such strains die out. Or, the mutants may have selective advantage, i.e., they infect more readily, replicate and also spread more easily. These variants are causing the surge in cases in certain areas.
- Mutations are changes in the genetic composition that occur naturally over time. Mutations cause variants.
- When variants of the same class develop different genome sequences due to mutation, they are called variants. They may either strengthen or weaken the virus.
- A distinct branch of viral classification is termed as part of a lineage.

- Clade means the different ways in which species of a virus relate to each other. It is used to track how the virus bounces around various geographical regions.
- Each variant mutation is named with letters and numbers. For e.g., D614G (earliest mutation that occurred in 2020 and is the most prevalent variant worldwide); N501Y, this mutation helps the virus to bind more tightly to human cells.
- Variant of interest: A variant with specific genetic markers that have been associated with changes to receptor binding, reduced neutralization by antibodies generated against previous infection or vaccination, reduced efficacy of treatments, potential diagnostic impact, or predicted increase in transmissibility or disease severity (*CDC*).
- Variant of concern: A variant for which there is evidence of an increase in transmissibility, more severe disease (e.g., increased hospitalizations or deaths), significant reduction in neutralization by antibodies generated during previous infection or vaccination, reduced effectiveness of treatments or vaccines or diagnostic detection failures (*CDC*).
- Variant of high consequence: A variant of high consequence has clear evidence that prevention measures or medical countermeasures (MCMs) have significantly reduced effectiveness relative to previously circulating variants (*CDC*).
- There is evidence of impact on diagnostics, treatments or vaccines for variants of concern. They interfere with diagnostic test targets, decrease susceptibility to neutralizing antibodies, reduce vaccine-induced protection from severe disease and increase resistance to treatment.
- The variants of concern are B.1.1.7 (first found in the UK), B.1.351 (first found in South Africa), P.1 (first found in Brazil) and B.1.617 (first found in India).
- B.1.1.7 variant is 50% more transmissible and has spread to other countries. Many mutations in this variant are present in the gene that encodes for the spike protein.
- The Pfizer, Moderna, AstraZeneca and J&J vaccines appear to protect against B.1.1.7.
- The B.1.351 was first detected in October 2020 in South Africa. It is the predominant variant in South Africa now. Some mutations are similar to that seen in B.1.1.7.
- The P.1 strain was discovered in Brazil. It has at least two key mutations that may make the strain more transmissible and more able to reinfect. It has the potential to make vaccines less effective.
- The B.1.617 or the "double" variant was first detected in India in the state of Maharashtra in October last year. It is very contagious and is spreading very rapidly and may soon become the dominant variant in Europe. It shows potentially slightly reduced susceptibility to neutralizing antibodies.
- Most antigen-based tests will continue to work with these variants as most test the N antigen of the virus, where there are fewer mutations. So far, the N antigen has remained conserved in these variants. However, efficacy of genome sequence testing is still unknown.
- 85.4% of diagnostic tests have targets other than the spike gene, so they should still be effective for these variants, and would not produce a "failed" test if the infection is caused by a variant with mutations in the spike gene. Of the remaining 14.6% of tests, 7.3% have multiple targets within the SARS-CoV-2 genome in addition to the spike gene, such as *ORF1ab* and *N* genes, so they should continue to yield accurate results; 90.1% of rapid antigen tests with EUA detect nucleocapsid protein, rather than spike protein, so they should be unaffected (*Johns Hopkins*).
- The percentage of cases that are being sequenced is very low. Hence, there is very little insight into emerging new variants.
- We still have a long way to go to ensure equitable distribution of vaccines in terms of the number of population.
- The Novavax vaccine (NVX-CoV2373) was tested against B.1.351 variant at 16 sites in South Africa in 4,387 participants. Two doses of the vaccine or placebo were administered 21 days apart. The overall efficacy of the vaccine was 49.4% and the efficacy against the variant in HIV-negative subjects was 51%. The Novavax vaccine was efficacious against COVID-19, including the B.1.351 variant.
- The efficacy of Pfizer-BioNTech was found to be 75% against B.1.351; the efficacy against B.1.1.7 was 89.5% 14 days after the second dose. Efficacy against severe outcomes against any variant was 97.4% (*NEJM*).
- The Moderna trial evaluated three types of booster vaccines: B.1.351, multistrain version and its original vaccine. The single dose of 1273 and 1273.351 had increased neutralizing titers against the virus and

two variants of concern (B.1.351, P.1). 1273.351 achieved higher titers against B.1.351 vs. 1273. Both booster doses were generally well-tolerated.

#2: Country Update

- **Singapore Update:** The B.1.617 is a concern. Four generations of spread from the Changi Airport cluster have been seen in just 8 days. The index case was detected on 4th May, the second-generation spread was estimated to be from May 3 to 7, the third-generation spread was estimated to be between 8th and 11th May and the fourth-generation spread between 10th and 12th May.
- **Bangladesh Update:** The country has the variant from India as well as South Africa. There are about 1,400-1,600 new cases every day. The country is under a lockdown but only educational institutes, public transport, markets are closed. Only about 50% people use masks. There is a shortage of vaccines in the country.
- **India Update:** The country is struggling with the second wave. More than 4 lakh new daily cases were recorded, though the numbers have started declining. Although the second wave had initially overwhelmed the healthcare system, the situation seems to be somewhat under control. Many states are under lockdown with different restrictions. The infection is spreading to the rural areas. Both vaccines in India (Covaxin and Covishield) appear to be effective against variants, though confirmatory reports are awaited.
- **Pakistan Update:** The country is experiencing the third wave; in some parts of the country, the numbers are rising, whereas they are decreasing in other parts. More than 4,000 cases were recorded in last 24 hours. Vaccines used are Sinopharm, AstraZeneca and Sputnik.
- **Malaysia Update:** More than 6,000 cases were recorded in 24 hours. There is lockdown called the "movement control order (MCO)" although businesses are allowed to operate. Five cases of the variant found in India have been detected. The Government is planning a 21-day quarantine for travelers coming from India.
- **Japan Update:** Japan is currently in the midst of the fourth wave. The IOC has said that the Olympics will be held, which is a concern.
- **Brazil Update:** Two cases of B.1.617 have been detected. The vaccines used are Coronavac, Pfizer and AstraZeneca.
- **South Africa Update:** The country is experiencing the third wave. More than 3,500 new cases are reported daily. People with comorbidities are more affected and their oxygen requirement is very early. The Pfizer vaccine is being used for the general public, but the vaccination is occurring at a slow pace.
- **Australia Update:** There are no community cases; there is some complacency and vaccine hesitancy. Poor logistics hampered vaccine rollout. There is battle between government zero tolerance strategy versus open up and back to normal living with the virus. The borders may be closed for much longer.

Take Both Doses of COVID Vaccine to Get Maximum Protection Against B.1.617.2 Variant

Pfizer and AstraZeneca COVID-19 vaccines are effective against symptomatic disease due to the B.1.617.2 variant detected in India, according to a new study conducted by Public Health England and reported as a preprint.

The two doses of the Pfizer vaccine showed 87.9% efficacy in preventing symptomatic disease due to the B.1.617.2 variant, while the two doses of the AstraZeneca vaccine demonstrated 59.8% efficacy against the B.1.617.2 variant.

Efficacy against B.1.1.7 (which first emerged in the UK during September 2020) was 93.4% with two doses of Pfizer vaccine as compared to 66% efficacy with two doses of the AstraZeneca vaccine.

However, the effectiveness 3 weeks after single dose of both vaccines amounted to only 33%.

The effect of vaccination on the B.1.617.2 variant was assessed using the following two approaches:

- First, a test negative case control (TNCC) design was used to estimate vaccine effectiveness against symptomatic disease with the B.1.617.2 variant compared to the B.1.1.7 variant over the same period.
- Second, the proportion of cases with the B.1.617.2 variant relative to the main circulating virus (the B.1.1.7 variant) was estimated by vaccination status.

The B.1.617.2 and B.1.1.7 variants were identified by whole genome sequencing as well as a 3-target polymerase chain reaction (PCR) assay (samples testing positive or negative on the spike gene target). A total of 12,675 sequenced cases were analyzed. Of these, 11.621 were B.1.1.7 variant, while B.1.617.2 was detected in 1,054 cases.

The study authors write, *"These findings suggest a modest reduction in vaccine effectiveness. Nevertheless, a clear effect of both vaccines was noted with high levels of effectiveness after*

two doses. Vaccine effects after two doses of ChAdOx1 vaccine were smaller than for BNT162b2 against either variant."

The B.1.617 has been declared as a variant of concern by the WHO and Public Health England. It has not only become the dominant strain (B.1.617.2) in India, it has rapidly crossed borders and spread to about 40 countries.

Besides increased transmissibility and disease severity, variants of concern interfere with diagnostic test targets, reduce susceptibility to neutralizing antibodies and increase resistance to treatment. Another concern is their ability to evade natural or vaccine-induced immunity.

The AstraZeneca vaccine is marketed as Covishield in India.

The results of this study are encouraging and reassure that the vaccines will be effective in reducing severe disease and prevent hospitalization and deaths. This study also reiterates the need for full vaccination, especially for the high-risk population groups. It is important that people take both doses of the vaccine to get maximum protection.

Source: Jamie Lopez Bernal, et al. Effectiveness of COVID-19 vaccines against the B.1.617.2 variant. Available at: https://www.medrxiv.org/content/10.1101/2021.05.22.21257658v1, Posted May 24, 2021. doi: https://doi.org/10.1101/2021.05.22.21257658.

Ischemic Stroke can be Indicative of Vaccine-induced Thrombosis and Thrombocytopenia

Stroke due to cerebral sinus thrombosis as a presenting feature of vaccine-induced thrombosis and thrombocytopenia (VITT) has been frequently reported earlier. However, ischemic stroke due to arterial thrombosis occurring after vaccination has now been identified as another presentation of VITT.

A study published online on May 25 in the *Journal of Neurology, Neurosurgery & Psychiatry* has reported the first cases of stroke due to large vessel arterial occlusion in 3 patients who had received the AstraZeneca COVID-19 vaccine and developed ischemic stroke due to VITT. One of the three cases had a fatal outcome.

- The first patient, a 35-year-old woman developed intermittent headache on the right side and around her eyes 6 days after vaccination. Five days later, she woke up in the morning with drowsiness and weakness on the left side of the body involving the face, arm and the leg. Right middle cerebral artery occlusion with extensive ischemia and right portal vein thrombosis was seen on imaging. The patient underwent urgent decompressive hemicraniectomy along with IV immunoglobulin and plasmapheresis and anticoagulant fondaparinux. But, she passed away within 2 weeks of onset of illness.
- The second patient was another woman, aged 37 years, who reported symptoms of diffuse headache, confusion, weakness in her left arm and visual field loss on the left side 12 days post-vaccine. Bilateral internal carotid arteries were found to be occluded; other features on imaging were left transverse sinus thrombosis, pulmonary embolism and thromboses of the left transverse and sigmoid sinuses, left jugular, right hepatic and both iliac veins. The platelet counts improved after treatment with IV immunoglobulin, methylprednisolone and plasmapheresis following which her platelet counts improved. She also received fondaparinux after which her condition improved.
- A 43-year-old man was the third patient reported in this series. He presented with dysphasia 21 days after taking the vaccine. Acute left frontal and insular infarct was evident on imaging; however, no blood clots were seen in the cerebral venous sinus. His condition became stable after treatment with platelets, IV immunoglobulin and fondaparinux.

A high index of suspicion is required for correct diagnosis as timely intervention can be life-saving.

VITT should be considered as a possible cause when any patient, especially a young patient, presents to the hospital with ischemic stroke within 1 month of taking the AstraZeneca vaccine. Urgent platelet count, D-dimers, fibrinogen and anti-PF4 (platelet factor 4) antibodies must be done as part of evaluation. All three patients in the above case series had very low platelet counts, elevated D-dimers and confirmed antibodies to PF4 findings typically associated with VITT.

A multidisciplinary approach should be adopted for managing such cases. Potentially life-saving treatments include IV immunoglobulin, methylprednisolone and plasmapheresis. Such patients need nonheparin anticoagulants (such as fondaparinux, argatroban) or direct oral anticoagulants.

Although VITT is a serious condition, it is very rare. Post-vaccine thrombotic complications are much less common than those reported with the disease (COVID-19) itself. Therefore, one must always keep in mind that the benefits of the vaccine still outweigh the associated risks.

Source: Al-Mayhani T, Saber S, Stubbs MJ, et al. Ischaemic stroke as a presenting feature of ChAdOx1 nCoV-19 vaccine-induced immune thrombotic thrombocytopaenia. J Neurol Neurosurg Psychiatry. 2021:jnnp-2021-326984.

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News and Views

Covaxin Found Effective Against Variant First Found in Brazil

The indigenous coronavirus disease 2019 (COVID-19) vaccine, Covaxin, can fight the variant first found in Brazil too, suggests a new study on the vaccine. Earlier, the vaccine was found to have the capability to fight the variant first detected in UK, B.1.1.7 and the double mutant, B.1.617.

The vaccine, developed by the Indian Council of Medical Research (ICMR) in association with Bharat Biotech, is therefore capable of fighting some of the major variants of concern (VoC), currently circulating in the country.

Researchers from the National Institute of Virology (NIV) and the ICMR assessed the neutralization efficacy of the variant first detected in Brazil, B.1.1.28.2, with convalescent sera of people with natural COVID infection and those who had been given two doses of Covaxin. It was noted that after receiving two doses of Covaxin, people's immunity was boosted against the variant… (*ET Healthworld – TNN*)

P.1 Variant may be More Transmissible, Says Study

A study published in *Science* says that the coronavirus variant first identified in Brazil seems to be much more contagious compared to the other versions of the virus.

The variant termed P.1 might also be able to evade immunity that people achieved after being infected with COVID-19 earlier. An article in *Science Daily* stated that nearly 75% of the individuals in Manaus were infected in the first wave in mid-2020. Experts believed that the city might have reached herd immunity. However, a second wave of infections hit the city in late 2020, and P.1 was the dominant strain.

Investigators noted that P.1 acquired 17 mutations, three being in the spike protein. The strain appears to be 1.7-2.4 times more transmissible than other strains and is capable of avoiding 10-46% of the immunity that people achieve from infection with other strains… (*Medscape*)

N440K Drove COVID Surge in Some Indian States

As scientists attempted to decode the potential fatality of the double mutant strain B.1.617 of the coronavirus, researchers from Hyderabad and Ghaziabad noted that the mutant N440K of the coronavirus was 10- to 1,000-fold more infectious than some other strains. This mutant appeared to have driven the second wave of COVID-19 infections in some areas.

First identified in Kurnool in Andhra Pradesh, the N440K mutant spread fast in some parts of the country. About a third of infections in Andhra Pradesh and Telangana had been reported to be due to this variant and in the second wave, its presence rose fast. Over the previous 2 months, Karnataka, Maharashtra, Telangana and Chhattisgarh contributed around 50% of samples with the mutant version, thus pointing to a geographically-localized spread… (*ET Healthworld – TNN*)

Most Hospitalized Vaccinated Patients Likely Acquired COVID-19 Infection before Development of Immunity

Most people who had taken the vaccine and were hospitalized for COVID-19 likely had developed the infection just before or about the time of the vaccination, as per a *BMJ* report.

Hospitalized vaccinated patients during the second wave of the UK were evaluated by the International Severe Acute Respiratory Infection Consortium Clinical Characterisation Protocol (ISARIC4C) using data available up to April 10, 2021. Of the 99,445 hospitalized patients enrolled in the study, 3842 (7.3%) had received the vaccine. Time to onset of symptoms and also mortality were analyzed for the vaccinated patients.

- 729 (40%) symptomatic patients developed COVID-19 symptoms 0-7 days after the vaccination.
- 352 (19%) developed symptoms 8-14 days post-vaccination.
- 211 (12%) patients developed symptoms 15-21 days after vaccination.
- 526 (29%) developed symptoms more than 21 days after vaccination.

Since the median incubation period for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is approximately 5 days, these observations suggest that the majority of patients had been infected before they developed fully immunity as this is not enough time (0-7 days) for the immunity to develop. And those who developed symptoms 8-14 days after the vaccine were infected before the immunity had fully developed. These infections are unlikely to be vaccine failures.

However, there is a possibility that those who developed symptoms 15-21 days or >21 days post-vaccine were cases of vaccine failure. But, this is along expected lines as vaccines were not 100% effective.

ISARIC4C report states that the "elderly and vulnerable people who had been shielding, may have inadvertently been exposed and infected either through the end-to-end process of vaccination, or shortly after vaccination through behavioral changes where they wrongly assume they are immune."

Among those who developed symptoms ≥21 days after the vaccination, 28% (113/400) died with COVID-19. Of these, 82 were in the "frail elderly" group. The report said, "Mortality appears to remain high for people in high risk vaccination tiers who are admitted to hospital with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection despite vaccination 21 days or more previously."

These findings reiterate the importance of maintaining social distancing, even after vaccination, to minimize the risk of infection as most infections had occurred within 14 days of vaccination before immunity fully develops.

Deborah Dunn-Walters, chair of the COVID-19 Taskforce at the British Society for Immunology and Professor of Immunology at the University of Surrey, said, "A very small number of people were hospitalized 21 days post-vaccination, and it's these people that we need to examine in more detail to understand why the vaccine did not afford them full protection."

(*Source: BMJ 2021;373:n1127, Published April 30, 2021*)

Pulse Oximeters More Useful Than Symptom-based Screening for COVID-19 in Older Adults

Pulse oximeters are more useful screening methods for COVID-19 in older adults compared to temperature measurement.

Fever is considered a classic presentation of COVID-19. However, a new research from the College of Nursing, Washington State University suggests that since older adults have a lower core body temperature (<98.6°F or even as low as 94°F), the standard definition of fever (≥100.4°F) may be a less useful indicator of infection in this population group. The study says "Lower baseline temperatures may result in overlooking fevers. In fact, upwards of 30% of older adults with serious infections show a mild or no fever."

In addition, COVID-19 symptoms such as fatigue, body ache, weakness, increasing loss of taste and smell may well be attributed to aging. Atypical symptoms are more often seen in older adults, which could be in the form of change in cognitive status or mobility. There is a delay in fever and respiratory symptoms.

The study cautions healthcare providers to look out for any fall in SpO_2 (3-5%) after mild activity/ambulation, room air and the presence of hypoxemia without tachypnea. This can be done in homes using a small, portable and an economical device, the pulse oximeter.

The authors recommend that pulse oximeters should be considered to screen for asymptomatic hypoxia in older adults, given their potential efficacy for detecting changes in SpO_2.

Since the absence of fever does not always rule out the presence of an infection, screening for "silent hypoxia" with pulse oximeters could help identify older adults with COVID-19 pneumonia.

(*Source: Frontiers in Medicine, April 14, 2021*)

AHA/ASA: Treat All Patients with Suspected CVST Due to a COVID-19 Vaccine with Nonheparin Anticoagulants

The American Heart Association (AHA)/American Stroke Association (ASA) Stroke Council leadership has issued guidelines on the management of cerebral venous sinus thrombosis (CVST) with vaccine-induced immune thrombotic thrombocytopenia (VITT), which have been published in the journal *Stroke*.

Let's first understand the definitions of these terms.

- CVST is formation of clots in the veins (*cf*. in most cases of stroke, clots are formed in the arteries of the brain).
- CVST and thrombocytopenia together are called thrombosis-thrombocytopenia syndrome (TTS).
- When TTS is linked to receiving a COVID-19 vaccine, it is called vaccine-induced immune thrombotic thrombocytopenia (VITT).

CVST may be roughly divided into four syndromes:

- Isolated headache or increased intracranial pressure
- Focal neurological presentations
- Subacute encephalopathy
- Cavernous sinus syndrome/multiple cranial neuropathies.

CVST is not easy to diagnose as its symptoms resemble several other neurological disorders and can include severe headache, blurry vision, fainting or loss of

consciousness, weakness, sensory changes, confusion or trouble speaking, seizures, abdominal pain, leg pain, difficulty breathing or shortness of breath.

If associated with the COVID-19 vaccine, cases of TTS/VITT occurred several days up to 2-1/2 weeks after being vaccinated with the Johnson & Johnson (Janssen) COVID-19 vaccine in the US, or up to 3-1/2 weeks after receiving the AstraZeneca COVID-19 vaccine in Europe. All patients who present to the ER with a suspected clot should be screened for a recent history of COVID-19 vaccine. However, the risk of CVST blood clots was 8-10 times higher following a COVID-19 infection as compared to the risk associated with a COVID-19 vaccine. The guideline also says that whether an association between the vaccine and platelet factor 4 (PF4) antibody, thrombocytopenia, and thrombosis exists or not is not definitive as at present there is no data about people who did not develop CVST, TTS or VITT after a COVID-19 vaccine for comparison.

Key recommendations

- All patients with suspected CVST due to a COVID-19 vaccine should be treated with nonheparin anticoagulants such as argatroban, bivalirudin, danaparoid, fondaparinux or a direct oral anticoagulant (DOAC). No heparin products in any dose should be given.
- Magnetic resonance imaging with a venogram (MRI/MRV) or computed tomography with venogram (CT/CTV) is recommended to accurately detect and diagnose CVST.
- Blood tests should include a CBC (complete blood count) plus: platelet count, peripheral smear, prothrombin time, partial thromboplastin time, fibrinogen test, D-dimer test and PF4 antibody ELISA test (PF4 antibodies are sometimes formed in the blood to fight against the anticoagulant heparin).
- Anticoagulation treatment doses may need to be tailored if platelet counts are extremely low (<20,000/mm^3) or if there is low fibrinogen.
- Anticoagulants should be used to treat CVST even if there is a secondary hemorrhage in the brain in order to prevent progressive thrombosis and to control bleeding.
- Platelet transfusion should be avoided.
- Once platelet counts return to normal (1,50,000-4,50,000/mm^3), most patients can be transitioned to an oral anticoagulant if there are no contraindications.
- Individual patient factors should be considered regarding the use of a DOAC or a vitamin K agonist (VKA) after there is full platelet count recovery.
- All cases of thrombosis after a COVID-19 vaccine should be reported to the US Department of Health and Human Services Vaccine Adverse Event Reporting System. This data will be important to understanding the incidence of CVST, TTS and VITT. *In our country, such ADRs (or any other) can be reported to PvPI.*

(*Source: AHA Press release, April 29, 2021*)

Strengthening Global Public Health Response to Prevent and Prepare for Future Pandemics

The COVID-19 pandemic has exposed the inadequacy and fragility of the global health infrastructure. The consequences have been devastating. However, in every adversity there lies an opportunity. The lessons learned from the ongoing pandemic are an opportunity to revise and reinforce the public healthcare system, especially in the rural areas.

In a research titled "Global Public Health Convention for the 21st Century", the Panel for a Global Public Health Convention (GPHC) has outlined 10 recommendations on how the world can better prevent and prepare for future pandemics by adopting a robust global public health convention. GPHC panel is an independent group of global experts from diverse disciplines such as public health, public policy, medicine, diplomacy and economics. It was officially launched on April 26 this year.

The 10 key recommendations are:

1. **Greater authority for a global governing body:** "The governance structure for a global public health system should grant necessary authority to one or more agencies, such as the World Health Organization (WHO), to coordinate pandemic prevention, preparedness and response globally, including across regions and countries."
2. **Improved ability to respond to pandemics:** "The global public health system (and its governing agency or agencies) should possess the capability to flexibly and rapidly respond to, instil protections for, formulate interventions against and mobilize and deploy resources for, a range of possible public health security threats and scenarios such as infectious disease outbreaks and pandemics... This flexibility includes the capacity to meet the diverse needs of countries at any given stage of an infectious disease outbreak or pandemic."

3. **Single source for technical expertise**: "An effective global public health security system requires a singular body with technical expertise in pandemic prevention, preparedness, response and recovery. This agency should represent the authoritative source for information, expertise and technical proficiency. The agency should be the single authoritative guide in case of emerging and re-emerging infectious disease outbreaks—the role that WHO is currently authorized to serve."
4. **Objective evaluation system for national core public health capacities**: "The capacity of objectively evaluating countries on their progress in achieving requirements and of providing or coordinating remediation for identified deficiencies should be built into a governing framework for a global public health system."
5. **More effective enforcement mechanisms:** "An effective global public health security convention requires a governing body (or bodies) to enforce the framework.... Enforcement mechanisms can include incentives for participation, penalties for noncompliance or both."
6. **Autonomy:** "The convention's governing body (or bodies) should possess independent decision making powers and be insulated from undue political interference. The body should have the ability to make decisions in the best interest of global health, rather than in the interests of individual stakeholders."
7. **Independent and sustainable funding:** "An effective global public health security framework requires a sustainable financing system that protects the governing body (or bodies) from political influence, possible retribution or the threat of inconsistent funding....Sustainable financing means perennial investments in all stages of infectious disease containment—especially prevention-related activities, before outbreaks occur."
8. **Representativeness:** "The governing framework must possess a high degree of transparency and accountability. The governing structure must be adequately representative of all countries. It should also include other relevant stakeholders from civil society, the public health sector, the private sector and academia, among others."
9. **Investment from multiple sectors:** "A formal pandemic prevention, preparedness and response system (including governing bodies) must involve multiple sectors at all levels of governance and action.... The public health sector alone is not enough to effectively prepare the world for a pandemic, nor does it typically have enough influence within countries to gather adequate national support."
10. **Commitment:** "For a global health security convention to be effective, all relevant parties participating in the system must understand the threat posed by pandemic infectious diseases; accept the gravity of this threat; acknowledge their own responsibility in contributing to effective prevention, preparedness and response; show a commitment to these efforts..."

(*Source: Lancet Public Health, Published Online May 5, 2021*)

Seropositive Healthy Young Adults Still at Risk of Reinfection

New research published in *The Lancet Respiratory Medicine* has found that seropositive healthy young adults are still at risk of reinfection.

A prospective cohort study was conducted as part of the COVID-19 Health Action Response for Marines (CHARM) study to examine the risk of reinfection in healthy young adults who were seropositive for a previous SARS-CoV-2 infection. The study included male recruits, aged 18-20 years, from the US Marine Corps. They were first put under a 2-week unsupervised home quarantine followed by a 2-week supervised quarantine when they returned to the marine quarantine facility.

- Seropositive young adults had lower risk of reinfection vis-a-vis the seronegative individuals. During the 6-week study period, 10% of seropositive participants (19/189) had at least one positive polymerase chain reaction (PCR) test for SARS-CoV-2. On the other hand, 48% of seronegative participants (1,079 of 2,247) tested positive for the infection.
- Reinfection in seropositive adults was found to be associated with lower spike protein immunoglobulin G (IgG) titers versus those who had higher IgG titers (hazard ratio [HR] 0.45 [95% confidence interval or CI 0.32-0.65]; $p < 0.001$).
- The infected seropositive subjects had at least 10 times lower viral load than that seen in the infected seronegative participants (*ORF1ab* gene cycle threshold difference 3.95 [95% CI 1.23-6.67]; $p = 0.004$).
- Baseline neutralizing titers were detected in 83% (45/54) of uninfected seropositive subjects and 32% (6/19) of the infected subjects.

These observations indicate that although antibodies produced as a result of the infection are generally protective, they do no ensure effective immunity against subsequent infection. A risk still exists albeit a small one. In previously infected young adults, vaccination further enhances the natural immune response to prevent reinfection and reduce transmission. Hence, an aggressive vaccination strategy needs to be pursued toslow down the pandemic.

(*Source: Lancet Respiratory Medicine, Published April 15, 2021*)

Not All Sinusitis in the Time of COVID-19 is Bacterial; It could also be Black Fungus Sinus Infection

Mucormycosis, or Black fungus as it is referred to in common parlance, is being reported in patients with COVID-19. It is a rare but serious fungal infection caused by a group of fungi called the mucormycetes. The overall mortality rate of mucormycosis is 50%. It is usually found in air and soil and in association with decaying organic matter, such as leaves, compost piles and animal dung.

The Health Ministry and ICMR have released an advisory for the screening, diagnosis and management of mucormycosis. According to the advisory, this fungal infection mainly affects individuals with impaired immunity. The predisposing factors are uncontrolled diabetes mellitus, steroids, prolonged intensive care, comorbidities, immunocompromised state (cancer or post-transplant). The sinuses or lungs are commonly affected after inhaling fungal spores from the air. Skin can also be affected after a cut, burn or other type of skin injury.

The advisory has defined the warning signs and symptoms, which include:

- Pain and redness around eyes and/or nose
- Fever
- Headache
- Coughing
- Shortness of breath
- Bloody vomits
- Altered mental status.

A diagnosis of mucormycosis should be suspected in case of following clinical presentations:

- Sinusitis – nasal blockade or congestion, nasal discharge (blackish/bloody), local pain on the cheek bone
- One-sided facial pain, numbness or swelling
- Blackish discoloration over bridge of nose/palate
- Toothache, loosening of teeth, jaw involvement
- Blurred or double vision with pain; fever, skin lesion; thrombosis and necrosis (eschar)
- Chest pain, pleural effusion, hemoptysis, worsening of respiratory symptoms.

To prevent mucormycosis, the advisory recommends use of masks, especially in dusty construction sites, cover yourself well (wear shoes, long trousers, long sleeve shirts and gloves) when handling soil or manure and maintain personal hygiene. It further advocates monitoring of blood sugar in COVID patients after discharge as well as in patients with diabetes, judicious use of steroids/antibiotics/antifungals and use of clean and sterile water for humidifiers.

Mucormycosis needs urgent attention and is best managed by a team of specialists comprising of a microbiologist, internal medicine specialist, intensivist, neurologist, ENT specialist, ophthalmologist, dentist, surgeon (maxillofacial/plastic) and biochemist.

Mucormycosis can be managed by controlling blood sugar levels (and ketoacidosis in diabetic patients), reducing steroids, stopping immunomodulating drugs and extensive surgical debridement to remove all necrotic materials. The advisory further recommends putting in a peripherally inserted central catheter, maintaining adequate systemic hydration, normal saline infusion and antifungal therapy for at least 4-6 weeks. The patient should be carefully monitored both clinically and with radio-imaging to evaluate response to treatment and to check if the disease is progressing.

The advisory cautions to stay alert for the warning signs and symptoms. Not all cases, especially in immunosuppressed and COVID-19 patients, with blocked nose should be thought of as having bacterial sinusitis. Investigate for fungal etiology and start treatment at the earliest.

(*Source: ICMR, Evidence based advisory in the times of Covid-19, Screening, diagnosis and management. https://www.icmr.gov.in/pdf/covid/techdoc/Mucormycosis_ADVISORY_FROM_ICMR_In_COVID19_time.pdf. May 09, 2021*)

First-phase Ejection Fraction may be a Novel Marker of Undetected Early Heart Damage in Hospitalized COVID-19 Patients

First-phase ejection fraction is a strong predictor of survival in hospitalized COVID-19 patients. New research published in the journal *Hypertension* says that

hospitalized COVID-19 patients with impaired first-phase ejection fraction were nearly 5 times more likely to die compared to patients with normal first-phase ejection fraction.

Heart function is traditionally measured by the ejection fraction. First-phase ejection fraction has been proposed as a new measure of heart function. It is a measure of the left ventricular ejection fraction (LVEF) until the time of maximal ventricular contraction. It can identify early, undetected or subtle damage to the heart (sign of heart failure) compared to the conventionally used ejection fraction.

The study examined mortality rates of hospitalized COVID-19 patients in Wuhan, China (n = 129) and in South London (n = 251). The echocardiography results of COVID-19 patients were compared to adult patients who had an echocardiography done pre-COVID and had otherwise similar health profiles.

- COVID-19 patients with a first-phase ejection fraction <25% had a nearly 5-fold higher risk of death versus patients in whom the ejection fraction was ≥25%.
- Patients who did not have COVID-19, but had similar risk factors also had low first-phase ejection fraction suggesting that the damage to the heart may be due to chronic pre-existing conditions and not COVID-19 infection.

These findings suggest first-phase ejection fraction can be used as a novel marker to identify high-risk COVID-19 patients. They can be closely monitored and death can be possibly prevented by preventing very early chronic damage to the heart. However, the researchers caution that more studies are needed to verify this.

(*Source: AHA News Release, Published: May 10, 2021*)

COVID-19 Patients with Neurological Complications have Higher In-Hospital Mortality

Neurological complications frequently occur in hospitalized COVID-19 patients and are associated with higher in-hospital mortality in comparison to patients who do not develop neurologic complications, according to findings from a global multi-cohort study.

This is the largest cohort study of neurological manifestations of COVID-19 to date, which included patients with clinically diagnosed or laboratory-confirmed COVID-19 at 28 centers, representing 13 countries and 4 continents. The study included consecutive patients in three cohorts who were hospitalized with COVID-19 between March 2020 and October 2020. The study population was derived from 2 large consortia: the Global Consortium Study of Neurologic Dysfunction in COVID-19 (GCS-NeuroCOVID) and the European Academy of Neurology (EAN) Neuro-COVID Registry (ENERGY). The findings are published online May 11, 2021 in *JAMA Network Open*.

Some key observations of the study

- Eighty-two percent of 3,744 hospitalized COVID-19 patients developed neurological manifestations.
- Overall, 80% of these patients exhibited at least 1 new neurological symptom, sign or syndrome, and 55% had at least 1 neurological sign or syndrome captured on clinical evaluation.
- The most common self-reported symptom was headache (37%). The incidence of self-reported anosmia (loss of smell) or ageusia (loss of taste) was 26%.
- Acute encephalopathy (49%) was the most commonly seen neurological sign or syndrome followed by coma (17%) and stroke (6%). The least common were meningitis and/or encephalitis (0.5%).
- Presence of clinically captured neurologic signs and/or syndromes was associated with a 6-fold increased risk of dying during hospitalization.
- Having a pre-existing neurological condition doubled the risk of developing COVID-related neurological complications.

(*Source: JAMA Network Open, Published May 11, 2021*)

Poor Sense of Smell may Signify a Higher Risk for Pneumonia Hospitalization in Older Adults

Having a poor sense of smell is associated with higher risk of pneumonia in older adults aged 65 years or above, says a new cohort study from the Michigan State University, published in the journal *Lancet Healthy Longevity*.

The study recruited participants from the Health, Aging and Body Composition study. Health data from 2,494 older adults, ages 71-82 years, was analyzed to look for any association between poor sense of smell and a higher future risk of developing pneumonia. The participants were given a Brief Smell Identification Test or B-SIT, using common smells such as lemons and gasoline to determine if their sense of smell was good, moderate or poor. They were followed up until the date of pneumonia hospitalization, death, last contact or the end of 13 years of follow-up, whichever came first with

annual clinic or home visits and semi-annual or quarterly telephone interviews to identify hospitalization due to pneumonia.

- Compared with participants who had a good sense of smell, those who had a poor sense of smell had almost 50% higher chances of being hospitalized with pneumonia at any time point during the follow-up.
- Among participants with a poor sense of smell who never had pneumonia before, the risk of having the first-ever pneumonia hospitalization was about 40% higher.
- Moderate olfaction was not associated with a higher rate of total or first-ever pneumonia.

The study is published *The Lancet Healthy Longevity*, May 1, 2021.

COVID-19 mRNA Vaccines are 94% Effective in Reducing Symptomatic Illness

The mRNA vaccines are highly effective in protecting against symptomatic COVID-19 among the healthcare personnel (HCPs) according to interim results from the largest COVID-19 vaccine effectiveness study conducted by the CDC. Among fully vaccinated HCPs, the two Food and Drug Administration (FDA)-approved mRNA vaccines - Pfizer-BioNTech and Moderna - reduced the risk of becoming sick with COVID-19 by 94%.

Data for this assessment come from a network covering 5,00,000 HCPs across 33 sites in 25 states in the US, providing additional robust evidence that mRNA vaccines are effective against symptomatic illness in real-world conditions..

In this study, the vaccination status of COVID-19 positive cases (n = 623) was compared with the vaccination status of those who tested negative, who served as controls (n = 1,220). Comparison of the odds of COVID-19 vaccination in cases and controls was used to calculate the vaccine effectiveness estimates.

The fully vaccinated (≥7 days after receipt of a second vaccine dose) HCPs had 94% less likelihood of developing symptomatic illness, whereas the partially vaccinated (≥14 days after receipt of dose one through 6 days after dose two) were 82% less likely to develop symptoms.

These observations support the recommendation that both doses (complete vaccination) are necessary to get maximum protection.

(*Source: CDC Press Release, May 14, 2021*)

Ebola Outbreak Declared Over in the DRC

The US CDC as well as the global health community have marked the end of the latest Ebola outbreak in North Kivu Province of the Democratic Republic of the Congo (DRC).

The DRC Ministry of Health (MOH) and the WHO declared it over after 42 days without any new cases after the last survivor tested negative and was discharged from a treatment unit. This was DRC's 12th Ebola outbreak, and was announced on February 7 this year. Recent Ebola outbreaks have highlighted that persistent infections in survivors can give rise to fresh outbreaks or set off new and ongoing transmission within an outbreak that is going on… (*CDC*)

Emergency Use Approval for Baricitinib to Treat COVID-19

Generic drugmaker Natco Pharma announced that it has received emergency use approval for baricitinib tablets from the Central Drugs Standard Control Organisation (CDSCO).

The company stated that baricitinib in combination with remdesivir is used in the treatment of COVID-19. In November 2020, the US FDA had granted an emergency use authorization (EUA) for baricitinib in combination with remdesivir for the treatment of suspected or confirmed COVID-19 in hospitalized patients who need supplemental oxygen, invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO). (*ET Healthworld*)

Study Detects Slightly Elevated Rates of Blood Clot After AstraZeneca COVID Vaccine

A study conducted in Denmark and Norway has noted slightly raised rates of vein blood clots among individuals who received a first dose of AstraZeneca's COVID-19 vaccine, including clots in the brain, in comparison with expected rates in the general population.

However, the investigators emphasized that such side effects are extremely rare, and the benefits of the vaccine still outweigh the risks in most circumstances. Norway had paused the rollout of the AstraZeneca vaccine on March 11 following some cases of blood clots with bleeding and low platelet levels. Denmark also halted the use of the vaccine.

The study, published in *BMJ*, assessed 2,80,000 individuals aged 18-65 years in Denmark and Norway who had been given a first dose of the AstraZeneca vaccine from the beginning of February till March 11… (*Reuters*)

Third COVID Wave Inevitable, Says Govt's Scientific Advisor

K Vijay Raghavan, the government's Principal Scientific Advisor, has said that the third COVID wave is inevitable in India. Addressing the media during the health ministry's briefing on the COVID-19 situation in the country, Raghavan said that a third wave is imminent, considering the high levels of circulating virus. He added that we should be prepared for new waves.

The officials also stated that the long COVID wave of such intensity that India is currently experiencing was not predicted. (*ET Healthworld – Timesofindia.com*)

Russia Authorizes Single-dose Sputnik Light COVID-19 Vaccine

Russia has given authorization for the single-dose Sputnik Light version of its COVID-19 vaccine for use, reported the Russian Direct Investment Fund (RDIF). The one-shot vaccine has been developed by Moscow's Gamaleya Institute, and the RDIF has stated that it is 79.4% effective against COVID-19 and is priced below $10 a dose. It has been designated for export and could enhance the proportion of people with partial immunity.

A Phase III clinical trial with 7,000 individuals was going on in Russia, the United Arab Emirates, Ghana and other countries, stated the RDIF. A potential use of this vaccine is that it can be shipped to a country fighting an acute outbreak that needs to be repressed quickly… (*ET Healthworld – Reuters*)

Moderna Vaccine Found 96% Effective in 12- to 17-year Olds

Moderna has reported that its COVID-19 vaccine has been found to be 96% effective among 12- to 17-year olds in its first clinical trials. Among the 3,235 participants in trials in the United States, two-thirds of the subjects were given the vaccine and one-third received a placebo. The vaccine efficacy against COVID-19 was shown to be 96%. The company stated that mRNA-1273 was well-tolerated with no serious safety concerns detected. There were 12 cases of COVID-19, 14 days after the first dose. For these intermediate results, participants were followed-up for on average 35 days following the second dose… (*NDTV - Agence France-Presse*)

Indian Government Says New Variant Tied to COVID Surge

The Indian Government stated that a new variant of the coronavirus first detected in the country in March may be tied to a deadly second wave.

Samples having the double mutant, or the B.1.617 variant, have been identified in many states with high case count.

Government's top scientific adviser also cautioned that a third wave is imminent and that we need to be prepared for future waves… (*BBC*)

Pfizer COVID Vaccine Tied to Fewer Asymptomatic Infections: Study

People administered the Pfizer COVID-19 vaccine at a US hospital had considerably fewer symptomatic and asymptomatic infections in comparison with their unvaccinated counterparts, reported a new study.

Published in the *Journal of the American Medical Association*, the study is among the first to indicate an association between COVID-19 Pfizer-BioNTech vaccination and fewer asymptomatic infections. The study included 5,217 employees at St. Jude, eligible under Tennessee state guidelines for vaccination from December 17, 2020, through March 20, 2021. Over 58% of employees were vaccinated during that period. Most workers received both vaccine doses. Vaccination was found to decrease the risk of asymptomatic and symptomatic infection by 79% in vaccinated employees compared to their unvaccinated peers, noted the investigators… (*ET Healthworld – PTI*)

Britain to be Free of COVID by August: UK Vaccine Task Force Chief

Coronavirus will no longer be circulating in the United Kingdom by August, said the departing vaccine taskforce chief Clive Dix to the Daily Telegraph.

Dix told the daily that sometime in August, there will be no circulating virus in the UK. He further stated that he believed the vaccine booster program could be pushed to early 2022. The government is evaluating which COVID-19 vaccines would serve as the best booster jab for vulnerable individuals later this year. He also expected everyone in the country to have been vaccinated at least once by the end of July. (*NDTV – Reuters*)

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Indian Journal of Clinical Practice, Vol. 32, No. 1, June 2021

Vedic Principles Behind Cognitive Behavior Therapy

What is counseling?

The mental process involves generation of a thought or idea, which is analyzed and then acted upon. Thought, analysis and action, are the three processes of human mind. Counseling encompasses actions at all the three levels.

What are different types of counseling?

Counseling involves two principles – Cognitive counseling and behavioral counseling. Behavioral counselling focuses only on the actions, while cognitive counseling focuses on the changes in either the thought process or in the interpretation of the thought process.

What is cognitive behavior therapy?

As opposed to pure behavior therapy where a person is counseled to do predefined things at regular intervals, cognitive behavior therapy is aimed at changing the actions by altering observations of the interpretation of a particular situation.

What is the origin of counseling in India?

The origin of counseling dates back to the Vedic era. Upanishads were nothing but textbooks on counseling based on the original knowledge of Rigveda, Yajurveda, Samveda and Atharvaveda.

Is there a relationship of Bhagavad Gita with counseling?

Bhagavad Gita is counseling done by Krishna that aims to resolve the conflict in Arjuna's mind whether to fight or not. Counseling at that time was done by the elders in the family.

Are the principles of Bhagavad Gita followed today?

All the principles of cognitive behavior therapy today have their roots in the principles that have originated from Bhagavad Gita.

What is the first principle?

The first principle is that counseling cannot be done in 1 or 2 sessions. It requires up to 18 sessions which is what Krishna did in Bhagavad Gita. Bhagavad Gita contains 702 dialogues in the form of Shlokas. A proper counseling involves in-depth conversation between the counselor and the patient.

What is the second principle of counseling?

The second principle of counseling is to listen to the patient in the first session in great detail. Krishna did the same in Bhagavad Gita. In Chapter 1, only Arjuna speaks and Krishna listens. A patient listening is half the healing done.

What is the third principle?

The third principle states that the second (first interactive) session between counselor and the patient should be the longest one. Chapter 2 of Bhagavad Gita is the gist of Krishna's counseling.

What is the fourth principle?

The fourth principle is that after giving a detailed counseling in the second session, the patient is expected to be confused. In start of Chapter 3, Arjuna says to Krishna "I am confused. Sometimes you are talking about one path and other time you are talking about another path. Guide me again." The third counseling session is the most important where one has to counsel slowly and in great detail.

What is the fifth principle?

The fifth principle is to give reasoning to the counseling. One should not take the patient for granted. Krishna discusses each and every aspect of life with Arjuna in great detail giving scientific reasoning at every stage.

What is the sixth principle?

Provide reassurance to the patient repeatedly. During his counseling, Krishna assures Arjuna on multiple occasions to do his job and not to worry. I am with you.

What is the seventh principle?

The seventh principle involves creating some fear in the patient's mind. This is what Krishna does while showing his viratswaroop. This especially works in patients of addiction. Some degree of fear with re-assurance from the counselor works well.

What is the eight principle?

The summing up counseling session should be as long as the second session. Chapter 18 of Bhagavad Gita is

as big as Chapter 2 where the whole Bhagavad Gita is summarized again.

What are the ingredients of counseling?

Counseling involves in-depth knowledge of dharma, artha, kama and moksha.

They are greatly described in Dharmashastra, Arthashastra, Kamasutra and Upanishads through various Vedas.

What is stress?

Stress is the reaction of the body or the mind to the interpretation of any situation.

How can stress be managed?

Stress can be managed by either changing the response of the body through yogic living, or changing the interpretation by understanding the principles of counseling or changing the reaction by wilful actions.

Are different nitis of our scriptures based on counseling?

Yes. Vidur Niti was the counseling given by Vidur to Dhritarashtra when he was not sleeping and Chanakya Niti involved how to rule a country. Yoga Vashishtha was the counseling given by Vashishtha to Rama to acquire higher levels of spiritual knowledge.

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A Risk Profile for Severe COVID-19 Infection in Patients with Diabetes

A study has identified older age, obesity, heart disease and use of steroids and sodium-glucose co-transporter-2 (SGLT2) inhibitors prior to hospitalization for COVID-19 as factors that increase the risk of severe COVID-19 in persons with diabetes. These findings from a retrospective study were presented at the recently concluded annual meeting of the American Association of Clinical Endocrinology (AACE) (May 26-29, 2021 virtual meeting).

Patients who had blood glucose levels out of the reference range had greater chances of developing severe infection. About 44% of diabetic patients with severe COVID-19 had glucose levels >180 mg/dL compared to 38% of those who did not have severe infection. Patients with severe COVID-19 also had more hypoglycemic episodes compared to patients who did not have severe infection (9.75% vs. 8.90%).

The multicenter study analyzed 1,818 people with diabetes who were hospitalized with COVID-19. Patients who required intensive care, or met clinical criteria indicating ARDS or tachypnea (respiratory rate >30) or SpO_2 <93% or PF ratio <300 or those who died were categorized as severe COVID-19.

History of use of an SGLT2 inhibitor (such as canagliflozin, empagliflozin, dapagliflozin) prior to hospitalization for COVID-19 was associated with an 85% greater chance of having a severe COVID-19 infection (OR = 1.85). A similar high risk of severe COVID-19 was observed with pre-hospitalization exposure to steroids (OR = 1.49). No such association was seen with use of angiotensin-converting enzyme (ACE) inhibitors (OR = 0.75) or statin (OR = 0.66).

Older people with diabetes (OR = 1.01) were more likely to have severe disease, as did males (OR = 1.37).

A significantly increased risk for severe COVID-19 infection was seen in obese persons with BMI >35 kg/m^2 (OR = 1.83) or those having neuropathy (OR = 1.65) or heart disease (OR = 1.3).

The study authors are hopeful that their findings would help in better triage of patients with diabetes at greater risk of severe COVID-19 for timely and intensive clinical interventions to improve outcomes in this group of patients.

(*Source: Medpage Today, May 28, 2021*)

A Great Story

A woman clad in the best of clothes walked up to a man sitting on the ground. "Good morning," she politely greeted him. The man slowly looked up. He thought that she wanted to make fun of him, like many others and just asked her to leave him alone.

The woman continued standing and asked the man if he was hungry. The man sarcastically said 'No'. He said that he had just had a meal with the President. Furious, he told her to go away. The woman smiled and held him from his arm to help him get up. The man resisted.

Just then a policeman came up and asked the lady if there was a problem. She asked the officer to help her get the man to his feet.

The officer wondered what business she had with him. The woman told the officer that she wished to get the man some food at the cafeteria nearby.

The homeless man resisted. But by then, he was brought to his feet by the officer.

The woman and the police officer got the homeless man into the cafeteria and sat him at a table in a corner. It was the middle of the morning, so most of the breakfast crowd had already left and there was still time for lunch.

The manager came to the table and asked the officer what was going on. The officer told him that the lady had brought this man in to be fed.

The manager replied angrily that it was not possible in that cafeteria. The homeless man smiled and told the lady that he knew this would happen. He got up and wished to leave.

The woman turned to the cafeteria manager, smiled and asked him if he was familiar with Eddy and Associates, the banking firm.

The manager said that he was. He told her that they hosted their weekly meetings in one of their banquet rooms. The woman went on to ask that they must be making a huge amount of money providing food at these weekly meetings. The manager was curious by now.

She went on to tell him that she was the President and CEO of the company. The manager was taken aback.

The woman smiled again. The officer was also giggling by now.

The woman offered the officer a cup of coffee. He gladly agreed. The cafeteria manager rushed to get his coffee.

The woman sat down at the table across from her guest. She stared at him and asked him if he remembered her. He looked closely at her and said that she looked familiar.

She said that she was a little older now from when she last met him when he worked at the same cafeteria. She told him that she came through that very door, cold and hungry on day.

She had come to the city looking for a job, but couldn't find anything. She was completely out of money and had been kicked out of her apartment. It was very cold and she was nearly starving. That's when she had walked into the cafeteria to try her luck and see if she could get something to eat.

The homeless man lit up with a smile. He recognized the woman. He remembered that she had come once and asked him if she could work for something to eat. The woman then said that he made her the biggest roast beef sandwich that she had ever seen, gave her a cup of coffee, and told her to go over to a corner table and enjoy it. She saw him put the price of her food in the cash register.

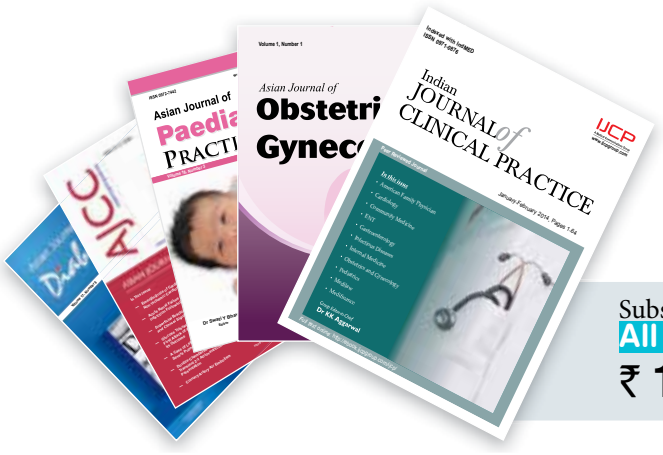
She went on to tell them that she got a job that very afternoon and worked her way up. She opened her purse, pulled out a business card and gave it to the homeless man. She told him to visit the personnel director of her company.

There were tears in the old man's eyes. He said that he could never thank her enough. She told him to thank God, because he led her to him.

As they walked out the cafeteria, the officer told the lady that he had seen a miracle, something that he will never forget.

God closes doors no man can open and opens doors no man can close.

■■■■



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Indian Journal of Clinical Practice, Vol. 32, No. 1, June 2021

Lighter Side of Medicine

HUMOR

Q: How does Juliet maintain a constant body temperature?

A: Through "Romeostasis!"

Q: What did one cell say to his sister cell when she stepped on his toe?

A: Ouch, "mitosis!"

Q: How do you eat DNA-spaghetti?

A: With a replication fork!

Q: Where do they send the criminal neurons?

A: To the chain ganglion!

Q: What's a pirate's favorite amino acid?

A: Arrrrrr-ginine!

Q: What's the difference between a dog and a marine biologist?

A: One wags a tail and the other tags a whale!

Employer: Do you have trouble making decisions?

Interviewee: Well … yes and no.

Q: What do a fudge cake and meditation have in common?

A: Both bring you a piece or peace of heaven!

Q: What kind of music should you listen to while fishing?

A: Something "catchy!"

Q: What goes up and never comes down?

A: Age!

Q: What did the ice cream say to the unhappy cake?

A: Hey, what's eating you?

Q: What did one candle ask the other?

A: Don't birthdays burn you up?

Bill struggled to get up early in the morning, and as a result, he was always late for work. His boss got fed up of his constant lateness and so threatened to fire him if he didn't get his act together.

So, Bill went to see his doctor who gave him a pill and told him to take it just before going to bed.

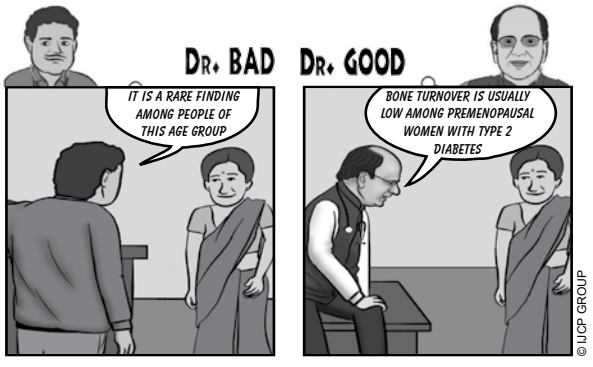
Bill did as advised and slept very well and actually beat the alarm clock by 2 hours. He fixed himself a nice breakfast and drove happily to work, with plenty of time on hand.

When he reached office, he said, "Boss, that pill the doctor gave me actually worked!"

His boss said, "That's all very well, but where were you yesterday?"

Dr. Good and Dr. Bad

SITUATION: A 44-year-old premenopausal woman with type 2 diabetes had low bone turnover.



LESSON: A cross-sectional study showed that premenopausal females with type 2 diabetes have lower bone turnover in comparison to those without type 2 diabetes. It was stated that significantly lower bone turnover process initiates relatively early in the premenopausal age, regardless of the duration of diabetes.

BMC Endocr Disord. 2017;17(1):72.

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The following information should be given:

- The statistical universe i.e., the population from which the sample for the study is selected.
- Method of selecting the sample (cases, subjects, etc. from the statistical universe).
- Method of allocating the subjects into different groups.
- Statistical methods used for presentation and analysis of data i.e., in terms of mean and standard deviation values or percentages and statistical tests such as Student's 't' test, Chi-square test and analysis of variance or non-parametric tests and multivariate techniques.
- Confidence intervals for the measurements should be provided wherever appropriate.

Results

- These should be concise and include only the tables and figures necessary to enhance the understanding of the text.

Discussion

– This should consist of a review of the literature and relate the major findings of the article to other publications on the subject. The particular relevance of the results to healthcare in India should be stressed, e.g., practicality and cost.

References

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Examples of common forms of references are:

Articles

Paintal AS. Impulses in vagal afferent fibres from specific pulmonary deflation receptors. The response of those receptors to phenylguanide, potato S-hydroxytryptamine and their role in respiratory and cardiovascular reflexes. Q. J. Expt. Physiol. 1955;40:89-111.

Books

Stansfield AG. Lymph Node Biopsy Interpretation Churchill Livingstone, New York 1985.

Articles in Books

Strong MS. Recurrent respiratory papillomatosis. In: Scott Brown's Otolaryngology. Paediatric Otolaryngology Evans JNG (Ed.), Butterworths, London 1987;6:466-470.

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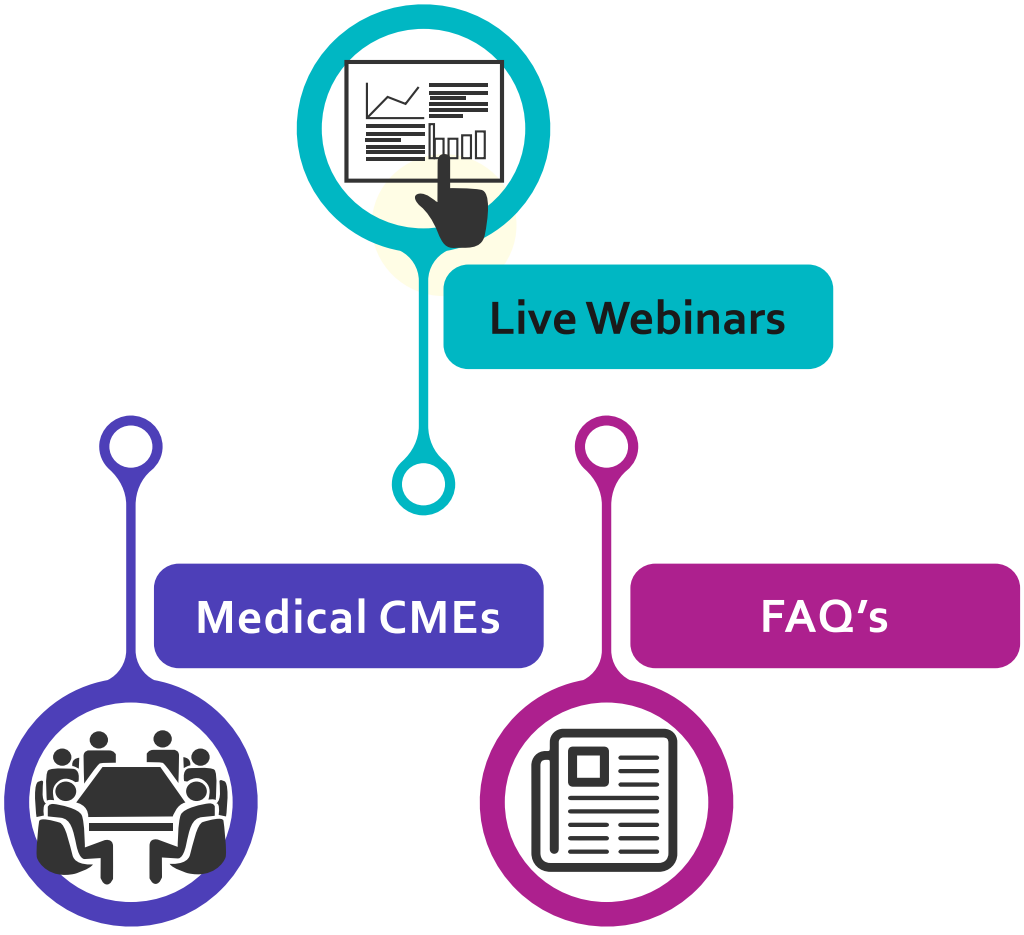

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