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Contents

(Continued next page)

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Contents

Editorial

Sarcopenia : Screening Made Simple

The 600+ skeletal muscles are an important organ-system of our body. The muscle is an organ which can be used to assess health (muscular fitness) and improve it (through exercise). It can be a target of disease (myopathy), and a target for drug action (anabolic steroids)[1]. In medical discourse, however, discussion on the musculoskeletal system is often limited to bones and joints. Muscle health is usually relegated to the background, even though muscle contributes to 40-50% of our body weight.

When muscle is fit and fine, it usually does not attract adequate attention. However, when muscle is diseased or has less than optimal functionally, it is of even less concern. Sarcopenia is a relatively new term, coined by Rosenberg in 1989[2], characterized by loss of skeletal muscle mass, quality and strength. This condition is associated with other components of frailty syndrome, and with adverse health outcomes[3].

Sarcopenia, and its associated disease, sarcopenic obesity, are common in India. A recent analysis of the data from the Longitudinal Ageing Study in India (LASI) Wave1 Survey (2017-18) reveals an overall prevalence of "possible" sarcopenia of 41.9%[4]. Sarcopenic obesity was found in 8.7% of all participants, with an overall obesity prevalence of 27.1%. Sarcopenia was more common in the oldest age group (65.1%), women (42.16), rural dwellers (43.6%), residents of south India (48.1%), those from poorest background (45.1%), with no education (44.7%), who were not working (53.9%) and not living in a union (52.1%). Other factors associated with sarcopenia included lack of physical activity (46.7%), and comorbidities like cardio vascular disease (51.4%), diabetes (44.1%), bone/joint disease (49.1%), neurological illness (45.7%) and multi-morbidity (45.6%).

In spite of this heavy burden on our health, sarcopenia has not been highlighted in medical curricula and continuing medical education programmes. Many factors contribute to this[5]. No medical or surgical specialty "owns" sarcopenia, and the disease thus gets an orphan-like treatment. There is no specific drug therapy for sarcopenia, and this, too, creates lack of interest amongst stakeholders. The main focus of sarcopenic care is prevention through nutrition and lifestyle modification, but these are given short shrift in today's world, which expects magic pills and injections for treatment.

The main reason for lack of interest, however, has been the criteria used for diagnosis of sarcopenia. Till recently, international guidelines required demonstration of reduced muscle mass to conclusively diagnose sarcopenia. This could be done only with the help of expensive imaging tools such as bioimpedance and DEXA scans (Dual Energy X-ray Absorptiometry)[6]. The role of reduction in muscle strength and muscle function, which can be assessed clinically, was limited to suspicion of

probable sarcopenia. This created a situation where sarcopenia assessment was limited to research settings in India.

This year, the South Asian Working Action Group on Sarcopenia (SWAG_SARCO), composed of experts from 11 countries, published a consensus on the screening, diagnosis and management of sarcopenia[7].

The authors define sarcopenia as a syndrome in which any two of the following three abnormalities are present in muscle strength, muscle function and/or muscle mass as shown in Table 1.

Table 1 — *Definition of sarcopenia: any two of the following three must be present*

Clinical modality	Clinical assessment
Muscle strength	Hand grip and lower limb muscle strength
Muscle function	Walking speed, sit-to-stand test, chair stand test and SPPB (Short Physical Performance Battery)
Muscle mass	Calf circumference, Mid arm circumference, Thigh circumference[7].

These can be supported by imaging techniques, if available. The rationale of these criteria is similar to that used in other syndromes such as PCOS (polycystic ovary syndrome) and metabolic syndrome, where the presence of a few (but not all) criteria is required for diagnosis.

The SWAG_SARCO guidelines facilitate community- and clinic-based screening and substantiation of sarcopenia, and thus allow timely institution of preventive and therapeutic interventions. These guidelines along with secondary data analysis of LASI survey will bring focus attention on this syndrome, and on its public health significance. The research data that will be generated by the use of South Asian diagnostic criteria will promote action to address muscle health, and its comorbidities.

In the meanwhile, as physicians, we must begin screening for primary sarcopenia in all elderly adults, and for secondary sarcopenia in all persons with comorbidities. Simple anthropometric measurements such as weight, waist circumference, mid arm circumference and mid-calf circumference must be incorporated into routine clinical evaluation. Tests for muscle strength and function should be made part of clinical examination in not only geriatric medicine and endocrinology, but family medicine as well. A concerted effort for timely diagnosis, associated with lifestyle, nutritional, metabolic and orthotic optimization, will lead to better muscle health, and better overall health, for all.

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Original Article

Telemedicine in Paediatric Subspecialty : A Low Cost Model for Developing Countries during the COVID-19 Pandemic

Mastakim Ahmed Mazumder[1], Sanjeev Gulati[2], Amrita Sengar[3]

Background : Telemedicine is the delivery of Health Care Services using information and communication technologies. Most models of Telemedicine in developed countries involve high-cost infrastructure. The COVID-19 pandemic imposed lockdowns and travel restrictions have highlighted the importance and the necessity of an economically viable model of telemedicine for resource-poor countries like India.

Methods : We conducted a prospective study to assess the feasibility, acceptability and effectiveness of low-cost model of Telemedicine services for regular follow-up as well as for triaging. A combination of WhatsApp/email using smartphones and Electronic Medical Records (EMR) system was used to provide Telemedicine services. At the end of the e-consult, the patient/ parents were asked to rate their experience on a scale of 0 to 10.

Results : A total of 155 children and 865 consults were included. The mean age of the children was 8.5 years. Forty-four consultations were given to 12 (7.7%) International patients. Thirty-eight (24.5%) patients were seen for the first time via Teleconsultation and the remaining 117 (75.5%) were follow-up patients. The most common diagnosis was Nephrotic Syndrome (51.6%) followed by Chronic Kidney Disease (21.9%), Urinary Tract Infection (10.3%), Kidney-transplant follow-up (6.4%), Acute Glomerulonephritis (3.8%), and Acute Kidney Injury (2.6%). Twenty-three patients were advised admission after the Teleconsultation and the remaining 122 children were advised follow-up e-consults. The mean satisfaction score reported for e-consults was 9.4.

Conclusion : Our low-cost Telemedicine model offered a viable modality for delivery of Paediatric Nephrology Services during lockdown period and can be replicated by pediatricians practicing other subspecialties as well.

[*J Indian Med Assoc* 2022; **120(7):** 11-5]

Key words **: Telemedicine, Paediatric Nephrology, Teleconsultation, COVID-19 pandemic.**

Access to paediatric subspecialty care has always been a challenge even for the developed world and the COVID-19 pandemic has made the traditional face-to-face outpatient consultation even more difficult[1]. Telemedicine has emerged as an effective alternative means to deliver Health Care Services using information and communication technologies[2]. Most of the studies evaluating the role of Telemedicine in paediatric Nephrology Care have been conducted in developed countries which had high infrastructure costs[3,4]. There is limited experience of Telemedicine for Paediatric care in India[5,6]. Moreover, studies evaluating the utility of Telemedicine for Paediatric Nephrology subspecialty in India is very rare[7]. In the wake of COVID-19 pandemic, the decision granting legal sanction to Telemedicine by the Governing Body of Medical Council of India (MCI) created a unique opportunity to evaluate the scope of Telemedicine in children[8]. However, there remains a lot of hesitation amongst pediatricians about the safety and applicability of Telemedicine in our country. This single centre prospective observational study was carried out toassess the feasibility, methodology, acceptability and effectiveness of Telemedicine services for regular follow-up as well as for triaging children with kidney diseases for admission, in setting of a countrywide lockdown.

Editor's Comment :

- Access to paediatric subspecialty care has always been a challenge even for the developed world and the COVID-19 pandemic made the traditional face-to-face outpatient consultation even more difficult, Telemedicine offered a viable modality for delivery of Paediatric Nephrology Services during pandemic period when access to healthcare was restricted.
- Another advantage is the minimal cost and infrastructure required making it user friendly and widely acceptable.
- Although this experience is with children with kidney diseases it is equally applicable to other pediatric subspecialties where there is limited access.
- Our study can help improve simplify and standardise the practice of telemedicine.

Materials and Methods

The study period was during the period of COVID-19 pandemic in our country from 1st June, 2020 to

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31st May, 2021. The parents were informed about the availability of Telemedicine services for Paediatric Nephrology through text messages sent from our patient data base as well through Social Media platforms like Facebook and WhatsApp. The patient data was stored in Electronic Medical Records (EMR) using the Healthplix platform. A combination of WhatsApp/email and EMR database was used to provide Telemedicine services during the study period. On receiving the request, a formatted message was sent to either of the parents' mobile number requesting for following information: current problems, weight, vital signs including temperature, blood pressure (whenever possible) as well as current and previous investigations.The records of follow-up patients was used to check whether patient was normotensive or hypertensive. Whenever required the parents family was asked to get BP recorded at their local pediatrician or nearest physician as in case of Acute Glomerulonephritis and Chronic Kidney Disease (CKD). All our kidney transplant children had been trained to measure and record BP at home.The diagnosis in case of new patients was confirmed by laboratory tests such as Kidney function tests and Urine protein/Creatinine ratio from a local laboratory. UTI is one of the commonest causes of fever and the diagnosis was made based on combination of clinical symptoms, urine examination and culture. The samples for Tacrolimus trough (T0) estimation of kidney transplant recipients were drawn at their nearby laboratory and couriered to the standard labs where testing is routinely done.The data was entered in EMR and electronic prescription was generated. This was sent over email or WhatsApp as per the family's preference. At the end of the e-consult the patient was asked to rate his experience on a scale of 0 to 10. The Study was approved by the Institutional Ethics Committee.

Results

The study group included patients from whom a request for Teleconsultation was received. During the 1-year study period a total of 865 e-consults were given. Eight-hundred-twenty-one (95.0%) e-consults were for domestic patients and 44 (5.0%) were for international patients. The domestic patients were from the states of Delhi, Uttar Pradesh, Bihar, Chhattisgarh, Madhya Pradesh, Punjab, Rajasthan, Uttarakhand, Gujarat, Assam and Karnataka.The domestic patients were predominantly (56.8 %) from Urban and metropolitan background, 27.1 % from semi-urban and 16.1% from Rural background. The study group comprised of 155 patients and there were 119 (76.8%) boys and 36 (23.2%) girls. Out of the 155 patients, twelve(7.7%) were International patients and 143 (92.3%) were domestic patients. All these children were provided Teleconsultation using a combination of WhatsApp text and WhatsApp / Google duo video call on smartphone and the e-prescription was sent via email or WhatsApp.

The distribution of the diagnoses was as follows Idiopathic Nephrotic Syndrome (80 patients, 51.6%), Chronic Kidney Disease (34 patients, 21.9%), Kidney Transplant follow-up (10 patients, 6.4%), Urinary Tract Infection (16 patients, 10.3%), Acute Glomerulonephritis (6 patients, 3.8%), Acute Kidney Injury (4 patients, 2.6%) and others (5 patients, 3.2%). The mean age of the patients in was 8.5 years (range 0.17-18 years). All the e-consults that were advised, opted in for Teleconsultation. Of the 155 children in the study, there were 38 (24.5%) new patients that were evaluated for the first time via teleconsultation. The remaining 117 (75.5%) were follow-up patients, previously being followed up in our OPD clinics. Of the 155 children that were given e-consults, 122 (78.7%) were advised follow-up e-consults and 23 (14.8%) were advised admission. Children with Acute Kidney Injury (6) and Acute Glomerulonephritis (4) were managed in co-ordination with the treating pediatrician. In one of these, where a biopsy was indicated, the parents were requested to come to our center and the biopsy revealed Mesangiocapillary Glomerulonephritis.

After a detailed history on a video/audio call and review of the clinical status as well as investigations, a digitalised signed prescription was sent to the child's family. Of the 865 e-consults, 817 (94.5%) e-consults were delivered directly to the patient's parents through a combination of text and WhatsApp, or a combination of audio call and email. In 48 (5.5%) e-consults, where a smart phone was not available, the assistance of a paramedical worker was sought and a video consultation done via a WhatsApp video call. The digital prescription was sent via WhatsApp to the paramedic who in turn printed and handed it over to the patient Majority of the patients opted for WhatsApp as a medium of e-prescription (727, 84.0%) while 138 (16.0%) e-consults were emailed through an inbuilt software. The mean satisfaction score reported by parents for e-consults was 9.4.

Discussion

Telemedicine, as defined by the World Health Organization, is: "the delivery of Health Care Services, where distance is a critical factor, by all Healthcare

Professionals. It involves using information and communication technologies for the exchange of valid information for diagnosis, treatment and prevention of disease and injuries, research and evaluation. It also encompasses, continuing education of Health Care Providers, all in the interests of advancing the health of individuals and their communities[2]. Telemedicine has been used as Healthcare Education tool in medicine for last many years. It can also be used for patient care delivery. It has been used extensively in radiology as well as pathology and to some extent in dermatology and paediatrics[3,4,9-11]. According to the interaction between the individuals involved, it is of the following types: (1) Health professional to health professional (giving easier access to specialty care, referral and consultation services (2) Health professional to patient (providing Healthcare to the unreached population by giving them direct access to a medical professional)[2].

One of the early Indian experience in Telemedicine in India has been from SGPGIMS, Lucknow, India[12]. Regular Tele-healthcare and Tele-educational services were conducted by them for the Postgraduate students of Medical Colleges of Orissa.13In paediatrics, most of the studies have been from US in the pre COVID era[4,9,14,15]. They have demonstrated the usefulness in pedaitric subspecialty care in rheumatology, weight management and emergency medicine. There is only 1 previous published study form Australia regarding the delivery of Telemedicine in Paedaitricnephrology which evaluated 168 patients over a 10-year period. This was retrospective in nature and also involved dedicated videoconference studios and experienced Telehealth coordinators who manage referrals, provide technical support and assist with the delivery of Telehealth services which makes it expensive and not suitable for developing countries[4]. In contrast, our study is prospective in nature, over a 1-year period and involved a much larger number of e-consults.

There is no previous published experience from developing countries like India which have unique technological and communication challenges. The growth of Telemedicine in India was limited by the cost of infrastructure as well as regulatory issues including some legal judgments delivered by courts against it[16]. The initial challenge for the commencement of the programme posed by the lack of a primary centre for practicing Telemedicine services in many remote areas was resolved with the kick-off of mobile Telemedicine units with satellite communication. Over the past several decades, as the use of wireless broadband technology has become more advanced and smartphone and internet use has become nearly ubiquitous. The recent pandemic highlighted the need of Telemedicine to bridge the gap of delivery of healthcare.

The Board of Governors responded promptly to the scenario and gave legal sanction to Telemedicine. Most Health insurance companies have also made Teleconsultation reimbursable. The MCI is also planning a certificate course to train medical personnel in the nuances of Telemedicine[8]. The Indian Academy of Pediatrics has also tried to promote Telemedicine by launching an app. The recent review article by Mahajan et al provides an excellent overview of the complexities of this practice[17]. The widespread smartphone penetration in our country makes it possible to deliver consultation through cell phone based applications. These applications include email and WhatsApp as well as Teleconsultation software. However, so far in our country we have followed a traditional Healthcare model which involves face-to-face patient physician contact with a history and good physical examination. However, the scenario is changing fast. Recent study form health-tech platform Practo showed that 50 million Indians have accessed online healthcare between March and May 2020 and there was 500% increase in e-consults and in-person doctor visits are down by 67%[18]. Interestingly, 80% of all Telemedicine users were experiencing it for the first time.

This is a single centre prospective pilot study, the first of its kind during this pandemic and the largest so far involving children with kidney diseases. It was conducted to evaluate the feasibility and applicability of Telemedicine services in management of children with kidney diseases. The low cost technology involved use of smartphones. Over the 1-year period, consults were given to parents of children with kidney diseases. There was a high acceptance of Telemedicine as evident form the fact that all the parents of these 155 children who were offered Telemedicine, consented to go ahead. It was effective across age groups in children ranging from 2-month old infant to an 18-year-old adolescent. It was also useful across a wide spectrum of kidney diseases ranging from simple renal problems like Urinary Tract Infections, Glomerular Diseases, Acute Kidney Injury, Chronic Kidney Disease and Kidney Transplant. We found this to be an effective modality in triaging patients for follow-up and admission. Based on Teleconsultation, 14.8% of the children were successfully triaged into admission. This obviated the need for outpatient-clinic visits in the rest 85.2% who were managed by

Telemedicine follow-up, thus sparing them from the logistical nightmare of travel to the hospital for paediatric nephrology consultation. As far as the modality of Telemedicine was concerned, we used a combination of Electronic Medical Record (EMR) system along withWhatsApp and or email. We found WhatsApp to be particularly suitable in the Indian setting in view of its widespread reach in Urban as well as Rural areas of the country. In the absence of a physical examination, the EMR data was of valuable assistance in tracking the trend of vital signs and laboratory values as well as the previous medications used. It also enabled the delivery of a signed digital prescription which is medicolegally appropriate as well as storage of the same for future reference as per Medical Council of India (MCI) Guidelines. A disclaimer was also added at the end of each consultation documenting the request of the same by the parents for medicolegal purposes. We found Telemedicine to be suitable both for new patients as well as for follow-up consultations.

Out of the 155 children, 76.8% were boys. It is possible that there was a selection bias as the gender distribution depended on the willingness of the parents to request for a Teleconsultation.Majority (94.5%) of the e-consults were delivered directly to the patients via either combination of text message and WhatsApp or audio call and email. Only 5.5% patients did not have a smart phone, where the assistance of a paramedical worker was sought for video consultation usingWhatsApp video call. Since the parents or family members of majority of the children could access WhatsApp/ email, most of the children possibly came from educated background. However, the data regarding the educational background was not collected in our study. In the 5.5% of e-consults where a smart phone was not available, it is likely that the educational and Socio-economic status of them were low.The digital prescription was sent via WhatsApp to the paramedic who in turn printed it and handed it over to the patient Majority (84.3%) of the patients opted for WhatsApp as a medium of e-prescription while rest were emailed through an inbuilt software. In our study, Telemedicine was found to have high acceptance and satisfaction by the parents as evidenced by a mean feedback score of 9.4 for e-consults.

Telemedicine services offer a win-win situation for both doctors as well as patients. The advantages for patients include better access (as during lockdown). This is also important for underserved areas and the services are convenient and available from the setting of patients own home without having to travel long distances. Another advantage is the reduced cost in terms of time as well as money spent on travel and stay by the parents, which sometimes exceeds the cost of treatment (consultation fee as well as medicines). It also has health benefits for the patient in view of the early diagnosis, detection of complications as well as better patient compliance with treatment. It can also be used for patient education, reminders for vaccination as well as investigations. There are benefits for doctors too in terms of getting access to new patients from distant areas, cross physician referrals as well as second opinions. It improves clinical outcomes because of improved patient compliance as well as easy and better follow-up. It expands the horizon as in our experience we were able to offer e-consults to 12 International patients, of which 4 were new patients. All this comes with enhanced patient satisfaction because of stronger doctor patient relationship and improved tracking of health.

Telemedicine can be used by pediatricians for new patients, follow-up patients and second opinions as well as cross referrals.

There are a variety of modes of Telemedicine delivery platforms (1) audio calls (telephone, WhatsApp or similar platforms) (2) Telemedicine platforms (3) Hybrid using a combination of audio chat/ call in combination with an electronic medical record.

The simplest and quickest form of Telemedicine is an audio call using a telephone or a WhatsApp. It has the advantages of being quick and easy to use, convenient both for the physician as well as the patient and at no, extra cost. The disadvantages include difficulty in identification as well as consent, difficulty in record storage as well as retrieval, also there is no formal prescription, the quality of the consent being poor as well there being an absence of payment gateway. There also a variety of Telemedicine platforms available. These have immense advantages in terms of making patient identification possible, having a recorded consent (for medicolegal purposes), secure record storage and retrieval, having a legal and digital prescription. The quality of Teleconsultation experience is also good as the availability of video consultation simulates live face to face experience. There is payment gateway present making the experience for the Nephrologist a financially viable. Over a long period, it also enables brand customisation. There a few disadvantages as well as it requires the patient to be a bit tech-savvy in terms of ability to download the application on his smartphone or laptop which could limit its use in developing countries like India. Another

disadvantage is the additional cost to the users which may impede its wider usage. A third alternative is using a hybrid of telephone/WhatsApp along with an Electronic Medical Record. This enables record storage and retrieval, a legal and digitalised prescription that can be emailed or sent via WhatsApp at the same time being simple and user friendly. Electronic payment can be requested by bank transfer or digital wallet payments. The biggest advantage is the widespread penetration because of using WhatsApp based prescription delivery and that too at no additional cost. In the current study we utilised the third option with excellent results. There was a wide patient acceptance as well as satisfaction as evidenced by a high feedback score.

So based on this prospective observational study, we conclude that Telemedicine offered a viable modality for delivery of paediatric nephrology services during pandemic period when access to Healthcare was restricted. Another advantage is the minimal cost and infrastructure required making it user friendly and widely acceptable. The decline in in person doctor visits shows the increasing acceptability of Telemedicine in most specialties. Although this experience is with children with kidney diseases it is equally applicable to other Paediatric subspecialties where there is limited access. Our study can help improve simplify and standardise the practice of Telemedicine. This experience can not only be used during the current as well future pandemics, but also during non-pandemic situations. It also opens up new vistas for the paediatric subspecialists to deliver consultations and follow-up patients in remote areas where currently paediatric subspecialty services are unavailable.

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Original Article

Prevalence of Malignancy and Incidental Carcinoma in Routine Histopathology of Gall Bladder after Cholecystectomy for Gall Stones in the Age Group 30-60 Years

Mayurpankhi Saikia[1], Junu Devi[2]

Background : Gall Bladder is the most commonly resected organ for various Pathological conditions and most common specimen received in the laboratory. Cholelithiasis is the most common cause of Cholecystectomy. Association of Cholelithiasis and Gall Bladder Carcinoma is strong. Gall Bladder Adenocarcinoma is a rare malignant tumor with incidious onset, rapid local invasion and progression. The frequency of incidental Carcinoma of Gall Bladder is also increasing and is estimated between 0.2% to 2.8%. Objectives of this study is to determine the various Gall Bladder lesion and detection of incidental Carcinoma in routine Histopathological study of Cholecystectomy specimens in 30-60 years age group.

Materials and Methods : Total 556 Cholecystectomy cases were enrolled in the study and it was done for a period of one year from August, 2015 to July, 2016. The specimens received were fixed in 10% formalin and were examine grossly and processed routinely. Sections were stain with Haematoxiline and Eosine stain and Microscopic findings were noted.

Results : out of 556 cases 124 were male 432 were female with M:F = 1:3.5. Most commonly affected age group is 30-40 years. Non-neoplastic (98.6%) cases are more than Neoplastic (1.4%) cases. Among Non-neoplastic cases most common Histopathological diagnosis was Chronic Cholecystitis (83.4%). All Neoplastic cases were malignant tumors involving the age group 40-60 years (P=0.04) and M:F=1:7. Histopathologically all were Adenocarcinoma. Prevalence of Gall Bladder Carcinoma was 1.4% and prevalence of incidental Carcinoma was 0.89%.

Conclusion : Routine Histopathological analysis of all Gall Bladderr specimens after Cholecystectomy operation is mandatory for detection of various Pathological conditions and diagnosis of Gall Bladder Carcinoma specifically incidental Carcinoma which help in proper management the cases. However more studies with large numbers of cases are recommended for evaluation of incidence of incidental Carcinoma.

[*J Indian Med Assoc* 2022; **120(7):** 16-20]

Key words **: Cancer, Gall bladder, Cholecystitis.**

Gall bladder is among the most common surgically resected organs and the numbers of Cholecystectomies have increased more than 50% in the past decade[1]. It is affected by variety of non-neoplastic and Neoplastic lesions. More than 90% of Biliary diseases are attributed to Gall Stones. Moreover the most important risk factor for Gall Bladder cancer (besides gender and ethnicity) is Gallstones which are present in 95% of cases. Chronic trauma and inflammation can induce epithelial dysplasia, Carcinoma in situ and invasive cancer but a cause and effect relationship is not proven[2]. In India, carcinoma of Gall Bladder is much more common in women in North and Central part than in the West and the South[3]. The frequency of incidental Gall Bladder Carcinoma diagnosis in routine Cholecystectomy is estimated between 0.2 and 2.8%. Routine Histopathological examination of all cholecystectomy specimen is mandatory because of significant risk of incidental Carcinoma. Aim of this study is to determine the frequency of malignancy and incidental Carcinoma in routine cholecystectomy specimens.

Editor's Comment :

- Gall stone is the most important risk factor for Gall Bladder Carcinoma.
- After Cholecystectomy thorough sampling of Gall Bladder specimen is mandatory for diagnosis of incidental Carcinoma.

Materials and Methods

The present study is a cross sectional study carried out in the Department of Pathology, Gauhati Medical College and Hospital,Guwahati done for a period of one year from August, 2015 to July, 2016. The study was approved by Institutional Ethical Committee of Gauhati Medical College and Hospital, Guwahati vide letter number NO.MC/02/2015/218. All total 556 cases (sample size) of Cholecystectomy Specimens (30-60

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years) received in the Department of Pathology, GMCH were included and analysed. Specimens received in a poorly preserved or autolysed State were excluded. Detail gross examination of formalin fixed specimens were done and subjected to histopathological processing and paraffin blocks preparation.

Sections were cut at 3-5 micron thickness and stained by Hematoxylin and Eosin and mounted in Dibutylphthalate Polystyrene Xylene (DPX) and examined under the microscope. Pathological diagnosis was made and classified.

Observations and Results

Out of 556 cases majority of cases (293, 52.7%) were in the age group of 30-40 years followed by 26.4% in 41-50 years age group and 20.9% in 51-60 years age group respectively. In gender distribution out of 556 cases 124 were male and remaining 432 were females with a M:F =1:3.4. Females are more commonly affected by Gall Bladder disease than males (Table 1, Fig 1).

Clinically patients had varied symptoms that included pain in right hypochondrium (91.9%), nausea or vomiting (5.9%), fever (0.9%), weight loss (0.7%), right hypochondriac mass (0.5%). In the present study maximum numbers of cases 548(98.56%) were non neoplastic in nature and 08 (1.4%) cases were neoplastic lesions. Among the non-neoplastic lesions 529(96.5%) cases were inflammatory lesions and rest 19 (3.4%) were pre-malignant lesions (Fig 2).

Among the inflammatory lesions we got maximum cases of Chronic cholecystitis, followed by other benign lesions. All 8 neoplastic lesions were malignant tumours and all of them were adenocarcinoma.

A total of 8 cases were diagnosed to have Gall Bladdercarcinoma by histopathological examination. The male to female ratio was 1:7. They were between the ages 40-60 years old. Only 3 out of 8 cases were clinically suspected to have Gall Bladder Carcinoma. Others were diagnosed as Chronic Calculus Cholecystitis clinically. Incidence of incidental Gall Bladder Carcinoma in our study was 0.89%. The patients had varied symptoms that included pain in right hypochondrium, vomiting and weight loss.

Table 2 — *Total Distribution of Gall Bladder S (non Neoplastic)*

Histopathological Diagnosis	No of cases	Percentage (%)
Chronic cholecystitis	464	83.45 %
Acute on chronic cholecystitis	14	2.52 %
Xanthogranulomatous cholecystitis	15	2.70 %
Chronic cholicystitis with cholesterolosis	16	2.88 %
Follicular cholecytitis	5	0.90 %
Eosinophilic cholecystitis	5	0.90 %
Empyema GB	1	0.18 %
Mucocele GB	3	0.54 %
Chronic cholecystitis with Intestinal metaplasia	8	1.44 %
Chronic cholicystitis with Antral metaplasia	6	1.08 %
Chronic cholicystitis with Epithelial Dysplasia	5	0.90 %
Chronic cholicystitis with Adenomyomatosis	5	0.90 %
Cholesterol Polyp	1	0.18 %
Neoplastic	8	1.44 %
Total	556	100 %

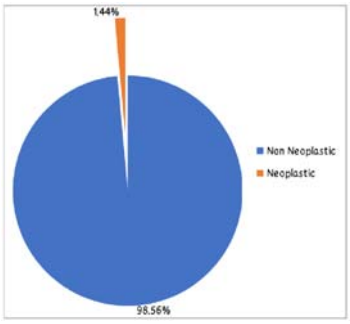

Fig 2 — Pie Diagram Showing Distribution of Gall Bladder Les

Table 1 — *Age and Sex Distribution*

Sex	Age Group (in years)			Total
	30-40	41-50	51-60	
Male	61	34	29	124(22.3%)
Female	232	113	87	432(77.7%)
Total	293(52.7%)	147(26.4%)	116(20.9%)	556(100%)

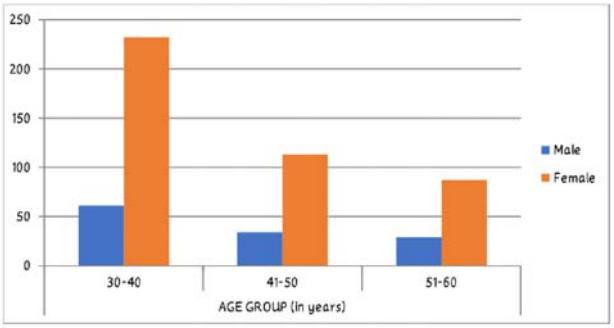

Fig 1 — Bar Diagram Showing Age and Sex Distribution of Gall Bladder Lesions

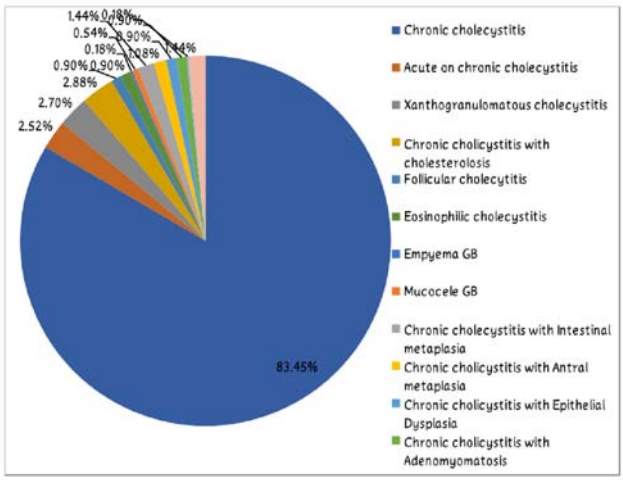

Fig 3 — Pie Diagram Showing Total Distribution of Gall Bladder Lesions

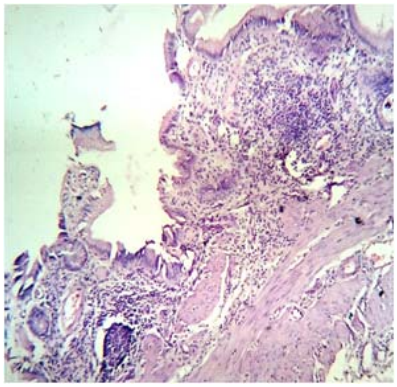

Fig 4 — Microscopic Image of Chronic Cholecystitis (10x40), H&E Stain

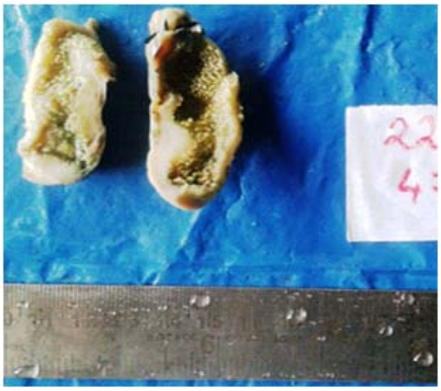

Fig 5 — Gross Picture of Strawberry Gall Bladder

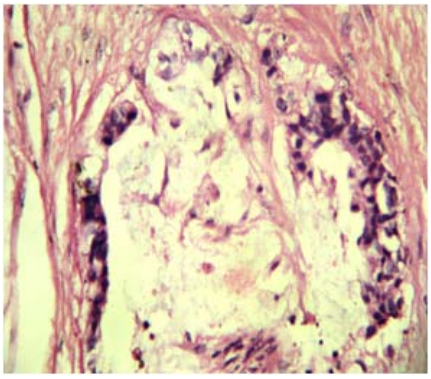

Fig 6 — Microscopic Image of Mucinous Adenocarcinoma Gall Bladder (10x40, H&E)

Macroscopically 2 of the 8 cases showed polypoidal growth, 1 case showed nodular mucosa and others showed thickened and normal Gall Bladder Wall. All of them were Adenocarcinoma histopathologically of which 3 cases were of well differentiated Adenocarcinoma, 2 cases each of moderately differentiated Adenocarcinoma and Papillary Adenocarcinoma and 1 case of mucinous adenocarcinoma.

In our study the p- value for the age of Neoplastic lesions is 0.04 which is <0.05 and it is statistically significant. Male to female ratio in Gall Bladder Carcinoma was found to be 1:7. Increased frequency of Gall Bladder Carcinoma in females suggested a possible role of hormonal factors.

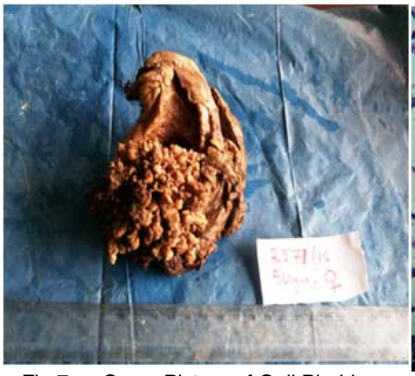

Fig 7 — Gross Picture of Gall Bladder Carcinoma

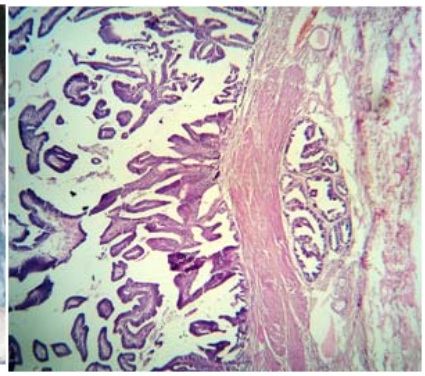

Fig 8 — Microscopic Image of Papillary Adenocarcinoma Gall Bladder (10x10, H&E)

Discussion

Frequency of Gallstones increases with age, more after 40 years of age and becomes 4 to 10 times more likely in older individuals. The risk factors predisposing to Gallstones formation include Obesity, Diabetes mellitus, Estrogen and Pregnancy.

In our present study, the peak age group among both male and female affected by Gallbladder diseases in general was 30-40 years group which is consistent with studies by Mohan H, *et al* (2005)[4], Nailesh Shah, *et al* (2010)[5], Sabina, *et al* (2013)[6]. But there are some studies like, Arati NA, *et al* (2013)[7]& Gajendra Singh, *et al* (2016)[8] who had maximum numbers of patients in the 41 to 50 years age group. In our study we found female pre-ponderance. The male to female ratio was found to be 1 : 3.5. which is consistent with the studies by Nailesh Shah, *et al* (2010)[5], Mustafa Mazlum, *et al* (2011)[9], Arati NA, *et al* (2013)[7].

In the present study out of 556 Cholecystectomy specimen, 464 specimen belong to Chronic Cholecystitis (83.45%) thus making it the most common histopathological findings and this value is similar with the other studies like Sabina, *et al* (2013)[6], Sunil Kumar KB, *et al* (2015)[10]. We got 15 cases of Xanthogranulomatous Cholecystitis (2.75%) which is consistent with the studies byTadasi Terada, *et al* (2013)[11], Gudeli Vahini, *et al* (2015)[12] & Nidhi Awasthi, *et al* (2015)[13]. Xanthogranulomatous Cholecystitis is diffusely infiltrated by macrophages and other inflammatory cells. On macroscopic examination, showed marked wall thickening and mimic with Carcinoma grossly. So its microscopic diagnosis is important.

In our study the incidence of Follicular Cholecystitis was 0.90% which is consistent with studies by Mohan, *et al* (2005)[4] & Gudeli Vahini, *et al* (2015)[12]. The incidence of Cholesterol Polyp was 0.18% which is consistent with the study reported by Faisal G Siddiqui, *et al* (2013)[14]. There were16 cases (2.87%) of Cholesterolosis

Table 3 — *Age Distribution of Gall Bladder Carcinoma*

Age in years	No of cases (%)
30-40	1 (12.5%)
41-50	6 (75.0%)
51-60	1 (12.5%)

Table 4 — *Charecteristics of Patients With Gall Bladder Carcinoma*

Pre-operative diagnosis of GBC	Clinical diagnosis	Macroscopic appearance	Type
Yes	Suspected GBC	Polypoidal growth	Papillary Adenocarcinoma extending up to serosa
No	Chronic calculus cholecystitis	Thickened GB	Well differentiated Adenocarcinoma extending up to muscle layer
No	Chronic calculus cholecystitis	Normal GB Wall	Well differentiated Adenocarcinoma infiltrating up to serosa
Yes	Suspected GBC	Nodular mucosa	Moderately Differentiated Adenocarcinoma
Yes	Suspected GBC	Polypoidal growth	Papillary Adenocarcinoma extending up to serosa
No	Chronic calculus cholecystitis	Thickened GB	Moderately Differentiated Adenocarcinoma
No	Chronic calculus cholecystitis	Normal GB Wall	Well Differentiated Adenocarcinoma
No	Chronic calculus cholecystitis	Thickened GB	Mucinous Adenocarcinoma

associated with Chronic Cholecystitis and was characterized by infiltration of foamy macrophages in the mucosa, which is consistent with studies by Nailesh Shah, *et al* (2010)[15], Mohammed Tayeb, *et al* (2015)[16]. Incidence of Eosinophilic Cholecystitis was 0.89% which is consistent with studies by Tariq Sarfaraz, *et al* (2015)[17], Gudeli Vahini, *et al* (2015)[12] . However, histopathological diagnosis of these Gall Bladder lesions has no prognostic value.

In the present study, it was observed that prevelance of non-neoplastic lesions were more. Among the non-neoplastic lesions maximum number of cases were inflammatory lesions (96.5%) rest were pre-malignant lesions. The occurrence of non- neoplastic lesion in Gall Bladder in present study is 98.55% which is consistent with studies by NT Damor a, *et al* (2013)[18] & Gajendra Singh, *et al* (2016)[8].

Cholelithiasis produces mucosal epithelial changes that represent the precursors lesions of carcinoma. A Gallstone mainly injure the Mucosal Epithelium and thus causes changes like Metaplasia, Dysplasia and Neoplasia. There is presence of inter-relationship between Antral Metaplasia, Intestinal Metaplasia, Dysplasia and Carcinoma. Hence Histopathological examination is important in every case of Cholecystectomy specimens.

Incidence of Gall Bladder Carcinoma (GBC) in our study was 1.43% which is consistent with the studies by Nailesh Shah, *et al* (2010)[5],Ghimire P, *et al* (2011)[19], Chin KF, *et al* (2012)[20] Mohammed A Bawaheb (2013)[21], Gulwani HV, *et al* (2015)[22], Taha MM, *et al* (2015)[23]. All the 8 cases of Gall Bladder Carcinoma were in the age range of 41 to 50 years and is found among females which is quite similar to other studies. Increased frequency in females suggested a possible role of Hormonal Factors.

Incidence of incidental Gall Bladder Carcinoma in our study was 0.89% which is consistent with studies by Dipti Kalita, *et al* (2013)[24], Hamdani, *et al* (2012)[25], Ghimire, *et al* (2011)[19], R Shreshtha, *et al* (2010)[26] & Medhi KB, *et al* (2016)[3].

Adenocarcinoma showing varying degrees of differentiation was the most common type of malignancy in our study which is consistent with findings of studies by Nailesh Shah, *et al* (2010)[15], Mustafa Mazlum, *et al* (2011)[9], Nissar Hussain Hamdani, *et al* (2012)[25], Mohammed A Bawaheb, (2013)[21], Faisal G Siddiqui, *et al* (2013)[14], Ramesh S Waghmare, *et al* (2014)[27],Gudeli Vahini, *et al* (2015)[17] & Taha MM, *et al* (2015)[10].

Conclusion

This study has highlighted the importance of proper histological examination for diagnosis of various lesions of Gall Bladder especially Carcinoma which was not suspected upon clinical nor macroscopic examination. GBC was not always associated with gallstones but may clinically mimic Gallstone disease. Adenocarcinoma was the predominant histological type of GBC. Increased rate of incidentally diagnosed Gall Bladder cancer was found in our study which reinforces the importance of thorough sampling and routine histopathological examination of all cholecystectomy specimens. Further studies with large sample size is recommended for determination of actual value of incidental Carcinoma.

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Original Article

A Prospective Study to Evaluate the Possible Role of Cholecalciferol Supplementation on Autoimmunity in Hashimoto's Thyroiditis

Biva Bhakat[1], Sumit Kumar Chakraborty[2], Sukdeb Das[3], Sahid Imam Mallick[4]

Introduction : Several studies have reported a low Vitamin D status in Autoimmune Thyroid Diseases (AITD), indicating association between Vitamin D deficiency (<20 ng/ml) and thyroid autoimmunity. If supplementation of Vitamin D decreases anti-TPO antibody titres, in future it may become a part of AITDs' treatment, especially in those with Vitamin D insufficiency (21-29 ng/ml) or deficiency.

Objectives : Our study aims to assess any potential therapeutic role of Vitamin D in the management of HT.

Study Design : It is a randomised, double blind, single centre, placebo-controlled study.

Results : Significant negative correlation between Serum anti TPO Antibody and Vitamin D level; statistically significant reduction of anti TPO Antibody titre in intervention group compared to Placebo group.

Conclusions : Vitamin D can be a therapeutic option in Hashimoto's Thyroiditis.

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Key words **: Randomised Controlled Trial, Negative Correlation, Hashimoto, Cholecalciferol.**

Hashimoto Thyroiditis (HT), an autoimmune disease in which thyroid cells are destroyed by antibody and call-mediated immune processes. Hashimoto Thyroiditis is the commonest cause of Goitre in iodine-sufficient regions[1].

The aetiology of Hashimoto disease is not clearly understood. Many patients form antibodies to different types of thyroid antigens, most commonly it is anti-thyroid peroxidase (anti-TPO). Some patients also develop antibodies to Thyroglobulin and TSH receptor (TBII). These antibodies damage the thyroid tissue resulting in diminished thyroid hormone production. Serum antibody may be negative in 10-15% of patients with clinically evident disease[2,3].

Vitamin D is linked with autoimmunity probably by virtue of its anti-inflammatory and immunomodulatory properties. The dendritic cells are antigen-presenting cells originating from bone marrow and also a primary target for the immunomodulatory activity of Vitamin D. 1,25[OH]2D has direct immunomodulatory effects at the level of the T cell Vitamin D receptor. Together, these immunomodulatory effects can lead to the protection of tissues, for example thyroid cells in autoimmune Thyroiditis. Considering that in HT, a T cell-mediated immune disorder, immunologic damage occurs when MHC class II HLA-DR antigens is expressed on the surface of thyrocytes, induced by the production of Th1 type inflammatory cytokines (eg, IFN-γ). Moreover, at another stage, after being activated by T cells, B cells' ongoing proliferation might be inhibited and apoptosis might be induced by 1,25[OH]2D. Thus, 1,25[OH]2D might decrease antibodies that react with thyroid antigens. The appropriate levels of Vitamin D that are sufficient to improve the immune regulatory function and lead to an effective immune response, should be determined.

Low Vitamin D status in Autoimmune Thyroid Diseases (AITD) or HT has been reported in several clinical studies. This indicates an association between Vitamin D deficiency and autoimmune thyroid disorder. If thyroid antibody titres is decreased by supplementing Vitamin D, It may become a part of the therapeutic regimens of AITD, especially in Vitamin D deficienct or insufficient patients[4]. So, our study tries to assess any potential therapeutic role of Vitamin D

Editor's Comment :

- Vitamin D has an important role to play in the pathogenesis of autoimmune disorder.
- Deficiency of Vitamin D is one of the important risk factor of Autoimmune Thyroid Diseases (AITD).
- Underlying pathogenesis of AITD can be reversed by supplementing Vitamin D.
- It could be a great therapeutic option in the management of Hashimoto's Thyroiditis as there is marked improvement of antibody titre and TSH level.

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in the treatment of Hashimoto's Thyroiditis.

Aims and Objectives

Low Vitamin D status has been linked with the pathogenesis of Autoimmune Thyroid Disorder, especially HT. However, there are only few preliminary interventional studies for HT. Vitamin D supplementation is beneficial or not for AITD or HT, should be evaluated. Treatment of HT focussed on mainly thyroid hormone supplementation, so if a therapeutic advantage of Vitamin D supplementation is identified/confirmed, it will be helpful in the treatment of HT and may be a part of treatment of HT patients.

So, the objective of our study is evaluating the role of Vitamin D on an excessive thyroid immune response.

Materials and Methods

(1) Study area : NRS Medical College and Hospital, Kolkata (Department of General Medicine).

(2) Study period : 1 year (January, 2019 to December, 2019)

(3) Sample size : 100 patients both Male and female.

(4) Sample Design : Patients attending outpatient Department in NRS Medical College and Hospital.

(5) Study Design : Prospective, Hospital based, Single centre study.

(6) Inclusion criteria :

Newly diagnosed patients (age >18 years and of both sexes) with HT and Vitamin D deficiency.

(7) Exclusion criteria: Patients suffering from:

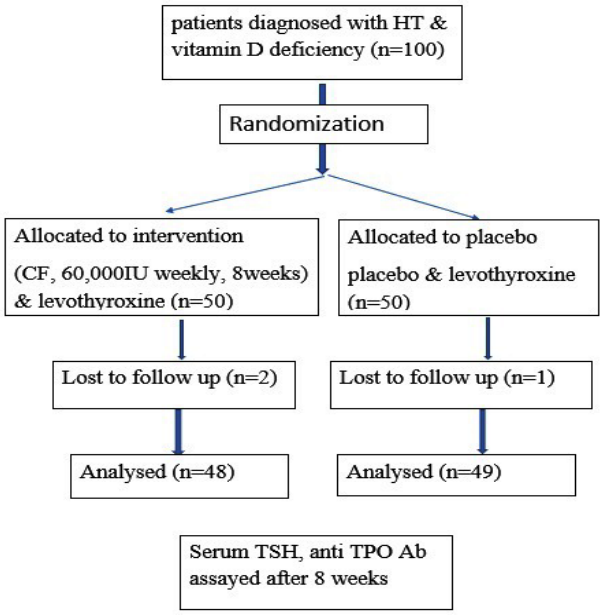
- Other Autoimmune Diseases
- Chronic illnesses like Diabetes Mellitus, Chronic Kidney Disease, Chronic Liver Disease, Malignancy.
- Pregnancy

(8) Study tools : Estimation from serum:

- TSH
- Free thyroxine (FT4)
- 25 hydroxy vitamin D
- Anti-thyroid Peroxidase (anti-TPO) antibody

(9) Study techniques :

This is a prospective study conducted in NRS Medical College and Hospital, Kolkata, India. Total 100 adult patients of both sexes diagnosed with HT and vitamin D deficiency (Vitamin D<30 ng/ml)[12], having none of the exclusion criteria and getting treatment on out-patient department basis, who gave informed consent were included in our study. Blood samples drawn for anti TPO antibody and 25hydroxy Vitamin D from all the participants. The correlations between serum Vitamin D and anti TPO antibody were measured and presented by correlation coefficient (r2). Study participants are randomly assigned into two groups by random permuted block. Cholecalciferol supplement given in the dose of 60,000 IU weekly for 8 weeks in one group (n=50). Another group (n=50) were given placebo (empty soft gelatine capsule). At the onset of the study, patients were requested to keep their habitual diet and routine level of physical activity throughout the study period and not to take any medication that might affect their reproductive physiology. Compliance to the consumption of supplement and Placebo was examined by empty blister packets. However, 2 patients from Cholecalciferol group and 1 patient from control group lost to follow up. After 8 weeks blood anti-TPO antibody level measured in both the groups (n=48 & 49 in 2 group). The change in the mean value of anti TPO antibody measured and statistical significance of the change checked. Results considered significant or non-significant when P> or <0.05, respectively.



Flowchart showing the Methodology of our Study

TSH, T4 measurement Performed with chemiluminescence using ADVIA Centaur XP Immunoassay System.

(10) Work plan : Study was done over 12 months. Data collected and compilation done and then statistical analysis done by standard statistical method.

(11) Statistical analysis : For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS (version 27.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 5. p-value = 0.05 was considered for statistically significant.

Observations

Laboratory parameters before intervention :

	Cholecalciferol group	Placebo group
TSH (mU/L), mean±S.D	50.8±21.18	43.7±25.99
Free T4 (ng/dl), mean±S.D	0.55±0.10	0.55±0.12
25 hydroxy Vitamin D (ng/ml)mean±S.D	11.53±2.05	11.69±3.85
Anti-TPO antibody (IU/ml)mean±S.D	545.06±230.82	686.97±290.19

Laboratory parameters after intervention :

	Cholecalciferol group	Placebo group
TSH (mU/L), mean±S.D	3.70±0.37	5.36±2.62
Anti-TPO antibody (IU/ml)mean±S.D	378.60±160.49	571.10±254.09

Correlation between Serum 25 hydroxy Vitamin D and Serum anti TPO antibody :

		Serum anti TPO antibody (IU/ml)
Serum 25 hydroxy Vitamin D (ng/ml)	Pearson Correlation Coefficient (r)	-0.775**
	p-value	<0.0001

Negative Correlation was found between Serum 25 hydroxy Vitamin D (ng/ml) *versus* Serum anti TPO antibody (IU/ml) which was statistically significant.

Correlation between Serum TSH and Serum 25 hydroxy Vitamin D :

		Serum 25 hydroxy Vitamin D (ng/ml)
Serum TSH (mU/L)	Pearson Correlation Coefficient (r)	-0.301**
	p-value	0.003

Negative Correlation was found between Serum 25 hydroxy vitamin D (ng/ml) *versus* Serum TSH (mU/L) which was statistically significant.

Distribution of mean serum anti-TPO antibody level (IU/ml) [mean±SD] in both groups before and after intervention (Fig 1) :

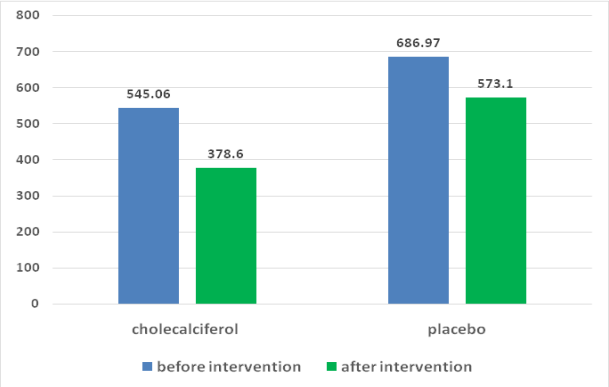


Fig 1 — Flowchart showing the methodology of our study

Reduction of serum anti -TPO antibody level in Cholecalciferol group is 30.5% and reduction of serum anti -TPO antibody level in Placebo group is 16.5%

Discussion

This study is carried out with the total number of 100 outdoor based patients of diagnosed Hashimoto's Thyroiditis (elevated Anti-thyroid peroxidase antibody) and Vitamin D deficiency (Vitamin D<30 ng/ml)[12] in Nil Ratan Sircar Medical College and Hospital within the mentioned study period. The study focussed on evaluating the role of vitamin D on an excessive thyroid immune response ie, the effect of supplementing Vitamin D on thyroid autoimmunity and that Vitamin D deficiency and the risk of HT are closely associated and the potential application of Vitamin D in the therapy of AITD.

The result demonstrates a negative Correlation between Serum 25 hydroxy Vitamin D (ng/ml) *versus* anti TPO antibody (IU/ml) (statistically significant). Pearson Correlation Coefficient (r)= -0.775, p value= 0.0001. Goswami *et al* conducted a community-based survey on 642 adults to investigate the relationship of serum Vitamin D concentrations and thyroid autoimmunity. Their results highlighted a inverse association (statistically significant) between Vitamin D and anti TPO Ab[40]. This inverse correlation was substantiated in the following studies[5-8].

Mackawy and co-workers demonstrated a strong negative association between serum vitamin D and TSH levels, leading to the speculation that Vitamin D deficiency in HT patients lead to progression into hypothyroidism ie, TSH > 5.0 m UI/l [45]. Our study also demonstrates negative Correlation between Serum 25 hydroxy Vitamin D (ng/ml) *versus* Serum TSH (mU/L) and the result was statistically significant. Pearson Correlation Coefficient (r)= -0.301, p value=0.003.

So, the results clearly indicates that Vitamin D deficiency is one of the important risk factor of Hashimoto's Thyroiditis.

Mean (mean± SD) Serum anti TPO antibody (IU/ml) before intervention was 545.06± 230.82 and after Cholecalciferol supplementation the mean value decreased to 378.6±160.49. So, there is a 30.5% reduction in the mean value of anti TPO antibody level. Difference of mean Serum anti TPO antibody (IU/ml) was statistically significant (p<0.0001).

In the Placebo group the mean Serum anti TPO antibody (IU/ml) (mean±SD) of patients was 686.97± 290.19 and after 8 weeks of Placebo the mean value was 573.1±254.09. So, in the Placebo group the reduction is only 16.5%. Difference of mean Serum anti TPO antibody (IU/ml) was statistically significant (p<0.0001).

Therefore, in line with the hypothesis the data contributes clearer understanding that supplementing Vitamin D helps in reduction of underlying autoimmune injury to thyroid gland. This result also supports the previous research. Simsek *et al* prospectively evaluated 82 patients with HT randomized in two groups: the first group treated with cholecalciferol for one month and the second group without vitamin D replacement. Their results indicated that TPO Ab and Tg Ab levels were significantly diminished by the vitamin D supplementation therapy in the first group [46]. These findings were also confirmed by other prospective studies and randomized controlled trials[9-11].

So, the result of our study clearly indicates that vitamin D supplementation could render a positive effect on thyroid function and thyroid autoimmunity.

Limitations :

(1) Vitamin D status could not be measured at the end of 8 weeks because of economic constraints. So, it is difficult to determine the optimal level of Vitamin D needed for improving the evolution of this immunological disorder.

(2) Cholecalciferol is used in HT patients in our study, although active form calcitriol might be more beneficial as Vitamin D binding protein level may affect the conversion of inactive Vitamin D form and thus alters its function on immune cells.

(3) HT patients with normal Vitamin D level have been excluded from the study, so from our study we cannot comment on beneficial effect of Vitamin D supplementation in HT patient with normal Vitamin D level.

(4) As we used empiric dose of levothyroxine in both the groups instead of a fixed dose, we could not analyze any role of Vitamin D supplementation in reducing the levels of serum TSH in HT

(5) There is still a gap in the knowledge regarding the effects of Vitamin D supplementation in the HT patients- whether it will help in decreasing the replacement dose of levothyroxine or whether it will stop the need of levothyroxine replacement if used in pre-clinical stages of HT.

Conclusions

- The 8 weeks randomized; double-blind, placebo-controlled clinical trial demonstrates a negative correlation between Serum 25 hydroxy Vitamin D *versus* anti TPO antibody level.
- Treatment with 60,000 IU cholecalciferol weekly for 8 weeks, is associated with significant decrease in antithyroid antibody titers. It also improved serum TSH level compared with the placebo, ie, supplementary treatment with cholecalciferol seems to have beneficial effects on AITD.
- However, large multicentre studies are needed to investigate further the impact of vitamin D supplementation on meaningful long-term clinical end points in AITD.

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Original Article

Study of Admitted Patients of Mucormycosis : Experience of A Tertiary Care Centre

Namita Goyal[1], Lakhan Poswal[2], Deepika Gupta[3], Neera Samar[4], Priyanka Parakh[5], Manisha Raut[6]

A prospective study was done during mid-April to mid-June 2021 to analyze the sudden rise in cases of Mucormycosis. We assessed characteristics, related comorbidities, disease locale, steroid administration and disease outcome in patients. Cases of Mucormycosis associated with RTPCR positive for Coronavirus disease (COVID-19) and Mucormycosis occurring in patients with negative RTPCR for COVID-19 were compared. A total of 103 Mucormycosis patients were analyzed, 84 (81.55%) were RTPCR positive. Uncontrolled Diabetes Mellitus (70.87%) was the most common comorbidity present among RTPCR positive and negative Mucormycosis patients. Rhino-orbital and Rhino-sinusoidal sites were equally involved (44.0%), followed by Rhino-orbital-cerebral (11.9%) region. We ascribe the spike in Mucormycosis episodes to the trio of diabetes, excessive corticosteroid usage in the face of the COVID-19 Pandemic.

[*J Indian Med Assoc* 2022; **120(7):** 25-9]

Key words **: Mucorales, Diabetes Mellitus, COVID-19, Coronavirus, Corticosteroids, Mucormycosis.**

Recently with the increasing trend associated with the second wave, we witnessed an increase in invasive Rhinosinusitis caused by Mucormycosis. On extensive search of previous five-year records of our institution RNT Medical College and associated group of Hospitals, we did not come across any case of Mucormycosis in first wave and in the near Pre-COVID era. This observation was a matter of concern which prompted us to analyze temporal dimensions of Mucormycosis, correlation with co-morbidities, therapies used for Coronavirus along with overall features and prognosis.

Materials and Methods

During the prospective study in a period of two months, from mid- April to mid-June 2021, all patients presenting with symptoms of Mucormycosis with or without Coronavirus history or an ongoing COVID-19 illness were included. The observational study was conducted at Rabindra Nath Tagore Medical College and associated hospitals, Udaipur, Rajasthan, India.

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Editor's Comment :

- Second wave of COVID-19 witnessed alarming increase in cases of Mucormycosis.
- Triad of SARS-CoV-2, Diabetes and Steroid are Ominous risk factors for Mucormycosis.
- Judicial use of steroids, good glycemic control and monitoring for immunosuppression following steroid use is imperative.

A Mucormycosis case was diagnosed based on their Clinico-radiological features and evidence of fungi either by conventional microscopy or culture of Mucorales from patient's tissue/ body fluids. Microscopy showed presence of broad, aseptate, ribbon like, irregular hyphae. Patients testing positive for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in respiratory specimens using Reverse Transcription (RT)-PCR were diagnosed to be COVID-19 positive. We divided patients with Mucormycosis in two groups based on RTPCR for COVID-19 as Mucormycosis in COVID-19 patients (Group A); and Mucormycosis in patients negative for RT-PCR (Group B). Antibody titer of patients was not available, so the presence of past asymptomatic COVID-19 could not be ruled out in patients with negative RTPCR.

Over the two-month period, the presenting complaints of patient, other co-morbidities including history/current COVID-19 infection, details of biochemical; microbiological; pathological; radiological investigations were obtained. Also, information regarding Diabetes and its control, use of steroids and patient's follow-up details were studied. Hierarchical model was used to classify various underlying illness.

For example, an individual with COVID-19 who is also a known case of uncontrolled Diabetes then, Diabetes was recognized as underlying primary disease.

Comparison between Mucormycosis cases as two Groups – RT-PCR positive and negative, along with underlying diseases, infection site, investigations and outcomes was the prime objective of study.

Tissues from anatomical regions affected by Mucormycosis were biopsied followed by processing using different methods and positive samples were identified based on their macroscopy and microscopy findings. Evaluation of potassium hydroxide tissue mounts was done by routine microscopy. Culture of samples was performed in two sets using SDA (Sabouraud's Dextrose Agar) one at 25°C and other at 37°C. Histopathological examination was done using stains like H&E (Hematoxylin-eosin), Periodic Acid-Schiff (PAS) / Grocott-Gomori's Methenamine Silver (GMS).

Data analysis was performed using Epi info. Descriptive statistics such as frequencies, arithmetic mean (SD), Median, Interquartile Range [IQR] were used. Categorical variables were compared by Chi-square test / Fischer's exact test. p-value of <0.05 was considered statistically significant.

Results

In the second wave of COVID-19 in 2021 a significant rise was noted; as during 2 months of study period, diagnosis of total 103 cases of Mucormycosis was made and admitted at our Institution. Of the 103 cases, 84 (81.55%) had Mucormycosis with RTPCR (+) for COVID-19 (Group A) and 19(18.45%) had Mucormycosis with RTPCR – for COVID-19 (Group B). The average of study population's age was 50.22 years (SD 11.906 years); age bracket in Group A was 30-81 years and in Group B was 35-70 years. 75.73% were men and 24.27% were women (Table 1). Patients in Group A had a higher proportion (79.76%) of males than in Group B patients. The presenting complaints of patients comprised of face and periorbital discomfort/pain, headache, sudden compromise in vision and nasal discharge.

On presentation 25 (24.27%) cases tested positive for Coronavirus; the remaining 59 (57.28%) were infected before and had thereafter recovered, while 19 patients had no present or previous episode of Coronavirus illness. Patients in whom minimum 2 weeks had passed, Post COVID-19 detection were characterized as Recovered/ Post-COVID.

Hyperglycemia (Pre-existing or new-onset DM or concomitant Diabetes and Hypertension) was the prime risk factor seen in 86 (83.5%) cases on presentation in patients suffering from Mucormycosis along with COVID-19. Uncontrolled DM (70.87%) with HbA1c values more than 7 percent was the most frequent underlying co-morbidity in both groups. Cases of newly diagnosed Diabetes Mellitus (DM) were more common in Group A (28/84 [33.33%]) than in Group B (2/19 [10.52%]; p = 0.0482). Singly COVID-19 was present as underlying illness in 10/84 (11.9%) of group A patients, among whom Glucocorticoid therapy was received by 07 (70%) patients for COVID management. Risk factors like Hypertension, CAD and HIV were also observed in some patients (Table 1).

A greater percentage of Mucormycosis patients with RTPCR + COVID-19 had hypoxemia during hospitalization than the patients with RTPCR (-). (Table 1). The Rhino-orbital and Rhino-sinusoidal region were equally involved Mucormycosis site (44.0%), followed by Rhino-orbital-cerebral (11.9%) (Table 1). However, both groups were identical in terms of the affected site.

Direct microscopy diagnosed Mucormycosis in 61/ 103 (59.2%) patients. Aseptate hyphae were visualized by Histopathology in 24/34 (70.59%) cases (Fig 3).

Among RTPCR (+) COVID -19 patients, 32 (38.1%) were hypoxemic. Glucocorticoids were given in 52 (61.91%) patients. As majority of the patients were Post-COVID, they had received treatment for COVID

Table 1 — *Baseline characteristics among patients with Mucormycosis with RTPCR for COVID-19 Positive (history of positive or active infection): Group A and Negative: Group B*

Variables	Group A, n=84	Group B, n=19	p value
Mean age± SD	50.47 ±11.91	49.10±12.12	0.862
Sex : Male	67 (79.76)	11 (57.89)	0.45
Female	17(20.24)	08 (42.11)	
Underlying disease	84 (81.55)	15 (78.95)	0.0001
COVID-19 only	10 (11.9)	0	0.113
Glucocorticoids for COVID-19	52/84 (61.91)	0	<0.0001
Oxygen for COVID-19	32/84 (38.10)	0	0.001
Remdesivir for COVID-19	29/84 (34.52)	0	0.002
Diabetes Mellitus	58 (69.05)	11 (57.89)	0.027
Diabetes Mellitus and Hypertension	15 (17.86)	2 (10.53)	0.436
Other†	1 (1.19)	2 (10.53)	0.028
None	0	4 (21.05)	0.0001
Site of involvement			0.636
Rhino-orbital	37 (44.05)	08 (42.1)	0.877
Rhino-orbito-cerebral	10 (11.9)	01 (5.3)	0.399
Rhino-sinusoidal	37 (44.05)	10 (52.6)	0.4975

*Values are no (%) except as indicated.
†Includes Hypertension, Coronary Artery Disease, HIV.

Fig 1 — Gross Specimen of enucleated eye including eyelids measuring anteroposterior diameter 3 cm, horizontal diameter 4 cm, vertical diameter 3.8 cm, optic nerve measured 2 cm in length

as per the protocol of the respective treating Institute. All patients receiving steroid in any dose and for any duration for COVID management were included in the study. However, on tracing back the data where available, parenteral dexamethasone was the commonest steroid used; minimum being 6 mg/day for 5-7 days. Remdesivir was administered to 29 (34.5%) patients for COVID-19 management. Other immunosuppressive drugs like Tocilizumab were used in very few patients so were not included in the study.

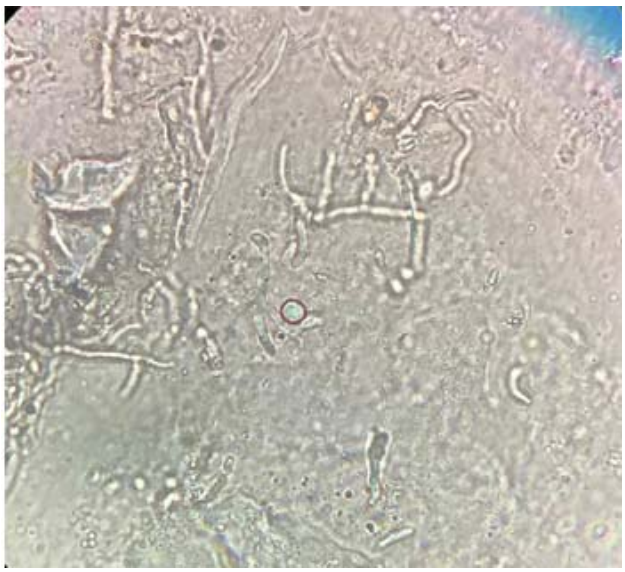

Fig 2 — Photomicrograph of KOH mount showing aseptate hyphae (KOH, 10X)

Majority of the patients (79.6%) had not received even a single shot of vaccination.

Discussion

Mucormycosis is now a notifiable disease. There was not a single case of Mucormycosis in the past five-year records of RNT Medical College and associated group of Hospitals comprising of near pre-COVID era and the following first wave. We observed a surge in Mucormycosis with 103 cases between mid-April and mid-June, 2021, indicating an epidemic along with COVID-19 pandemic. A series of 18 cases in a South Indian City also reported a significant risk in COVID-19 associated Mucormycosis[9]. Hypoxemia owing to Coronavirus and inadvertent Glucocorticoids usage were both separately related with Mucormycosis development in RT-PCR (+) COVID-19 patients.

In our study, 75.73% patients of Mucormycosis were males, which is similar to previous studies[10]. There is no gender or age dependency of Mucormycosis incidence. However, the notably increased incidence of Mucormycosis amongst males in our study may reflect the higher prevalence of Coronavirus illness in men in India. In India nearly 66.8% cases of COVID-19 were males until May 25, 2020[6].

Mucormycosis within a time period of four weeks or less causes Hyphal Sinus invasion[11]. Atypical clinical manifestations like complicated Rhinosinusitis

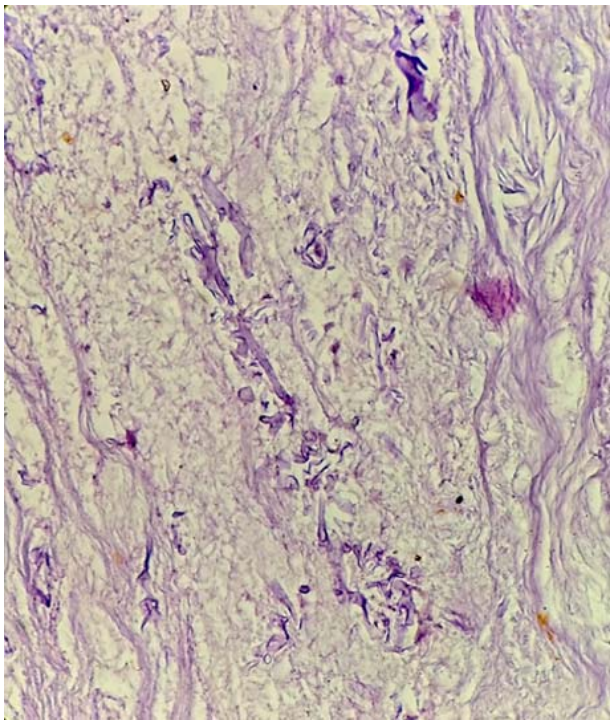

Fig 3 — Photomicrograph of Section examined show broad aseptate irregularly branching fungal hyphae (H and E, 40X)

comprising of Nasal Blockage, Ophthalmoplegia, proptosis, headache, fever, pain in facial region, edema and neurological symptoms may be present in Rhinocerebral Mucormycosis[12]. Black eschar is commonly present over hard palate and in nasal cavity; however, it is not typical[13]. Histologically blood vessels show Mycotic infiltration, Thrombosis, Vasculitis; also there is hemorrhage, neutrophil infiltration and infarction of tissue[14]. Although CT (Computed Tomography) is used as the initial diagnostic modality to analyze the sinus status; however, MRI (Magnetic Resonance Imaging) is the best technique to determine extra-sinus dissemination[13]. Site involved by Mucormycosis was comparable in both groups, which is in corroboration with other studies[10].

Spores of Mucorales germinate in an environment with increased glucose levels (DM, hyperglycemia either steroid induced or new onset), decreased oxygen (hypoxia), acidic medium (DKA – diabetic ketoacidosis, metabolic acidosis), increased ferritin levels, and reduced phagocytosis by leucocytes because of immunosuppression (corticosteroid mediated / iatrogenic / SARS-CoV-2 mediated / co-morbidities / AIDS / hematological cancers / organ transplantation) combined with other factors like usage of mechanical ventilation and extended hospitalization[15].

Commonest underlying disease in both Groups A and B mucormycosis patients was Diabetes Mellitus. SARS-CoV-2 affects pancreatic beta cells, leading to metabolic derangements, and perhaps resulting in Diabetes mellitus[16]. More frequent diagnosis of diabetes mellitus alone or with hypertension in Group A (86.9%) compared with Group B patients (68.4%); it is unclear if this is due to COVID-19 infection, glucocorticoid treatment or a coincident. A multicenter retrospective study across India in September to December, 2020 compared epidemiology among patients of COVID associated Mucormycosis also reported uncontrolled diabetes to be the commonest underlying illness among both CAM and NCAM (non-CAM) cases[10].

In the study of 103 patients, 84 patients of Mucormycosis with RTPCR (+), among them 10 (11.91%) had COVID as sole underlying illness; of them 3 cases had not received any Glucocorticoids / Immunomodulatory therapy; rest had received steroids for COVID management. Inappropriate usage of Glucocorticoids was observed to be related with Group A patients. These findings are in corroboration with other studies[8-10,15]. It is unknown if COVID-19 induces immunological dysregulation by itself and thereby predisposing individuals to Mucormycosis[17]. CBC analysis showed presence of Neutrophilia in 36 (42.86%) Group A patients (Table 2). Wang *et al* also showed a rising Neutrophil count and a falling Lymphocyte count during the severe phase in several COVID-19 patients[18]. Altered innate immune response owing to decrease in T lymphocytes (both CD4+ and CD8+ T lymphocytes) due to immune dysregulation, leads to increase in likelihood of subsequent fungal infections[8]. Both group A and B had comparable sites involved by Mucormycosis.

Table 2 — *Baseline investigations among patients with Mucormycosis with RTPCR for COVID-19 positive (history of positive or active infection): Group A and negative: Group B*

Variables		Group A, n=84	Group B, n=19	p value
Diabetes‡‡:	Uncontrolled	62/73 (84.93)	10/13 (76.92)	0.4712
	Controlled	11/73 (15.07)	3/13 (23.08)	
Microscopy (KOH) :	Positive smear	49 (58.3)	12 (63.2)	
	Negative smear	29 (34.5)	05 (26.3)	
	Not available	6 (7.1)	2 (10.5)	
Histopathology diagnostic of Mucormycosis‡		20/27 (74.07)	04/07 (57.14)	0.381
WBC Analysis :	Neutrophilia	36 (42.86)	09 (47.37)	0.7758
	Lymphocytosis	10 (11.90)	03 (15.79)	
	Normal	38 (45.24)	07(36.84)	
NLR Ratio:	Raised	68 (80.95)	14 (73.68)	0.4776
	Normal	16 (19.05)	05 (26.32)	
Platelet Analysis:	Thrombocytopenia	12 (14.29)	02 (10.53)	0.7366
	Thrombocytosis	08 (9.51)	01 (5.26)	
	Normal	64 (76.2)	16 (84.21)	
IL-6:	Raised	45 (53.6)	09 (47.4)	0.0482
	Normal	39 (46.4)	10 (52.6)	
Serum ferritin :	Raised	31 (36.9)	06 (31.6)	0.662
	Normal	53 (63.1)	13 (68.4)	
Vaccination :				0.8456
	First dose	13 (15.5)	2 (10.5)	0.5807
	Second dose	05 (6.0)	01 (5.3)	0.9078
	None	66 (78.6)	16 (84.2)	0.5817
Outcome:	Death	03 (3.57)	0 (0)	0.403
	Discharged	03 (3.57)	01 (5.26)	0.730
	Admitted	70 (83.33)	15 (78.95)	0.649
	Shift to ICU	02 (2.38)	01 (5.26)	0.499
	LAMA	06 (7.14)	02 (10.53)	0.618

(‡Histopathological examination was performed in 34 cases, 27 in the mucormycosis with RTPCR (+) for COVID -19 and 07in mucormycosis with RTPCR (-) for COVID-19.IL -6 (>400ng/ml) and Serum Ferritin (>4.4pg/ml). NLR Ratio (>3). ‡‡Diabetes includes patients with only diabetes as well as patients with diabetes and hypertension.

Timely management of Mucormycosis by antifungals like Amphotericin B Liposomal and Isavuconazole along with surgical excision, when possible are imperative[19]. Mortality rates did not differ between both groups. However, COVID associated increased mortality risk could not be excluded for RT-PCR(+) COVID-19 patients. The exact effect of vaccination and its bearing on COVID-19 and Mucormycosis needs further analysis and research as limited data is available, and vaccination is still under process in our country.

Our study showed Diabetes to be an important risk factor for developing Mucormycosis, like in other studies from China, Bangladesh, Mexico etc[20]. Individual exact dosage of steroid and effect of Mucormycosis treatment medical/surgical having an impact on outcome could not be analyzed. Increase in Mucormycosis prevalence in India may be due to undetermined variables, such as genetic susceptibility.

Conclusion

The triad of SARS CoV-2, Diabetes and steroid are ominous risk factors for occurrence of Mucormycosis. Usage of Glucocorticoids in the wake of COVID-19 outbreak in India along with existence of co-morbidities, such as Diabetes etc. supports the hypothesis of necrosis of tissue and fungal invasion caused by heightened immune dysregulation. Presence of Diabetes and its poor control are risk factors for Mucormycosis, therefore early diagnosis and good glycemic control are imperative.

Limitations :

- Small sample size
- Short period of study

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Original Article

Comparative Study of Expected Date of Delivery on the basis of Last Menstrual Period and Ultrasonographic Evaluation in Pregnancy

Smita Kumari[1], Gunjan[2], Sipra Singh[3], Rizwan Karim[4]

Accurate determination of gestational age is essential in care and management of pregnant woman. The most widely used and accepted method for prediction of expected date of delivery is by the use of Naegele's formula. Present study was done in 500 pregnant women to compare the Naegele's formula and Ultrasound in estimation of gestational age, and to find out the most reliable method. Most of the patients in present study were second gravid in the age group of 20-30 years. In majority of the cases scanning was started in first trimester. In 60% of studied cases the EDD predicted by USG and LMP corresponded to each other within a range of ± 0ne week. Only 50% of cases delivered within 7 days of EDD calculated by LMP. EDD predicted on the basis of first and second trimester scan didn't differed much but EDD predicted by third trimester scan differ significantly from the first trimester scan.

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Key words **: Gestational age, Trimester, LMP, EDD**

Accurate determination of gestational age is essential in care and management of pregnant woman. The most widely used and accepted method for prediction of Expected Date of Delivery (EDD) is by the use of Naegele's formula. It is observed that that almost 50% of woman deliver within one week of EDD predicted by this method. However, exact date of last menstrual period is essential to use this formula. Most of the woman in our country are still don't bother to remember their LMP, thus using Naegeles formula for calculation EDD becomes difficult. Similar problem arises if patient conceives in lactational amenorrhoea or post pill amenorrhoea.Occasionaly, even in woman with known LMP, the biological age of fetus may differ significantly from menstrual age, because the ovulation which has resulted in pregnancy could have taken place long time after menstruation. In woman with irregular menstrual cycle, woman in whom pathological amenorrhoea precedes physiological amenorrhoea of pregnancy or woman who misinterpret implantation bleeding as menstruation in such cases, the value of LMP becomes dubious. Without the knowledge of gestational age, the pregnancy cannot be managed properly. Ultrasound has now become an integral part of Obstetrics with the increasing use of Ultrasound, most of the pregnant woman have now two independently derived estimates of delivery dates; one based on ultrasound findings and other on the basis of date of Last Menstrual Period (LMP). Sometimes these dates may vary significantly creating dilemma for the obstetrician.

Editor's Comment :

- Ultrasound is simple and non invasive method for accurate assessment of gestational age. First trimester ultrasound provides the most accurate estimation of gestational age.
- Prior to any intervention for termination of pregnancy ultrasonic fetal dating should be employed in all cases where exact date of last menstrual period is not known.

Aims and Objective

(1) To compare the predictive value of Naegele's formula and Ultrasound in the estimation of gestational age.

(2) To find out most reliable method of estimation of gestational age.

Material and Method

The present study was done in Katihar Medical College and Hospital, Katihar from January, 2014 to December, 2014. In 500 pregnant women who attended Antenatal OPD and labour room were included in study, irrespective of their age, parity and religion. Complete details of patient particulars, Obstetrical history, Menstrual history, Past history, Family history,

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Personal history, Contraceptive history and Drug history were recorded.

Inclusion criteria :

(1) Woman with known LMP and have normal menstrual cycle of 28 days.

Exclusion criteria :

(1) Woman taking oral contraceptive pills.

(2) Woman with medical or obstetrical complication at the time of examination.

Observation and Results

Most of the patients in present study were second gravid in the age group of 20-30 years. In majority of the cases scanning was started in first trimester.In 60% of studied cases the EDD predicted by USG and LMP corresponded to each other within a range of ±0ne week. Only 50% of cases delivered within 7 days of EDD calculated by LMP. EDD predicted on the basis of first and second trimester scan didn't differed much, but EDD predicted by third trimester scan differ significantly from the first trimester scan.

Discussion

The purpose of this study was to assess the predictive value of Ultrasonic fetal measurements in estimation of gestational age and its comparison with conventional method of predicting EDD on the basis of LMP.

The observation of this study has been shown in different tables.

Table 1 shows distribution of cases in different age groups. It is evident from this table that incidence of adolescent pregnancy is still high in our state.

Table 2 shows distribution of women according to parity. Primi and second gravida constituted the maximum number of cases (79%).

Table 3 shows the number of cases scanned in different trimesters. It shows that in majority of cases scanning was started in first trimester and only 95 patients were scanned for the first time in third trimester. O'Brien, *et al* (1980), Benett KA, Crane JM (2004), Max Mongelli, Mark Wilcox (2012) have scanned their patients during first trimester of pregnancy and have found good correlation between crown lenth and gestational age.

Table 4 shows difference between LMP based EDD and EDD predicted by first trimester Ultrasound. In 60% of cases these two dates corresponded to each other within a range of one week. Correlation between menstrual age and Ultrasonically determined age by Robinson in 1973 concluded that difference between these two mentioned ages was not more than 4 days. Robinson and Fleming in 1975 also found similar result taking crown rump length in consideration.

Kramer, *et al* (1988), Maratha S, Winqate, *et al* (2007) also compared these two dates and concluded that in some cases they correspond to each other and with actual date of delivery, but in others ultrasonically derived dare was more accurate.

Table 5 shows difference between LMP based EDD and actual date of delivery. Only 52% delivered within one week of predicted date and 88% delivered within two weeks.

Table 6 shows difference between USG based EDD and actual date of delivery. In 83.6% of cases delivery occurred within seven days of predicted date which is significantly greater than predicted by LMP. Rossavik and Fishburne (1989) found that estimation of gestational age on the basis of LMP is more reliable

Tabe 1 — *Distribution of cases in different age group*

Age (in years)	No of cases	Percentage (%)
15-20	105	21
20-30	280	56
30-40	100	20
40-45	15	3
Total	500	100

Table 2 — *Distribution of cases according to parity*

Parity	No of cases	Percentage (%)
Primi	160	32
Second	235	47
Third	85	17
Fourth and above	20	4
Total	500	100

Table 3 — *Distribution of cases scanned in different trimesters*

Trimester	Total no cases scanned	No of cases scanned for the first time
First	220	220
Second	385	185
Third	450	95

Table 4 — *Shows difference between LMP based EDD and EDD predicted by first trimester USG*

Difference (in days)	No of cases	Percentage (%)
Nil	40	8
1-7	260	52
8-14	175	35
More than 14 days	50	10
Total	500	100

Table 5 — *Shows difference between LMP based EDD and actual date of delivery*

Difference (in days)	No of cases	percentage (%)
Nil	30	6
1-7	230	46
8-14	180	36
>14	60	12
Total	500	100

Table 6 — *Shows difference between EDD predicted by first USG and actual date of delivery*

Difference (in days)	No of cases	Percentage (%)
Nil	60	12
1-7	358	71.6
8-14	66	13.2
15 days and above	16	3.2
Total	500	100

than ultrasound dating.

On the contrary, Becke and Nakling (1994) observed that most of the deliveries were significantly closer to USG predicted date than

those calculated by LMP. Similar findings were observed by TM Mongelli, *et al* (2003) and Max Mongelli and J Gardosi (2012).

Conclusion

Ultrasound is simple, hazardless and non invasive method for accurate assessment of gestational age. For getting accurate results, Ultrasonic fetal dating should be done in first trimester.

Its predictive value is greater than that predicted by LMP. So, ultrasonic fetal dating should be employed in all cases who are not sure of her last menstrual period. Even in women with known LMP it is wise precaution to assess gestational age ultrasonically prior to any intervention because of the fallacies associated with menstrual period.

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Original Article

Effectiveness of Self-directed Learning to Teach Biochemistry in Phase 1 MBBS Students

Soma Gupta[1], Alka Rawekar[2], Abhijit Bhakta[3], Maitreyi Bandyopadhyyay[4]

The effectiveness of introducing Self-directed Learning (SDL) activity in teaching Biochemistry in Phase 1 MBBS Students was studied by measuring learning gain before and after SDL session. The SDL sessions were conducted among 3 groups of Students (Group A, n = 88; group B, n = 66 and Group C, n = 46; Total, n = 200) according to their learning needs. SDL was found to improve test scores significantly in all three groups. The perception of the Undergraduate Medical Students on SDL was also collated in this study by close ended question (in Likert scale) and open-ended questions. Perception analysis showed that majority of the Students agreed that SDL sessions are beneficial and interesting. However, thematic analysis showed that most of the Students considered SDL to be more time consuming. The questions were found to be reliable in present setting by calculating Cronbach's alpha coefficient (0.893). It seems to be essential to find out the topics where students need special guidance and which topics will be chosen for SDL.

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Key words **: SDL, Biochemistry, Learning gain, Perception.**

The introduction of competency-based Medical Education Curriculum in India has endorsed many new concepts, one of which is Self-directed Learning (SDL). In SDL, the students are expected to take the initiative to diagnose their learning needs, formulate their learning goals, identify resources for learning and evaluate their learning outcomes. Thus, SDL is primarily a higher order active learning technique where onus of learning lies with the Students[1]. The design of SDL sessions and their successful implementation is still a challenge. The effectiveness of the particular strategy must be evaluated properly to make sure that the process has been implemented successfully. Selection of competencies in Biochemistry that can be taught by SDL to Students of Phase 1, should be identified.

This study was undertaken to find out effectiveness of introducing self-directed learning activity in teaching Biochemistry in Phase 1 MBBS Students by measuring learning gain of the undergraduate medical students. Moreover, the perception of the Undergraduate Medical Students on SDL was also collated.

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Editor's Comment :

- This study shows that SDL significantly improves scores of tests but it is much time consuming. Thus, it appears that it is not an alternative to didactic lecture but it is a supplementary to it.
- It is essential to find out the topics where students need special guidance and which topics will be chosen for SDL.

Material and Method

This cross-sectional study was conducted in a Government Medical College of West Bengal on the Phase1 MBBS Students, who after finishing the whole syllabus of Biochemistry approached the faculties to revise some topics. We planned to take some of these topics by SDL following the steps described by Badyal DK[2].

The study was approved by Institutional Ethics Committee. All students of the 1st phase MBBS were introduced briefly to the objectives and the methodological workflow of the study by an interactive lecture. All willing students were included in the study. Those Students, who were absent on that day were excluded for the study.

Selection of topic: By discussion with the Students and reviewing competencies[3] in the curriculum, 3 suitable topics were selected for 3 groups (competency, BI 11.17):

- **Group A :** Explain the basis and rationale of biochemical tests done in Diabetes Mellitus (DM)
- **Group B :** Explain the basis and rationale of biochemical tests done in Thyroid disorder
- **Group C :** Explain the basis and rationale of biochemical tests done in Acute Myocardial Infarction

1st contact session : A pre-test on each topic was taken for each group. Then the topic was given to the students setting the learning goal and time limit.

Intersession period : During this time students were supposed to find and explore resources, read the topic and approach facilitator as needed.

2nd contact session : A post-test on the same topic was taken.

Then to collate the perception of the students on SDL, they were asked to fill out a pre-validated questionnaire, where 7 questions were given in Likert scale and 3 questions were open ended. For open ended questions, Students were supposed to write what they liked and disliked most regarding SDL session and their suggestion to improve the sessions[4]. This was carried out by Google Form.

Statistical analysis :

All data were analysed using SPSS software version 22. To assess the effectiveness of SDL on the learning gain, marks of pre-test and post-test were tabulated and compared by student t test. P value <0.05 was considered as significant.

Perception analysis of the students were done by calculating frequencies with percentage for all response. For open ended questions, thematic analysis was performed[5]. Reliability was calculated by Cronbach's alpha coefficient.

Observations

A total of 222 Students approached for SDL with following distribution. But ultimately a total of 200 Students (88, 66 and 46 respectively for Group A, B and C) completed all the sessions.

Table 1 shows comparison of score of pre-test and post-test, which shows significant improvement in all 3 topics. Table 2 shows Item statistics and Reliability Statistics (Cronbach alpha 0.893) regarding perception of students about SDL. Fig 1 shows the graphical response of student perception on SDL, as obtained on Likert scale. Table 3 shows Frequency distribution of response about perception of students regarding SDL.

More than half of the Students strongly agreed that SDL session is beneficial for their examination (54.5%), as well as their future study (55%). Almost half of the Students strongly agreed that SDL improved team work and they got adequate support from their facilitator. Though majority agreed that SDL causes better understanding of the subject, only 44% strongly agreed and 39% agreed the statement. Strong agreement was not found regarding improvement of leadership skill in communication ability.

Table 1 — *Learning gain by SDL*

Topic	Pre test Mean±SD	Pre test Mean±SD
Explain the basis and rationale of biochemical tests done in Diabetes Mellitus (DM) (n = 88)	9.37±2.05	12.37±1.84*
Explain the basis and rationale of biochemical tests done in Thyroid disorder (n=66)	8.23±2.9	12.01±1.73*
Explain the basis and rationale of biochemical tests done in Acute Myocardial Infarction (n = 46)	10.13±3.13	11.92±2.26*
OVERALL	9.16±2.69	12.10±1.9*

*Significant at p <0.05

Table 2 — *Item statistics and Reliability Statistics of Perception analysis*

Question	Mean	STD. Deviation	Cronbach's Alpha
Question 1	4.4523	0.70100	
Question 2	4.4523	0.72229	
Question 3	4.4422	0.72852	
Question 4	4.3568	0.76432	0.893
Question 5	4.0603	0.93007	
Question 6	4.2663	0.77487	
Question 7	4.3568	0.77742	

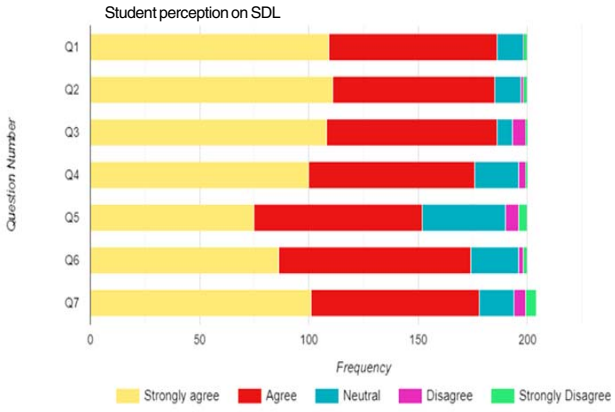

Fig 1

So far open-ended questions are concerned, the students revealed that SDL session cleared their concept, which they liked most (71%). Some commented that the topics dealt in SDL helped them in revision (19%), while some wrote that they became curious to read further (7%).

Almost 65% students found that SDL sessions take a lot of time, which they disliked most. Approximately 20% students wrote that questions set in tests were tough and some were out of syllabus. So, they had to work hard. Another point of disliking was "Non participation of some Students". The most relevant and common suggestions for improvement were inclusion of more clinically oriented topics and to conduct the sessions in smaller groups. Some suggested for provision of a Manual.

Table 3 — *Frequency distribution of response in analysis of perception of students regarding SDL*

Question	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
I think it is beneficial for my examination	109 (54.5%)	77 (38.5%)	12 (6%)	0 (0%)	2 (1%)
I think it is beneficial for my study in future	111 (55.5%)	74 (37.0%)	12 (6%)	1 (0.5%)	2 (1%)
I think it causes better understanding of the subject	108 (44%)	78 (39%)	07 (3.5%)	06 (3%)	1 (0.5%)
I think it improves team work	100 (50%)	76 (38%)	20 (10%)	03 (1.5%)	1 (0.5%)
I think it increases my leadership skill	75 (37.5%)	77 (38.5%)	38 (19%)	6 (3%)	4 (2%)
I think it improves my communication skill	86 (43%)	88 (44%)	22 (11%)	02 (1%)	2 (1%)
I think I got adequate support from my facilitator	101 (50.5%)	77 (38.5%)	16 (8%)	05 (2.5%)	1 (0.5%)

Discussion

The learning gain of the students by SDL was found to be significant. Certain topics of Biochemistry demand integration of basic knowledge of Biochemistry with laboratory finding. In these conditions, SDL is supposed to work better. This finding is in accordance to the findings of Pai *et al*[6].

Perception analysis shows that SDL is a good method for acquisition of knowledge, particularly among Phase 1 MBBS Students[7]. Studies have also shown that Case based learning by SDL is an effective method of introducing clinical correlation[8]. Previous studies on perception analysis showed that SDL causes better understanding of the subjects like Anatomy[9], Physiology[6] or Biochemistry[10]. Our study is in accordance to this finding.

Agarwal *et al*[10] reported that majority of Students have found SDL more interesting, more enthusiastic and an enjoyable form of learning a topic in Biochemistry. Moreover, it provided sufficient opportunity to interact with the Faculty. Our study also supports the finding of Agarwal et al.

Thematic analysis revealing that SDL takes longer time appreciated by our study team also. So, though it clears concept, only some selective topics can be covered by SDL. We need to work hard to select the topics to be taken by SDL and to plan accordingly so that time can be utilised optimally.

In open ended questions they were also asked to give suggestion to improve SDL sessions. Most of the students were in favour of incorporation of case-based learning, which is appreciated as good suggestion. It was also reported by previous study[11], but due to the threat of SARS Cov 2 infection, it could not be carried out.

Limitation of this study is that the result solely depends on Self-assessment of the students. We have no scope to verify whether it is correct or not. It must be emphasised that questionnaire used to analyse students' perception of SDL was pre-validated by a number of subject experts and through a pilot study in 10 Medical Students. But a detailed Psychometric analysis of the items has not been done. This may be considered as another limitation of this study.

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Original Article

A Comparative Study of Common Bile Duct Drainage by T-tube and Choledochoduodenostomy in Cases of Common Bile Duct Stones

Pranaya Kunal[1], Kumar Koustuv[2], Neha Gupta[3]

To study and compare the cases of 'T'-tube drainage and Choledochoduodenostomy done for Common Bile Duct stones.

Methods : A prospective study was conducted from October 2019 – September 2021 (24 months including follow-up period) in patients diagnosed to have Choledocholithiasis in MGM Medical College and Hospital, Kishanganj, Total 50 patients were Included in this study. Those patients in whom CBD stones detected incidentally on investigation like Ultrasonography upper abdomen done for chronic calculus cholecystitis or detected during surgery for cholecystectomy ie, asymptomatic stones were also included in this study.

Results : In the cases of our study, most of the patients (62%) didn't has sludge. Choledochoduodenostomy was more frequently performed when sludge was present (P=0.043), whereas 'T'-tube drainage was performed when sludge was absent. only 19 cases (38%) had sludge. And also it was present more commonly with larger diameter CBD (P value =0.016).

Conclusion : In this study, both the surgical procedures did not produce any mortality. Some patients developed complications. This could be because much of the study population was elderly and most of the complications were noted in patient with acute cholangitis. In both the group, wound infection was noted to be most common complication. All of the patients treated conservatively successfully. [*J Indian Med Assoc* 2022; **120(7):** 36-40]

Key words **: Cholelithiasis, Common Bile Duct, Choledochoduodenostomy, T-tube drainage.**

Cholelithiasis is frequently associated with stones in the Common Bile Duct (CBD). From varying published data it can be seen that of all patients subjected to cholecystectomy for gallstone, Atleast 15% of patients with cholelithiasis have Choledocholithiasis conversely, 95% of patients with CBD stones also have Gallstones[1]. The presence of this stone in the CBD increases the morbidity and mortality of patients, particularly those presenting with jaundice and pancreatitis.

External drainage of the common duct is the oldest and most widely practised procedure of draining the CBD. But surgeons soon began to think of some other methods of drainage which would avert the unnecessary loss of bile into exterior and which would lower the incidence of over looked stones and subsequent obstruction of the CBD. Choledochoduodenostomy was soon discovered and was designed with the idea of draining the bile internally into the duodenum and that residual stones, if any, would pass into the duodenum through the stoma. Though it is almost more than 90 years from now that the operation was first performed and published and though quite a number of papers were published subsequently from various centres in its favour, it is still to be accepted universally as an effective procedure in cases of benign biliary obstruction. The uncertainty is probably due to the fact that the long-term effects of this operation on the CBD and the liver has not been analysed satisfactorily on any large group (Capper, 1961).

Editor's Comment :

- This study evaluates the efficacy and safety of T-tube drainage method of CBD repair after Common Bile Duct exploration and provides more evidence for duct closer after choledocholithotomy in cases of Common Bile Duct stones.

Choledochoduodenostomy which is described as an anastomosis between the lower end of the CBD and duodenum has limited but specific indications. This procedure has been described long back but the indications have remained the same over years[2].

The present series consists of 50 cases where CBD was explored for stones of which in 30 cases Choledocholithotomy followed by T-tube drainage was performed and in the rest 20 cases lateral Choledochoduodenostomy was the choice of operative procedure. All the patients were admitted in MGM Medical College & Hospital during the period of 2017 - 2019 in the Department of Surgery. All the patients were investigated thoroughly during the pre-operative period, by biochemical and radiological methods. The choice of operation was decided upon the findings at

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pre operative investigation and during exploration. All the patients were assessed post operatively with regard to recurrence of jaundice, deterioration of liver function and ascending infection by clinical, biochemical and radiological investigation. Finally, quite a number of literatures on this topic were reviewed and the results of the present series were corroborated with the other published series.

Materials and Methods

A prospective study was conducted from October 2017 – September 2019 (24 months including follow-up period) in patients diagnosed to have Choledocholithiasis in MGM Medical College and Hospital, Kishanganj, a tertiary hospital of northern India. They were followed up for a period of 3 months. The cases were recruited from surgical outdoor patients or emergency services. Patients who presented with signs and symptoms (like pain in right hypochondrium, biliary colic, fever with or without chills and rigor, vomiting and past history of or presence of Jaundice) suggestive of stones in the CBD were included in the study. Those patients in whom CBD stones detected incidentally on investigation like Ultrasonography upper abdomen done for chronic calculus cholecystitis or detected during surgery for cholecystectomy ie, asymptomatic stones were also included in this study. The cases of benign ampullary stenosis which were detected only after exploration were also included in this study. Cases of biliary obstruction like biliary stricture, carcinoma of CBD or periampullary carcinoma etc. were excluded from the study. Those cases in which no stone was found within the common duct on exploration were also excluded from this study.

Number of cases — 50 cases (prospective)

Much attention was given to differentiate surgical from medical jaundice from the history clinical examination and investigations

A total of 50 cases were prospectively recruited in the study. After enquiring the patient's particulars, a detailed history was taken. Chief complains like pain in abdomen, fever, jaundice, nausea or vomiting and their duration were noted. The onset of pain, its character, radiation, aggravating or relieving factor, relation with food were noted carefully. History of jaundice, its onset, duration and progression (gradually deepening or fluctuating) were noted. History of fever with or without chills and rigor, nausea, vomiting, colour of stool, and itching were also noted. In regards to past history previous attacks of biliary colic, jaundice, typical fever, and recurrent blood transfusion were noted. Any history of surgical intervention in the past was also noted. History of any major medical illness or history suggestive of diabetes mellitus, hypertension, and ischemic heart disease were also noted. Personal history of dietary habits and any addiction was enquired. In female patients obstetrical history like parity, number of living children or abortion, if any was enquired. History of taking oral contraceptive pills was also noted.

Every patient was clinically examined very carefully and systematically. In general examination the Built of Patient, Weight, Pallor, Oedema, Jaundice, Pulse, Blood Pressure, Respiration, Temperature, etc were noted.

On local examination of abdomen, abdomen was inspected especially for its shape, its movement with respiration, presence or absence of any lump. On palpation tenderness and temperature were noted especially in right hypochondrium. Presence of any lump and any other organomegaly was noted Other systemic examination of cardiovascular system, respiratory system and nervous system was done carefully.

Observations

All the patients were followed up on 4th post operative week and then 3rd postoperative months. In case of any abnormality in any follow up, patients were followed up closely depending on clinical, blood and radiological investigations.

Both group of patients were followed up by –

(1) Clinical examination — All of the patients were examined and asked for history of pain, fever or jaundice, urine and stool colour.

(2) Liver function test — All of the patients were investigated for serum Bilirubin (total,direct and indirect) and serum Alkaline phosphatase.

(3) Ultrasonography upper abdomen — It was done only when clinical examination or liver function test showed any abnormality.

Statistical Methods :

Data analysis was done using Epi Info Software and appropriate tests were applied where applicable.

Results

A total of 50 cases were recruited in the study, in which 30 cases (60%) underwent T-tube drainage and 20 cases (40%) underwent Choledochoduodenostomy.

Out of total cases, 16 (32%) were males and 34 (68%) were females (Table 1).

Table 1 — *Showing the gender distribution of cases*

Sex	No of Cases	Percentage
Male	16	32
Female	34	68
Total	50	100

The incidence of choledocholithiasis was found to be more (46%) in the age group of 40-49 years.

Choledochoduodenostomy was more frequently performed in older (more than 50 years) age group whereas T-tube drainage was performed more commonly in relatively younger age group (less than 50 years) (Table 2).

Table 2 — *Showing the age distribution of choledocholithiasis and the type of surgery performed in different age group*

Age (Year)	T-tube drainage		Choledochoduo-denostomy		Total No	Percentage
	No	%	No	%		
<20	1	2	0	0	1	2
21-29	4	8	3	6	7	14
30-39	5	10	3	6	8	16
40-49	13	26	5	10	18	36
50-59	4	8	7	14	11	22
≥60	3	6	2	4	5	10
Total	30	60	20	40	50	100

Both the surgeries T-tube drainage as well as Choledochoduodenostomy were performed more common in absence of cholangitis, but statistically Cholangitis was not found to be the important factor in decision making of procedure performed (P= 0.630) (Table 3).

Table 3 — *Showing the relation of Cholangitis with the procedure performed*

Procedure	Cholangitis (Fever)				Total	%
	present	%	Absent	%		
'T' tube drainage	10	20	20	40	30	60
Choledochoduo-denostomy	8	16	12	24	20	40
Total	18	36	32	64	50	100

χ^2 = 0.231, P value = 0.6304

Cholangitis was found to be more common (15 out of 18 cases *ie,* 83.33%) when CBD was dilated more than 10 mm (P=0.007), whereas 20 out of 32 cases (62.5%) has shown CBD diameter less than 10 mm in absence of cholangitis (Table 4).

Table 4 — *Showing the relation of common bile duct diameter (mm) with cholangitis*

CBD diameter	Cholangitis (Fever)				Total	%
	Present	%	Absent	%		
≤10 mm	03	06	20	40	23	46
11-15 mm	09	18	07	14	16	32
> 15mm	06	12	05	10	11	22
Total	18	36	32	64	50	100

χ^2 = 9.751, p Value= 0.007

T-tube was performed more commonly when CBD diameter was less than 10 mm. Choledochoduo-denostomy performed only when diameter of CBD was more than 12 mm. When CBD diameter was more than 15 mm, only choledochoduodenostomy was performed (Table 5).

Table 5 — *Showing the relation of CBD diameter with the surgical procedure performed*

Procedure Performed	CBD diameter (mm)			Total	Percentage
	≤10	11-15	>15		
'T' tube drainage	23	07	00	30	60
Choledochoduo-denostomy	00	09(>12mm)	11	20	40
Total	23	16	11	50	100

χ^2 = 33.594, p Value = <0.001

In this study, it was found that the number of stones didn't affect the CBD diameter. No association was seen between multiplicity of stone and CBD diameter (P =0.663) (Table 6).

Table 6 — *Showing the relationship of number of stones with CBD diameter*

Number of Stones	CBD diameter (mm)						Total	
	≤10 mm		11-15 mm		>15mm			
	No	%	No	%	No	%	No	%
Single	12	24	06	12	05	10	23	46
Multiple	11	22	10	20	06	12	27	54
Total	23	46	16	32	11	22	50	100

χ^2 = 0.820, p Value= 0.663

In the cases of our study, most of the patients (62%) didn't has sludge. Choledochoduodenostomy was more frequently performed when sludge was present (P=0.043), whereas 'T'-tube drainage was performed when sludge was absent (Table 7).

Table 7 — *Showing the frequency of sludge in relation to surgery performed*

Procedure	Sludge				Total	
	Present		Absent			
	No	%	No	%	No	%
'T' tube drainage	08	16	22	44	30	60
Choledochoduodenostomy	11	22	09	18	20	40
Total	19	38	31	62	50	100

χ^2 = 4.089, p Value= 0.043

Mean duration of surgery was significantly lower in T-tube drainage by 48 minutes (Table 8).

Table 8 — *Showing the average duration of surgery*

Operation	Time (minutes)
T-tube drainage	78
Choledochoduodenostomy	126

Hospital stay was calculated from the day of surgery performed till the patient was in dischargeable condition. Average hospital stay duration was around 4 days longer for T-tube drainage surgery (Table 9).

Table 9 — *Showing average number of days of hospital stay after the surgery*

Operation	Hospital Stay (Day)
T-tube drainage	14.4 days
Choledochoduodenostomy	10.7 days

In our study, wound infection was more common with T-tube drainage (20% *versus* 15%). A total of 6 cases (4 in each T-tube group and 2 in Choledochoduodenostomy group) were developed bile leak in postoperative period. One case of bile leak developed with T-tube in situ, whereas 2 cases developed after T-tube removal. One case of leak occurred due to dislodgement of upper tip of T-tube outside of CBD, when T-tube was in situ and was diagnosed by T-tube cholangiogram. On 10th postoperative day leasubsided within 2-3 days of removal of T-tube. Bile leak occurred after removal of T- tube was stopped within 3 days. However, all of these patients were asymptomatic and treated conservatively. There were 2 cases of missed stones in T-tube drainage (10%) (Table 10).

Table 10 — *Showing various postoperative complications of the surgery*

Complication	T-tube		Choledochoduodenostomy	
	No	%	No	%
Wound infection	06	12	03	06
Residual Stones	02	04	00	00
Cholangitis	00	00	00	00
Bile leak	03	06	02	04
T-tube dislodgement	01	02	00	00

2 cases of bile leak occurred after choledochoduodenostomy (10%). In both cases the diameter of CBD at the time of anastomosis was 13mm and 16mm. However both patients were asymptomatic and treated conservatively and bile leak stopped within 4-5 days. There were no complications of bile collection, bile peritonitis, cholangitis, anastomotic stricture or sump syndrome.

There was no mortality noted in both the group of our study.

Follow up :

Out of 50 patients, 46 patients (92%) came for one month follow up, and 38 patients (76%) came for 3 months follow up. All the patients in both the groups didn't complaint any symptoms in the follow ups. Clinical examinations didn't revealed jaundice, tenderness and hepatomegaly. Liver function of all the patients in both the group was normal in the follow ups. Ultrasonography was not required for any of the patients.

Discussion

Incidence of Choledocholithiasis has been found to be higher in females compared with males in our study (2.125:1). This was in accordance with the study conducted by Way, *et al,* who reported female: male ratio of 3:1[3] and by Kumar, *et al* with reported ratio of 2:1 to 1:1[4]. However, Soon, *et al* reported male preponderance in their study with female male ratio of 1.3:1.

In our study, the most common age group affected is between 40 to 49 years. The mean age of the patients is 42.92 years. The incidence and prevalence of choledocholithiasis tends to increase with age. Nathanson, *et al* have reported the median age affected to be 59.6 years[5]. Sgourakis reported the age range to be between 46 to 89 years[6]. Hermann has shown that the incidence that begins in childhood, progresses steadily with a sharp increase between 35 to 55 years and continues to show a gradual increase after 55 years[7]. With the proper indication and meticulous technique, it can be performed even in younger patients. Our study showed incidence choledocholithiasis maximum in middle aged women probably because of geographical variation and local dietary habits.

It is the most important criteria in decision making of drainage procedure.

L H Blumgart, suggests that a dilated duct is the sin qua non for the choledochoduodenostomy. It should not be performed with ducts less than 1.4 cm in diameter & a duct narrower than 1.2 cm is absolute Contraindication. Thus Two technical criteria are essential for a proper choledochoduodenostomy a common duct of 1.4 cm in diameter at the minimum & a stoma size of 2.5 cm.

Wood MD, Glidman ML, 1981 showed in his 200 cases of Choledochoduodenostomy that when the calculus containing CBD measures 1.2 cm in internal diameter & anastomotic width is at least 2.5 cm, Choledochoduodenostomy is an excellent procedure[8].

Similar results were shown by George A Degenshein MP, *et al* 1974 who published the study of 175 consecutive cases of Choledochoduodenostomy among which 153 were for benign biliary disease.

In our study, 15 out of 18 (83.33%) patient with cholangitis had CBD diameter more than 10 mm, whereas in the absence of cholangitis, only 12 out of 32 patients had CBD diameter more than 10 mm. this was in accordance with the study conducted by Tomizawa *et al*, in which 70.13% of (11.2±2.9mm)[9]. CBD dilatation aids in the diagnosis of acute cholangitis[10]. The sensitivity of cholangitis is 95 to 100% for CBD stones[11].

The most popular and age-old method of draining the common duct after exploration is a T-tube drainage. The bile is a most irritating fluid to the peritoneum. It produces an intense inflammatory reaction, which is mostly followed by dense peritoneal adhesion and if the extravasation is large, septic peritonitis follow which eventually leads to fatality. By draining the common duct such complications can be avoided. The drain should be left in place till its track is safely sealed off from the general peritoneal cavity which takes about 10 days (Sir Ogilvie[12], 1957).

Operative Cholangiogram is a relative safe guard against residual stones, particularly when there are multiple stones in the common duct. Where the facility of operative cholangiogram is not available, it appears that choledochoduodenal bypass prevents subsequent bile duct obstruction by any residual stone which, if small, will pass into the duodenum through the stoma easily.

The primary objection of many to perform Choledochoduodenostomy is that it, pre-disposes to ascending cholangitis, from intestinal contents passing into the biliary tract. But this objection is not borne out by any confirmatory factual clinical data. Madden, *et al* (1970), in a convincing experiment, proved that in none of the 20 animals subjected to biliary – colic anastomosis did cholangitis develop, although barium enema studies demonstrated an immediate reflux of the barium into the biliary system. This has been convincingly proved by many authors that cholangitis really occurs in cases of stomal obstruction where the outflow of bile is impeded and not due to regurgitation of intestinal contents. Florcken, as early as in 1923 stated that the danger of cholangitis was purely theoretical and the objections came only from those who never did the operation or those who made a small anastomosis. Madden[13] *et al*, in a collected series of 1,255 Choledochoduodenostomy, found only 5 patients (.4%) with recurrent cholangitis.

Mortality rates in patients undergoing surgery for CBD calculi ranges from 1% in relatively fit younger patients to 28% in the unfit and the elderly[14]. It increases to 12-14% in younger patients undergoing surgery for Cholangitis[14]. Moreover the mortality/morbidity is increased if a drainage procedure is included[15].

In our study, both the surgical procedures did not produce any mortality. Seventeen (34%) patients developed complications. This could be because much of the study population was elderly and most of the complications were noted in patient with acute Cholangitis.

In both the group, wound infection was noted to be most common complication. There were 3 cases (10%) of bile leak in T-tube drainage group. One was due to dislodgement of upper end of T-tube and other two developed after removal of T-tube. However, all of the 3 cases recovered over next 2-3 days and fistula stopped. In Choledochoduodenostomy group there were only 3 cases of wound infection (15%) and 2 cases of bile leak (10%). All of the patients treated conservatively successfully.

Mean duration of surgery was significantly lower in T-Tube drainage. The mean number of days of hospital stay for the patients who underwent treatment by T-Tube was 14.4 days and those who underwent choledochoduodenostomy was 10.7 days, which was significant in our study ($p<0.001$).

Conclusion

In this study, both the surgical procedures did not produce any mortality. Some patients developed complications. This could be because much of the study population was elderly and most of the complications were noted in patient with acute cholangitis. In both the group, wound infection was noted to be most common complication. All of the patients treated conservatively successfully.

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Conflicts of Interest : Nil

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Review Article

Oral Manifestations of Chronic Renal Disease

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Chronic Renal Disease is a Global Health Problem which has multiple clinical features which are problematic to the patient, reduces their life expectancy and changes their way of living. It is mainly comprised of hematuria, proteinuria and progressive loss of kidney function. If it reaches end-stage that means there is 90% loss of the kidney function. At times, it also gives rise to oral manifestations which are misdiagnosed and as a result go untreated. This review article deals with the oral manifestations of Chronic Renal Disease so that proper awareness of this problem can be met among Dentists as well.

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Key words **: Chronic, Renal, Oral manifestations, Hematuria, Proteinuria.**

Chronic Kidney Disease (CKD) is a major health issue in today's time around the Globe. It is the 12th leading cause of death Globally and 17th leading cause of disability[1]. It is defined as "structural or functional abnormalities of the kidney, with or without decreased GFR, manifested by pathological abnormalities or markers of kidney damage, including abnormalities in the composition of the blood or urine or abnormalities in imaging tests[2]." As it progresses it can lead to gradual loss of kidney function which further gives rise to different conditions such as bony changes, altered immune status which can be of significance to every diagnostician.

Floege J, *et al* (2010) classified CKD (Table 1) on the basis of Glomerular Filtration Rate (GFR)[3]:

The end stage of CKD is End-Stage Renal Disease (ESRD). The main causes of ESRD are Diabetes Mellitus and Hypertension which themselves can cause problems of their own. The commonest cause of death in patients with ESRD is Cardiac failure, followed by infection and malignancy[4]. The analysis in 2017, suggests that prevalence of CKD globally was 9.1% (697.5 million cases). Nearly 1/3rd of all cases were in China (132.3 million) or India (115.1 million)[5].

The oral manifestations primarily include generalized pallor of oral mucosa, platelet alteration in such patients can lead to renal anaemia[6]. Due to platelet defects there may be formation of ecchymosis and petechiae. Xerostomia is also reported in such patients[7].

Editor's Comment :

- A health practitioner should have a understanding of the renal diseases and their manifestations to have an updated approach and dental treatment protocol against patients with CKD and put them into practice for the betterment of society.

Table 1 — Classification of CKD on basis of GFR

CKD Stage	Definition
1	Normal or Increased GFR, some evidence of kidney damage reflected by microalbuminuria, proteinuria and hematuria as well as radiologic or histologic changes
2	Mild decrease in GFR (89-60ml/min per 1.73m^2) with some evidence of kidney damage reflected by microalbuminuria, proteinuria and hematuria as well as radiologic or histologic changes
3 3A 3B	GFR 59-30 ml/min per 1.73m^2 GFR 59 to 45 ml/min per 1.73m^2 GFR 44 to 30 ml/min per 1.73m^2
4	GFR 29- 15 ml/min per 1.73m^2
5	GFR < 15 ml/min per 1.73m^2, when renal replacement therapy in the form of dialysis or transplantation has to be considered to sustain life
The suffix p has to be added to the stage in proteinuric patients (proteinuria > 0.6g/24h)	

These patients also have a characteristic smell in oral cavity known as "Uremic Fetor". There is also altered taste sensation due to high content of urea in the saliva[8].

Discussion

As far as oral cavity is concerned the renal diseases affect both the soft and hard tissues.

Soft Tissue :

One of the first symptoms that can be seen in the soft tissue is a generalized pallor of the oral mucosa.

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Advanced Renal Diseases can lead to anemia because of reduced erythropoietin, that's why the generalized pallor[7]. Chronic Renal Failure (CRF) can cause dry mouth as there is limited fluid intake in CRF, the adverse effect of the associated drugs and low salivary flow rate[8]. Another symptom which we see is 'uremic fetor' in the oral cavity which occurs due to conversion of urea (high concentration in the saliva) into Ammonia. Patients with CKD are hospitalized for a longer period of time which may result in more plaque accumulation in the patient and that lead to Gingiva inflammation. However, the signs of inflammation can be masked by the generalized mucosal pallor[9].

One of the most important manifestation of CKD is Uremic Stomatitis (Fig 1). This condition occurs secondary to uremia and is seen in patients with Advanced Renal Failure and Blood Urea Nitrogen (BUN) levels above 300 mg/ml[10].

It is of two types:

- Erythe-mopultaceous form
- Ulcerative form

The erythe-mopultaceous form is characterised by erythematous mucosa which is covered with a grayish pseudo membrane. The ulcerative form shows marked ulceration along with erythema. Painful lesions are also seen on the ventral surface of tongue. Uremic Stomatitis heals spontaneously once the causative uremia and elevated BUN levels are normalized[10].

Uremic Frost (Fig 2) are the white patches seen on skin and is caused due to formation of crystals of urea on the epithelial surface after sweating and evaporation of sweating. Theses patches can also be seen intra orally and that occurs after evaporation of saliva[11].

In patients who have undergone Renal Transplant are generally immuno- compromised. This condition can give rise to Oral Candidiasis. It may present as angular Cheilitis, erythematous, atrophic or pseudomembranous type. Even Herpes Simplex infection are also prevalent in patients with CKD[12].

In patients with CKD, gingival hyperplasia is also evident. This enlargement occurs secondary to usage of anti-hypertensive medications such as calcium-channel blockers (amlodipine, verapamil) and also due to immune- suppresive agents such as tacrolimus, which is given in patients with renal transplant[13].

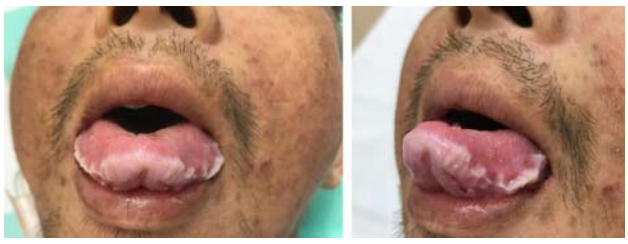


Fig 1 — Uremic Stomatitis

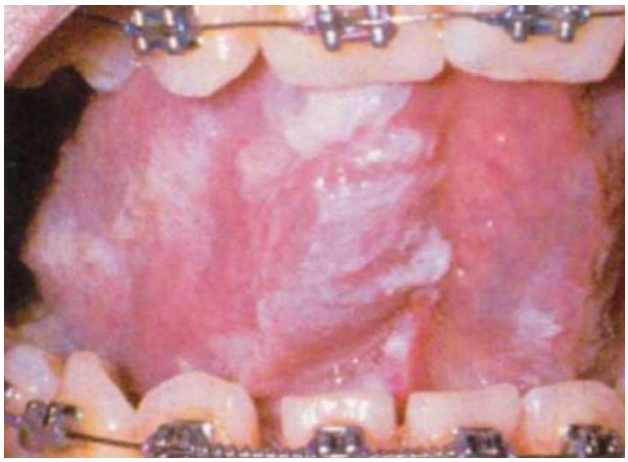


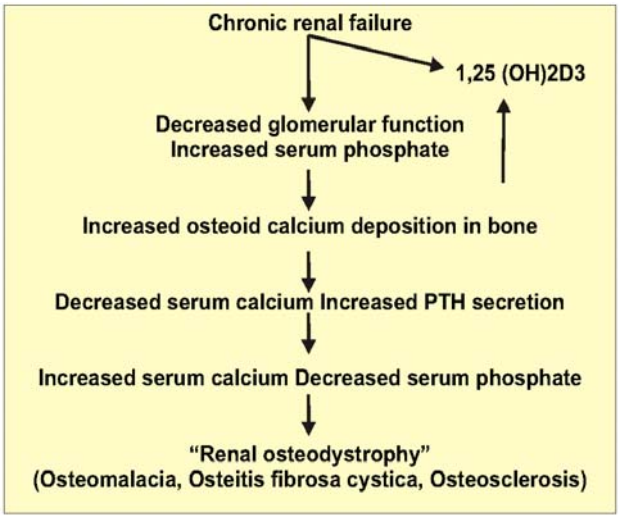
Fig 2 — Uremic Frost

Alteration in platelet function can lead to gingival bleeding, ecchymosis and petechiae.

Hard Tissue :

Chronic Renal Diseases (CRD) patients, both deciduous and permanent dentitions are affected. In deciduous dentition, it can cause problems in mineralization, histodifferentiation, etc. leading to enamel hypoplasia[14]. According to different studies, the range of enamel hypoplasia in children with CKD ranges from 31-83% depending upon nutritional, socio economic status and ethnicity of child's parents[15]. In deciduous teeth, the formation of enamel starts around 14th week of Intra-Uterine Life (IUL) and is completed by the end of 1st year of life. As a result, any kind of enamel defects in deciduous dentition indicates a pre or early post-natal damage affecting ameloblasts. In children with CRF during first month of infancy leads to defects in Vitamin D metabolism, Calcium and Phosphorus metabolism; which may result in enamel defects. Jaffe, *et al* (1990) and Martins, *et al* (2008) in their respective studies have reported delayed eruption of permanent teeth in children with CKD[9,16].

In cases of CRF, kidneys cannot convert Vitamin D to 1,25 dihydroxy cholecalciferol which is the active form. CRF also results in retention of Phosphate and all these things leads to decreased Serum Calcium level. The systemic manifestations of this whole process leads to Renal Osteodystrophy. Levels of fibroblast growth factor 23 (FGF-23), a key regulator of Phosphorus and Vitamin D metabolism, also increase and result in inhibition of osteoblast maturation and matrix mineralization. The progression of osseous changes is as follows: osteomalacia (increased unmineralized Osteoid Bone Matrix)



(Flowchart Showing Pathophysiology of Renal Osteodystrophy)[17]

followed by Osteitis Fibrosa (bone resorption with lytic lesions and marrow fibrosis) and finally, Osteosclerosis of variable degree (enhanced bone density)[17].

The Parathyroid Gland undergoes a compensatory hyperactivity leading to reduction in excretion of Calcium in urine, increased excretion of Phosphates and increased Calcium released from bone. Renal osteodystrophy leads to bone pain, fatigue, Osteomalacia. In the jaw region, the demineralization of the bone leads to reduction in trabeculation which ultimately leads to a radiographic"ground glass appearance" (Fig 3), a generalized loss of lamina dura, radiolucent Giant Cell lesions, enlargement of skull base[18]. It also leads to malocclusion, pulp stones, problem in healing after extraction, tooth mobility. Deciduous dentition may demonstrate brown discolouration due to underlying uremia[19].

Secondary to Renal Osteodystrophy, symmetrical non-painful enlargement of both the maxilla and mandible occurs. This distortion of the facial structure in human beings is secondary to renal secondary Hyperparathyroidism. This typical facial feature is called as uremic leontiasis ossea. This facial feature can be seen in patients of any age[20]. Patients with CKD also have an increased risk of caries formation which may be due to poor oral hygiene, xerostomia, carbohydrate rich diet (this diet is necessary to reduce the renal work load)[19].

Since gingival enlargement is a common finding in patients with CKD, it leads to more accumulation of plaque and calculus which ultimately leads to periodontal destruction.

Considerations in Dental Treatment :

Proper considerations has to be followed in the dental clinics while dealing with patients of CKD as in all those systemic diseases which has oral manifestations, the main goal should be to treat the primary disease and then the symptomatic treatment. Proper evaluation and risk assessment of the patient has to be done and always a medical opinion is must. Blood Pressure monitoring should also be done as hypertension is commonly present in patients with CKD, also before any invasive procedure screening for Bleeding Disorders should be done in patients with CKD as excessive bleeding is reported in patients with poorly controlled CKD. If the GFR rate is <50ml/min then dose adjustments of Analgesics and antibiotics has to be done. Analgesics like morphine and pethidine are dependent on renal function; while their alternatives like fentanyl, levomethadone are independent of renal function. Adjustments in the drug doses are considered in antimicrobials (eg. ampicillin, cefazoline), antivirals (eg. Acyclovir), chemotherapeutic and cytotoxic drugs. Patients with CRF are immunodeficient because of altered B-cell and T-cell activity. They present with several bacterial and fungal infection secondary to inability to produce sufficient antibodies and hence antibiotic prophylaxis before any dental treatment should be considered. If the patient is on hemodialysis; it's best to avoid giving appointment to the patient on the day of dialysis and it's better to treat the patient the day after the dialysis[17].

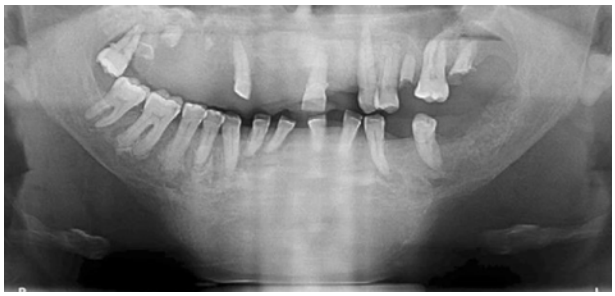


Fig 3 — Ground Glass Appearance Seen In Patients With CKD

Conclusion

CKD being one of the prime diseases in World today is a problematic venture for the patient. Through this review and different literature which is available, we have seen that it has numerous oral manifestations. As per oral diagnosticians, it is our prime duty that these manifestations don't get misdiagnosed. A proper diagnosis is the only way for a proper treatment plan.

Conflict of Interest :

There is no conflict of interest among the authors and this review has been written by the contributions of all of them.

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Review Article

Imaging in Tuberculosis

Bhoomi Angirish[1], Bhavin Jankharia[2]

Tuberculosis is a leading cause of mortality in our country. Our article highlights the imaging appearances of tuberculosis in various organs with emphasis on its pulmonary involvement. The spectrum of presentation of active and latent tuberculosis infection in the lungs is discussed. The commonly practised algorithms for diagnosis and follow up of tuberculosis in routine clinical practise are summarized. Tuberculosis in cardiac, central nervous system, musculoskeletal and gastrointestinal system is also discussed briefly.

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Key words **: Tuberculosis,**

Tuberculosis (TB) is a common health problem, particularly in our country. Although pulmonary involvement is the most common manifestation, tuberculosis can involve any of the organ systems. Timely diagnosis of the disease with the help of imaging can affect treatment decisions, such as the duration of therapy[1]. Early diagnosis promotes effective treatment and leads to reduced onward transmission of TB[2]. Chest radiographs are used to stratify for risk and to assess for asymptomatic active disease[1]. Though computed tomography scan is frequently employed in the diagnosis and follow-up of TB, it is not a part of the national and international guidelines[3].

Chest Tuberculosis :

It manifests in active and latent forms. Active disease occurs as primary tuberculosis - developing shortly after infection, or postprimary tuberculosis, developing after a long period of latent infection. Primary tuberculosis commonly presents with lymphadenopathy, pulmonary consolidation, and pleural effusion. Postprimary tuberculosis manifests with cavities, consolidations, and centrilobular nodules. Miliary tuberculosis refers to hematogenously disseminated disease that is more commonly seen in immunocompromised patients. Latent tuberculosis is an asymptomatic infection that can lead to postprimary tuberculosis in the future[1,3].

Primary Tuberculosis :

Parenchymal disease — Manifests as consolidation in a segmental or lobar distribution (Fig 1a). Cavitation occurs in a minority of patients with primary tuberculosis- 29% in one series and when cavitation occurs, it is known as progressive primary disease[1]. This cavitation occurs within existing consolidation and thus does not demonstrate an upper lung zone predominance, in contrast to postprimary disease. Resolution of pulmonary consolidation is slow and residual opacities are seen. After resolution, parenchymal scarring can be seen at sites of prior consolidation in 15%–18% of patients and is referred to as a Ghon focus, or Ghon tubercle[1].

Editor's Comment :

- Tuberculosis can involve any organ system and has a wide spectrum of presentation. Imaging plays a key role in the disease course from diagnosis to treatment response and follow up.

Lymphadenopathy — Lymph node and pleural involvement is part of extra-pulmonary tuberculosis (EPTB)[2]. Mediastinal and hilar lymphadenopathy is the most common radiologic manifestation of primary tuberculosis presenting as low attenuation central necrosis with peripheral enhancement on contrast CT scan (Fig 1b). Lymphadenopathy is a common manifestation of tuberculosis in pediatric population. At resolution of lymphadenopathy, calcified normal-sized lymph nodes may be seen[1].

Pleural Effusion — It is seen in approximately 25% of primary tuberculosis cases in adults and are predominantly unilateral. Tuberculous empyemas are loculated and associated with pleural thickening and enhancement (Fig 1c). Tuberculous empyemas may be complicated with bronchopleural fistula or extension into the chest wall (empyema necessitatis). An air-fluid level within an empyema in the absence of intervention is suggestive of a bronchopleural fistula. Residual pleural thickening with calcification can develop, potentially leading to fibrothorax as post treatment sequelae (Fig 1d)[1].

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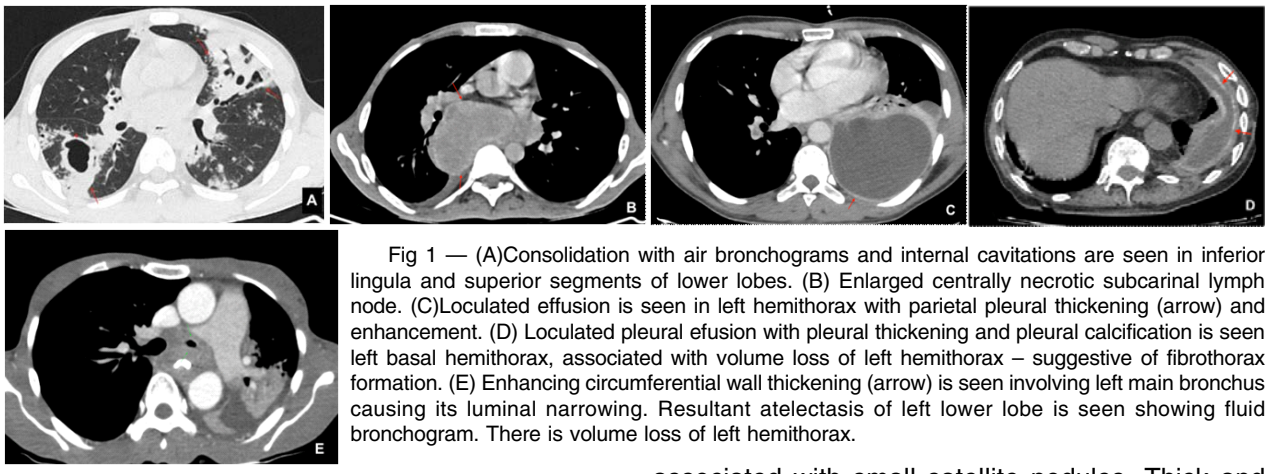

Fig 1 — (A)Consolidation with air bronchograms and internal cavitations are seen in inferior lingula and superior segments of lower lobes. (B) Enlarged centrally necrotic subcarinal lymph node. (C)Loculated effusion is seen in left hemithorax with parietal pleural thickening (arrow) and enhancement. (D) Loculated pleural efusion with pleural thickening and pleural calcification is seen left basal hemithorax, associated with volume loss of left hemithorax – suggestive of fibrothorax formation. (E) Enhancing circumferential wall thickening (arrow) is seen involving left main bronchus causing its luminal narrowing. Resultant atelectasis of left lower lobe is seen showing fluid bronchogram. There is volume loss of left hemithorax.

Airway Disease — Bronchial wall involvement may be seen in primary and postprimary tuberculosis. Bronchial stenosis occurs in 10%–40% of patients with active tuberculosis . The main radiographic features of proximal airway involvement include segmental or lobar atelectasis, lobar hyperinflation and postobstructive pneumonia. At CT, airway involvement can manifest as long segment narrowing with irregular wall thickening, luminal obstruction, and extrinsic compression (Fig 1e)[1].

Postprimary Tuberculosis :

Postprimary tuberculosis result from reactivation of dormant *M Tuberculosis* infection or may result from a second infection with a different strain.

Consolidation and Cavitation — Strong predilection for the apical and posterior segments of the upper lobes as well as the superior segments of the lower lobes in postprimary tuberculosis. In 3%-6% of cases, a noncalcified nodule known as a tuberculoma (ranging from 5 mm to 40 mm in dimension) may be the predominant manifestation associated with small satellite nodules. Thick and irregular walled cavities, often seen within an area of consolidation is a common finding in postprimary tuberculosis (Fig 2a)[1]. Residual cavities may persist after treatment, that predispose to bacterial superinfection, mycetoma formation, or erosion of adjacent vasculature resulting in hemoptysis[3].

Centrilobular Nodules — are seen due to endobronchial spread of infection. At CT, centrilobular nodules are seen in approximately 95% of cases of active tuberculosis, some showing tree-in-bud branching pattern (Fig 2b)[1].

Miliary Tuberculosis :

Hematogenous dissemination , especially in immunocompromised patients, results in miliary tuberculosis. Miliary disease may occur in primary or postprimary tuberculosis. It manifests as diffuse 1–3-mm nodules in a random distribution (Fig 2c)[1].

Imaging findings in sequelae of tuberculosis —

Inactive tuberculosis is characterized by stable fibronodular lesions, fibroatelectatic bands,

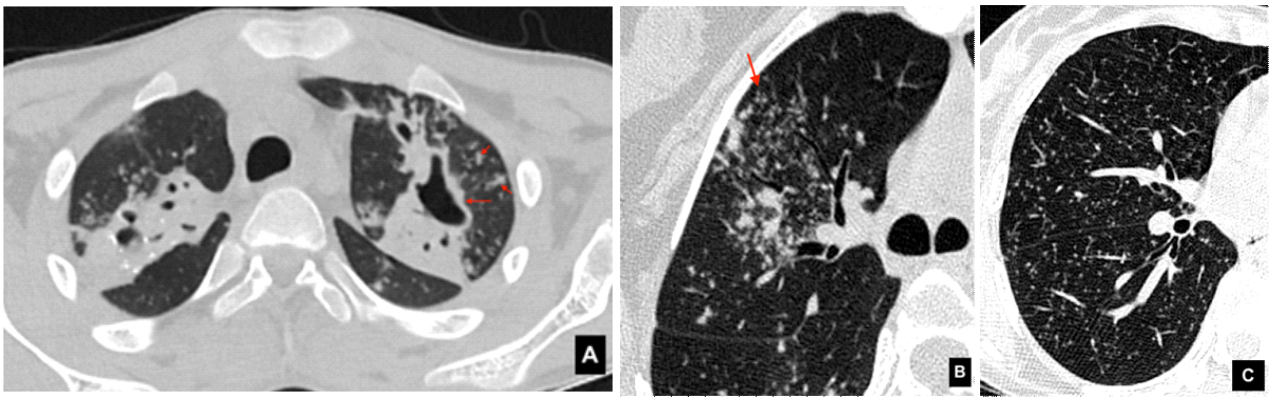

Fig 2 — (A) Consolidation with internal irregular cavity (arrow) is seen in apicoposterior segment of left upper lobe with surrounding discrete centrilobular nodules (short arrow) suggestive of reactivation of tuberculosis. Fibronodular and fibrobronchiectatic changes with calcification are seen in right upper lobe. (B) Multiple discrete centrilobular nodules are seen, some showing tree-in-bud branching pattern representing endobronchial spread of infection. (C) Widespread discrete 2-3 mm sized nodules are seen in random distribution pattern representing miliary tuberculosis.

peribronchial fibrosis, bronchiectasis and architectural distortion (Fig 3)[1]. Thin-walled cavities and well-defined nodules may persist for a long time after completion of antituberculous treatment. Tuberculomas and small calcified lung nodules also suggest prior infection. Calcified lymph nodes and pleural thickening (with/without calcification) are also imaging features of healed TB[3].

Persistent lesions at the end of anti-tuberculous treatment —

The activity of residual lesions needs to be resolved using imaging and/or laboratory parameters (Fig 4a). The residual inactive lesions, which are stable on follow up imaging, do not require further treatment. In case of partial or no response, ATT is prolonged as per guidelines. The persistent lesions may represent drug-resistant TB, in which case drug susceptibility testing is recommended. Appearance of new lesions may represent reactivation of tuberculosis. Stability of radiographic findings for 6 months distinguishes inactive from active disease[1].

Imaging algorithm for diagnosis of pulmonary tuberculosis —

As per the RNTCP guidelines, any person with cough for 2 or more weeks is a Pulmonary TB suspect. In addition to sputum smear examination, all such patients should be subjected to a CXR, wherever feasible.

If the radiographic findings suggest active TB (Fig 4b), ATT may be started in concordance with clinical scenario. In case the X-ray findings are equivocal and not specific for TB, confirmation with non-contrast or contrast enhanced CT scan is needed (preferably contrast enhanced).

If the CXR suggests healed TB, then comparison with prior imaging is required to document stability, failing the availability of previous imaging, a CT is usually done to confirm the absence of active infection.

Based on the CT scan findings, radiologist should categorize the patient into active, healed or indeterminate categories.

In case CT scan is indeterminate for disease activity, other parameters like BAL, lab parameters, or tissue sampling play an important role[3].

Protocol for follow-up of pulmonary tuberculosis —

Follow-up is done at the end of intensive phase/continuation phase (IP/CP). In case of no response to treatment, follow-up is repeated after extension of IP/CP as per the RNTCP guidelines.

(1) CXR is done at the completion of IP of the treatment regimen. If there is significant / near

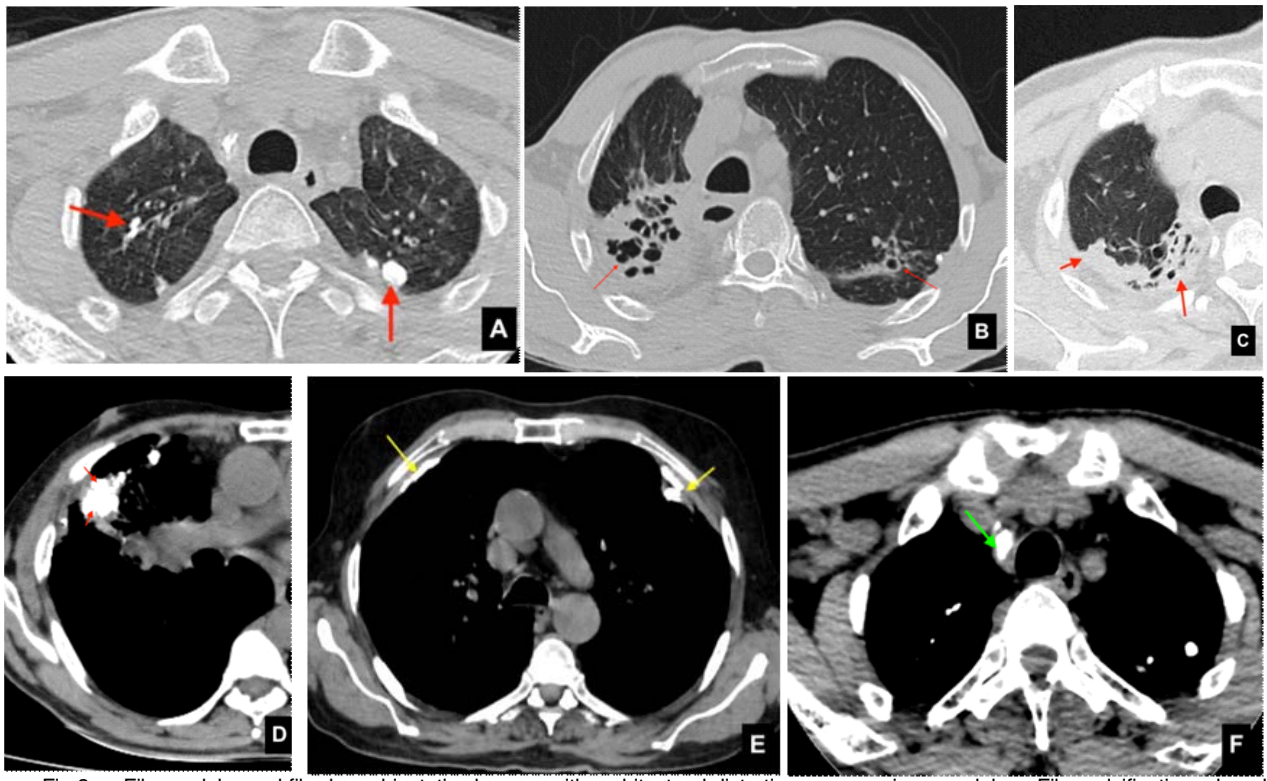

Fig 3 — Fibronodular and fibrobronchiectatic changes with architectural distortion are seen in upper lobes. Fibrocalcification, pleural thickening with calcification and calcified lymph nodes are also seen as sequelae of old tuberculous infection.

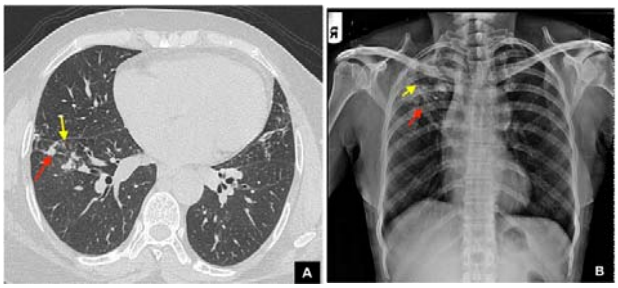

Fig 4 — (A) Fibronodular changes (red arrow) are seen in right lower lobe with surrounding discrete nodules (yellow arrow), the activity of the nodules cannot be decided in absence of previous imaging . Clinical workup and follow up CT scan after 3 months is indicated in such cases. (B) Consolidation with internal cavitation is seen in right upper zone. There is widening of bilateral paratracheal strip (due to mediastinal lymphadenopathy). These findings are in favour of active tuberculosis.

complete resolution of findings or CXR depicts only sequelae of prior infection, then no further imaging is needed at the end of treatment regimen, provided there is clinical improvement as well.

(2) If the CXR shows residual findings or is indeterminate and the patient is improving clinically, then a follow up CXR is recommended at the end of ATT course. The follow up CXR if shows findings as mentioned above, then ATT can be stopped. However, if the follow up CXR still shows residual findings, ATT maybe prolonged depending on clinical scenario.

(3) In case of no definite response on CXR and absence of clinical improvement, CT may be done to assess disease activity. Non-contrast CT is sufficient for follow-up of parenchymal lesions, but contrast administration is required for follow-up of nodal disease. ATT may be prolonged in case CT suggests residual active disease or if CT is indeterminate but clinical and laboratory parameters do not suggest any treatment response[3].

Apart from lungs, tuberculosis affects other organs presenting in various typical and atypical manifestations. A brief overview of extra-pulmonary tuberculosis is as mentioned below:

Cadiac Tuberculosis :

This accounts for only 0.5% cases of extrapulmonary tuberculosis. Pericardial involvement is more common than myocardial involvement.

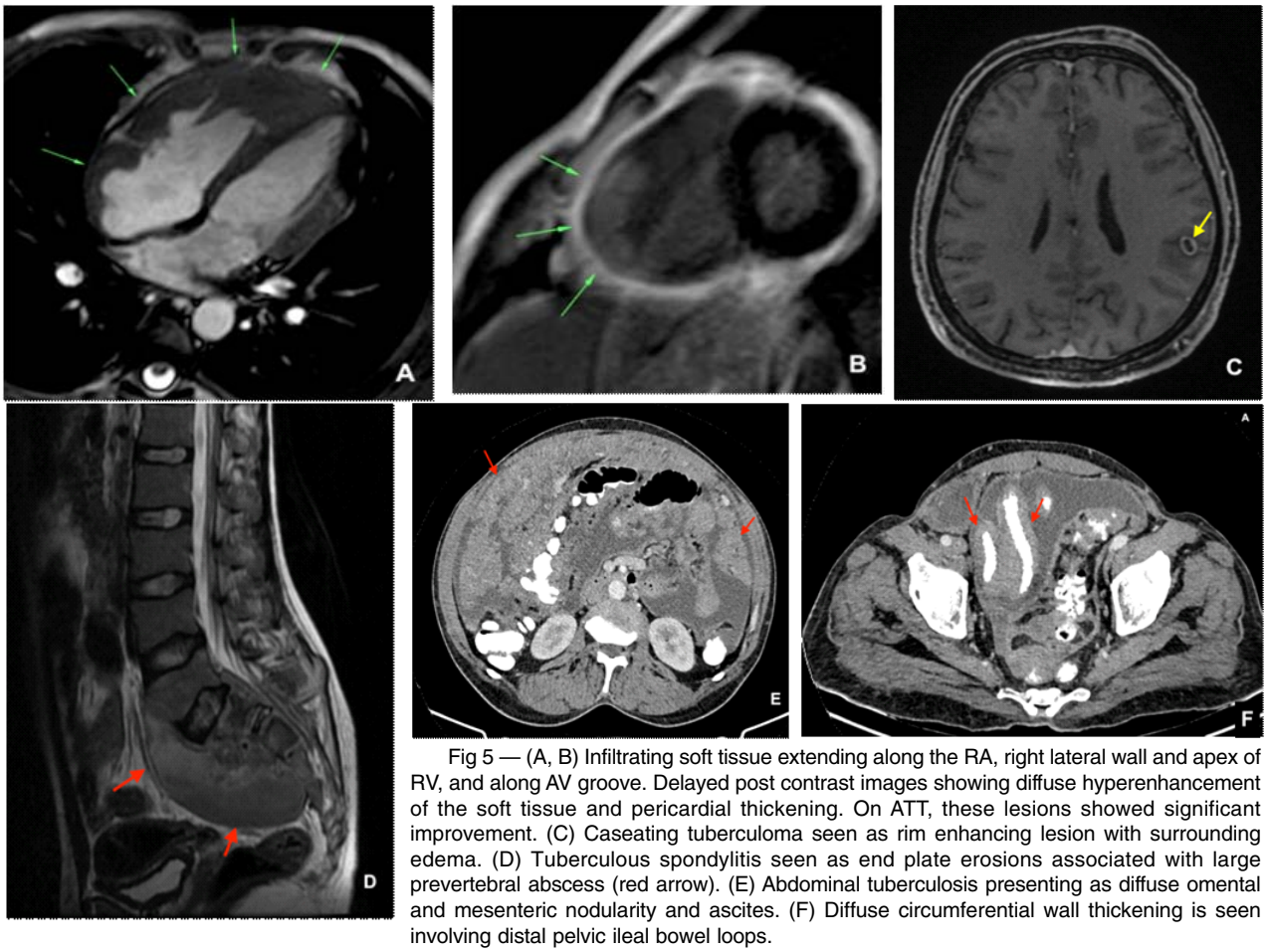

Fig 5 — (A, B) Infiltrating soft tissue extending along the RA, right lateral wall and apex of RV, and along AV groove. Delayed post contrast images showing diffuse hyperenhancement of the soft tissue and pericardial thickening. On ATT, these lesions showed significant improvement. (C) Caseating tuberculoma seen as rim enhancing lesion with surrounding edema. (D) Tuberculous spondylitis seen as end plate erosions associated with large prevertebral abscess (red arrow). (E) Abdominal tuberculosis presenting as diffuse omental and mesenteric nodularity and ascites. (F) Diffuse circumferential wall thickening is seen involving distal pelvic ileal bowel loops.

Tuberculous pericarditis presents as pericardial thickening of more than 3 mm, frequently associated with mediastinal lymphadenopathy. Tumefactive tubeculosis of myocardium (Fig 5a,b) presents as infiltrating masses which need to be differentiated from other lesions such as angiosarcoma and lymphoma[2].

CNS Tuberculosis :

CNS tuberculosis can manifest in a variety of forms, including tuberculous meningitis, tuberculomas, tuberculous abscesses, tuberculous cerebritis, and miliary tuberculosis. TB meningitis presents as abnormal meningeal enhacement (more marked in basal cisterns and within the sulci). The common complications are communicating hydrocephalus and ischemic infarcts.

A noncaseating tuberculoma is hypointense relative to gray matter on T1-weighted images and hyperintense on T2-weighted images, with homogeneous enhancement while caseating tuberculomas are isointense to hypointense on both T1- and T2-weighted, have a variable amount of surrounding edema and show rim enhancement on post contrast study (Fig 5c).

Head and Neck Tuberculosis :

Most commonly it presents as cervical lymphadenitis, initially homogeneous but later undergo central necrosis. These nodes may be difficult to differentiate from the necrotic nodes seen in metastatic head and neck squamous cell carcinomas. Nodal calcification often develops late in tuberculosis. Extranodal tuberculous disease in neck most commonly involves the larynx, temporal bone, and pharynx[2,4].

Musculoskeletal Tuberculosis :

Tuberculous spondylitis most commonly affects the lower thoracic and upper lumbar vertebrae. Infection usually begins in the anterior part of the vertebral body adjacent to the end plate with subsequent end plate erosion and involvement of intervertebral disc. There may be associated prevertebral, bilateral paravertebral and epidural abscess as well (Fig 5d). Psoas abscess are also commonly known to occur. If left untreated, the infection eventually results in vertebral collapse , anterior wedging, leading to kyphosis and gibbus formation. With healing, ankylosis of the vertebral bodies occurs, with obliteration of the intervening intervertebral disc[6].

Tuberculous osteomyelitis usually affects the metaphyses of involved bones. It presents as poorly defined lytic lesions with surrounding sclerosis and may be associated with abscess formation.

Tuberculous arthritis is characteristically a monoarthritis affecting large weight-bearing joints. It presents as osteopenia, synovitis, marginal erosions, and varying degrees of cartilage destruction. Joint space narrowing is usually delayed. The end result is usually fibrous ankylosis of the joint[2,6].

Abdominal Tuberculosis :

Abdomen is the most common site of extra-pulmonary tuberculosis. There is a varied presentation of abdominal tuberculosis dependenting on the organ of involvement. It may present as an isolated organ involvement or as a combination of findings.

Abdominal lymphadenopathy —

Abdominal lymphadenopathy is the most common manifestation of abdominal tuberculosis, presenting as enlargement of mesenteric and peripancreatic lymph nodes. The enlarged lymph nodes show homogeneous attenuation or are centrally necrotic. Calcifed mesenteric lymph nodes are seen in healed stage of disease.

Tuberculous peritonitis —

Wet type peritonitis is the most common presentation, seen as free or locualted ascites. Fibrotic peritonitis presents as omental and mesenteric cake-like masses with matted bowel loops. Peritoneal thickening and fibrous adhesions are also seen (Fig 5e).

Gastrointestinal tuberculosis —

The most common imaging finding is concentric mural thickening showing enhancement. Ileo-cecal junction is commonly involved. Skip areas of concentric mural thickening with associated luminal narrowing with or without proximal dilatation can also occur elsewhere in the small bowel (Fig 5f).

Hepatosplenic and adrenal tuberculosis —

Hepatosplenic tuberculosis is common in patients with disseminated disease and presents as innumberable 0.5-2.0 mm nodules, often not detected at CT scan and appear hypointense on MRI images. The CT signs of active tuberculous involvement of adrenals are bilateral enlarged glands associated with large, necrotic areas, with or without calcification.

Genitourinary tuberculosis —

Renal tuberculous involvement presents as “moth-eaten” calyx which progresses to papillary necrosis. Dilated calices may be due to infundibular stricture within the collecting system. Calcifications in a lobar distribution are often seen in end-stage tuberculosis.

Ureteric tuberculosis is characterized by a thickened ureteric wall and strictures. Urinary bladder tuberculosis commonly manifests as reduced bladder volume with wall thickening, ulceration, and filling

defects due to granulomatous material.

Genital tuberculosis involves the fallopian tubes in women usually causing bilateral salpingitis with obstruction and multiple constrictions of the fallopian tubes and endometrial adhesions or deformity of the cavity.

Summary :

Imaging plays an important role in the diagnosis and follow up of tuberculosis. Categorisation into active, healed and indeterminate disease activity can be confidently done with imaging. Good response to anti-tuberculous treatment and suspicion of drug- resistant tuberculosis can also be commented upon with the help of follow up scans, which affects treatment regimen and duration. Radiological modalities go hand in hand with clinical and pathological workup for evaluation of tuberculosis, however there are no imaging guidelines for the diagnosis and follow up of such cases.

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Case Report

Two Cases of Secondary Hypertension with Rare Aetiology

Arnab Bhattacharyya[1], Tapan Haldar[2], Jyotirmoy Pal[3]

Secondary Hypertension comprises approximately 5% of Systemic Hypertension[1]. Renal parenchymal, Renovascular and Endocrine Diseases are amongst the common causes of Secondary Hypertension. Takayasu's Arteritis is a rare form of Primary Systemic Vasculitis that appears to be commoner in Asia than Europe or North America[2] and in contrast to Japanese patients, who have a higher incidence of aortic arch involvement, the series from India reports higher incidences of thoracic and abdominal involvement. In general, patients from Indian subcontinent tend to have greater prevalence of Pan-aortic Disease (both above and below the diaphragm) when compared with the west. In India the women : men ratio is around 1.5:1. Takayasu's Arteritis most frequently affects young women[3]. Therapeutic intervention like Percutaneous Transluminal Angioplasty (PTA) and Stenting, By-pass Surgeries or surgical reconstruction should be performed when disease is made inactive by the use of effective immunosuppressive Therapy[4].

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Key words **: Takayasu's Arteritis (TA), Descending Thoracic Aorta (DTA), Diethylenetriaminepentacetate (DTPA).**

Case 1

A twenty three year old female presented with occasional attacks of Malaise, Fatigue, Palpitation, Headache for about six months duration. There was no history of fever, joint pain, seizures, blurring of vision or history suggestive of limb claudication, or weight loss / chest pain. Her menstrual cycles were normal and she had no addiction and there was no significant past history. Her father is diabetic.

Examination — She was found to be hypertensive with Blood Pressure (BP) - Right / Upper Limb (UL)-160/92, Left/UL-158/94, Rt/Lower Limb (LL)-120/90 and Lt/LL -134/90, pulse 98 per minute regular. Carotid, brachial, radial pulses were well palpable but femoral, popliteal, posterior tibial and arteria dorsalis pedis were less palpable. No carotid /subclavian/abdominal bruit. CVS- S_1, S_2(normally audible), no murmur, no added sound; chest- Nothing Abnormal Detected (NAD), abdomen – NAD, CNS - NAD.

Investigations — Hb-11.7gm%, ESR-09mm, TWBC-6500/cumm, CRP-0.59mg/l (<6), K^+- 4.4mmol/l, USG of whole abdomen – NAD, Cr-0.77mg%, Glucose (fasting)-84mg/dl, LFT-WNL, TSH-1.59, HB_SAg-negative, ECG-sinus tachycardia, ECHO-NAD, LVEF-68%.

She was put on anti-hypertensives (diuretics, amlodipine, beta-blockers). But her BP was not controlled. So Renal Artery Doppler was done which showed increase AT in Bilateral Renal Arteries and Interlobar Arteries with concentric wall thickening of aorta with focal stenosis involving supracoeliac part. CT Angiography of aorta (Fig 1) showed – Long segment (about 8.5cm in length

Editor's Comment :

- Diagnosis of TA is often delayed and so there must be high index of suspicion for young female patients of Indian origin suffering from hypertension — so, as to treat them early with medical and surgical intervention.

Fig 1 — CT Angiography of aorta

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with inferior extent 4cm above the coeliac trunk) moderate stenosis of thoraco- abdominal aorta, -features likely to suggest TA-there was also mild stenosis at the origin of coeliac trunk. Aortic root, ascending aorta (max. diam. of 27mm), aortic arch and its branches (no plaque/ stenosis), Bilateral Renal Arteries, Superior and Inferior mesenteric arteries and infrarenal and juxtarenal abdominal aorta appear normal, with normal aortic bifurcation.

Visualised illiac arteries appear normal. On conventional Angiography all are normal except long segment stenosis of maximum 70% severity of Descending Thoracic Aorta (DTA) and coeliac ostial discrete lesion of 90%.

Final diagnosis — Takayasu's Arteritis type-III.

Patient was put on immunosuppressants first, followed by, Angiography and Stenting. After Stenting of DTA – BP was better controlled with lesser dose of anti-hypertensives.

Case 2

A twenty five year old female was incidentally detected to have hypertension during pre-anaesthatic check up for a sialoadenoscopic evaluation for her right submandibular duct stone. There was no history of headache, palpitation, abdominal pain, vomiting, fever, joint pain, muscle pain, convulsion, blurring of vision, weakness of limbs, weight loss, limb claudication and chest pain. She had no addiction. Her menstrual cycles were regular. There was no significant Family history or past history.

Examination — Mild pallor was there but there was no cyanosis, no clubbing, no pedal oedema and JVP was not raised. BP was – (Rt/UL-164/90), (Lt/UL-160/94), (Rt/LL-154/90), (Lt/LL-150/92); PULSE – 96/min, equally palpable in all four limbs. Both carotids are equally palpable. There was no carotid/subclavian/abdominal bruit. Chest-NAD, CVS-S_1, S_2 (normally audible), no murmur, no added sound; CNS-NAD, abdomen-no ascites or organomegaly.

Investigations — Hb-9.2gm%, ESR-102mm, TWBC-7720/cumm. DC- normal, CRP-7.2mg/l (<6) , Na^+-141, K^+-4.2 , Cr-0.82mg%, SGPT-10units/l, ECG- Within Normal Limits (WNL), ECHO-NAD.

Renal Artery Doppler —There was intimal thickening of aorta, extending into the origin of Left Renal Artery, leading to luminal stenosis. Right renal artery appears normal. Impression-left proximal renal artery stenosis. CT Angiogram of Abdominal Aorta (Fig 2) -small left kidney (72mm), large right kidney (108mm), there was tight stenosis (99%) of proximal left renal artery including ostium with post stenotic dialatation and poor opacification of left kidney, mild narrowing of right renal artery sparing ostium. There was also concentric wall thickening of aorta causing mild narrowing with involment of superior mesenteric artery.

MR Angiogram — Vertex to toe-all vessels were normal except in the perirenal aorta there was uniform

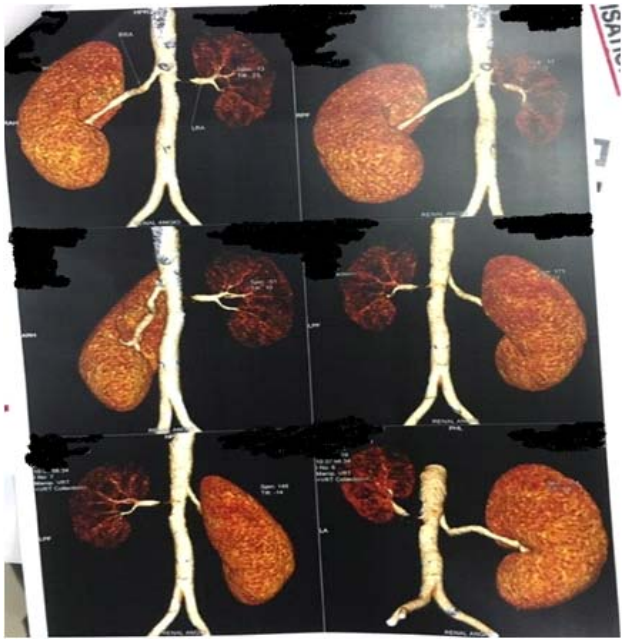

Fig 2 — CT Angiogram of abdominal aorta

circumferential thickening with mid segment narrowing (30%) of Right Renal Artery and Left Renal Artery showed tight stenosis at its origin. Left kidney was reduced in size. Visualised Pulmonary arteries appeared normal. Impression-Takayasu's arteritis-type-IV. Diethylenetriaminepentacetate (DTPA) Renal scan-relative function-left kidney (22%), right kidney (78%). DTPA clearance –left kidney (18 ml), right kidney (61ml). Left kidney was contracted-severely impaired perfusion and parenchymal function; right kidney-good parenchymal function and drainage. Patient was put on anti-hypertensives (amlodipine+metoprolol), immune suppressants (deflazacort + mycophenolate mofetil+ tocilizumab), followed by Angiography and stenting of Left Renal Artery.

Final diagnosis — Takayasu's Arteritis type-IV with Left Renal Artery Stenosis. After Renal Artery Stenting her blood pressure is now normal without any anti-hypertensive medication.

Discussion

TA is more commonly seen in women[5] than men in India and Asia. In clinical practice the diagnosis of TA is almost always secured by an imaging procedure[6] that demonstrates the characteristic abnormalities of the aorta and its major branches. Unfortunately the diagnosis of TA is often delayed. Many of these delays can be prevented by remembering that TA should be included in the differential diagnosis of any person younger than 40 years, who present with FUO, aortic regurgitation, hypertension or unequal or absent pulses. Once an imaging test demonstrates disease of the aorta or its major branches, the differential diagnosis narrows to a set of disorders that are usually differentiated by their

clinical features and other investigations. Most rheumatic diseases that can affect the aorta are distinguished by their associated features. For example, Cogan's syndrome typicaly produces ocular inflammation (especially Keratitis) and vestibuloauditory dysfunction . Giant Cell Arteritis (GCA) can be distinguished from TA by its age range (50years or more – average age of onset – 72 years), visual loss (10%-30%) and less involvement of aorta (25% in GCA whereas 100% in TA)[7]. Infection of the aorta is rare. Tertiary Syphilis can be excluded by a negative fluroscent treponemal antibody test. Other diseases of the aorta are usually readily seperated from TA by the history and physical examination. There has been much speculation about the role of Mycobacterium Tuberculosis in the aetiologies of TA, especially in India[8]. It remains possible that this is simply coincidence of a common infection with a rare vasculitis. In India Numano Types IV and V are most frequent.

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Case Report

Hypokalemic Rhabdomyolysis — A Rare Presentation

Praveen Kumar Yadav[1], Snigdhendhu Ghosh[2]

Hypokalemia leading to Rhabdomyolysis is a potentially fatal disorder if not identified and treated early. In this case report we present a patient who had one week history of asymmetric painful Quadriparesis with neck drop and preserved reflexes. Evaluation revealed Hypokalemia with raised creatine.

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Key words **: Hypokalemia, Rhabdomyolysis, Quadriparesis, Neck drop.**

Hypokalemia is a common condition seen in clinical practice however, persistent asymmetric weakness, neck drop and Rhabdomyolysis is an uncommon feature of Hypokalemic muscle weakness. We present a patient with these uncommon manifestations in this case report.

Case Report

A 48-year-old hypertensive male on presented with history of weakness of both lower limbs leading to difficulty in walking since last four days. He also had weakness of right hand and difficulty in holding neck erect due to neck muscle weakness since one day. He also complained of pain in the proximal arm and lower limbs since two days.

Examination — His vitals were stable. His higher mental functions were normal. He had neck extension weakness with neck drop. Cranial Nerve Examination showed normal fundus, no ptosis, normal extraoccular movements, no facial muscle or bulbar weakness. Upper limb examination revealed normal tone with no wasting and asymmetric weakness, Right upper limb had grade 2 power proximally and grade 4 power distally. Both lower limbs had grade 3 power proximally and grade 4 power distally. Reflexes were well ellicitable. Plantars were flexor. His single breath count was 25 and respiratory rate was 15 with no Orthopnea. Other system examination were normal. The possibilities considered were Acute Neuropathy like Guillain Barry Syndrome, Neuromuscular Junction disorders like Myasthenia gravis, Hypokalemia related weakness. In view of asymmetric weakness a cervical cord pathology was also kept in the differential diagnosis. However, the absence of sensory symptoms and absent upper motor signs were against this localization and diagnosis. Patient was evaluated with Routine Blood Counts, Renal, Liver Function and Thyroid Function Tests were normal. His sodium was 145 mmol/L and potassium was 2.1 mmol/L. Arterial blood gas analysis showed PH-7.471, Pco2-45.6mmg, Po2-92 mm Hg, bicarbonate of HCO3-30.8 mmol/L. ECG showed presence of U waves. Patient was also evaluated with nerve conduction studies and repetitive nerve stimulation test which were normal. His S Creatine Kinase (CPK) was 7500 U/L (39-308). Work up for cause of hypokalemia was done. Spot urinary sodium was 89mmol/L(40-220), Urine potassium was 4.6 mmol/L(25-125), Urine chloride 84mmol/L(18-209). His serum aldosterone levels were normal and the renin to aldosterone ratio was found to be normal. Viral serology for HIV, HBsAG and HCV was normal. SARS-COV2 PCR was negative. His urine myoglobin was postitive however, there was no high coloured urine.

There was no past history or family history of episodic weakness. There was no history of muscle pain or cramps in the past. No history of any diuretic intake or use of medications precipitating Hypokalemia or muscle damage. No history of Renal diseases, Diarrhea or vomiting. No history of any Sicca symptoms, joint pain, raynauds, arthritis or oral ulcers.

Patient was started on intravenous correction of potassium with regular serum potassium monitoring. There was quick recovery of weakness and muscle pain resolved within two days. His neck weakness and limb weakness improved dramatically. His repeat Creatine Phospho Kinase (PK) also had a decreasing trend over one week. He was discharged from hospital after he became asymptomatic. Thus the final diagnosis of Hypokalemic Muscle weakness and Rhabdomyolysis was considered.

Editor's Comment :

- Hypokalemia is a very important and reversible cause of flaccid limb weakness and neck drop. Rarely it can lead to complications like rhabdomyolysis. Early detection and treatment can give good outcomes.

Discussion

Rhabdomyolysis is a condition in which there is severe muscle pain and weakness which leads to

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release on toxic intracellular products like Myoglobin, Creatine Kinase[1-3]. It presents with the key features of muscle rigidity, muscle pain and high coloured urine[4]. There are many causes of rhabdomyolysis like trauma, direct compression, non traumatic events like seizures, heat stroke, extreme muscle exertion, medications, toxins, Infections, endocrine disorder mediated, Insect bites and dyselectrolemias. Hypokalemia however, is a rare cause of this fatal condition. Hypokalemia is a very common medical condition however it leads to Rhabdomyolysis very rarerly[5,6]. The postulated mechanism of this condition is the muscle ischemia related to hypokalemia which in turn leads to changes in permeability of the Sarcolemma[7].

Rhabdomyolysis may be complicated with Acute Renal Failure in 4-33% of the cases and it does not correlate with the serum CPK (Creatine Phosphokinase) levels. Myoglobinuria is not seen in all the cases and is not essential for diagnosis of this condition[8].

In our patient the asymmetric weakness of limbs and neck drop was very atypical. Patients weakness was probably related to Hypokalemia and the muscle pain was due to Rhabdomyolysis.

Conclusion

This is a potentially treatable and reversible condition if diagnosed early. Delay in diagnosis can lead to life threatening complications like Acute Renal Failure and cardiac dysrythmias and disseminated intravascular coagulopathy. Neck drop should make us suspect hypokalemia weakness apart from the other causes of neck weakness like myasthenia gravis, polymyositis and anterior horn cell disease

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Corrigendum

The Editor's Comments of the article "Intracranial Calcification in a Case of Seizure Disorder", JIMA, January, 2022, pp 50 should be read as “Idiopathic Intracranial Calcification should be considered as an important, albeit rare differential in a patient with seizures when no other apparent secondary cause can be as certained."

— Hony Editor

Special Correspondence

Strike Omicron before you Captures It !

M V Raghavendra Rao[1], Dilip Mathai[2], Vijay Kumar Chennamchetty[3], V Raghunandan Reddy[4], Manick Dass[5]

Omicron is currently shaking the world to its core. The disease is mainly transmitted via the respiratory route when people inhale droplets and small airborne particles (that form an aerosol) that infected people exhale as they breathe, talk, cough, sneeze, or sing. "UK becomes first country in Europe to pass 1,50,000 COVID deaths Omicron clouds forecasts for Covid end game.Omicron is a variant of nSARS-CoV-2 that has been identified initially in COVID-19 patients in Botswana and South Africa. The chief of the World Health Organization (WHO), Tedros Adhanom Ghebreyesus, has said that the combination of Delta and Omicron variants of coronavirus is driving a tsunami of COVID-19 cases. The statement came as record new cases were reported from the United States and countries across Europe. France recorded the highest ever daily numbers in Europe for the second consecutive day, at 208,000 new cases.Vaccines offer strong protection from serious illness.

[*J Indian Med Assoc* 2022; **120(7):** 56-60]

Key words **: Deltacron, National Institute of Infectious Diseases (NIID), Tocilizumab (TCZ), Tocilizumab (TCZ), Itolizumab, Nucleic Acid Amplification Test (NAAT) - Astra Zeneca, Moderna.**

The pandemic impacted global health for many other conditions. Hospital visits fell.SARS-CoV-2 is a newly discovered virus that is closely related to bat coronaviruses.Several variants have been named by WHO and labelled as a Variant of Concern (VoC) or a Variant of Interest (VoI). They share the more infectious D614G mutation

New threat in coming days

Genome progression of Omicron variant

The Omicron variant was sequenced from a viral isolate collected from Gauteng, South Africa in early November 2021 (The variants were named by WHO according to the letter order of the Greek alphabet.

U S-Epsilon (B1.249, B1.427 (March 2021) Iota (B 1.526) (March 2021)

Peru (C 37)-(Lambda)

Columbia-August-2021(B1.621 (Mu)

Brazil—(March 2021) (P2) (Zeta) (January 2021) (P.1) (Gamma)

U K (Alpha) (B.1.1.7) (December 2021)

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Editor's Comment :

- Omicron illness has affected several million patients in all age groups throughout the world.Omicron is a blessing in disguise variant that causes mild infections like common cold with rapid spread and is an indication for the end of Pandemic. The WHO experts are satisfied the new omicron variant is superior to mild. Vaccines are a powerful weapon to fight against Covid.

UK and other countries - (Eta) (B.1.525) (March 2021)

South Africa (December-2020) (B.1351) (Beta)

November (B.1.1.529) Omicron (Botswana and other countries)

April 2021) (B.1.6171) (Kappa) (March 2021) (B.1.617.2) (Delta) (India)

Philippines (Theta) (P3) (March 2021)

Deltacron'—Cyprus—January—2022

G. A new Covid-19 variant——Marseilli-France

Something to be worried about at the moment, a media report said.Kostrikis also emphasized that the variant has a similar genetic background to the Delta variant, as well as some of the mutations from Omicron. As on 10/January/2022,25 cases of Deltacrons were detected.

Variant of Concern :

According toa PIB press release published on 9/1/2022,1.79 lack new cases were recorded in just 24 hours.

It should have the following conditions

(1) Transmission is very high

(2) Severity of illness is very high

(3) Efficacy of drug is low

(4) Decrease efficacy of vaccine

Scientists race to work out how dangerous is the variant :

Omicron is now found in two dozen countries.

In US 10 lack cases recorded on 4/1/2022

As the COVID surge continues in India, AIIMS chief DrRandeepGuleria has told The Indian Express that the Omicron variant mainly affects the upper respiratory tract and airways, and people without comorbidities should not panic and should not block the hospital beds.He emphasized that the focus should be on home isolation as the recovery time for the new variant is much faster. Omicron now is fueling a rise in cases again, and the country in January will roll out vaccine boosters for frontline workers.

Clinical Symptoms :

Omicron is a blessing in disguise variant that causes mild infections like common cold with rapid spread and is an indication for the end of Pandemic. The WHO experts are satisfied the new omicron variant is superior to mild. Patients experience a severe headache, nausea, dizziness and high pulse rate, according to hospitals and medics across South Africa.

Immunity :

Memory B cells are one of those layers, cells that live for years in the bone marrow, ready to swing into action and produce more antibodies when needed. But first those memory cells get trained in immune system boot camps called germinal centers, learning to do more than just make copies of their original antibodies.

In a new study, Ellebedy's team found Pfizer vaccinations rev up "T helper cells" that act as the drill sergeant in those training camps, driving production of more diverse and stronger antibodies that may work even if the virus changes again **(Hindustan times, January, 2022).**

The immunity after COVID-19 infection or after vaccination lasts for about nine months, said the director general of Indian Council of Medical Research (ICMR), DrBalram Bhargava, as he cited evidence from several global and Indian studies.Dr Bhargava said that evidence also indicates that a strong response was mounted through hybrid immunity which developed among people who were vaccinated after recovering from natural COVID-19 infection.

The immunity confirmed by COVID-19 vaccine particularly to prevent infections falls over time.Common cold protects against covid.People with higher levels of T cells common cold corona viruses are less likely infected.

Mutations :
Omicron from mice

Mutations are not found in Alfa, beta gamma,and delta.B1.1 variant show highest sequence similarities to omicron.Normal rate of mutations in spike protein RNA is 0.45 mutations /month.During missing time for omicron 27mutations accumulated in spike protein RNA during 18months.3.3 faster than average rate of other mutations.Omicron has criptically spread.and circulated in population.Second hypothesis is omicron could have evolved in a chronically infected Covid-19 patients.The third hypothesis is omicron could have accumulated mutations from non-human host and jumped into human.

New Coronavirus Variant Identified In France, May Have 46 Mutations :

Amid the surge of Omicron variant of SARS-CoV-2 across the globe, scientists have now identified a new strain of the virus in Southern France.Named as IHU, the B.1.640.2 variant has been identified by researchers at institute IHU Mediterranee Infection in close to 12 cases. The variant has been linked to travel to the African country Cameroon.

Thousands of schools in the United States postponed the scheduled school openings this week after the holiday break or switched to online learning as the Omicron variant continued to surge.In other school districts, officials pressed on with reopening plans, including in New York City, where one in every three COVID-19 tests over the last week returned positive. According to the Mayo Clinic, on average 18% of tests are returning positive across the country.New York City Mayor Eric Adams intended.

As India witnesses a third COVID wave, a large proportion of Omicron cases have been reported from big cities, stated the head of India's vaccine task force, Dr NK Arora.Dr Arora said that big cities like Mumbai, Delhi and Kolkata together have a 75% share of infections due to the Omicron variant.

"Could Natural COVID Immunity be better than Vaccinated Immunity?"

The Omicron variant is nearly 3 to 4 times more infectious than the Delta variant among vaccinated persons if a household member becomes infected, suggests a preprint study from Denmark. The booster vaccinated persons are less likely to spread the infection.The transmission of the Omicron variant in households was investigated, which covered 11,937 households

"Beat Omicron Before You Catch It !"

Omicron is now circulating widely in many countries quickly taking over from Delta.It has

doubling time of only three days which means cases double every three days.It will soon become a dominant variant around the world.This virus can jump from human to animals and back.Omicron shows common symptoms like runny nose,headache,fatigue,sore throat and sneezing.

Monoclonal antibodies :

Monoclonal antibodies are usually produced in an animal in response to a simple antigen are heterogeneous as they are synthesized by several different clones of cells ie, they are polyclonal. Antibody produced by single antibody forming cell or clone directed against single antigen or antigenic determinant is called monoclonal antibody.

Spike proteins of the virus have access with ACE-2 receptors. The purpose of MAB is to lock off spike proteins, and prevent the entry of virus into the cell. These are the neutralizing antibodies. Infusion of MAB medicines prevent hospitalization.

Tocilizumab (TCZ) is a humanized IgG1 recombinant monoclonal antibody used for the treatment of cytokine release syndrome (CRS) associated with rheumatologically conditions and was postulated to have some role in patients with a severe or life-threatening COVID-19 disease.

Itolizumab is a recombinant monoclonal antibody against CD6 (Cluster of Differentiation 6) of IgG1 (Immunoglobulin G1). Based on the mode of action, it has been used as treatment option for COVID-19 infection. However, moreclinical data is awaited to establish its role in severe COVID-19.

Immunosuppressants which are under trial include Anakinra (AKR) which acts on endogenous elevated IL-1 levels in patients with COVID-19. Baricitinib is a selective inhibitor of Janus Kinase (JAK)1 and 2.

Ancient science needs to be put into modern tests

Direct—

(1) Antigen detection

(2) RTPCR (Reverse Transcriptase Polymerase Chain Reaction)

(3) Truenat

(4) Gene Xpert - Cartridge based nucleic acid testing (CBNAT)

Indirect :

Antibody detection— Not recommended for diagnosis. Useful for seroprevalence estimation

Saliva swabs detected Omicron variant more accurately compared to the nasal swabs, according to a study from South Africa, published as a preprint on medRxiv.1 In this study, researchers from the University of Cape Town enrolled 382 acutely symptomatic, non-hospitalized patients who came for Covid-19 test. The data was collected between August and December 2021. Nasal (mid-turbinate) and saliva swabs were collected for RT PCR testin

RT-PCR based Assay for screening of Omicron variant (B1.1.529.1) of SARS-COV-2 developed at IIT Delhi. Currently, the identification or screening for Omicron is done world-wide using next generation sequencing based methods, which require over three days. By using this RT-PCR based assay, it will be possible to test for the presence of Omicron variant within 90 minutes.

Bharat Biotechnology Research Centre (GBRC) has developed a PCR based method to detect the Omicron variant of SARS-Co2 within 8 hours Whole genome sequencing can otherwise take up to 72 hours. Constant RT-PCR.

Research did at Imperial College London, UK propose that long COVID-19 could before long be analyzed by a straightforward blood test.

Nearly 80% COVID positive samples sent to genome sequencing laboratories in Calcutta have been found to contain the BA-2 sub lineage of Omicron variant nick named the "Stealth version"as it cannot be detected by RT-PCR tests. Interestingly almost all these found infected with BA.2 , had no immediate history of foreign travel :The sub lineage B.1 has detected in those travelled abroad in the recent past said a senior health official. From the original B.1.1.529,first detected in South Africa. Omicron now split into three types. BA.1,BA.and BA.3.BA.3 isnot identified in India.InMaharasrra BA.1 is dominately circulating.BA.2 cannot be identified in the primers of RT- PCR test.

Break through treatments

It was the initiator in human history where a clinical identification was executed very early in the case of a pandemic. Several antiviral drugs, anti-inflammatory agents, immune modulators, and vitamins were used to control COVID19 disease.

The anti-inflammatory drugs and immune regulator agents are advantageous in lessening the effect of the cytokine storm. Corona drugs are doubtful for the Omicron variant.

Covid Vaccines

- 'GERMAN–US' vaccine: Pfizer-BioNTech; BNT162b2; New messenger RNA (mRNA) platform
- 'US' vaccine: Moderna; mRNA-1273 for spike protein; New messenger RNA (mRNA) platform.
- 'British' vaccine: Oxford-AstraZeneca; ChAdOx1 nCoV19 / Covishield; Traditional inactivated virus platform
- 'Russian' vaccine: Gamaleya Institute; Sputnik V

'Indian' vaccine: Bharat Biotech, Hyderabad / ICMR's National Institute of Virology, Pune; Covaxin;

Booster dose trial

Sub group immunogenicity, analysis by age for anti-spike IgG and cellular response at 28 days post third dose between study vaccines and controls for the Ch/ Ad,Ch/Ad-primed population.

Omicron can evade protection offered by vaccines, antibody treatment: Study

Omicron can evade the protection offered by COVID-19 vaccines and natural infection, according to a peer-reviewed study, published in the journal Nature. The variant is also resistant to the antibody treatments currently being used, noted the study.The study assessed the potential of antibodies evoked by vaccination to neutralize the Omicron variant in lab tests.

Multivitamins, paracetamol only treatment given to Omicron patients at hospital in Delhi

26th December 2021 Pathology & Lab Medicine Pulmonary Medicine

Omicron patients at Delhi's LokNayak hospital have been given only multivitamins and paracetamol as treatment thus far, said doctors. The hospital has reported 40 Omicron cases till now,

The ongoing COVID-19 pandemic was first reported in December 2019. Since then it has spread globally and affected millions of people. Transmission of the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) is via respiratory droplets and contaminated surfaces and objects (fomite transmission). The reservoirs of the virus are the nasal cavities, nasopharynx, oral cavity and oropharynx

A preprint study from Scotland has shown that infection with Omicron is associated with fewer hospitalizations with Omicron when compared to delta infections. It has further shown that the booster dose provides considerable protection within two weeks of administration compared to two doses received 25 or more weeks ago.1In this preliminary study, researchers from the University of Edinburgh, University of Strathclyde and Public Health Scotland analyzed data from 23,840 patients with Omicron

Will the Vaccines Stop Omicron? Scientists are running against to Find Out.

Dr. Penny Moore, virologist at the National Institute for Communicable Diseases in South Africa, is working with her team to test how vaccines respond to Omicron. She and her colleagues are preparing to test blood from fully immunized people against a synthetic version of the Omicron variant *(The New York Times).*

COVID vaccines can be mixed for booster shots, says WHO's provisional report

Based on availability, mRNA vaccines (Pfizer, Moderna) can be used as subsequent doses after an individual has been administered AstraZeneca's vectored vaccine as their first dose and vice versa, the WHO report said. AstraZeneca and the mRNA vaccines can also be used after initial doses of Sinopharm's inactivated vaccine, the global health body said.

Why is pandemic Policymaking still short of science?

We have to focus on improving scientific temper among both the population and policymakers. This is necessary to improve compliance with science based decisions ,and more importantly for the public to question policymakers' unscientific decisions. There are supporters of science among policymakers and we need platforms for them to unite. We need to mandate transparent policy development mechanisms which also allow public scrutiny before and after decision.An independent body to scrutinize every policy decision and its evidence base and put this in the public domain needed.Will government bite this bullet?If not who do we go to?Courts or philanthropists? DrAnanda Krishnan, has expressed his personal views at the center of community medicine, AIIMS, NewDelhi.

Australia hits COVID-19 case record

Australia registered a record high of daily COVID-19 cases for the third day in a row on Wednesday, further increasing the pressure on hospital resources and testing facilities, as anger grew among people over the handling of the Omicron outbreak.A record number of 64,758 new infections was reported on Wednesday, with the majority being in New South Wales (NSW) and Victoria

CDC updates COVID-19 isolation recommendations

it is best to use a rapid test toward the end of their 5-day isolation period. The agency faced criticism and pressure to include a testing component in the new decreased isolation period.

India sees higher spread of COVID-19 than second wave peak: Govt official

India is witnessing an exponential increase in the number of COVID-19 cases, believed to be largely driven by the Omicron variant, said the Center. It stated that the R naught value in the country, which is an indicator of the spread of the infection, stands at 2.69. This is higher than the value of 1.69 recorded during the peak of the second COVID wave in the country.At a press conference, Director General of the Indian Council of Medical Research (ICMR), DrBalram Bhargava, said that.

Italy to Make COVID-19 Vaccine Mandatory for Everyone above 50 Years

Italy is set to mandate vaccination against COVID-19 for all people 50 years of age and over, in a bid to

reduce the pressure on its healthcare services and decrease deaths, revealed a draft decree on Wednesday. The draft seen by Reuters states that the move will be effective immediately and will continue till June 15. If confirmed, it would make Italy one of the few countries in Europe to take similar steps.

Risk factors for severe Covid-19 among vaccinated persons

Findings of the CDC's latest Morbidity and Mortality Weekly Report published Jan. 6, show that severe COVID-19 outcomes or death were rare in vaccinated persons. And, all vaccinated persons who developed severe outcomes had at least one risk factor and most of the vaccinated patients who died had a minimum of four risk factors.

Risks posed by new variant still unclear

Omicron rapidly dominating in SA

Dataon omicron contagiousness "with in days"

"Latest data, looking good"

"Omicron symptoms "totally different" from Delta COVID-19 variant.The high proportion covid incidental admissions may reflect higher rates of community transmission compared to previous waves.The threat of the Omicron variant poses Canada.

WHO raises alarm over Omicron spread

The chief of the World Health Organization (WHO), TedrosAdhanomGhebreyesus, has said that the She added that as the case numbers rise, it will strain the healthcare systems

Amid growing concerns over the rapid spread of Omicron variant of the coronavirus, Israel has announced that the country will **offer a fourth dose of the COVID-19 vaccine to people aged above 60 years**.An expert panel of the Health Ministry recommended offering a fourth vaccine dose and the move was welcomed by Prime Minister Naftali Bennett who called it a news that will help the country overcome the Omicron wave

Omicron causes crippling staff shortage.

Hospitals in UK and US are running short of staff. "You are entering the Omicron wave.Hospitals in UK and US are running short of staff. | Omicron Variant. India will witness a peak in the number of Covid-19 cases by next month with the expectation of reporting five lakh cases per day, a US-based health expert said

The bottom line

COVID and its variant pandemics has given humanity a very hard blow. Almost all countries in the world have been devastated. Economy has received a severe setback. Many have lost their near and dear ones. Omicron illness has affected several million patients in all age groups throughout the world. Vaccines are the powerful weapon to fight against COVID.

Suggested Reading :

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Voice of the Expert

Patient Centered Health Care

S Arul Rhaj

Prof (Dr) S Arulrhaj is a renowned physician. He is the Past National President, IMA, Past National President, API & Past Commonwealth President, CMA, UK.

JIMA interviewed Dr S Arulraj for his expert opinions regarding Patient Centred Care

Q 1 : How to define in a formal way Patient Centered Care ?

Ans : The IOM (Institute of Medicine) defines patient centered care as: **"Providing care that is respectful of, and responsive to, individual patient preferences, needs and values, and ensuring that patient values guide all clinical decisions."**

Patient centered care respects and integrates a patient's values, preferences, and goals into clinical decision-making and outcome assessments. This partnership between caregiver and patient addresses the physical, mental, spiritual, and social determinants of a patient's health to achieve better outcomes.

Centricity in Healthcare

- **Doctor centric – Patients**
- **Disease centric – Doctors**
- **Hospital centric – Corporate**
- **Patient centricity – Need of the Hour**

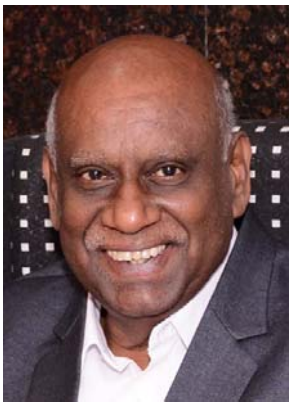
Q 2 : What is Patient Centricity?

Ans : Patient centricity should be defined as 'Putting the patient first in an open and sustained engagement of the patient to respectfully and compassionately achieve the best experience and outcome for that person and their family'.The patient-centric approach involves providing special medical services fashioned to cater to the individual values, needs, and preferences of a patient in addition to professional consultations and guidance of a health expert. There is a paradigm shift in the healthcare system.

Q 3 : When you are mentioning Patient Centric Focus, in this context would you please let us know about Patient-centric Culture and what are the fundamentals of Patient Centered Care ?

Ans : In a patient-centric culture, employees are able to see beyond their own roles and contribute to delivering what patients need, even if it's outside the scope of their job descriptions.

The Fundamentals of Patient-centered care (PCC)



Prof (Dr) S Arulrhaj
MD, FRCP (Glasg)

Health care is a service industry. This may sound like mere common sense, but if truly embraced and built into the health care system, it is a transformative idea. In important ways health care is unlike commercial services like hair salons and hardware stores.

Sick people are not shoppers and their relationship with providers is qualitatively different from their relationship with sales clerks. But one concept fundamental to the commercial world is relevant to health care: **the customer is always right.**

Q 4 : If we accept the concept that "the patient is always right" then we need to know what Patients Want from us?

Ans : The Change Foundation in Ontario has done a lot of work on PCC. A major literature review confirmed that there is very little research that examines health care integration from the patient perspective. The Foundation conducted a series of focus groups to get a better understanding of the patient experience. Many implicit definitions of the elements of PCC emerged, among which were:

(1) Comprehensive care – all of their needs, not just some, should be addressed

(2) Coordination of care – someone is in charge, there is someone to go to who knows you and will help you navigate the system

(3) Timeliness – they should get care when they need it and where a sequence of services is required, the intervals should be short

(4) Functioning e-health – provide information once, ensure that it is accessible to those who need it, give patients access to the records and the opportunity to add

(5) Clear and reliable communication – listen, explain, clarify, ensure that the provider team members are on the same page, consistency of messages, access to phone or internet consultations

(6) Convenience – minimize the need to go to different physical locations for services; open access, same day scheduling; no unnecessary barriers or steps to getting to the right provider

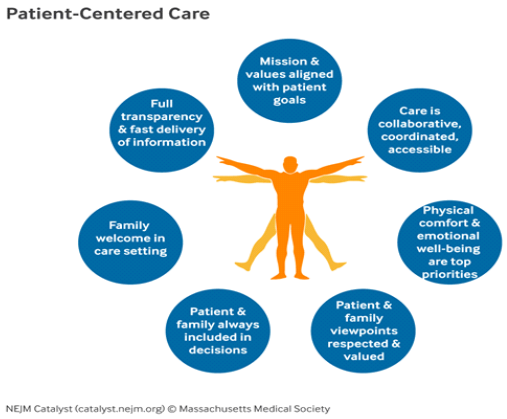
(7) Respect – for their time, intelligence; for the validity of their stories; for their feedback about quality and effectiveness; for their environment and family caregiving partners

Q 5 : What are the Key Elements of Patient Centered Care ?

Ans : Patient and family centered care encourages the active collaboration and shared decision making between patients, families, and providers to design and manage a customized and comprehensive care plan:

- The health care system's mission, vision, values, leadership, and quality-improvement drivers are aligned to patient centered goals.
- Care is collaborative, coordinated, and accessible. The right care is provided at the right time and the right place.
- Care focuses on physical comfort as well as emotional well-being.
- Patient and family preferences, values, cultural traditions, and socioeconomic conditions are respected.
- Patients and their families are an expected part of the care team and play a role in decisions at the patient and system level.
- The presence of family members in the care setting is encouraged and facilitated.

Information is shared fully and in a timely manner so that patients and their family members can make informed decisions.



Q 6 : When we are discussing about Patient Centered Care, Picker's Eight Principles are extremely crucial to acknowledge. Would you please let us know briefly about these principles?

Ans :

(1) Respect for patients' values, preferences and expressed needs

(2) Coordination and integration of care

(3) Information and education

(4) Physical comfort

(5) Emotional support and alleviation of fear and anxiety

(6) Involvement of family and friends

(7) Continuity and transition

(8) Access to care

To promote ideal patient care, follow these evidence-based directives:

Make healthcare accessible

You can't implement patient-centered care if the people who need it can't locate or travel to your office, clinic, or hospital. To get ambulatory service, your future patients must know about your facility and the transportation options available to reach it. You should also make sure the referrals you provide to accessible specialists are clear and easy to follow**.**

Respect patients' values, needs, and preferences

- Set aside what you may have learned in medical school and open your mind to the continually evolving integrative health care landscape your patients live and work in.
- If they've researched and successfully applied botanical medicine in the past, integrate it into your medical care plan.
- If your patient's family has been traumatized by the opioid crisis and they prefer pain management via acupuncture, follow their lead.
- If their religious or cultural values promote or reject certain treatments, respect that fact.what you may have learned in medical school and open your mind to the community.

Coordinate care

Focus groups at the aforementioned research centers have documented how illness caused vulnerability makes patients feel powerless. You can empower them by actively participating in and fully understanding their care plan. When you coordinate frontline patient care, clinical care, ancillary care, and support services, be flexible. Follow up to ensure each clinician is informed about each step in the patient's care plan.

Inform and educate your patients

Curious, intelligent patients often feel their providers patronize and condescend when informing them about their condition, prognosis, or treatment. Not telling them all the details can cause patients to become suspicious, angry, and bitter. They may lack the motivation to follow your care plan if they fear you don't truly care about or respect them. You can easily counter this fear by providing thorough but easy-to-read information on their clinical status, progress and prognosis, care processes, and autonomous selfcare. People who feel they're in control of their healthcare tend to take control of their healthcare.

Provide emotional and physical comfort

Ideal patient care requires acute attention to the healthcare environment. If your office, clinic, or hospital is unsterile, cold, cluttered, fluorescently lit, or garishly and uncomfortably furnished, it can negatively impact mood and even induce anxiety.

Once they're physically comfortable and calm, your patients may be more likely to discuss their take on pain management and disclose their need for assistance with daily activities. Listen and resolve any issues immediately before their trust wanes. If you comfort and reassure them, they'll trust you. Why is reassurance important in health and social care? If patients aren't confident you have their best interests at heart, they'll turn elsewhere—and walk away from an optimal health outcome.

Finances are a huge source of anxiety that can be reduced with a bit of research and budgeting.

Involve Family and Friends

- You can dramatically improve the patient experience by accommodating family and close friends at your facility.
- Involve them in your decision-making if you see they are your patient's deeply trusted advocates.
- Make sure you explain your patient centered care plan to all of them so they can participate and ensure consistency.
- Provide any logistical resources or emotional support needed to caregivers, who so often experience burnout and health issues.
- Demonstrate that you recognize their needs and are available to act as their trusted consultant and supporter.

Ensure continuity of care

- Patient centered care does not end when the patient leaves your clinic or hospital room.
- Make sure the patient's family and caretakers are fully vested in your care plan and understand the patient's physical limitations, dietary requirements, and medication schedules.
- Help them coordinate ongoing treatments and ensure they're informed about access to physical, financial, clinical, and social support.
- Nurses often provide the first touchpoint with patients to set the stage for these new expectations. What is patient centered care in nursing, and how can it be implemented?
- According to the Journal of the American Academy of Nurse Practitioners[4], effective patient centered care practices require consistent communication, shared decision-making, and dedicated patient education—which is often first introduced to patients by nurses.

DIRECTIVES :

- **To Make healthcare accessible**
- **To Respect patients' values, needs, and preferences**
- **To Coordinate care**
- **To Inform and educate your patients**
- **To Provide emotional and physical comfort**
- **To Involve Family and Friends**

Q 7 : Please let us know about a few examples showing beneficial effect of Patient Centered Care

Ans 7 :

- Research conducted by **Horizon Blue Cross Blue Shield** in 2014 revealed that patients who participated in patient centered programs had a 9% lower total cost than those who participated in traditional fee-for-service care models.
- A study conducted in **Sundaram Arulrhaj Hospital, Tuticorin** between 2020-2021 shows,Patients who received patient centered care were 9% less likely to be admitted to a hospital and 6% less likely to end up in the emergency room.
- A study at **Aruls Diabetic Centre, Tuticorin** shows 14% better TIME IN RANGE with continuous glucose monitoring managed according to patient centered care compared to traditional care.
- A study at department of cardiology **Idhayalaya, Sundaram Arulrhaj Hospital, Tuticorin** shows 13% less readmission for follow up cases of heart failure with reduced ejection fraction participating in patient centered care compared to traditional care.

Q 8 : How Patient Centered Healthcare Can Improve Quality

Ans 8 :

- Healthcare is evolving from a model in which the physician made almost all treatment decisions, unquestioned, and based on clinical experience, to a

patient centered model. Under the new but still-evolving model, patients are active participants in their own care. Increasingly, clinicians are treating patients who make decisions about healthcare services based on their own needs and preferences.

- IOM has identified patient-centeredness as one of the six domains that define quality care — the others being safety, timeliness, effectiveness, efficiency, and equity.
- Patient centered care has enjoyed increased attention recently. Over the past 30 years, an increasing proportion of Americans have collectively and individually demanded a greater say in decision-making and many other areas. In addition, patient centeredness is a goal of the Value-Driven Health Care Initiative, a major effort by the U.S. Department of Health and Human Services to stimulate quality improvement.

The essence of patient centered care is captured in the maxim, **"Nothing about me without me"** (Delbanco, 2001)[7]. In its landmark report, *Crossing the Quality Chasm,* the Institute of Medicine (IOM) defined patient centered care as **"care that is respectful of and responsive to individual patient preferences, needs, and values and [ensures] that patient values guide all clinical decisions"** (Institute of Medicine, 2001).

Q 9 : would you please tell us about Physicians' Role in Patient Centered Care?

Ans : We have a long way to go in offering patient centered care. The Commonwealth Fund recently surveyed physicians nationally, examining practices that are commonly accepted as patient centered, and arrived at some disturbing conclusions about the **low frequency of patient centered practices** (Audet, 2006):

- Only about one-half (54%) of all physicians send reminder notices for preventive or follow-up care.
- Just over one-third (36%) of primary care physicians (PCPs) conduct patient surveys and use the data to improve their practice.
- Only 26% of PCPs have medical records and lab tests readily available.
- Less than a quarter (23%) of PCPs have electronic medical records.
- Barely one in five (21%) of PCPs "always or often" furnish patients with information on the quality of care of referral physicians.
- Only 18% of all physicians give patients the opportunity to ask questions and transmit information through e-mail.

Q 10 : What are the different roles of Patientin Patient Centered Health Care

Ans : Individually, each of these statistics would be startling. Taken together, they paint a clear picture of a healthcare system that does a poor job of placing the patient at the center of their own care. This must change. We must recognize that patients are the best source of information about their own bodies and about how they prefer to be treated. They should be active participants in decisions about their treatment.

Patients' day-to-day activities, such as diet, medications, exercise, habits and sleep, have a substantial impact on their health (Wu, 2000). When patients play an active role in their healthcare, they are more likely to comply with their treatment and enjoy **safer care.**

Q 11 : We often hear about Shared decision making, how it is important in patient centered care?

Ans : Shared decision making takes into account the findings from current evidence-based practice, in addition to the patient's values, desires, and preferences.

- Patients should be actively involved in making decisions about their care.
- Shared decision making is a process by which nurses help patients make **informed healthcare decisions. Eg; Surgeries, PCI, Chemotherapy etc.**
- **Shared decision making improves patient autonomy.**

Patients have to make many healthcare decisions during hospital stays and throughout care. These decisions can vary dramatically in context and severity. For example, one patient may need to choose the type of facility, he or she will be discharged to and another may need to make a simple medication or activity decision.

Patient involvement in Clinical decisions

Patient participation means involvement of the patient in decision making or expressing opinions about different treatment methods, which includes sharing information, feelings and signs and accepting health team instructions.

Q 12 : Is there any way to Measurethe results of patient-centered care?

Ans : The first standardized survey in the US is the Hospital Consumer Assessment of Healthcare

Providers and Systems Survey (CAHPS®). This data collection tool was developed by The Centers for Medicare & Medicaid Services (CMS) and the Agency for Healthcare Research and Quality (AHRQ). It measures patient experience by asking discharged patients whether they got the care they needed quickly enough and whether they enjoyed thorough, compassionate communication with doctors, care providers, and customer service representatives. These ratings are critical to the health of your practice.

Q13: Would you briefly enumerate the importance of AHRQ in Patient Centered Care?

Ans : Quality as we know it is an elusive concept for even sophisticated consumers. To help bridge the gap, the **Agency for Healthcare Research and Quality (AHRQ)** has provided tools to foster patient centeredness and consumer participation in healthcare decision making.

AHRQ's SHARE Approach is a **five-step process** for shared decision making that includes exploring and comparing the benefits, harms, and risks of each option through meaningful dialogue about what matters most to the patient.

Q 14 : How patient-centered care will help your care team thrive?

Ans : Despite its name, patient centered care offers just as many benefits for providers. This holistic healthcare approach will help your care team:

- Improve patient outcomes
- Reduce expenses and total cost of care:Research conducted by Horizon Blue Cross Blue Shield in 2014 revealed that patients who participated in patient centered programs had a 9% lower total cost than those who participated in traditional fee-for-service care models
- Enhance reputation
- Boost staff satisfaction
- **Streamline resource allocation**

Q 15 : In this era of newer Technologies, how could we utilize them for patient centered healthcare?

Ans : Advances in genetic analysis and bioinformatics show promise in the development of personal diagnosis and treatment that will become an integral part of the patient record. The Internet has made world-wide access to the medical record possible. In addition, the Internet provides the means for remote diagnostics and intervention.

Smart Care: Integrating Blockchain Technology into the Design of Patient centered Healthcare Systems[11]

Cross institutional sharing of medical data is essential to provide effective collaborative treatment and clinical decisions for patients. Medical data privacy involves ensuring only authorized parties may access the health records under the awareness and approval of patients in any circumstances. This is crucial to any healthcare system because the protection of patients' clinical data is not only an ethical responsibility but also a legal mandate.

Q 16 : Can Artificial intelligence Boost Efficiency in this regard?

Ans : Today, much of a doctor's daily routine is administrative and logistical, rather than patient centric. One study even found that physicians spend twice as much time updating electronic health records (EHRs) as they do providing direct care to patients.

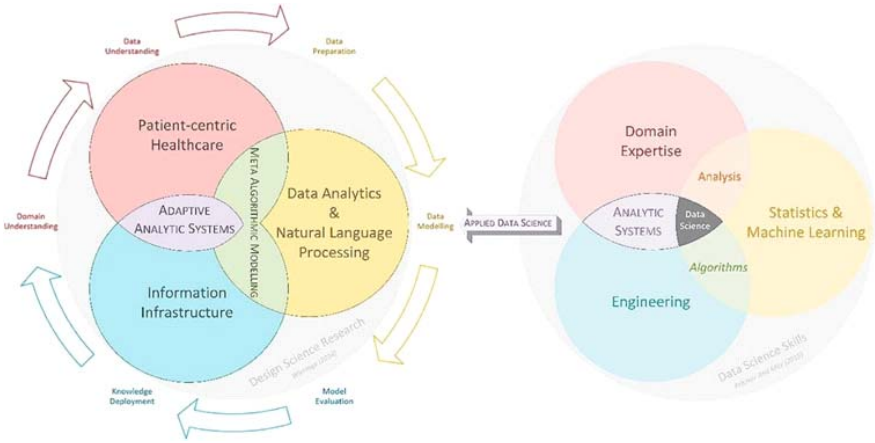
AI has the potential to improve the efficiency of interpreting x-rays, Scans. Advances in computer imaging have made it so that AI can automatically sort through images to find the best match, which it then presents to the radiologist with a few neighboring options. AI could also play a significant role in the development of new drugs and treatments especially previously unknown or unidentifiable treatments for chronic conditions and genetic disorders at a significantly lower cost.

Q 17 : Applied data science is extremely important in patient centric healthcare. How Adaptive analytic systems could empower both physicians and patients?

Ans :

- Applied data science for healthcare empowers physicians and patients.
- Applied data science focuses on adaptive analytic systems to improve daily care.
- Adaptive analytic systems for patient centredness enable personalised medicine.

- Empowerment of physicians and patients accelerates healthcare innovation.
- Meta-algorithmic modelling provides a framework for the post-algorithmic era.



Q 18 : Please summarize Benefits and advantages of patient centered care.

Ans : The primary goal and benefit of patient centered care is to improve **individual** health outcomes, not just **population** health outcomes, although population outcomes may also improve. Not only do patients benefit, but providers and health care systems benefit as well, through:

- Improved satisfaction scores among patients and their families.
- Enhanced reputation of providers among health care consumers.
- Better morale and productivity among clinicians and ancillary staff.
- Improved resource allocation.
- Reduced expenses and increased financial margins throughout the continuum of care.
- Improved patient satisfaction
- Improved reputation for your organization

Better job satisfaction for staffImprove your care team's job satisfaction, promote ideal patient care, and attract new patients by designing a holistic, patient centered, software-enabled care plan. Then, enjoy the benefits.

Outcomes of PCC are :

- **Violence on Healthcare will decline**
- **Doctor Patients Relations will improve**
- **Doctor will command more respect in society**
- **Healthcare become an effective appreciable companion of human life**

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Thank you again Dr Arul Rhaj for your time. We are sure our readers will love to go through this insightful perspective of *Patient Centred Care*.

We hope to speak with you again in the future.

Drug Corner

A Prospective, Cross-sectional, Multicenter, Observational, Questionnaire-based Survey to assess the Knowledge, Awareness, Attitude and Practice of Physicians while Prescribing Proton Pump Inhibitor (PPI) Drugs for Acid Peptic Disease

Kranthi Kiran Pebbili[1], Bharadwaja Pendurthi[2], Seema Bhagat[3]

Goal : This is a subjective survey to assess the knowledge, awareness, and practices (KAP) of physicians while prescribing Proton pump inhibitors (PPI) in acid peptic disorder (APD) patients in India.

Background : APD represents a variety of gastric anomalies in which PPIs form the mainstay of management. Many of the APD patients are associated with comorbidities, resulting in polypharmacy and increased risk of drug-drug interactions. Therefore, it is essential that physicians be aware of PPI drug interactions while prescribing them to patients with comorbidities. In developing countries like India, studies assessing the KAP of Physicians are limited.

Study Design : This questionnaire-based study consisted of 3 domains: (A) Study objectives and consent; (B) Participants' socio-demographic details; (C) Questions on KAP of Physicians around various aspects of APD management and PPI usage.

Results : A total of 110 Physicians completed the survey. 92% observed stress as the most common risk factor; Obesity (46%), Diabetes Mellitus (41%) and Cardiovascular Disease (33%) as the most frequent comorbidities, in APD. Almost all Physicians (99%) considered patient's comorbidity important while choosing PPI. 84% participants felt that anticoagulants when co-prescribed with PPI have higher chance of drug-drug interactions. 60% ranked Rabeprazole in the top, in terms of safety and tolerability among PPIs.

Conclusion: The present study mapped the awareness of Indian Physicians on APD, PPI usage, their adverse effects, drug-drug interactions; patient compliance and satisfaction with PPIs. These findings can be used to plan future interventions targeting HCPs, to ensure safe and appropriate use of PPIs.

[*J Indian Med Assoc* 2022; **120(7):** 67-74]

***Key words* : Acid peptide disorder, Awareness, Attitude, Knowledge, Proton pump inhibitor.**

Acid Peptide Disorder (APD) is a term that represents a vast variety of gastric anomalies including Gastric Esophageal Reflux Disease (GERD), Peptic Ulcer Disease (PUD), Gastritis, Zollinger-Ellison syndrome (ZES), Meckel's diverticulum, and other hyper secretory conditions, which are believed to be caused by gastric acid acting on diminished gastric mucosa[1].

The prevalence of GERD is probably under-estimated, as most of the epidemiological studies on GERD are symptom based (heartburn, regurgitation). According to the first consensus on GERD from India by the Indian Society of Gastroenterology Task Force (ASGTS), the prevalence of GERD is approximately 10% among the Indian population[2]. PUD, another major type of APD, has an annual incidence rate between 0.10-0.19% for physician-diagnosed PUD and between 0.03-0.17% from hospitalization data. The 1-year prevalence of PUD on the basis of a medical diagnosis was 0.12-1.50 % and that based on hospitalization data was 0.10-0.19%[3].

Since the first Proton-Pump Inhibitor (PPI) Omeprazole was introduced in 1989, PPIs have been proven to be safe and effective agents for the treatment and prophylaxis, in a variety of acid-related disorders affecting the upper gastrointestinal tract[4]. As of 2021,

Editor's Comment :

- In this KAP study almost all physicians felt that stress is the most common risk factor associated with APD. Obesity, Diabetes Mellitus, and CVD were noted as the most common comorbid conditions in APD patients. Efficacy and safety are the most important attributes considered while choosing a PPI and Rabeprazole is rated at the top in terms of safety and tolerability. It is important to choose a PPI with less chance of drug to drug interactions and have a reasonable certainty in providing response in majority of the APD patients.

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6 PPIs have been approved by USFDA namely: Pantoprazole, Rabeprazole, Esomeprazole, Omeprazole, Lansoprazole, and Dexlansoprazole. Adaption of PPI use has dramatically increased among the health care providers (HCPs), and their presence is ubiquitous within the prescriptions of various specialties. The world has seen a substantial, continuing, and unexplained rise in prescription and usage of PPIs.

A recent meta-analysis concluded that the prevalence of comorbid conditions (diabetes mellitus, coronary artery disease, malignancy, arthritis, HIV, respiratory, hepatic, and renal diseases) are high among APD patients[5]. This coexistence of APD and comorbid conditions have resulted in a consistent increase in co-prescription of PPIs along with the drugs used to treat these comorbidities. A recent study which evaluated the drug utilization pattern in cardiovascular diseases reported surprisingly high prescription rates of pantoprazole among patients suffering from cardiovascular disorders. Similarly, various drug utilization studies have reported high prescription rates of PPIs among patients with comorbidities including diabetes[6,7], cancer[8], arthritis[9], HIV[10,] CKD[11] and cirrhosis[12]. Such a wide usage of polypharmacy (including PPIs) among comorbid patients may potentiate the risk of drug-to-drug interactions and can result in the occurrence of Adverse Drug Reactions (ADRs). This risk is higher especially among hospitalized elderly patients in whom the prevalence of polypharmacy is approximately 31.8%, which increases their susceptibility towards experiencing an ADR[7,13,14]. Furthermore, there is a growing concern on the usage of PPIs beyond their approved duration[7,15] and irrational prescribing practices while treating patients with multiple ailments. Various recent epidemiological studies conducted in countries like Jordan, Greece, and China have reported 86%, 81%, and 82% use of PPIs in an inappropriate indication respectively[7]. Therefore, physicians should be made aware of PPIs' drug-drug interactions while prescribing them to a patient who is on treatment for multiple diseases.

In developing countries like India, drug utilization or surveillance studies assessing the knowledge, awareness, and prescribing practices of HCPs are lacking. The main objective of this survey is to access and map the knowledge, awareness, attitude, and practice of physicians while prescribing PPIs for APD in India.

Materials and Methods

Questionnaire Design :

A questionnaire was designed on web-based forms and the link generated was shared on WhatsApp or Emails to physicians (doctors treating APD). The purpose of the study was stated in the questionnaire and the participants were asked to fill the questionnaire after giving their consent via the web link by clicking the "Agree to Participate" option. The Participants were assured of the confidentiality of their information, and that it would be used only for the purpose of this study. All the participants were asked to fill the questionnaire only once to avoid duplication of data and that their participation in the study was entirely on voluntary basis. A structured questionnaire was used based on the variables of interest and guided by the study specific objectives. The questionnaire had questions assessing demographics of the Physicians, the knowledge, awareness, and attitude of respondents on APD and associated risk factors and the respondents' knowledge, awareness, attitude and prescribing practices on choice of therapy for APD and factors associated with the choice of therapy.

The questionnaire consisted of mainly 3 domains: (A) Information to the participants about the objectives of the study and their consent for participation; (B) Socio-demographic details of the participants; (C) Questions on the knowledge, awareness, attitude and prescribing practices of respondents on APD, associated risk factors, choice of therapy and factors influencing the choice of therapy. Time spent for the completion of the questionnaire was approximately 10-20 min.

Inclusion Criteria :

(1) Doctors registered with Medical Council of India and having MBBS Degree and Above

(2) Doctors having a minimum of 5 years of experience in clinical practice.

(3) Doctors treating Acid Peptic Disease patients.

(4) Doctors prescribing Proton Pump Inhibitor (PPI) drugs

(5) Doctors who are willing to voluntarily participate in the survey and provide the Consent.

Exclusion Criteria :

(1) Doctors not treating APD patients.

(2) Doctors not prescribing PPIs

(3) Doctors not providing the consent for participation.

Dropouts :

Those Participants who have not responded after

providing consent were considered as dropouts. Incomplete questionnaires have not been included in data analysis.

Sample size :

The survey questionnaire was shared to the eligible participants via email or other appropriate means of communication. A total of 110 responses were received from the physicians and included in the analysis.

Statistical Analysis :

All data was cleaned and validated before analysis. Absolute (n) and relative frequencies (%) were presented for qualitative variables and mean (±SD) was used for continuous variables. Statistical analysis was performed using STATA v15.0 and Microsoft Office (Excel).

Results

Demographic characteristics of survey participants and APD patient characteristics based on the participants' responses :

A total of 110 respondents from various clinical settings have completed the survey and their responses were considered valid and suitable for analysis. Among these 110 respondents, 95% (105) were male and only 5% (5) were female. The highest responses received were from physicians aged between 31-40 years of age and the mean age of respondents was 45.42 ± 9.82 years old. 55% (60) of respondents were currently practicing in a hospital with a mean clinical experience of 16.73 ± 9.83 years. The demographic characteristics of the respondents are provided in Table 1.

Based on the responses received, an average of 306 APD patients visit various clinical settings per month. 88% (97) of the physicians have expressed their opinion that patients commonly experiencing APD symptoms are aged between 25-54 years and approximately 81% physicians opined that male patients experience more symptoms when compared to female APD patients. 55% Physicians responded saying that patients commonly experiencing APD symptoms belonged to "Upper/Upper Middle" socioeconomic class and 64% Physicians opined that they are white collar workers. Physicians' awareness regarding socio-demographic details of APD patients are provided in Table 2.

The Knowledge, Awareness, Attitude and Prescribing practices of participants on APD and Associated Risk Factors :

Among the total respondents, 56% (62) are doing a monthly patient follow-up and prescription review.

Table 1 — *Demographic characteristics of the survey participants*

Parameters	Participants (N=110)
Gender n (%) :	
Male	105 (95.45%)
Female	5 (4.55%)
Age (years)	45.42 ± 9.82
21-30	1 (0.91%)
31-40	40 (36.36%)
41-50	39 (35.45%)
51-60	20 (18.18%)
61-70	10 (9.09%)
Highest Medical Qualification n (%) :	
Graduate	20 (18.18%)
Postgraduate	45 (40.90%)
Postgraduate diploma	4 (3.64%)
Doctorate	40 (36.36%)
Data not available	1 (0.91%)
Current clinical practice (type) :	
Hospital	60 (54.55%)
Clinic	49 (44.55%)
Data not available	1 (0.91%)
Clinical Experience (years)	16.73 ± 9.83

Table 2 — *Physician awareness regarding demographics of APD Patients*

Parameter	Responses (N= 110)
APD patients / month	306.41 ± 316.82
Age (Years) :	
24 years and below	1 (0.91%)
25-54	97 (88.18%)
55-64	12 (10.91%)
>65	0 (0.00%)
Gender :	
Male	89 (80.91%)
Female	21 (19.09%)
Typical symptoms observed :	
Heart Burn	101 (91.82%)
Dyspepsia	99 (90.00%)
Flatulence/Bloating	84 (76.36%)
Socio-economic class :	
Upper	5 (4.555)
Upper middle	56 (50.91%)
Lower middle	40 (36.36%)
Upper lower	6 (5.45%)
Lower	3 (2.73%)
Type of employment :	
Blue-collar workers	39 (35.45%)
White-collar workers	71 (64.55%)

92% (101) physicians have observed stress to be the most common risk factor associated with APD patients. 46% (51) perceived obesity as the most common co-morbid condition among APD patients followed by Diabetes Mellitus, Cardiovascular Disease (CVD), and arthritis with 41%, 33%, and 31% responses respectively. Among total respondents, 92 %, 90%, and 76% selected heartburn, dyspepsia, and flatulence/bloating as the most commonly observed symptom respectively.

The Knowledge, Awareness, Attitude and prescribing practices of participants on the choice of Therapy and Factors associated with the choice :

A total of 63% (70) respondents have mentioned that efficacy is the most important attribute while choosing a PPI and ranked Esomeprazole and Rabeprazole as the most efficacious ones among the PPIs. Further, approximately 60% (66) of respondents ranked Rabeprazole in the top, in terms of safety and tolerability among the PPIs for the treatment of APD.

For questions investigating the dosage regimen and effectiveness, 88% (97) respondents considered "effective acid suppression with once-daily dosing" as the most important attribute in determining the efficacy of a PPI. While 70% (78) of participants opined that Rabeprazole 20 mg and Esomeprazole 40 mg were effective as once-daily dosing regimens, 72% (80) of participants felt that twice-daily regimen has a greater effect on gastric acid suppression.

For the question concerning the usage of the drugs by the APD patients other than the drugs used for APD treatment, 28% (30) of respondents mentioned that NSAIDs are the most commonly used class of drugs. Also, 67% of participants responded that H2 receptor antagonists are the most prescribed class of drugs for APD management, after PPIs.

When asked about the importance of a patient's co-morbidity in deciding the PPI, almost all the Physicians (99%) considered a patient's comorbidity important while choosing a PPI and 88% (97) responded that cardiovascular disease is the most assessed co-morbid condition before prescribing a PPI.

Regarding the co-prescription, around 55% of study participants responded saying that co-prescription of a PPI affects the efficacy and safety of other medications prescribed for chronic health conditions. 84% (92) participants felt that anticoagulants when co-prescribed with a PPI have a higher chance of drug-drug interaction. 98% (108) participants felt that NSAIDs require a co-administration of PPI, and 89% agreed that PPIs act as a prophylaxis for NSAID induced peptic ulcers or gastric ulcers.

Regarding the adverse events with PPIs, around 64% (70) of participants considered diarrhea as the most common adverse event observed with the usage of PPIs and 81% (89) felt that there is a significantly increased risk of vitamin-B12 deficiency with long-term usage of PPIs.

For the questions pertaining to the reasons for PPI switching, 40% (44) of study participants considered "lack of immediate symptom relief" as the most important factor that influenced the switch of one PPI to another and 59% (65) agreed that this factor also influenced the change in the dose of the PPI.

For the questions pertaining to the patient satisfaction with PPIs, 50% of the responders reported that "Immediate relief from symptoms" is the most important factor influencing patient satisfaction and more than 55% (61) of participants responded saying that the patients are "very satisfied" with PPI treatment.

Discussion

APD significantly impacts the Quality Of Life (QOL) of the patients and causes considerable stress on the health services. Several population-based studies have reported poor QOL among patients with APD[16,17]. QOL worsens if APD is not treated in a rational way and it increases the cost of treatment for the patient, which includes repetitive consultation costs, investigations, medications, and additional complications. Therefore, it is of utmost importance for the physicians to have sound knowledge and awareness regarding the characteristics of APD patients and their management with PPIs. To understand the above-mentioned parameters, this questionnaire-based KAP survey was designed. This was a subjective survey of perception among HCPs on acid peptic disorders and PPI usage.

Our survey evaluated the Physicians' awareness on the demographics of the APD patients and the risk factors associated with APD. As per the Physicians' response, patients commonly experiencing APD symptoms belong to 25-54 age group and male patients experience more symptoms compared to female APD patients. Majority of the physicians opined that the patients commonly experiencing APD symptoms belong to 'Upper/Upper Middle' socioeconomic class and are white collar workers. Coming to the risk factors for APD, more than 90% of the Physicians mentioned stress as the most common risk factor associated with APD. Previous clinical studies have reported stress as a major risk factor for the development of APD, particularly in individuals aged 20's through 50's, who are more susceptible to stress[18,19]. The individuals in this age group form the major part of active work force and may be more susceptible to work related stress compared to other age groups. Based on this evidence from real world practice through our survey, it appears that 25-54 year old male white collar workers belonging to upper/upper middle socioeconomic class are more prone to stress, probably work related, which can increase their risk of APD.

While evaluating the Physicians' perceptions on

Table 3 — *KAP of respondents on associated risk factor with APD*

Questions (N= 4)	Responses (N=110)
What are the common risk factors observed in your routine clinical practice for Acid Peptic Diseases?	Stress (91.82%)
What tests do you recommend in order to arrive at a diagnosis of APD?	Upper G.I. Endoscopy 65 (59.09 %)
Which of the following comorbid conditions are seen frequently in APD patients treated by you?	Obesity 51 (46.36 %)
At your clinical practice how often do you follow-up the patient and review their prescription for treatment of APD with PPI?	Monthly - 62 (56.36 %)

Table 4 — *The respondents KAP on choice of therapy and factors associated*

Questions (N = 12)	**Responses (N=110)**
How important is a patients' comorbidity in deciding a PPI?	Important 109 (99.09 %)
Please rank the proton pump inhibitor according to your perception of its efficacy in treatment of APD?	Esomeprazole (Ranked1) 53 (48.18 %)
Please rank the proton pump inhibitor according to your perception of its safety and tolerability in treatment of APD?	Rabeprazole (Ranked 1)
Which of the following PPIs are effective as once daily dosing?	• Rabeprazole-20 mg - 78 (70.10 %) • Esomeprazole 40 mg - 78 (70.10 %)
Which co-morbid condition do you assess before prescribing a PPI?	Cardiovascular diseases 97 (88.18%)
In your clinical experience which drugs require coadministration of PPI?	NSAIDs 108 (98.18%)
In your clinical experience apart from drugs for APD treatment which other concomitant medications are frequently used by APD patients?	Nonsteroidal Anti-Inflammatory Drugs 30 (27.52 %)
In your clinical experience, which drug may have a higher chance of drug-to-drug interactions when given along with PPI?	Anticoagulants 92 (83.63 %)
Apart from PPI's which other class of drugs do you prescribe during treatment of APD?	H2-receptor antagonists74 (67.27 %)
Which attributes are important for you in choosing a PPI?	Efficacy 70 (63.63%)
For which conditions do you prescribe PPIs as prophylaxis?	Prevention of peptic ulcers or gastric ulcers induced by NSAIDs - 98 (89.09%)
Which of the following frequency of PPIs has greater effect on gastric acid suppression?	Twice daily (BID)80 (72.73 %)
Which risks do you observe with long-term use of PPIs?	Vitamin-B12 deficiency89 (80.90 %)
In your opinion which of the following attributes determine efficacy of a PPI?	Effective acid suppression with once daily dosing. 97 (88.18 %)
Which of the following factors make you switch a PPI with another one?	Lack of immediate symptom relief – 44 (40%)
What are the factors which prompt you to change the dose of PPI?	Lack of immediate symptom relief - 65 (59.09%)
What are the common adverse events observed in your routine clinical practice when PPIs are prescribed?	Diarrhoea 70 (63.64 %)
In your opinion what are the top factors of satisfaction for a patient who is using a PPI?	Immediate relief from symptoms (Ranked-1) 55(50.00 %)
At your clinical practice, what percentage of patients do you think strictly follow and use PPI as per your advice?	71-80% patients- 27 (24.54 %)
How would you rate the overall patient satisfaction with PPI treatment?	Very satisfied 61 (55.45 %)
In your clinical experience, does co-prescription of PPI has an effect on efficacy of other medications prescribed for chronic health conditions ?	Agree 59 (53.64 %)
In your clinical experience, does co-prescription of PPI has an effect on safety and tolerability of other medications prescribed for chronic health conditions?	Agree 60 (54.55 %).

the association of APD with various comorbid conditions, Obesity, Diabetes Mellitus, and CVD were noted by the respondents as the most common comorbid conditions observed in APD patients. Previous studies have reported that PUD is strongly associated with obesity[20,21]. In 2017, a study has established a correlation of increased weight and high BMI in women with PUD[22]. Further, some of the researchers have reported that PUD patients have a higher prevalence of DM and CVD, with increased threat for developing a variety of complications during the course of disease[23,24]. The current study provides real world evidence of observation of these comorbidities in APD patients, by the physicians.

Majority of the respondents in our survey reported that efficacy and safety are the most important attributes considered while choosing a PPI. As per

the study results, Esomeprazole and Rabeprazole are considered to be the most efficacious PPIs and majority of the respondents ranked Rabeprazole at the top among the PPIs in terms of safety and tolerability, in the management of APD. This adds up to the existing evidence, as Rabeprazole was reported in multiple earlier studies as highly effective PPI compared to other PPIs[25-27]. Another important attribute of PPIs is their once daily dosing. More than two thirds of the respondents reported that Rabeprazole is effective as OD dose. OD dosing is reported to be safer for long-term use of PPIs. Previous studies have also reported the good tolerability profile of Rabeprazole in OD dosing regimen[28,29]. Our study results have reiterated the existing evidence of Rabeprazole's efficacy, safety and the effectiveness as once daily dosing regimen through this evidence from real world practice.

In terms of safety, the adverse effects associated with PPI long-term use, as observed by more than 50% of the respondents were, vitamin B_{12} deficiency, risk of fractures and hypomagnesemia. The evidence connecting vitamin B_{12} levels and PPI use remains controversial. Though multiple studies have reported the possible effect of chronic PPI treatment in vitamin B_{12} levels[30,31], the others have reported no such association[32,33]. For the risk of fractures, multiple recent studies have reported a positive association of PPIs with an increase in fracture risk which may be due to hypergastrinemia and hypochlorhydria[34]. The presence of mineral deficiencies, particularly hypomagnesemia, which may be due to the inhibition of active absorption of magnesium, is commonly reported in PPI users[35,36]. The observation of these adverse effects in the clinical practice by the respondents in our study is in concordance with the available scientific literature.

Another important aspect of PPI safety is the drug-to-drug interactions, particularly with the medications prescribed for longer duration in comorbid conditions like CVD and Diabetes. It should be noted that almost all the respondents in our survey reported that patient's comorbidity is important while choosing PPI for APD. This is crucial since PPIs tend to interact with certain medications used for the management of Diabetes and CVD[22,37-40], probably due to the shared enzymatic metabolic pathway of CYP2C19[41]. Previous studies have reported an increase (Ex-Digoxin) or decrease (Ex-Ketoconazole) in the absorption of certain drugs, greater number of adverse effects of inactivated drugs (Ex-Citalopram),and reduced therapeutic efficacy due to inhibition in the conversion of prodrug to active metabolite (Ex-Clopidogrel), with concomitant use of PPI[42-44]. However, unlike other PPIs, Rabeprazole gets metabolized predominantly through non-enzymatic pathway and hence, have less chances of DDIs. In a meta-analysis published in 2016 evaluating the risk of Major Adverse Cardiovascular Events (MACE) in patients with coronary artery disease receiving a combination of Clopidogrel and PPIs, all PPIs have shown increased risk of MACE except Rabeprazole[45]. In fact, USFDA has recommended avoiding Omeprazole and Esomeprazole in patients taking Clopidogrel, as these PPIs can interact with Clopidogrel, resulting in adverse clinical outcomes[46]. This highlights the point that all PPIs are not same in terms of safety and drug to drug interactions and physicians should be made aware that co-prescriptions of PPIs can affect the efficacy, safety and tolerability of other medications prescribed for chronic health conditions. In our study, approximately three-fourth of the respondents have reported their awareness on these co-prescription hazards, more than 80% have mentioned that anticoagulants may have higher chance of drug to drug interactions when given along with a PPI and most respondents have ranked Rabeprazole in the top among PPIs in terms of safety and tolerability, reiterating the existing evidence, through this evidence from real world practice.

One of the major issues with PPI treatment is lack of therapeutic response in many patients. For the factors which influence the switching of the PPI or change of the dose of PPI, "lack of immediate symptomatic relief" has come up as the top reason in this survey. As discussed earlier, most of the PPIs get metabolized predominantly through the CYP2C19 enzymatic pathway. Several studies have highlighted the genetic polymorphism which exists in the CYP2C19 enzyme, which results in individuals with multiple CYP2C19 phenotypes and their differential response to the PPIs. In some phenotypes a standard once daily dosing of PPI may be sufficient for adequate acid suppression, whereas in other phenotypes a higher or more frequent dosing may be required. But evaluating these phenotypes in day to day clinical practice and individualizing the PPI dose is practically not possible. This uncertainty in response to PPI can probably be avoided by choosing a PPI like Rabeprazole, which doesn't depend on the CYP2C19 pathway for metabolism and consequently its acid suppressing effect doesn't vary with the enzymatic phenotype. The current survey has highlighted the challenge of patients' variable response to PPI treatment and the need to address this uncertainty.

The introduction of PPIs into the clinical practice

has revolutionized the management of APD[52,47]. In our survey, the patients' satisfaction with PPI, as reported by the HCPs, was very high, with more than half of the respondents reported that their patients are very satisfied with PPI use. However, Physicians should exercise reasonable caution in prescribing PPIs, particularly in patients with comorbid conditions, where long term use of PPIs can increase the risk of drug to drug interactions. It is important to choose a PPI with less chance of drug to drug interactions and have a reasonable certainty in providing response in majority of the APD patients.

Conclusion :

In conclusion, the present study has mapped the awareness of Indian HCPs on acid peptic disorders, PPI usage, their adverse effects, drug to drug interactions, patient compliance and satisfaction with PPIs. These findings can be used to plan future interventions targeting HCPs, to ensure appropriate prescription of PPIs, according to the risks and benefits in individual patients.

Study Limitations :

Firstly, the assessment of parameters such as knowledge, awareness, attitude, and practice through self-reported instruments may introduce reporting bias which can overestimate positive responses of these parameters. Second, our sample size is relatively small and limited to India which limits generalization of the results. A wider national/international survey with larger sample size may be needed to confirm our findings. Finally, our study only included responses from physicians. Future studies encompassing responses from diverse hospital departments, including nurses and pharmacists, may provide more detailed insights to the prescription practices of PPIs for APD.

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Drug Corner

Pharmacological basis of Evening Primrose Oil in Premenstrual Syndrome — An evidenced based approach

Ashwini Bhalerao Gandhi[1], Anish Desai[2],

Premenstrual Syndrome (PMS) is a recurrent luteal-phase condition associated with somatic emotional and behavioral symptoms. Frequently reported symptoms include breast discomfort, mood swings, fluid retention and food cravings. The exact etiology of PMS is unknown; however, the underlying mechanism is a complex interaction between fluctuations in ovarian steroids and central neurotransmitters as well as peripheral effects of hormones. Therefore, surprisingly a wide range of treatments are not available with satisfactory outcomes. Evening Primrose Oil (EPO) is one of the most popular for the management of PMS. EPO is a valuable fixed oil extracted from the *Oenothera biennis* seeds. It comprises essential fatty acids, including linoleic acid, Gamma-Linolenic Acid (GLA), and Vitamin E, which have been used in various treatments. It has been clinically shown to improve psychological (mood and sleep disturbances) and physical symptoms (breast pain/tenderness, bloating, fatigue) in women suffering from PMS. The rationale put forward for investigating the use of EPO in PMS is thataffected women appear to have abnormal levels of essential fatty acids; hence administrating linoleic acid and GLA in the form of EPO could potentially alleviate the symptoms of PMS.

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Key words **: Evening Primrose Oil, Premenstrual Syndrome, GLA.**

The onset of a phase with one or more symptoms before the menstrual cycle that causes an imbalance in a woman's lifestyle and everyday routines is known as Premenstrual Syndrome (PMS). Although most of the symptoms are mild, 5-8% of women experience moderate to severe symptoms that are linked to severe distress or functional impairment. Prospective and retrospective studies report that less than 10% of women with hormonal cycles experience moderate to severe symptoms[1,2]. Moreover, the prevalence of PMS is estimated to vary between 14.3% to 74.4% in India. Surprisingly, adolescents showed a comparatively higher prevalence, negatively impacting their quality of life[3]. Increased irritation, stress, depressed mood, soreness in the breasts, bloating, and weight gain are some symptoms of PMS.Premenstrual disorders significantly affect the quality of life by causing significant distress or interfering with daily activities like work, school, or socializing[4,5]. Treatment options for PMS include hormonal interventions [Gonadotropin-Releasing Hormone (GnRH) agonists and combined oral contraceptives], antidepressants [Selective Serotonin Reuptake Inhibitors (SSRIs)], and lifestyle changes[6].

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Editor's Comment :

- Evening Primrose Oil (EPO) is made from the seeds of the flowers of Oenothera biennis, which has traditionally been used to treat various conditions.
- Over the past few years, interest in EPO has risen due to its supposed benefit in managing PMS.
- The oil contains Gamma-Linolenic Acid (GLA) and other omega-6 fatty acids that have both anti-inflammatory and pain-relieving properties.
- Studies demonstrate that EPO helps significantly relieve the symptoms of Premenstrual syndrome (mainly mood disturbances, breast pain, fatigue).

Selecting a suitable treatment option is further complicated due to available therapies' serious side effect profiles.Supplements like Vitamin B6, Calcium, Vitamin D and Magnesium, Psychotherapy and Dietary changes are less researched alternative treatment options for the management of PMS[7]. With current treatment options lacking efficacy and safety, more research into alternative treatments for PMS management is required. Evening Primrose Oil (EPO) is one of the treatment options that has lately been reported to be beneficial in PMS[8]. This article aims to report the characteristics of EPO and its role in the management of PMS.

EPO and Its Applications :

The oil is derived from the evening primrose seeds (Oenothera biennis), which compriselinoleic acid, Gamma-Linolenic Acid (GLA), and Vitamin E. The

reputation of EPO is related to its chemical components[9,10]. EPO is currently the most essential source of GLA, which is in high demand for its therapeutic and pharmacological applications due to the presence of essential fatty acid and precursor of prostaglandin E1 and its derivatives. EPO contains two types of omega-6 fatty acids: linoleic acid (60-80%) and GLA (8-14%), both of which are considered essential fatty acids since they are not synthesized in the body[11,12]. Disorders for which EPO has been tested in controlled clinical trials include atopic dermatitis, rheumatoid arthritis, diabetic neuropathy, multiple sclerosis, various cancers, Raynaud's phenomenon, ulcerative colitis, and pre-eclampsia, menopausal flushing, breast cysts, mastalgia, Sjogren's syndrome, schizophrenia and hyperactivity[8,13] (Fig 1).

Management of PMS :

Although the etiology of PMS is unknown, various biological theories have been proposed to explain this syndrome.The gonadal hormones have been proposed as causative factors, with theories involving decreased and increased progesterone levels and changes in estrogen or an imbalance between these two hormones.Prolactin, which rises at the time of ovulation and remains high during the luteal phase, is another hormone that has been implicated[14,15].The findings suggested that women with PMS may have abnormal fatty acid metabolism[16]. According to the results of Watanabe's study from 2005, women with PMS had a significantly lower rate of GLA. Decreased prostaglandin E1 increases sensitivity to luteal phase prolactin and other hormones in women with PMS[17,18]. GLA supplementation is believed to improve microcirculation by improving cell membrane function, which results in decreased viscosity. According to the findings of one study, patients' PMS symptoms could be significantly reduced by herbs comprising GLA acid[15]. Studies have shown that consuming 180 mg of GLA-containing vegetable oil daily reduced PMS symptoms considerably and increased plasma phospholipid GLA levels. The findings of these studies suggest that GLA can effectively treat PMS symptoms and that GLA in plasma phospholipids plays an essential role in the onset of PMS[17,19].

Pharmacology of EPO :

Significant components of EPO include linoleic and GLA, from which GLA, an essential fatty acid, is the crucial active ingredient of this oil. These essential fatty acids are not synthesized endogenously and are necessary for the normal structure of cell membranes[20]. EPO's therapeutic activity is linked to the direct influence of its essential fatty acids on immune cells and an indirect effect on eicosanoid synthesis.The action of highly unsaturated fatty acid in tissues and eicosanoids is hypothesized to be involved in its inflammatory activity[21]. EPO contains essential fatty acids that are essential for the formation of PGE. The presence of GLA allows the synthesis of anti-inflammatory substances such as 15-hydroxy-eicosatrienoic acid and PGE1. Supplementation with EPO is assumed to lead to increased concentrations of GLA and DGLA in blood, thereby supporting anti-inflammatory responses. In fact, studies on the effects of GLA supplementation in humans and rodents have demonstrated that the synthesis of the anti-inflammatory PGE1 was substantially elevated. However, a measurable biomarker for the possible efficacy of EPO has not yet been described[22].

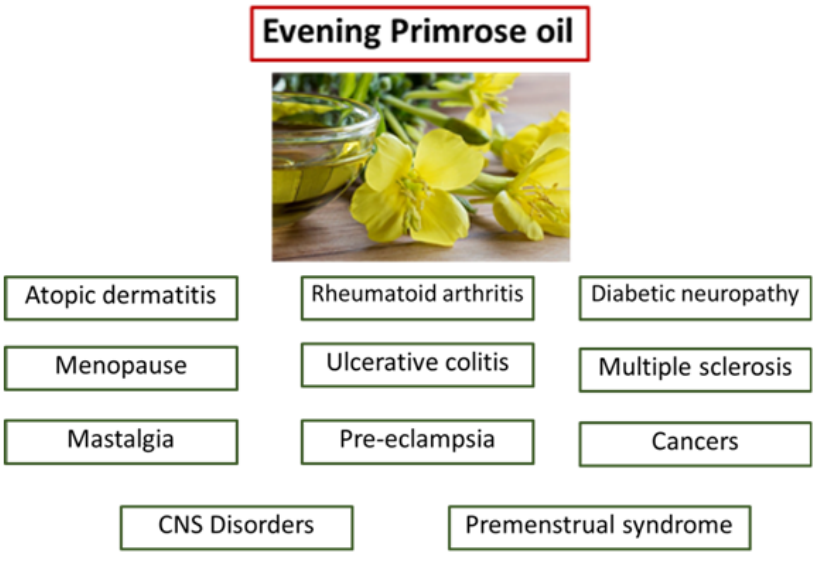

Fig 1 — EPO and its applications

In addition, there is evidence that PGE1, derived from dietary essential fatty acids, is able to attenuate the biological actions of prolactin. Women suffering from PMS may be abnormally sensitive to normal levels of prolactin,and this phenomenon may be related to low PGE1 levels, which in turn may interact with ovarian hormones[23]. Moreover, High prolactin levels associated with low estrogen

levels may cause mood disturbances and other premenstrual symptoms[24]. The essential acids in the EPO help this oversensitivity to prolactin by decreasing the effect of prolactin.Thus administration of linoleic acid and GLA in the form of EPO could potentially alleviate the symptoms of PMS (Fig 2).

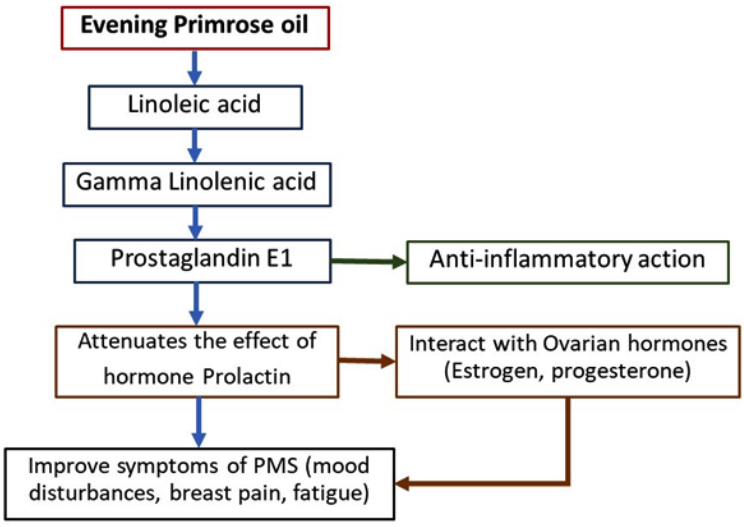

Fig 2 — Mechanism of action of EPO in PMS

Role of primrose oil in PMS :

Many clinical trials have investigated EPO's therapeutic potential in treating PMS (Table 1). Linoleic acid stimulates prostaglandin synthesis and relieves symptoms of PMS. The conclusion of EPO in PMS in clinical trials conducted over the years has been limited[25]. The alleviating effect of 180 mg/day GLA on clinical symptoms of women suffering from PMS in three luteal phases was compared with the placebo in a randomized, double-blind placebo-controlled parallel design.The duration and severity of symptoms were compared in groups using blood samples collected over three cycles. The levels of stearic acid, oleic acid, and Dihomo-Linoleic Acid (DGLA) levels in plasma phospholipids decreased significantly during the follicular and luteal phases. The most common symptom of PMS in women was irritable bowel syndrome, followed by breast swelling, drowsiness, avidity and facial eruption.After treatment, the patients in the GLA group had higher GLA and DGLAlevels in plasma phospholipids compared to the placebo group. Compared to the placebo group, the severity and duration of PMS (Physical, Mental and Social) and irritability improved in the group supplemented with GLA[17]. In another clinical trial, patients were divided into two groups and given either 1.5 g EPO or a placebo daily for three months. EPO significantly reduced PMS severity scores after the intervention when compared to before. After three months of interventions, the EPO and placebo groups saw a significant difference in PMS symptom severity scores[16]. In other studies, 3g of oral EPO or 600 mg of oral vitamin E were given to women

Table 1 — *Clinical trials of EPO in PMS*

Trial	Partici-pants	Intervention	Results
Randomized double-blind placebo-controlled parallel design,	N=28	180 mg GLA orally during the luteal phase	Increase in GLA, DGLA in plasma phospholipid, Improvement of PMS severity and duration (P<0.05)[31]
Placebo randomized control trial	N=80	1.5 g EPO for 3 months	Significant reduction in PMS severity score(p<0.001)[32]
Placebo-controlled,randomized crossover study	N=30	500 mg EPO twice dailystarting on the 15th dayof the cycle and continuing until the nextmenstrual period.	Improvement in PMS score (breast tenderness, abdominal bloating, and breast engorgement)[33]
Double-blind, crossover, placebo-controlled study	N=80	NA	Both psychologicaland physical symptoms improved significantly[26]
Randomized, double-blind, placebo-controlled crossover study.	N=38	500 mg EPO Eight capsules daily for 3 months	Reduced PMS scores after 3 months[28]
Double-blind trial	N=70	1000 mg EPO thrice for 60 days	Significant reduction in stress symptoms (p=0.004), sleep disturbance (p=0.019), appetite for sweets (p=0.014), sore breasts (p=0.025), bloating (p<0.001)[30]

with cyclical mastalgia as a supplement. Vitamin E or EPO therapy significantly improved breast pain scores and decreased pain intensity[26].

Essential fatty acids, linoleic acid and GLA promote prostaglandin synthesis, which has anti-inflammatory and immune-regulating properties and can alleviate the symptoms of PMS. There is some evidence that prostaglandin E1 (PGE), derived from dietary essential fatty acids, can minimize the biological effects of prolactin which has an outsized impact on the absence of PGE[23,27]. Other studies found that treating PMS with EPO for at least six weeks resulted in a significant difference in scores between the EPO and placebo groups, primarily on mood symptoms, feeling of illness, and breast stimulation.According to studies, a daily intake of 2 mg primrose over a three-month treatment period can reduce breast stimulation more than other PMS symptoms. The results from Cornish's analysis indicated that EPO caused a remarkable reduction in agitation, fatigue and depression after the first treatment cycle[28,29]. Moreover, EPO showed better efficacy in managing the symptoms of PMS when compared to Vitamin E supplementation[30].

Safety of EPO :

Clinical studies on the efficacy of EPO on women's health showed its safe therapeutic potential for PMS. EPO was found to be safe upto 6g daily dose in volunteers with PMS[8,34]. EPO is not associated with severe side effects; however, some patients complain of bloating and gastrointestinal problems, nausea, headache,diarrhea, and weight gain after administration of EPO[35,36]. EPO capsules should be taken with food, milk, or liquid to minimize the risk of side effects. There are no known drug interactions. Steroids and nonsteroidal anti-inflammatory drugs may potentially interfere with essential fatty acid metabolism[37].

Conclusion :

The results from studies show that oral supplementation of EPO is effective in the treatment of PMS.The immediate results should not be expected from EPO; therefore, it should be regularly used for up to 4 or 6 months. EPO, which contains linoleic acid, and a considerable amount of GLA, can reduce and alleviate the symptoms of PMS. Many trials to date have been crossover studies in small numbers of patients. Nevertheless, EPO is an exciting substance with promising outcomes in managing PMS. Designing large multi-center clinical trials on the effectiveness of EPO on different ailments,including PMS among women, is needed for future studies.

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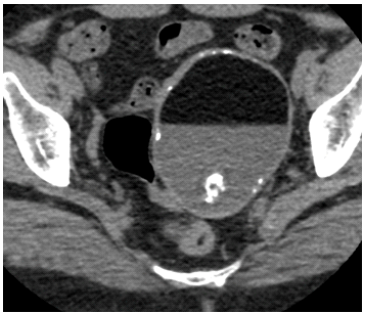
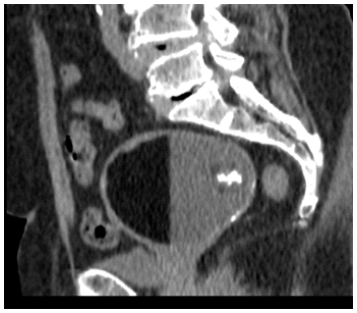
Image in Medicine

Bhoomi Angirish[1], Bhavin Jankharia[2]

Quiz 1

A 52 year Old Female Presented with Lower Abdominal Pain.





Questions :

(1) What is the Diagnosis ?
(2) What are the Imaging findings?
(3) What are complications of this lesion?

Answers :

(1) A well defined lesion showing fat fluid levels and calcification is seen in pelvis in left adnexal region. These findings are suggestive of mature cystic ovarian teratoma or ovarian dermoid cyst.

(2) Pelvic ultrasound is the preferred imaging modality. Ovarian dermoid cyst is seen as cystic adnexal mass with mural hyperechoic nodule (rokitansky nodule). It shows echogenic calcific components, fluid-fluid levels, thin echogenic bands caused by hair in the cyst (dermoid mesh). CT images well demonstrate the fat, fat-fluid levels and calcification within the lesion.

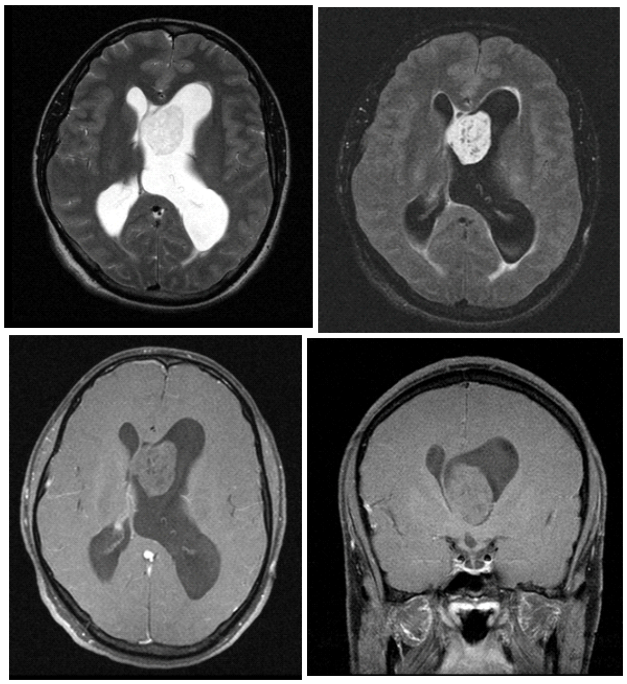
(3) The commonly known complication is ovarian torsion, which occurs in 3-16% of cases and more often in large lesions. Other less common complications are rupture which presents as fatty fluid in anti-dependant pockets in the peritoneum. Malignant transformation of the soft tissue component can also occur.

Quiz 2

A 31 year male presented with headache and giddiness since 3 months.

Questions :

(1) What is the Diagnosis?
(2) What is the Imaging features?
(3) What are the differential Diagnosis?



Answers :

(1) Well defined altered signal intensity lesion is seen within left lateral ventricle attached to septum pellucidum. These imaging findings are suggestive of central neurocytoma.

(2) Central neurocytoma are neuroepithelial intraventricular tumors with fairly characteristic imaging features. Calcification is seen in over half of cases. Cystic areas are frequently seen in larger tumors. These tumors usually show mild to moderate contrast enhancement. Associated ventricular dilatation is often present.

(3) The differentials of intraventricular tumors are :

A) Ependymoma- more commonly in 4th ventricle. Supratentorial tumors have significant extraventricular component. More common in children.

B) Intraventricular meningioma- homogeneous contrast enhancement.

C) Subependymoma – in 4th ventricle. Usually in older age group.

D) Subependymal giant cell astrocytoma – in patients with tuberous sclerosis.

E) Choroid plexus papilloma – intense contrast enhancement. Commonly seen in children.

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Student's Corner

Become a Sherlock Holmes in ECG

M Chenniappan[1]

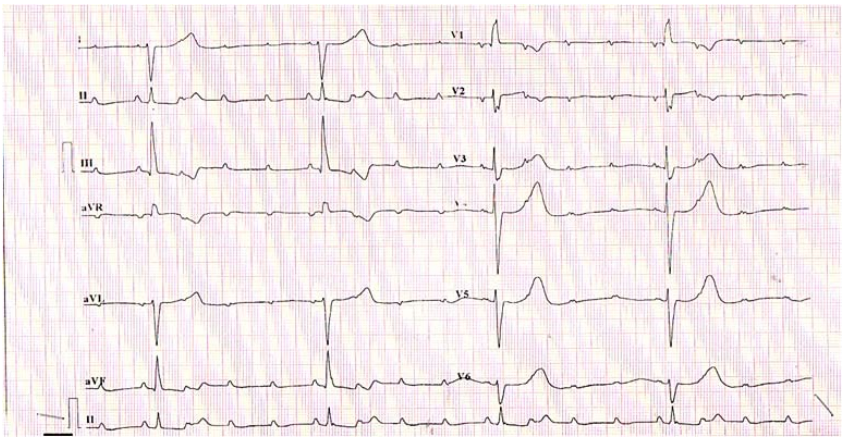
Series 7 :

"Aim High to Diagnose and Treat"

This is the ECG of 69 years old known hypertensive with recent onset breathlessness. No syncope.

Questions :

(1) Describe all ECG changes
(2) Why is this clue ?
(3) What are Practical Implications ?



1mv STD;25mm/sec.

Answers :

(1) ECG FINDINGS :

This ECG shows Bradycardia with wide QRS complexes. The atrial rate is about 100/mt and ventricular rate is about 30/mt. Whenever atrial rate is more than ventricular rate with bradycardia one should suspect Atrio Ventricular Block (AVB). If two or more successive P waves are blocked, as in this ECG, Complete Heart Block (CHB) or High Degree AVB (HDAVB) should be suspected. The most important differentiating point between HDAVB and CHB is the presence of complete Atrio Ventricular Dissociation (AVD) which indicates CHB, where there is no fixed relationship between P and QRS throughout the ECG. But in this ECG, there is definite fixed P–QRS relationship (constant PR interval) for all the beats throughout the ECG and in the rhythm strip. So, this is HDAVB where every fourth P wave is conducted to the ventricles with constant PR. In addition, patient has complete RBBB, Left Posterior Fascicular Block (LPFB). So, the only conducting fascicle is Left Anterior Fascicle (LAF) which is also partially blocked as it blocks 3P waves and conducts only the 4th P wave. The combination of RBBB, LPFB with partial block in LAF makes it a Trifascicular Block.

The other ECG findings are :

(1) Tall Broad T wave with Prolonged QT(?Recent SA Attack)

(2) Progressive decrease in R wave amplitude from V4-V6 (Probable Anterolateral MI–ALMI)

(3) In V1, the terminal negative complex of P is prominent and there are bifid Pwaves inanterior chestleads – (possible Left Atrial Abnormality)

The summary of all ECG findings:

(1) Brady cardia (Atrial Rate >Ventricular Rate)
(2) High Degree AVB with 4:1 conduction
(3) RBBB, LPFB, HDAVB-Trifascicular block
(4) Broad T with Prolonged QTc (?SA Attack)
(5) Probable ALMI
(6) Possible Left Atrial Abnormality

CLUE:

Most often this ECG will be diagnosed as CHB. The Important clue is the absence of AV Dissociation in the presence of fixed PR for conduction beats–which makes it a HDAVB. Because of this, "Aim high to diagnose" is given for suspecting High Degree AVB. Breathlessness in the presence of ALMI and LAA may indicate Heart Failure (HF), most often with preserved Ejection Fraction (HFpEF). This patient definitely requires a Permanent Pacemaker Implantation. Because of the possibility of HFPEF, one should always plan a Dual Chamber Pacemakeras the stiff ventricle needs atrial support. In single chamber pacemaker, there is Atrio Ventricular dissociation where a trium and ventricles are beating independently. So, pacing must include Higher chamber (Atrium) also. So, you have to also "Aim High for treatment". Because of both the above reasons, the clue of "Aim high to diagnose and treatment" is given.

PRACTICAL IMPLICATION:

In addition to dual Chamber Pacemaker, patient requires management for CAD and appropriate treatment for HF especially for HFpEF.

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Medical History

Medicine in Art

Rudrajit Paul[1]

[Over the ages, the medical profession has been described and portrayed in various ways by artists. It is worthwhile to look at those portrayals in order to understand the relation between a society and its healers.]

This oil painting (Fig 1) by American artist **Thomas Eakins** shows a doctor (Dr Gross) performing a surgery in his clinic in 1875. As is seen here, the doctor is performing his surgery while also teaching his students. The very concept of antisepsis during surgery was absent then. So, the surgeons are dressed in full formal suits with no face mask or cap or gloves. Also note the fact that all the doctors and students (in the gallery) were male. No nurse is shown anywhere. The patient's mother is sitting right beside the operation table, cringing. Far before the advent of modern consumer-court based protocols, it was very common to keep the patient's relatives in the same room while performing gory procedures.

Fig 1 — The clinic of Dr Gross (Public domain)

Fig 2 — Doctor's Office : Norman Rockwell

The figure of the surgeon is portrayed almost like a painter at work, thereby showing the finesse required for the procedure. This painting is considered one of the greatest examples of American art of the nineteenth century. But operation theatre culture was changing quickly and this casually dressed surgeon would soon be a thing of the past.

The Fig 2 is a painting by one of the most famous twentieth century American painters : **Norman Rockwell.** This shows a boy standing on a chair while the doctor is preparing an injection, probably a vaccine. The boy is apprehensive and is peering at the certificates of the doctor hung on the wall, presumably to assess his authenticity and expertise!! This wonderful painting is a glimpse of a family physician's clinic in mid-twentieth century USA, before medical profession became a hospital-based juggernaut.

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Letters to the Editor

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

Argatroban for the Management of Heparin induced thrombocytopenia in COVID-19 Cases

Sir, — We congratulate A Chandra *et al* for their case report on Thrombocytopenia in COVID-19. The situation of thrombocytopenia in COVID-19, poses a great diagnostic and therapeutic challenge in addition to it being a predictor of bad prognosis. Mild thrombocytopenia is common, but if there is severe thrombocytopenia while on heparin, one has to consider Heparin Induced Thrombocytopenia (HIT). As the patient showed sign of acute kidney injury Low Molecular Weight Heparin (LMWH) had been switched to Unfractionated Heparin (UFH). Heparin induced thrombocytopenia is more likely with UFH than with LMWH. As per Patell *et al* the prevalence of HIT antibodies is higher than in other situations[1].

Both the factors, COVID-19 infection and HIT, are prothrombotic state. It is a real dilemma how to manage venous thromboembolism in presence of thrombocytopenia. As per few case reports and literature, direct thrombin inhibitors may be considered for anticoagulation. The anticoagulants in this category are fondaparinux, argatroban, danaparoid and bivalirudin. Ogawa et al and Lingameneni et al had successfully managed a case each with argatroban[2,3]. Argatroban has a short half life of 24 minutes and require parenteral infusion at a rate of 1-2mcg/kg/minute. It requires monitoring to keep a target aPTT of 1.5 to 3 times the initial value. One has to consider the risk of bleeding as Patell et al found that 3 of their patients had developed major bleeding. If there is a risk of bleeding it may be initiated at a much lower dose, especially if the patient has liver dysfunction.

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A Comparative Study of the biochemical components of Human Umbilical Cord Blood and Adult Peripheral Blood

Sir, — Human umbilical cord blood is a massive and potential resource useful in combating many chronic diseases like anemia, leprosy, tuberculosis etc. Cord blood, being fetal in nature, is predominantly rich with hematopoietic stem cells, enriched with cytokines, growth factors and progenitor cells that can have a profound effect against chronic diseases, genetic disorders and many more. This study aimed to determine whether there was any difference between the biochemical components of Human umbilical cord blood & adult peripheral blood. 5 test samples are taken from both the Human umbilical cord blood and the adult peripheral blood and first undergo microscopic examination through a blood smear test to determine the size, shape and different types of blood cells. Secondly, hematological examination such as CBC, ie, Complete blood count, haematocrit value. Thirdly, serum metabolites value (like glucose, albumins, bile acids, bilirubin, cholesterol etc) Also, cytokine studies such as IL-6 (Interleukin- 6) determine whether it acts as a pro-inflammatory or anti-inflammatory cytokine. This study should be conducted in every institute for the betterment of Human race. It is a futuristic medicine approach through which we can achieve some of the greatest things of all time. This modern medicine study shows you what we can use from the garbage material to turn it into gold.

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Colchicine In COVID-19

Sir, — As wave after wave of the COVID-19 pandemic catches us off guard, more than ever is the need for a medicine that can rapidly, effectively, and decisively, changes the course and turn the tide of this devastating disease. The authors, hereby, wish to discuss the role of Colchicine for COVID-19 disease.

Colchicine is an alkaloid derived from the bulb-like roots of plant *Colchicum autumnale,* also known as *Autumn crocus*. Traditionally, it has been specifically used for suppressing gouty inflammation, for which it has been credited to be the fastest drug to control an acute attack[1]. Dose is 0.5mg 1-3 hourly, with a total of 4 doses in a day; maximum 6 mg in a course spread over 3-4 days may be given[1]. The response is dramatic, and may even be considered diagnostic. It is also used in Familial Mediterranean fever, Behcet's disease, pericarditis and atrial fibrillation[2].

Colchicine suppresses the inflammatory response by[1,3] : (a) preventing granulocyte migration to the site of inflammation, (b) inhibiting the release of glycoproteins, which is responsible for aggravating inflammation by forming lactic acid and releasing lysosomal enzymes,

(c) binding to intracellular protein 'tubulin', and causing depolymerization and disappearance of microtubules in granulocytes, causing metaphase arrest. As a result of this, migration of granulocytes into the area of inflammation is not only distorted but prevented, thereby interrupting the vicious cycle. Colchicine treated neutrophils develop a "*drunken walk*". Colchicine has the distinctive feature of accumulating in inflammatory cells at the site of inflammation, and reaching a higher concentration than plasma levels, with a markedly longduration of action[4]. It is rapidly absorbed orally, undergoes enterohepatic circulation and ultimately is disposed in urine and feces over many days[1,3]. Concurrent use of inhibitors of CYP3A4 and P-glycoprotein such as erythromycin, tetracycline, grape fruit juice, lopinavir and ritonavir, ketoconazole, diltiazem, verapamil, cimetidine, amiodarone, tamoxifen, quinidine, tacrolimus and cyclosporine can cause colchicine toxicity[2].

Colchicine has a narrow therapeutic index and toxicity is dose related. Nausea, vomiting, diarrhea and abdominal cramps (neurogenic stimulation of gut motility) occur as dose limiting adverse effects. Accumulation of the drug in intestine and inhibition of mitosis in its rapid turnover mucosa is responsible for the toxicity. In overdose, colchicine produces bloody diarrhea, throat pain, kidney damage, CNS depression; death is due to muscular paralysis and respiratory failure[1,3].

For COVID-19 disease, currently, oxygen, steroids and low molecular weight heparin have been the most used drugs, at a time when we still search for an anti-viral that can actually make a difference. With the experience of more than one year, it has been seen that the best time to start a steroid is the onset of inflammatory phase when hypoxemia starts setting in, with or without breathlessness. But like all medicines, steroids too have their limitation in terms of wide array of side effects that they cause. Their effect is non-specific and covers all components and stages of inflammation[1].

Ten colchicine clinical trials are currently in various stages of progress for the treatment of SARS-CoV-2 treatment and are listed on clinicaltrials.gov[4]. They differ in the timing of initiation as well as the dosing of colchicine. Some studies begin treatment in the outpatient setting and others in early inpatient setting. Dose varies from 0.5mg twice daily for three days followed by 0.5 mg for next 27 days to others like 0.5 mg or 0.6mg twice daily for 14 days or until discharge. Colchicine is cost effective and can prove to be a game changer when given during the early pulmonary phase of COVID-19, coinciding with the rise of inflammatory markers like CRP (C-reactive protein) and worsening of radiological severity. One suchrandomized controlled trial conducted in 2020 in adults with moderate or severe forms of COVID-19, with a total of 72 patients (including placebo group), showed improvement in terms of need for oxygen and length of hospitalization[5]. Researchers used the dose of 0.5 mg thrice daily for 5 days, then 0.5mg twice daily for next 5 days; if body weight was more than or equal to 80 kg then first dose was 1 mg. Dose was reduced in chronic kidney disease. Majority of adverse events were mild. While new or worsened diarrhea was more frequent in intervention group (17% *versus* 6%), none of the patients suffered dehydration, and the diarrhea was controlled with prescription of an anti- secretory drug (ex. racecadotril).

It is hereby proposed that colchicine may be considered in moderate COVID disease as the first anti-inflammatory agent, to which steroid may be added later as hypoxemia worsens. It may be given in both outpatient and inpatient setting, especially in high risk individuals by informed clinicians.

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