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MGMJMS

MGM Journal of Medical Sciences

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From the Editor's Desk

National Medical Commission (NMC) Bill, India, 2019: Long-awaited Change with a Mixed Response

NMC bill 2019 was passed by both the Houses of Parliament in August 2019 and got President's assent too. Now it is a law. Health Minister of India has recently announced that the detailed rules under this law will be worked out in the next six months. We have been expecting serious reforms in medical education for quite some time. A positive response from medical fraternity was expected, but there was a mixed reaction once the bill was moved in the Parliament. There were demonstrations too against the certain provisions of the bill. I think, we need not be impatient; probably it is too early to understand the full implications of the bill. There were some misconceptions too which were clarified by the Health Minister later. In my opinion, we should wait for the publication of rule book by the government before summarily rejecting it.

The NMC bill or now it can be referred to as the NMC law has replaced the existing Medical Council of India (MCI). The MCI came into existence in 1934 under 'Medical Council of India Act 1934. Its sole purpose was to set the standards and regulate medical education in India. MCI has always been in limelight for the wrong reasons. Corruption charges were leveled against it time and again. In the education field too it failed to deliver. The question at the moment is: Is NMC a cure for ailing medical education in India? The MCI was an autonomous body with more than two-thirds of its members (100+) were directly elected by the medical fraternity. The elections were said to be rigged. There were lobbies working in the interest of vested parties rather than for patient care and medical education. The new body 'the NMC' will have 25 members with no directly elected member. We hope, it will be effective and will remain corruption-free.

Let's have a look at the salient features of the NMC bill. The creation of four Boards to take care of different functions:

1. Board for undergraduate education
2. Board for PG education
3. Board for rating and medical assessment
4. Board for ethics. It will also maintain national register of medical practitioners and community health providers (CHPs).

Creation of these Boards may seem alright but once we go into details, there are a few new provisions, which catch our imagination (1) CHPs, (2) NEXT (National Exit Test), (3) 50% seats allocated to the management of private medical colleges, (4) Flexibility to medical colleges:

1. The CHPs would be the new class of authorized medical personnel who could provide primary care to the deprived population in the villages and other backward areas. Their total number will be restricted to one-third of the medical practitioners. In India, there is a gross disparity between the availability of medical care at the village level, town level, city level, and megacity level. The availability of community health providers at the village and town levels may be of help to the local community. However, there are other views too. The apprehension of IMA (Indian Medical Association) about CHP is that "They may not have sufficient background in the study of anatomy, physiology or pathology, etc. which form the basis of modern medicine. Besides, their significant presence will endanger patient safety and dilute health care in the country, especially in rural areas."
2. National Exit Test (NEXT): Earlier, only NEET was required for entry into PG courses. No separate exam was required to getting permission or license to practice medicine after passing the university exam. With a new bill, NEXT will be mandatory after final MBBS to practice medicine. This may place additional stress on the students but will create uniform national standards and remove bias. I talked to many undergraduates about it, most of them were apprehensive and were misinformed that they can appear only once for NEXT and it will start from 2020. Health Minister later clarified that a student can appear any number of times and NEXT will start three years from now. The extremely low number of PG seats is another worry of the students. We must appreciate that time has changed. It is difficult to practice effectively and provide optimum health care even in remote areas only after MBBS. Postgraduation, especially in clinical subjects, is a must for improving the health standards of the deprived population. Therefore doubling the PG seats from existing 23,000 to at least 50,000 should be done on a priority basis.
3. Fees structure for 50% of seats in private medical colleges can be fixed by the management. Some people see it as a bonanza for the private medical colleges but my sense is that it will add additional medical and hostel facilities in these colleges and start a competition to attain better ranking to attract students. At the moment, most of the private medical colleges are struggling with resource crunch. However, there is a caveat to this. The Health Minister says "The NMC would control the fees and other charges of 50% of seats in private medical colleges. The states would have the authority to come up with state amendments regarding the regulation of fees for the remaining 50% seats" in private colleges. At present, the state decides fee structure for 85% seats and 15% are left for the college management.
4. The NMC bill includes several path-breaking recommendations to provide greater flexibility to medical institutions, increasing the number of doctors while ensuring quality. For instance, one-time permission will be required by medical colleges for establishment. It will also be possible for them to increase the number of seats on their own up to a cap of 250 and start postgraduate courses. Additional changes are needed in presently very stringent regulatory standards to start and run a medical college. The cost of starting a new medical college is about Rs. 5 crore per bed. The land requirement and infrastructure needs are too extensive and can be reduced. The minimum standard requirements of the number of patients in OPD, IPD, major and minor surgeries, deliveries, imaging, lab investigations are irrational. The requirement is considerably higher than that of developed nations like USA and UK. These mandatory requirements are considered the biggest roadblock in the development of medical colleges in India.

To conclude, the NMC bill, 2019, is a new beginning in medical education and health care in India. Better training will produce better doctors. However, we do recommend increasing undergraduate and postgraduate seats so as to fulfill the aspiration of India's young population for medical education and the deprived masses for health care. The main strength of India is its young generation who could be trained in health care with global standard and may become global healthcare provider.

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Contents

ORIGINAL ARTICLE

Predictors of Mortality in Vasculotoxic and Neurotoxic Snakebite Patients in a Tertiary Care Institute in Jharkhand, India

Kanishka Kumar[1], Prashant Upadhyay[2], Rajendra Jha[3], Sushil Kacchhap[4]

Abstract

Introduction: The paper presents a study carried out in vasculotoxic and neurotoxic snakebite cases to find out the predictors of mortality in the state of Jharkhand.

Materials and methods: An estimated 58 snakebite patients who fulfilled the inclusion criteria were enrolled into the study. The clinical parameters and epidemiological data were noted during admission. Patients were followed up during their stay in the hospital for the progress of the symptoms and the treatment effects. Data obtained were analyzed using SPSS and Microsoft Excel.

Results: There was a significant positive association between the occurrence of GI bleed/epistaxis, DIC, or shock with an increased mortality in vasculotoxic snakebite cases. In the cases of neurotoxic snakebite, the occurrence of cardiac arrhythmias or respiratory failure was foretellers of an increased chance of mortality. Amongst the patients with vasculotoxic snakebite, local bleeding was present in all the patients and the infection was found in 94% of them. The complications included DIC in 36% of patients, GI bleed in 9%, epistaxis or gum bleed in 9%, shock in 21%, acute renal failure in 50%, and neurotoxic signs in 6% of the patients. In the neurotoxic subset, the most frequent symptoms were ptosis and blurring of vision, both in 100% of the cases, generalized paralysis in 79%, and local pain with swelling in 67%. Respiratory failure was seen in 50%, infection in 45%, cardiac arrhythmias in 33%, shock in 12%, and hepatotoxic features in 20%. Most of the patients required 30 vials or less of anti-snake venom serum (ASVS).

Conclusion: GI bleed/epistaxis, DIC, or shock are positive predictors of mortality in vasculotoxic snakebite cases, while the occurrence of cardiac arrhythmias or respiratory failure are markers of a poor prognosis in neurotoxic snakebite cases.

Keywords: Emergency medicine, Snakebite, Venom.

MGM Journal of Medical Sciences (2019): 10.5005/jp-journals-10036-1233

Introduction

Snakebite is a common occurrence in a country such as India[1] and more so in a tribal state such as Jharkhand, where the majority of the population lives in either villages or hilly areas.

Fatalities due to snakebite is due to wide snake species, poverty, shortage of anti-snake venom, poor compliance with treatment protocols, and a lack of public awareness along with a general state of ignorance about emergency management of snakebite cases across all regions within India. The overenthusiastic and overzealous reliance on faith healers due to a generally low level of social education is another frontier that needs to be crossed for improving care practices.

This study was done to ascertain the factors related to mortality during the course of the disease and treatment.

Aims and Objectives

- To study the clinical presentation and complications of snakebite.
- To find out the relationship between clinical features, complications, treatment modalities, and mortality

Materials and Methods

Patients admitted to the department of medicine who fulfilled the inclusion criteria were taken for the study and were evaluated using the proforma. Patients were followed up for their duration of stay in the hospital with a close watch being kept on the development of clinical features and complications and the treatment being given. Standard laboratory tests were used in the quantification and diagnosis, as was guided by the proforma of the study.

The data so obtained were represented in the form of a master chart using Microsoft Excel and were classified in groups for an easy statistical classification and analysis. IBM SPSS was used for the statistical evaluation. Pie charts and bar figures were used for representation of frequency and the Chi-square test was used for testing of association between various variables (Figs 1 and 2).

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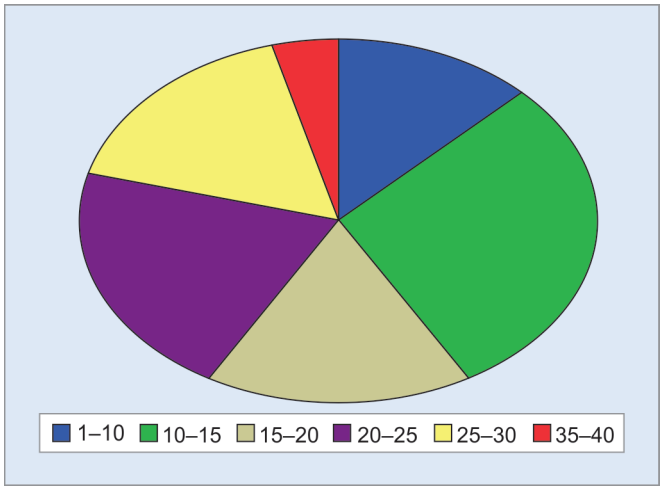

Fig. 1: Use of anti-snake venom serum (ASVS)

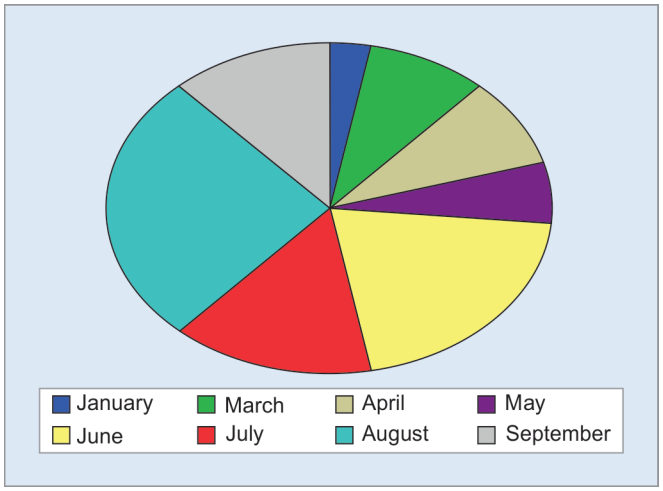

Fig. 2: Months of bite

Results

Fifty-eight cases were examined, of which 24 (41%) turned out to be neurotoxic and 34 (59%) vasculotoxic snakebite cases. The mean age in both groups was around the 30-year mark, which tells us that the effective management of snakebite cases is all the more important because most of the patients involved are in the peak of their productive life. While most of the neurotoxic bites occurred in the evening and night (84%), the vasculotoxic bites (57%) were reported to occur in the evening and night with the rest of them happening during the daytime. There were no major sex differences in the cases of snakebites amongst both vasculotoxic and neurotoxic groups, with both males and females being affected equally. Maximum cases occurred while the patient was sleeping: neurotoxic (75%) and vasculotoxic (50%). The limbs formed the major site of the bite, with the hands being the most common among the neurotoxic and the legs amongst the vasculotoxic group.

Majority of the cases of neurotoxic bites got to the hospital within the first 4 hours (58%) while it was only 35% in the vasculotoxic group. However, if we take 8 hours as the marker of getting to the hospital quickly for a state such as Jharkhand, where there is a dearth of local transport availability and bad terrain almost 75% of neurotoxic cases and 67% of vasculotoxic cases got to the hospital and had been started on treatment.

Fang marks were identifiable only in 46% of the patients. Most of these and subsequent findings are concurrent with those of other recent papers. In the neurotoxic subset, the most frequent symptoms were ptosis and blurring of vision, both in 100% of the cases, generalized paralysis in 79%, and local pain with blistering in 67%. Respiratory failure was seen in 50%, infection in 45%, cardiac arrhythmias in 33%, shock in 12%, and hematotoxic features in 20%. Ninety-five percent of the patients required less than 30 vials of ASVS with 42% requiring less than 15 vials. Mortality was seen in 4/24 cases (Fig. 3). Looking into the neurotoxic cases, the predictors of outcome and complications were looked into.

There was no significant association with:

- The time of bite
- The part of the body bitten
- The time taken to get to the hospital
- Infection

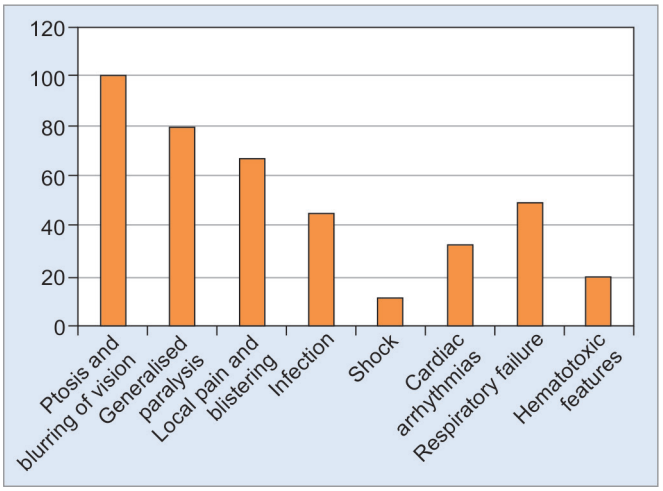

Fig. 3: Symptoms amongst neurotoxic bites

- Blurring of vision
- Ptosis
- Generalized paralysis
- Clotting time, or
- The amount of ASVS used.

However, a positive association was found among cardiac arrhythmias ($p = 0.01$), respiratory paralysis ($p = 0.02$), and mortality.

In the vasculotoxic subset, the whole blood clotting time at admission was deranged in about 80% of patients. Amongst the symptoms and signs of snakebite, local bleeding was present in 100% while the infection was present in 94%. DIC (36%), GI bleed (9%), epistaxis/gum bleed (9%), shock (21%), ARF (50%), and neurotoxic signs in 6% of the cases formed the complications (Fig. 4). Most (97%) of the patients required less than 30 vials of ASVS.

Testing for the parameters that may foretell the prognosis of the case and the likelihood of discharge or complications, there was no significant association with:

- The part of body bitten
- The time taken to get to the hospital
- Local treatment given
- The amount of ASVS used
- Neurotoxic features

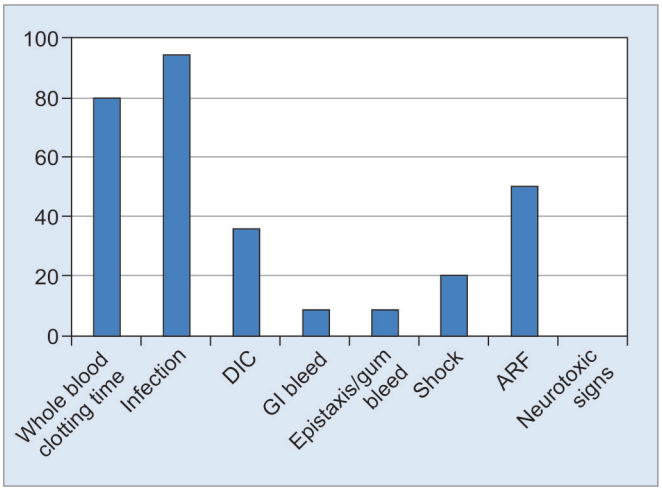

Fig. 4: Symptoms amongst vasculotoxic bites

- ECG changes, or
- Local infection.

Even the presence of acute kidney injury did not have a significant association with mortality. This may be due to the life-saving use of hemodialysis.

However, the development of DIC ($p = 0.014$), shock ($p = 0.000$), and epistaxis/gum bleed ($p = 0.000$) all had a positive association with a bad prognosis.

Discussion

Snakebite as has already been talked about is a grave danger for a country such as India and more so for a state such as Jharkhand, where the majority of the population lives in villages that are hilly in terrain and often difficult to access and is prone to incidence of snakebite.[1]

Amongst 58 patients evaluated, 24 had neurotoxic snakebite and 34 had vasculotoxic snakebite. The mean age of the patients was 30 years. This group is the most active; hence they have more probability of snakebites.

In the vasculotoxic group, the maximum bite incidence occurred between 6 am and 6 pm (41%) and another 32% indicidence is found to occur in the evening. This can easily be explained by the fact that cobra and krait (i.e., the neurotoxic snakes) are active at night, while the vipers are active in the daytime. The neurotoxic snakes may also bite during the day if disturbed while they are looking for food.

In both the groups, we saw that the maximum people were bitten while they were asleep and more so in the neurotoxic group (75%) than in the vasculotoxic group (50%). This has important implications, as it is a modifiable variable where a person may reduce his/her risk of a bite by not sleeping on the floor and trying to build a pucca house, which has fewer avenues for the snakes to come in. In cases of neurotoxic, the incidence of bite occurs on hands (50%), which is higher than in vasculotoxic (35%). Bite on the legs was much more common in vasculotoxic snakebite cases (67%) probably because of the more daytime bites and bites while the patient was either walking or working. In the neurotoxic subset, there were a few (3) cases of bites on the trunk and head neck area, which are considered rare and much more dangerous. Time to get to the hospital varies a lot with the types of bites. In the neurotoxic set, 58% of patients were brought to the hospital within the first four hours and no patients were brought later than 24 hours after the incident. In the vasculotoxic group, we see that only 35% of patients were brought within the first four hours and some patients (15%) were brought in later than a day.

The symptoms in the cases of neurotoxic snakebites are much more dramatic. Ptosis, respiratory failure, and generalized paralysis along with other symptoms lead the patients and attendants to rush to the hospital as soon as possible, whereas in the vasculotoxic group, the swelling of the part bitten, bleeding from various sites, shock, and acute kidney injury take some time to get established and therefore the patient is brought in a little later.

Pain and blistering is a common sign that occurs very early and was found to be present in 68% of the patients. It is one of the symptoms which are important because it draws the attention of the patient as well as attendants before the patient's condition becomes unsalvageable.

It is very interesting to note that 100% of the patients in the neurotoxic group had blurring of vision; therefore, this could be an important marker for being sure about the neurotoxicity of the case. Ptosis like a blurring of vision was also present in 100% of the patients. Generalized paralysis was present in 80% of the patients involving the limbs, which recovered on ASVS treatment. Respiratory failure (one of the most dangerous complications) occurred in exactly half of the patients studied. These patients needed mechanical ventilation for a duration of 1–7 days using GE Engstrom Carestation machine and made a good recovery.

Cardiac arrhythmias (67%) range from ST changes to arrhythmias, and in one case, frank ST-elevation myocardial infarction was seen. It may be due to cardiotoxins present in the snake venom. The hemodynamic shock was present in a few patients (3/24).

Visible fang marks were present in only 46% of the patients, and 54% of the patients had no fang marks. Therefore, fang marks can be considered as a reliable sign of envenomation.

Thirteen percent of patients got relief with a mere 10 vials of ASVS, which is only the first dose. An estimated 43% patients were treated in 15 vials and almost 60% in 20 vials. Totally, 80% of the patients needed less than 25 vials and only 5% needed more than 30 vials. In neurotoxic snakebite, the toxin is injected all at once and therefore a lesser number of ASVS is required for the treatment.

Clotting time was deranged in 71% of patients with vasculotoxic snakebite compared to 42% in a neurotoxic bite.

Like blurring of vision and ptosis were present in 100% of the patients of neurotoxic snake bite, local bleeding from the site of bleed was present in 100% of the vasculotoxic cases. Infection was present in 94% of the patients. Infection is very common in vasculotoxic cases because while the snake releases the toxins there is a grater chance of infection from the flora of the snake's teeth. The incidence of infection is much more in vasculotoxic than in neurotoxic cases (46%) as the toxin is present in the local tissue for a long time and leads to severe necrosis of the local tissue with subsequent gangrene and more avenues for infection. Higher and more prompt institution of antibiotics is important in the cases of vasculotoxic cases as otherwise there are other complications owing to sepsis. Disseminated intravascular coagulation (DIC) is a frequent manifestation of vasculotoxic snake bite owing to consumptive coagulopathy caused by the toxin especially in cases of vasculotoxic snakebite cases. It leads to severe bleeding from both external sites and tissue, including visceral bleed, retroperitoneal hemorrhage, cerebrovascular accident (commonly hemorrhage but in a rare

case a patient had parietal infarct) and system damage owing to hypoperfusion. DIC is also precipitated by the increased incidence of septicemia that is a frequent accompaniment in cases of vasculotoxic snakebite cases. It rapidly changes the treatment paradigm because now the coagulopathy is not only due to the direct effect of the toxin but as a result of the cascade of consumptive coagulopathy that is set into motion. Prompt ASVS therapy with well-targeted antibiotics and blood products such as fresh frozen plasma, cryoprecipitate are the mainstay of the treatment. Along with it the patient is treated for any system failure that might ensue most commonly the renal system. The incidence of GI bleed and epistaxis was very less, which about 9% each in the patients surveyed. The shock was found in about 21% of the patients and is more common in vasculotoxic cases compared to 13% in neurotoxic. The mechanism is a little different. While in neurotoxic the shock is caused by a direct cardio depressant effect and autonomic disturbances, the shock in vasculotoxic cases is caused by increased vascular permeability, leading to leakage of fluid into extravascular spaces and increased exudation. There is vasodilation and resultant hypotension, often leading to tissue hypoperfusion and failure of various systems. ARF or acute renal failure is another common complication in case of vasculotoxic snakebite cases. The incidence was 50% of the total patients.

Neurotoxic features that is ptosis, blurring of vision, and difficulty in breathing are generally signs of neurotoxic snake bite cases, but in a few cases (2/34), these features were also found in the vasculotoxic subgroup. The effects are well documented in some cases of bites by *Dabiola russeli*, which is the most common vasculotoxic snake found in our part of the world.

The mortality rate in cases of vasculotoxic cases were about 9%, which was mostly due to shock and acute kidney failure that did not even respond as a result of vigorous renal replacement therapy.

Testing for association between two-factor Chi-square and Fischer exact test were applied and the cross-tabulation was done.

Vasculotoxic Snakebites

There was a positive association between the part of the body bitten and the whole blood clotting time amongst vasculotoxic cases ($p = 0.04$) with more cases with deranged clotting time were bitten on the hands. Testing for the parameters that may foretell the prognosis, there was no significant association with

- The part of the body bitten
- The time taken to get to the hospital
- Local treatment given
- The amount of ASVS used
- Neurotoxic features
- ECG changes or
- Local infection.

Even the presence of acute kidney injury did not have a significant association ($p = 0.07$), which is most probably due to the widespread use of hemodialysis. However, the development of DIC ($p = 0.014$), shock ($p = 0.000$), and epistaxis/gum bleed ($p = 0.000$) all had a positive association with a bad prognosis. Amongst the other factors (the amount of ASVS required, the time taken to get to the hospital, the part of the body bitten, the time of the bite or whether the person was sleeping or awake), no strong association was found.

Neurotoxic Cases

Looking into the neurotoxic cases, the predictors of outcome and complications were looked into. There was no significant association with:

- The time of bite
- The part of the body bitten
- The time taken to get to the hospital
- Infection
- Blurring of vision
- Ptosis
- Generalized paralysis
- Clotting time or
- Amount of ASVS used.

However there were following strong associations:

The occurrence of respiratory paralysis ($p = 0.02$) and cardiac arrhythmias ($p = 0.01$) have a significant positive association with a worse outcome.

Sharma et al.[2] presented a study of 142 snakebite cases. Neuroparlalytic cases were predominant, with their number being 86; there were 52 vasculotoxic cases. Average time to arrival at their hospital after the bite was 9 hours and the mean duration of hospital stay was 8 days. Twenty-seven cases had acute renal failure and 75% of all neurotoxic bites required assisted ventilation. The average dose of antivenom was 51.2 vials for neurotoxic bites and 31 vials for haemotoxic bites.

Bawaskar et al.[3] in their 91 snakebite cases at Mahad of Mumbai in western Maharashtra found that Forty-five (49.5%) patients had snakebite without envenoming. Twenty-six (28.6%) patients were paralyzed and ten (11.0%) patients died.

In the study of Suchithra et al.,[4] 200 (34%) of 586 cases with snakebites had envenoming. Snake species could be identified in 34.5% of the venomous bites. 93.5% had signs of local envenoming. Failure of coagulation, respiratory failure, and intracerebral bleed were the determinants of mortality.

Bawaskar et al.[5] did a study on 182 snakebite cases. Totally, 55 (30.2%), 38 (20.8%), 48 (26.3%), 41 (22.5%) cases were bitten by *Echis carinatus* (Eh), Russell's viper (Rv), krait (Kr), and cobra (Cr), respectively.

In Hayat et al.[6] study, one hundred (100) cases from both genders, from 8 years to 55 years age were reviewed. There were 57 (95%) hemotoxic having hemostatic abnormalities and 3 (5%) neurotoxic bites presented with neuroparalytic symptoms. The average dose of anti-venom was 60 vials for viper bites and 10 vials for elapid bites. The overall mortality rate was 4%. An estimated 13 (86.66%) patients had respiratory paralysis requiring ventilatory assistance. Totally, 17 (19.31%) patients had clinical and laboratory parameters favoring DIC. A total of 12 (13.62%) patients had ARF in the study, and 2 (2.27%) patients succumbed amongst vasculotoxic snakebite cases.

Bawaskar et al.[7] studied 30 subjects of presumed snake envenoming (krait = 23 cases, cobra = 7 cases). Of the 23 subjects (11 male, 12 female) bitten by kraits, 2 were deceased upon arrival, 7 died in the hospital, and 14 recovered. Of the 14 survivors, 4 required artificial respirations. Of the 7 subjects (5 male; 2 female) who encountered cobras, 2 were deceased upon arriving at the hospital, and 1 died suddenly of an apparent cardiac arrest. Four subjects recovered with ASV, anticholinesterase drugs, and/or artificial respiration.

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ORIGINAL ARTICLE

Telemedicine as a Cost-effective Tool for Cardiovascular Diseases in Rural India: A Pilot Study in Delhi-NCR

Nisha[1], Shridhar Dwivedi[2], Suresh K Gupta[3]

Abstract

Objective: Telemedicine is an economical tool for providing healthcare to remote areas. So far, not much is known about such endeavors targeting rural parts of India. The National Heart Institute, New Delhi joined hands with an NGO at Jewar, Greater Noida (predominantly a rural area) to provide teleconsultation to patients attending the Community Health Center. The present study aims to evaluate the direct and indirect cost of treating cardiovascular diseases using teleservices at Jewar.

Materials and methods: It is a prospective, observational, and questionnaire-based study regarding the rural India. The demographic and complete clinical profile is noted in the telemedicine e-sanjeevani portal by a patient coordinator. A plausible clinical diagnosis is made at the NHI end after interacting with a patient on television and reviewing relevant investigations followed by instructions about drug treatment. At the end of the telesession, the direct cost (including medication, lab-investigation, consultation, transportation, any adverse drug reaction, internet, and setup cost) is calculated. The indirect medical cost was worked out using the human capital approaches such as the productivity loss of both the patient and attendants.

Results: A total of 100 consecutive cardiovascular patients (including diabetes cases attending telemedicine sessions at NHI) were studied. There were 53 males and 47 females. The mean age of patients was found to be 55.29 ± 11.6 years (mean ± SD). The common cardiovascular diseases noted were found to be diabetes alone (48%), hypertension and diabetes (24%), diabetes and other comorbid conditions (9%), hypertension alone (9%), diabetes with two cardiovascular conditions (4%), diabetes, hypothyroidism and cardiovascular diseases (3%), hypertension associated with coronary artery disease (2%), and coronary artery disease alone (1%) in that order. The average treatment cost per patient (direct as well as indirect) for 10-month duration for diabetes alone was INR 6,302.22 (630.22/month), diabetes and hypertension together cost INR 10,546.71 (1,054.67/month), diabetes with other comorbid condition cost INR 12,086.62 (1,208.66/month), hypertension cost INR 15,505.63 (1,550.57/month), diabetes and other two cardiovascular diseases cost INR 8,376.91 (837.69/month), diabetes and hypothyroidism and cardiovascular diseases cost INR 13,899.80 (1,389.98/month), hypertension and coronary artery disease cost INR 8,844.33 (884.43/month), and coronary artery disease cost INR 2,125.34 (212.53/month). The overall total cost direct as well as indirect for this telemedicine project was around INR 9,09,095.63, including direct, indirect, set-up and internet charges for 10-months tenure.

Conclusion: Telemedicine for rural people is a feasible proposition. Diabetes was found to be the most prevalent disease, thus possesses the maximum overall economic burden. The treatment for diabetes alone costs less than for diabetes associated with other comorbidities. Government telemedicine initiatives in India will further reduce the direct medical cost burden on rural patients substantially. Women empowerment is another important aspect of telemedicine. Adoption of this telemedicine model by health policymakers in India will lead to the better and affordable treatment to rural patients suffering from cardiovascular diseases.

Keywords: Cardiovascular diseases, Cost-of-illness, Diabetes, Rural health care, Telemedicine.

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Introduction

Telemedicine, as per World Health Organization (WHO), is the delivery of healthcare services, where distance is a critical factor, by all healthcare professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment, and prevention of disease and injuries, research and evaluation and for the continuing education of healthcare providers, all in the interests of advancing the health of individuals and their communities.[1] It was first started in the 1960s when two healthcare projects incorporated the principles of telemedicine in healthcare delivery in the United States.[2–4] The interest in telemedicine has increased over the past four or five years, with application of newer telecommunication technologies.[5] The first telemedicine project was started in India by Indian Space Research Organization (ISRO), Bengaluru, India in collaboration with Apollo Hospitals Group in 2001. 2016 has been a great year of telemedicine expansion as a memorandum of understanding (MoU) is established with ISRO to expand its telemedicine network to remote places.[6] Other centers in India that effectively run telemedicine centers are located in All India Institute of Medical Sciences (AIIMS), New Delhi, India; Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS), Lucknow, India; Postgraduate Institute of Medical Education and Research, Chandigarh India; A Coronary Care Unit in Siliguri; and Bankura Sammilani Hospital. The latest to start such a venture was Medanta Medi City Hospital.[7] However, not much is known about the cost-effectiveness of telemedicine as a therapeutic

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and preventive tool for cardiovascular diseases (CVDs). Our study addresses the cost-effectiveness and utility of telemedicine in CVDs for the rural population with limited financial constraints.

Two types of telemedicine technology are being used. The first one is "store and forward," which is used to transfer digital images taken and stored from a camera and then sent to another location. Teleradiology, telepathology, and teledermatology are some examples.[8] The second is "Real-time consultation," which involves the use of a video-conferencing equipment at both locations. Departments such as psychiatry, internal medicine, rehabilitation, cardiology, pediatrics, obstetrics and gynecology, and neurology are based on real-time streaming.[9] India is a developing country with a population size of 1,339,180.127 billions,[10] of which 68% of the population still lives in rural areas.[11] India's total annual budget is around Rs. 24.42 lakh crore. The budgetary expenditure collectively on health, education, and social protection for 2018–19 is Rs.1.38 lakh crore.[12] Astonishingly, public health expenditure is only 1% of the total GDP in India. Healthcare is a serious issue in our county; yet the government is unable to spend more on it because of financial constraints. Telemedicine appears to provide a new healthcare opportunity to treat cardiovascular patients effectively within limited resources.

The purpose of the present study was to know the cost of therapy for cardiovascular diseases using telemedicine as a tool in a rural setting. The cost of illness studies are descriptive: to itemize, value, and sum the costs of a particular problem with the aim of giving an idea of its economic burden.[13] The cost of illness aims to calculate the direct, indirect, and intangible dimensions in monetary units.[14] The prevalence-based method is commonest to estimate the total cost of a disease incurred in a year.[15] This study is being done from the societal perspective by a joint venture of a private corporate hospital and an NGO collaboration with the hospital.

Materials and Methods

It is a prospective, cross-sectional, observational, and questionnaire-based study used in the overall cost estimate for cardiovascular patients at the rural-end located at Noida, Jewar. Study centers include an urban center—National Heart Institute (NHI), community center, East of Kailash, New Delhi-110065, where teleconsultation is delivered to all patients through telemedicine portal (e-sanjeevani)—and a rural center—Community Health Center, Kanigarhi road, Jewar, Noida, where patients were called, enrolled, investigated, and given treatment advice by a senior cardiologist from the NHI side. Patients visit the telemedicine center twice a week for the treatment of various cardiovascular ailments. This is a pilot study spanning for 10 months. A total of 120 patients were chosen for this study, of which only 100 patients who had cardiovascular problems/diabetes have been included. A study performa was prepared to pass through a rigorous and strict content-validation process.

Inclusion Criteria

- Patients belonging to the age group of 20–85 years have been included in the study
- Patients who were diagnosed or known to have any cardiovascular disease visiting the telemedicine center are included in the study
- Participants ready to participate and sign the informed consent were included in the study

Exclusion Criteria

- All terminally ill patients were excluded
- Patients not willing to participate were also excluded

Process of Patient Enrollment

Patient coordinator at the rural end arranged the prospective cases at the Jewar Health Centre. List of all telemedicine patients was made available to an NHI consultant before the start of the television. The demographic details like height, weight, blood pressure, and blood sugar levels fasting as well as postprandial were noted before the start of session and the information was conveyed to the NHI center at the time of telesession (Flowchart 1). Once the tentative diagnosis was made on the basis of history and clinical details, the patient was advised for essential investigations, prescribed medicines and lifestyle measures—particularly tobacco cessation and appropriate diet, etc. The patient was then asked to come for a review with reports after 2 weeks. This is the time when cost calculations (direct as well as indirect) were made for each patient. The patients were followed up as per necessity on the telemedicine portal for assessing medication, investigation, consultation, and adverse drug reactions (if any).

Telemedicine Components (Flowchart 1)

NHI-end-components

A telemedicine portal (e-sanjeevni), a consultant, an IT professional, Pharmacy Postgraduate works in Unit, Internet access, a computer with an inbuilt camera, and headphones.

Jewar-end-components

A telemedicine portal (e-sanjeevni), a Chief Medical Officer, Patients, a patient coordinator, and an NGO coordinator, Internet access, a computer with an inbuilt camera, and attachable headphones.

Cost Parameters in Study

Direct Medical Cost

It includes the cost of medication, lab-investigations, consultation, adverse drug reaction (if any) and surgery. However, under the telemedicine project, all kinds of medications, lab investigations, and consultation fee were free.

Direct Non-medical Cost

It includes a computer setup, software and transportation cost.

Indirect Medical Cost

Patient and caregiver productivity losses.

Assumption

Medication charges are kept on a 40% discount from MRP to know the cost borne by the government/NGO to treat patients (medicine tender rate is confidential); all lab-investigation charges were calculated as per CGHS rates. Consultation and staff cost are based on the salary slabs as per the existing salary at both ends (Table 1).

Results

Demographic Profile

A total of 120 cases attended these telesessions, of which a total of only 100 patients (53% males and 47% females) had some kind of cardiovascular problems (Table 2). The mean age of all patients

Flowchart 1: Pictorial view of telemedicine session

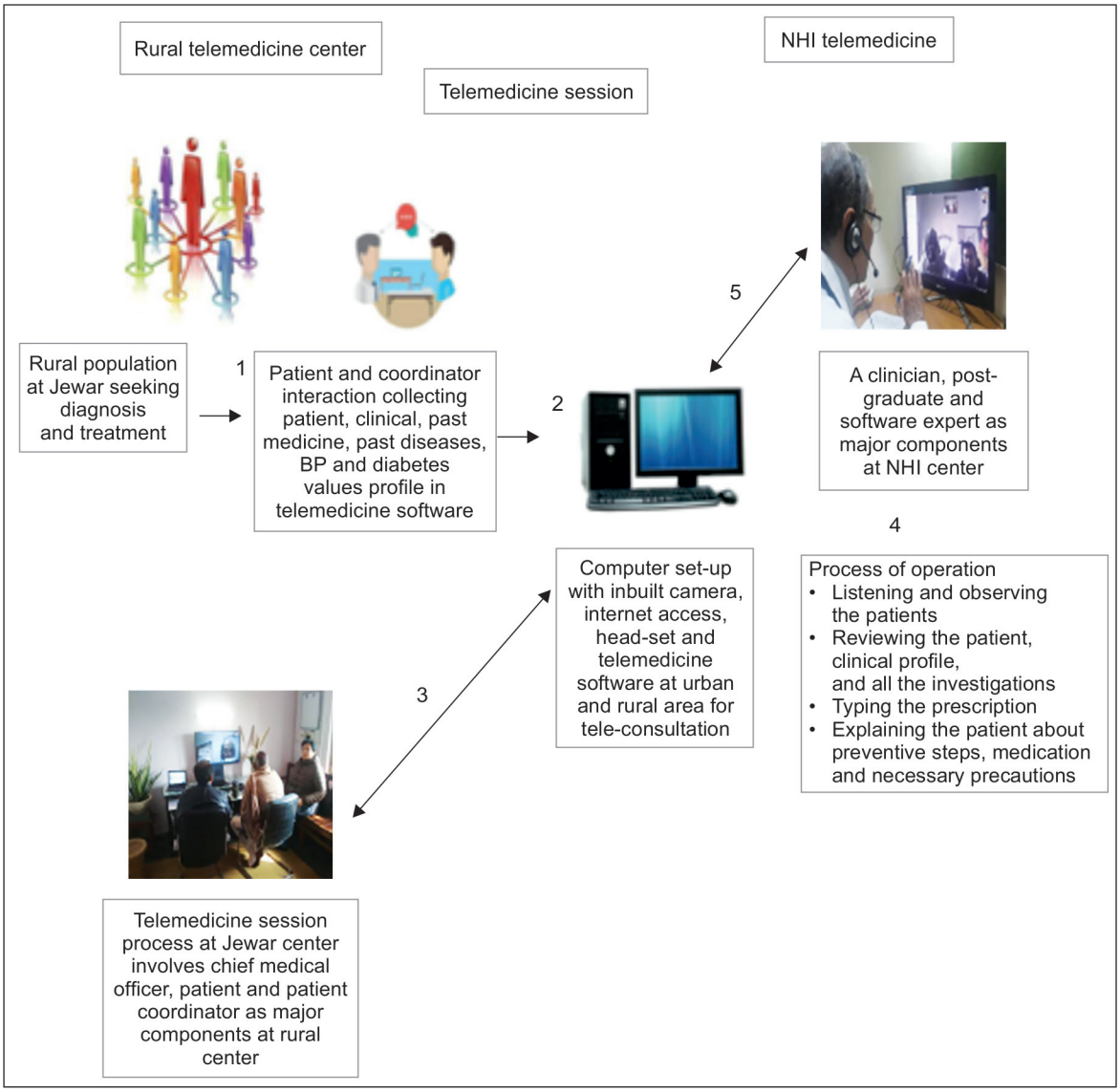

Table 1: Cost calculation and cost calculation formulas[16]

Direct cost:
Average medical cost = Total medical cost of telemedicine patients affected by specific disease/Total number of patients affected by the disease.
Average non-medical cost = Total cost non-medical items for patients affected by a specific disease/Total number of patients affected by the disease.
Indirect cost:
Average of indirect cost = Total cost of productivity loss for telemedicine patients and attendants/Total number of patients affected by the disease.
Total healthcare cost of respective diseases:
Average total cost of all CVD = Total of all direct and indirect cost for all patients affected by CVD/Total number of patients affected by the disease.

was found to be 55.29 ± 11.6 years respectively (male 55.29 year, female 55.19 year). The majority (81%) of patients were between the ages of 41 years and 70 years. More than half (53%) of our patients were noted to have a higher BMI, of which 29% were males and 24% females. About 79% of patients belonged to socioeconomic status IV, while 21% were from socioeconomic status III. None of our telepatients belonged to status I and II. The majority (81%) of them were Hindus, while 19% were Muslims. An estimated 77% of patients visiting these sessions were below the matrix, of which 46% were females. About 52% of patients were found to have the

Table 2: Demographic profile

Gender	*Male (%)*	*Female (%)*
Count (100)	53 (100)	47 (100)
Age		
≤30	1 (1.87)	–
31–40	4 (7.54)	6 (12.7)
41–50	12 (22.65)	13 (27.64)
51–60	20 (37.74)	16 (34.04)
61–70	9 (16.99)	11 (23.50)
71–80	5 (9.43)	0 (0)
≥80	2 (3.78)	1 (2.12)
BMI (kg/cm^2)		
Underweight >18.5	2 (3.78)	1 (2.12)
Normal 18.5–24.9	22 (41.51)	19 (40.42)
Overweight 25.29.9	22 (41.51)	14 (29.79)
Class I obesity 30–34.9	7 (13.20)	10 (21.28)
Class II obesity 35–39.9	–	3 (6.39)
Class III obesity ≥40	–	–
Socioeconomic status		
III	18 (33.97)	03 (6.38)
IV	35 (66.03)	44 (93.62)
Marital status		
Married	53 (100)	47 (100)
Unmarried	–	–
Emotional stress		
Widow/widower	2 (3.77)	13 (27.65)
Religion		
Hindu	45 (84.90)	36 (76.60)
Muslim	8 (15.10)	11 (23.40)
Education		
Postgraduate	1 (1.87)	–
Graduate	1 (1.87)	–
Intermediate	7 (13.20)	–
Metric	13 (24.57)	1 (2.12)
Below matrix	31 (58.49)	46 (97.88)
Occupation		
Government job	8 (15.09)	–
Private job	8 (15.09)	–
Business	7 (13.20)	–
Farmer	23 (43.39)	–
Housewife	–	47 (100)
Retired	1 (1.87)	–
Unemployed	6 (11.36)	–
Blood pressure (mm Hg)		
Normal (120/ 80)	23 (43.39)	25 (53.19)
Pre-stage (120–139/80–89)	10 (18.87)	9 (19.15)
Stage I (140–159/90–99)	10 (18.87)	10 (21.28)
Stage II (≥160/≥100)	10 (18.87)	3 (6.38)

blood pressure at the pre-stage, stage I and stage II as per JNC VII guidelines; majority of them were males (30%).

Disease Profile

Diabetes, hypertension, coronary artery diseases, hypothyroidism, and combinations were found to be the most prevalent diseases. It was found that diabetes alone (48%) was the most commonly occurring disease; diabetes and hypertension (24%) together with the second observed condition; hypertension (9%) and diabetes with other comorbid condition (9%) was next to diabetes. Diabetes and cardiovascular diseases (4%); diabetes and hypothyroidism and cardiovascular diseases (3%); hypertension and coronary artery disease (2%); coronary artery diseases (1%) were found to be less prevalent (Table 3). Hypothyroidism along with the other CVS disease was another important condition noted through telesessions.

Cost Computations

The average cost of disease and total cost of disease (within brackets) for a 10-months duration have been mentioned. The cost of treating diabetes alone was INR 6,302.22 (INR 3,03,758.16). Diabetes and hypertension together cost INR 10,546.71 (INR 2,53,122.27). Diabetes with other comorbid conditions required INR 12,086.62 (INR 99,944.47). Hypertension costs INR 15,505.63 (INR 56,949.08). Diabetes with two cardiovascular diseases cost 8,376.91 (INR 33,507.66). Diabetes and hypothyroidism and cardiovascular diseases cost (INR 13,899.80). Hypertension and coronary artery disease cost 8,844.33 (INR 17,688.65). Coronary artery disease costs 2,125.34 (INR 2,125.34) (Table 4). The cost of additional stuff such as setup (One time cost) was INR 1,20,000 and total Internet charges was INR 20,000 for 10 months, including both the rural and urban side. Overall, the total cost for this telemedicine project was around INR 9,09,095.63 for 10 months.

The individual cost per month for diabetes alone was found to be around INR 630.22; diabetes and hypertension cost INR 1,054.67; diabetes with another comorbid condition cost INR 1,208.66; hypertension INR 1,550.57; diabetes with two cardiovascular diseases cost INR 837.69; diabetes and hypothyroidism and cardiovascular diseases cost INR 1,389.98; hypertension and coronary artery disease cost INR 884.43; coronary artery disease cost INR 212.53. A linear relationship was observed between cost and number of comorbid conditions (Table 5).

Discussion

Telemedicine has spread over various parts of the world and is being used for more than two decades in our country. Various academic and corporate hospitals have started many patient-centered initiatives using this new tool.[17] Furthermore, it has also penetrated its roots in many Indian states through close networking. However, there is a paucity of literature on the economic burden over patient and government in treating cardiovascular diseases using telemedicine as a tool for health care. This is a boon for elderly and female patients in rural areas because they have to travel long distances for their cardiovascular problems.[18,19] Telemedicine is a strong means of women empowerment. In our study, almost 47% of the cases belonged to the fair sex. Our study brings out the cost of different cardiovascular diseases in rural India, using telemedicine.

The high prevalence of diabetes and hypertension alone and in combination in our study indicates the emergence of non-communicable diseases deep into the rural India. This is an important observation because cardiovascular conditions and diabetes are the main cause of death in all parts of India, including the poorer states and rural areas in India.[20,21] More than half (51%) of patients accepted the telemedicine very well as the visiting frequency of individual patient in a short span of ten months was more than three times.

Table 3: Cardiovascular and comorbid disease profile observed in rural population

Disease profile	*Male (%)*	*Female (%)*	*Total visits completed by patients in 10 months*
Diabetes alone (48%)	23 (47.92)	25 (52.08)	119 (39.9)
Hypertension and diabetes (24%)	11 (45.83)	13 (54.17)	84 (28.18)
Diabetes and other comorbid conditions (9%)	05 (55.55)	04 (44.45)	32 (10.7)
Hypertension alone (9%)	06 (66.67)	03 (33.33)	26 (8.72)
Diabetes with two cardiovascular diseases (4%)	04 (100)	0	12 (4.02)
Diabetes, hypothyroidism and cardiovascular disease (3%)	01 (33.33)	02 (66.67)	16 (5.36)
Hypertension and coronary artery disease (2%)	02 (100)	0	08 (2.68)
Coronary artery disease alone (1%)	01 (100)	0	1 (0.33)
Total	53	47	298

Table 4: Overall economic burden for 10 months on rural healthcare—direct and indirect cost (INR: Indian rupees)

Disease profile	*Direct medical av. cost (total cost in INR)*	*Direct non-medical av. cost (total cost in INR)*	*Indirect cost av. cost (total cost in INR)*	*Total cost av. cost (total cost in INR)*
Diabetes alone	5,802.91 (2,78,792.37)	44.18 (2,209.15)	455.13 (22,756.64)	6,302.22 (3,03,758.16)
Hypertension and diabetes	7,660.31 (1,83,848.04)	38.50 (924.23)	2,847.9 (68,350)	10,546.71 (2,53,122.27)
Diabetes and other comorbid conditions	9,712.60 (87,413.41)	1104.4 (1104.4)	1,269.62 (11,426.66)	12,086.62 (99,944.47)
Hypertension alone	6,179.72 (55,617.66)	5.91 (295.87)	9,320 (1,035.55)	15,505.63 (56,949.08)
Diabetes with two cardiovascular diseases	6,155.66 (24,622.66)	38.75 (155)	2,182.5 (8,730)	8,376.91 (33,507.66)
Diabetes and hypothyroidism and cardiovascular disease	12,834.57 (28,503.93)	31.90 (95.71)	1,033.33 (3,100)	13,899.80 (31,699.64)
Hypertension and coronary artery disease	8,244.33 (16,488.65)	0 (0)	600 (1,200)	8,844.33 (17,688.65)
Coronary artery disease alone	2,125.34 (2,125.34)	0 (0)	0 (0)	2,125.34 (2,125.34)
Overall total medical and non-medical cost	28,715.44 (6,77,412.06)	1,263.64 (4,784.36)	17,708.48 (1,16,598.85)	77,687.56* (7,67,095.63)*

*Cost of setup (1,20,000 INR) and internet (20,000 INR) at both the centers are excluded. Overall cost 9,24,795.27INR

Table 5: Average cost per person per month in (INR: Indian Rupees)

Disease profile	*Per month cost (av. cost in INR)*
Diabetes alone	630.22 (6,302.22)
Hypertension and diabetes	1,054.67 (10,546.71)
Diabetes and other comorbid conditions	1,208.66 (12,086.62)
Hypertension alone	1,550.57 (15,505.63)
Diabetes with two cardiovascular diseases	837.69 (8,376.91)
Diabetes and hypothyroidism and cardiovascular disease	1,389.98 (13,899.80)
Hypertension and coronary artery disease	884.43 (8,844.33)
Coronary artery disease alone	212.53 (2,125.34)

This observation is in accordance with the study by Khadanga et al.[22] The better response on behalf of the patients is due to several reasons, namely the easy accessibility of a consultant ant's opinion, enjoying the pleasure of high technology, free investigation, almost free drugs for 4–12 weeks depending upon the case, and repeated counseling about the disease and risk factors such as tobacco, smoking, a lack of physical exercise, and alcohol. These may be the reasons that more than 72% of females were regular in their visits. In our study, another significant finding is that the patient is not only satisfied with the treatment but also aware of disease risk-factors such as smoking, tobacco, and alcohol intake. Our model also provided the random blood sugar and blood pressure levels to the patient at the arrival so that they get sensitized about the status of their blood sugar and blood pressure. Patients with uncontrolled sugar and blood pressure were found to be faltering on taking medicine.

Patient awareness does play an important role in its treatment, thereby helping them to gain the knowledge, education, and training for the prevention of the diseases that are supported by various studies. The village environment is considered to be simple and less stressful. Notwithstanding this usual notion, 15% of patients were found to be suffering from some form of emotional stress (such as being single due to spouse death, no family support, and no children to take care); moreover, 13% were widows.

This promising joint venture will also help the e-data-collection of all patients such as patient demographics, disease profile, prescriptions, lab investigations, all visit follow-up date, and consultant opinion. This will go a long way in fulfilling the principle of a smart card.[23]

The individual cost per month was calculated; the cost of diabetes alone was around INR 630.22, diabetes and hypertension cost INR 054.67, diabetes with other comorbid condition cost INR 1,208.66, hypertension INR 1,550.57, diabetes with two cardiovascular diseases cost INR 837.69, diabetes and hypothyroidism and cardiovascular diseases INR 1,389.98, hypertension and coronary artery disease cost INR 884.43, and coronary artery disease cost INR 212.53. An almost linear relationship was observed between cost and a number of comorbid conditions. As the comorbid condition increases, the average cost per the person also increases. Telemedicine is found to be the most economical way of treating and diagnosing patients in rural areas.[24]

Our Telemedicine initiative has provided an opportunity to use generic medicine available at rural health center, thus reducing the cost of drugs. It is a better and convenient method for patient treatment, as all the medication (mostly generic cost with the assumption of a 40% discount for cost calculation from the government side) and lab investigations (done at the center or nearby hospitals considered at CGHS rates for cost calculations) provided to them are free. Only traveling and productivity losses were borne by patients, which were very minimal. The out-of-pocket expenditure is found to be less than that in the conventional settings, which provides the patients some relief.

A model like ours will help policymakers to provide health care to remote corners of the rural areas. This can be easily replicated in other parts of the country using the services of apex hospitals/medical colleges adopting a rural center for extending telemedicine facility to the adjacent villages. Such a venture costs less than ten lakhs for all sessions, including medical cost, non-medical cost, and indirect medical cost for a 10-month period.

Limitation

The study has been conducted on a pilot basis. The cardiovascular and diabetes patients were primarily brought for teleconsultations. High-Tech Technologies such as echo and CT were not available for further workup.

Conclusion

This study provides an insight into prevalent cardiovascular diseases in rural areas adjacent to the National Capital Region. It is clear that diabetes and hypertension are no more diseases appearing only in cities. It is an issue spreading to villages also. Furthermore, they no longer present as a single disease entity but as a cluster of diseases such as coronary artery disease, cervical spondylitis, hypothyroidism, benign prostatic hypertrophy arthritis, which ultimately increases the economic burden of the patients. In view of the paucity of specialized health services in rural areas, telemedicine is a useful, beneficial, and economical way of creating awareness among people, including healthy lifestyle and cost-effective medical treatment and prevention. The study site is a less researched area in India. Telemedicine also provides medical and paramedical staff a convenient platform for teaching and learning opportunities and for acquainting themselves with a rural healthcare picture.

Despite the current health policy for rural health in India, infrastructure, medical and paramedical staff, and availability of specialist medical services are still big concerns. It all requires a huge cost, other than those involved for curing the disease occurred. The study provides a model wherein a telehealth session provided by government initiative, NGO and hospitals will provide cardiovascular OPD care, reducing the maximum cost burden over the patients and families. Private corporate hospitals will certainly reduce the maximum cost burden of the patient and his/her family. Telemedicine is an emerging tool to handle most of the cardiovascular diseases. More such initiatives will help the rural India to stand equally for specialized medical services, diagnosis, and treatment. This study will help the policymakers to add some values to implement effective health planning in rural areas.

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ORIGINAL ARTICLE

Investigation on Lipid Profile in Affective Disorder at a Hospital Clinic in Kolkata, West Bengal, India

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Abstract

Aim: Prior research has shown that particular types of mental states contribute to one's risk for depression, and that abnormal blood lipid levels can be associated with the manifestation of mood dysfunction. The role of lipid metabolism in the pathophysiology of depressive behavior has received particular attention recently. As depressive disorders vary in regard to etiology and diagnostic marker, the present study aimed to explore any lipid-profile disparity among the sample of depressive patient groups visiting a clinic for treatment.

Materials and methods: The study group consisted of 80 patients diagnosed with three types of depressive disorders—endogenous, reactive, and dysthymic types. Groups were tried to match according to age, gender, and education.

Results: The demographical difference between marital status and economic status revealed among patients. The present study reveals the difference among serum lipid levels among groups in regard to LDL cholesterol (lipoproteins of low-density). Further after adjusting the confounding factors such as age and BMI, the ratio of HDL (lipoproteins of high-density)/cholesterol and also the ratio of LDL/HDL were found to be significantly different among the groups.

Conclusion: The present study shows the difference in lipid profile such as LDL cholesterol, HDL/cholesterol, and HDL/LDL ratios among psychogenic, reactive, and dysthymic groups. The psychogenic group reflects lower LDL and lower LDL/cholesterol, HDL/cholesterol ratios while compared to others.

Clinical significance: This study highlights how the lipid profile can act as a biological marker in distinguishing depression subgroups and assessing associated cardiovascular risks.

Keywords: Cholesterol, Depression, High-density lipoprotein, Lipid profile, Low-density lipoproteins.

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Introduction

The role of lipid status in patients with affective disturbance as depressive disorders has been investigated for the last few years. While various genetic, environmental, and social factors are found to have influences in the pathophysiology of depression, the search for biological precursors continued.[1] Most of the essential human physiological molecules that are related to affect human mood status (such as the neurotransmitters serotonin or dopamine, vitamin D, and steroid and sex hormones, including DHEA, testosterone, and estrogen) are directly or indirectly linked to the available quantity of cholesterol molecule. Some studies indicate that suppression or availability of serotonin (a neurotransmitter that modulates brain functioning, resulting in behavior changes) is somehow being connected to a low serum-cholesterol level.[2]

Some studies indicated a significant relationship between mood disorder and serum cholesterol levels. A lower level of cholesterol has been found to be mostly related to the prevalence of depressive disorders. Other findings reflect a close relationship between lipid profile components such as triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-cholesterol), and low-density lipoprotein cholesterol (LDL-cholesterol),[3] with various psychiatric disorders such as depression, bipolar disorder, anxiety disorders, aggressive and impulse control disorder, post-traumatic stress disorder (PTSD), and even schizophrenia.[4–6] A number of findings referred to a low cholesterol level being associated with deliberate self-harming attempts and suicide.[6]

The question as to whether an agressive treatment to lower serum cholesterol level in patients with cardiac risks may develop other conditions such as depression, increased violent behavior, suicide, bipolar disorder, anxiety, and Parkinson's disease still remains unanswered. Sometimes, in general practice, lowering of blood cholesterol may be considered, keeping in mind other psychological risks.[5,6]

While functions of cholesterol in the human body have been evaluated, cholesterol remains as one of the main constituents of central nervous system participating in various functioning as being in neuronal membrane and having a role in the process of neurotransmission and in the second messenger system in the brain.[7] Additionally, some investigations have indicated that neuronal dysfunction due to changes in microviscosity of the cellular membrane or disorders in signal transduction cause vulnerability to depression.[8,10] While many studies showed the relationship between serum cholesterol level and affective state of the human mind, not all authors agreed with this observation. Low serum cholesterol levels have been observed by researchers

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in patients with low-mood symptoms,[7–10] and a correlation among cholesterol levels in serum and with symptoms of self-harming and suicide in a group of psychiatric patients.[8]

In an attempt to investigate the components of lipid profile other than cholesterol in psychiatric patients, the role of triglyceride, LDL, and HDL cholesterols have been examined.[10] Comparing with a healthy control group, depressive patients showed a significantly lower concentration of serum cholesterol, HDL-cholesterol, and cholesterol/HDL-cholesterol ratio.[11] Some authors have found difference between groups of depression (as in patients with melancholic symptoms and atypical depression symptoms) in regard to levels of triglycerides, very-low-density lipoprotein cholesterol (VLDL-cholesterol), and HDL-cholesterol.[10] Some contradictory findings reflect no difference in levels of triglycerides in depressive patients and control group but found a significantly lower LDL-cholesterol level in depressive patients than in the control group.[12]

The depressive disorder has several subtypes (Diagnostic and Statistical Manual, DSM-5) and although a number of studies have been conducted in establishing relationships among serum cholesterol levels and low mood symptoms, very few studies investigated variation in serum cholesterol levels and types of depressive disorders. Among group-wise studies, some detected no significant differences in serum lipid levels of patients with types of depressive disorder such as melancholic and non-melancholic depression,[11,13] or in patients with psychogenic and atypical depression.[14] In contrast in another study (including psychogenic and atypical depression groups), Huang et al. indicated a significant difference in the concentrations of triglycerides, VLDL-cholesterol, and HDL-cholesterol.[10]

No confirmatory finding in case of a lipid profile of depressive patients of the eastern part of India has yet been established. While treating patients with depressive symptoms, three diagnostically different types (psychogenic, reactive, and dysthymic types) are often encountered in Kolkata hospital clinic outdoors. Thus, the present study aims to investigate whether there is any difference in regard to serum lipids (cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, and VLDL-cholesterol) and lipid fraction ratios (cholesterol/HDL-cholesterol and LDL-cholesterol/HDL-cholesterol) in three types of depressive disorder—namely psychogenic, reactive, and dysthymic groups.[3]

Materials and Methods

Subjects

Totally, 80 subjects (males: 32; females: 48) with detected depressive disorders who came for treatment at a hospital clinic in Kolkata, West Bengal during the period of April 2015 to March 2017 have been included in the present study. The demographics indicated that sample mean age ± SD was = 46 ± 10 years and the disease onset was (mean ± SD) was 40 ± 11 years, while disease duration (mean ± SD) was 8 ± 5 years. The detected mean body mass index (BMI) (mean ± SD) was 24.60 ± 5.49 kg/m^2. The socio-demographic features of the patients were duly summarized and presented in Table 1.

Besides the inclusion criteria for depressive disorders such as DSM-5, the exclusion remained for psychiatric addictive symptoms (substance abuse disorders—alcohol, cannabis, and other types) and other comorbid psychiatric symptoms/disease (such as bipolar affective types, psychotic manifestations, obsessive–compulsive features, and neurocognitive disorders). Additionally, medical problems such as cardiovascular diseases, hypertension, thyroid disorders, diabetes mellitus, lipoprotein metabolism disorders, organic brain syndrome, and nutrition disorders are excluded. As the patients came for treatment to the clinic, some pharmaceutical interventions had been offered. Antidepressants in SSRI groups (such as sertraline, fluoxetine, fluvoxamine, paroxetine) or in TCA group (such as clomipramine) are used for necessary remission of symptoms. Among other drugs, anxiolytics of benzodiazepine group (such as clonazepam, alprazolam, oxazepam) and diazepam are used for controlling low-mood-related symptoms. Those drugs have no detectable altering effect on serum lipid-level concentrations.[15]

Since dietary habits and physical activity may affect test results, all tests were conducted during the same treatment time and at the same time of the day as far as practically possible. The instruction was given to maintain a uniform diet and a uniform level of physical activity for 48 hours during testing in all subjects. All subjects signed their written consent for participation in the study, and the study was approved by a competent ethical committee.[3]

Psychiatric Assessment for Diagnosis

Inclusion criteria established according to the diagnosis of depressive disorders of the Diagnostic and Statistical Manual for Mental Disorders, 5th revision (DSM-5),[16] Hamilton rating scale for depression (HAMD-17)[17] had been used for diagnostic purposes. Subtypes of depression (psychogenic, reactive, and dysthymia) was assessed using a structured clinical interview (by trained clinical psychologist/psychiatrist) and diagnostic questionnaire based on the DSM-5 criteria.[16,18] Subjects were divided into groups based on diagnostic categories and double-checked by clinicians for grouping purposes, as showing psychogenic characteristics, or reactive characteristics, or with dysthymic symptoms.

Biochemical Measures

Subjects were asked to fast for 12 hours before the venipuncture procedure was carried out by certified technicians. Venous blood samples were collected and within 30 minutes of blood collection, the samples were centrifuged at 2,000*g* for 15 minutes at 4°C after adding EDTA and sent for preservation at the laboratory. Cholesterol oxidase method was used for HDL cholesterol estimation. Triglyceride concentrations were measured using a glycerol-blanked enzymatic method. The total cholesterol, HDL cholesterol, and triglycerides laboratory coefficient of variations (CVs) were 1.6%, 2.9%, and 4.0%, respectively. The Friedewald formula is used for calculation of LDL cholesterol. The ratio of two indices (total/HDL cholesterol ratio and LDL/HDL cholesterol ratio) was also calculated for the purpose of this study.

The height and weight of each patient, who was barefoot and in light clothes, were measured in a standing position on a medical scale that measures height and weight. Body mass index (BMI) was calculated by dividing kilograms by squared height in meters.[3]

Statistical Analysis

For collection and storing of data, MS Access 2000 database has been used. For running statistics, SPSS statistical program (SPSS for Windows 16.2, SPSS, Chicago, IL, USA) was used for needed analysis. One-way analysis of variance (ANOVA) was used to test differences in the serum lipid level between three depressive groups. While for assessing differences between individual groups, a *post hoc* analysis is used; covariance analysis (ANCOVA) was applied to control the effect of age and body mass index on investigated

Table 1: Sociodemographic features of the study group patients

Variables	*N*	*%*	X^2	*p*
Gender				
Men	32	39.5	3.37	0.66
Women	48	60.5		
Qualification				
Primary school education	17	21.1	30.73	<0.001
Secondary school education	49	63.2		
University degree	14	15.8		
Marital status				
Married	54	68.4	10.32	0.001
Single	26	31.6		
Employment status				
Employed	30	36.8	0.74	0.692
Unemployed	24	28.9		
Pensioners	26	34.2		
Residence				
Village	20	27.3	13.64	<0.001
Town	60	72.7		
Economic status				
Low	25	32.4	0.11	0.947
Middle-class	30	35.1		
High	25	32.4		

Table 2: Serum lipids (mean ± SD) in patients with three types of depressive disorders

	Type of depressive disorder				
	Reactive	*Psychogenic*	*Disthymic*	*F**	*p*
Triglyceides (mmol/L)	1.90 ± 1.41	1.43 ± 0.40	1.80 ± 0.45	1.62	0.153
Cholesterol (mmol/L)	6.03 ± 0.86	5.92 ± 1.33	5.42 ± 0.61	2.87	0.086
HDL-cholesterol (mmol/L)	2.11 ± 0.43	2.04 ± 0.42	1.68 ± 0.39	0.24	0.689
LDL-cholesterol (mmol/L)	4.82 ± 0.89	5.11 ± 0.71	3.24 ± 0.51	5.13	0.014
VLDL-cholesterol (mmol/L)	0.28 ± 0.35	0.29 ± 0.20	0.38 ± 0.11	2.19	0.162
Cholesterol/HDL-cholesterol ratio	5.12 ± 1.84	4.21 ± 0.45	3.48 ± 1.12	0.89	0.481
LDL-cholesterol/HDL-cholesterol ratio	3.31 ± 0.88	3.52 ± 1.20	3.11 ± 1.10	1.73	0.341

*One-way ANOVA

parameters. Normality and stem leaf for descriptive statistics checked for the data as far practicable and to assess differences in sociodemographic data. Some nonparametric analysis for sample distribution was tested by Kolmogorov–Smirnov test. For the present analysis, a $p < 0.05$ probability level was considered statistically significant.

Results

Serum lipid concentrations in relation to the type of depression have been indicated in Table 2. Analysis of the results shows that the psychogenic depression group reflects a significantly lower LDL-cholesterol level when compared with the dysthymic group (F (2.63) = 5.14, p = 0.014, ANOVA; p = 0.010, *post hoc* test). This trend continued when adjustments for age and BMI were made (ANCOVA F (2.61) = 8.46; p = 0.011, ANCOVA). A comparison among three groups in regard to other lipid estimates indicated no significant difference using a one-way analysis of variance. Thus, the serum level of triglycerides, cholesterol, and cholesterol/HDL ratio and LDL-cholesterol/HDL-cholesterol ratio in patients with psychogenic and reactive depression and dysthymia are in the same range. The serum lipid concentration ratios in depressive groups have been summarized and presented in Table 2.

As age and BMI could be confounding factors, an analysis controlling those was worth testing. While those adjustments were done for age and BMI statistically, certain explicit variations were indicated. However, after age and BMI adjustments, a comparison among groups with reactive and dysthymia (F (5.13) = 3.94; p = 0.024, ANCOVA). In regard to cholesterol/HDL-cholesterol ratios, patients with psychogenic depression showed a lower ratio than in reactive and dysthymic patients (F (2.61) = 4.52; p = 0.014, ANCOVA). Also, in regard to LDL-cholesterol/HDL-cholesterol ratios, the psychogenic group reflected a significantly lower ratio (F (2.61) = 6.13; p = 0.004, ANCOVA) (Table 3) than the reactive depression group and dysthymia group. Serum lipids' concentration ratios after age and BMI adjustments have been summarized and presented in Table 3.

Table 3: Serum lipids (mean (95% CI) after age and BMI adjustment in patients with three types depressive disorders

	Type of depressive disorder				
	Reactive	*Disthymic*	*Psychogenic*	*F**	*p*
Triglyceides (mmol/L)	1.90 (1.61–2.14)	1.86 (1.12–1.08)	1.82 (0.24–1.08)	1.82	0.157
Cholesterol (mmol/L)	6.20 (5.59–6.89)	6.86 (5.30–6.47)	5.87 (5.21–5.96)	3.94	0.024
HDL-cholesterol (mmol/L)	1.71 (1.56–1.73)	1.62 (1.22–1.31)	1.88 (1.43–1.82)	2.11	0.312
LDL-cholesterol (mmol/L)	4.12 (3.56–3.77)	5.6 (4.02–4.33)	3.01 (3.10–3.40)	8.46	0.001
VLDL-cholesterol (mmol/L)	0.60 (0.42–0.48)	0.36 (0.20–0.46)	0.34 (0.27–0.38)	1.80	0.173
Cholesterol/HDL-cholesterol ratio	5.13 (4.12–4.58)	5.11 (3.88–4.32)	4.10 (3.27–4.12)	4.52	0.014
LDL-cholesterol/HDL-cholesterol ratio	3.51 (2.18–3.23)	3.18 (3.11–4.12)	2.30 (2.10–2.83)	6.13	0.004

*One-way ANOVA

Discussion

Recent researches highlight the lipid profile influencing the behavioral aspects of human subjects. Indication about lower values of lipid profile components in cases with impulse control disorder has somewhat been established. A series of studies indicated psychiatric patients with suicidal attempts show lower levels of cholesterol. Some authors proposed that low total cholesterol can be a marker for suicidal behavior or risk. The connections between low cholesterol and various risk-taking behaviors have been highlighted in recent research, which suggested that a low total cholesterol level can be used as a marker for various risk-taking behaviors, including suicide or harming others. The present study indicated lower cholesterol values for certain depressive groups of patients, and a possibility of impulsive acting out can be considered for future treatment purposes.

The proposed mechanism possibly works by lipid microviscosity reduction in neural membranes in these subjects. Owing to a decreased neural membrane lipid micro-viscosity, serotonin receptor exposure on the membrane surface may be reduced, resulting in hypo-function of those receptors.[19] Several studies indicated that lower concentrations of 5-hydroxy in doleacetic acid (5-HIAA) in the cerebrospinal fluid (CSF) can be linked to impulsive act outs such as suicides and suicide attempts. Thus, the proposed link between low total cholesterol and serotonergic system is being recognized as having a central role in impulse control behaviors.[19,20]

Analysis of the results of this the study points that a comparison among three selected depressive groups in regard to some components of lipid profile as serum levels of triglycerides, HDL-cholesterol, and VLDL-cholesterol did not reveal significant differences. Findings show a fairly similar profile in regard to above components among patients with reactive depression, psychogenic depression, and dysthymia. While the noteworthy finding in this study reflects that in the psychogenic depressive group, estimations of LDL-cholesterol, cholesterol, cholesterol/HDL-cholesterol ratio, and LDL-cholesterol/HDL-cholesterol ratios were significantly lower compared to reactive and dysthymia groups. Huang and Chen worked on psychogenic and melancholic depressive groups of patients to found that serum concentration of triglycerides, VLDL-cholesterol, and HDL-cholesterol might be used as biological markers for group differentiation. The distinction among those groups was revealed after doing the statistical adjustments of age of the samples.[10] Some other studies observed similar findings on lipid components, but those have not been shared by all authors.[14] Applying similar statistics and after adjustment of BMI in another study, patient groups with melancholic and psychogenic characteristics of depressive disorder indicate no difference in serum lipid concentration.[14] Considering those differences in previous studies, we applied the analysis of covariance and age and BMI adjustments to find any difference among groups. When the confounding factors of age and BMI were adjusted, the results of the present study validated the fact that lipid profile may have a role as a possible biological marker of depressive groups. In our study, levels of cholesterol, LDL-cholesterol, cholesterol/HDL-cholesterol ratio, and LDL-cholesterol/HDL-cholesterol ratio are found to be possible indicators for differentiation between certain clinical subtypes of depressive disorder and thereby predicting some risk-taking behavior as well.

The relationship between cholesterol and depression or suicide is also complex. For example, studies from France and Canada linked low cholesterol levels to an increased incidence of suicide, and research from the Netherlands and Turkey reported an association between low cholesterol levels and depression. On the other hand, data from Hawaii found the reverse: high cholesterol levels were connected with an increased risk of suicide.

Since so many lifestyles and health factors influence both the body's metabolism and the mind's function, it is not surprising that population-based observational studies have produced conflicting results.[21] Randomized clinical trials of cholesterol-lowering medications avoid many of these pitfalls, and here the results are reassuring. Placebo-controlled trials of lovastatin and simvastatin (which can cross into the brain) and of pravastatin (which does not) have not identified any adverse effects on cognitive function or psychological well-being. In fact, a long-term use of statin drugs has been associated with reduced risks of anxiety, hostility, depression, and suicide, perhaps because of the improved physical health that results from these medications. Similarly, a meta-analysis of 19 trials of cholesterol-lowering interventions found no effect on the risk of death from suicide, accidents, or violence. And men who claim that a heart-healthy diet will drive them over the edge should note that dietary interventions that lower cholesterol is as psychologically friendly as medications. Thus diet has a greater role to play in psychiatric patients.

Another clinical significance of the present study is the prediction of atherosclerosis, which may in the long term indicate coronary heart disease. It has been speculated that values of total estimates of cholesterol, HDL-cholesterol, and LDL-cholesterol concentrations have lesser predictive value in assessing atherosclerosis or coronary risk. More prognostic value for risk factors for the onset of coronary heart disease have been entitled to ratios such as cholesterol/HDL-cholesterol ratio and LDL-cholesterol/HDL-cholesterol ratio.[15] As the present study disclosed a statistically significant variation

in regard to serum levels of triglycerides, HDL-cholesterol and VLDL-cholesterol and significantly lower values of LDL-cholesterol, cholesterol, cholesterol/HDL-cholesterol ratio, and LDL-cholesterol/HDL-cholesterol ratio in certain patient groups, consideration of a future cardiac risk related to the progression of atherosclerosis in those groups of depressive disorder can be anticipated.

Various mechanisms may be responsible for depressive symptoms as well as serum cholesterol concentrations. Recent investigations undoubtedly established the neurotransmitter serotonin dysfunction as one major cause of the mood disorder. That serotonin dysfunction can be somewhat related to a decline in the serum cholesterol level may lead directly to a reduction in cerebral 5-HT activity by various mechanisms such as changes in concentrations of 5-hydroxy tryptamine (5-HT) of the 5-HT receptor, and in 5-HT transporter activity. Other mechanism possibilities can be free-disturbed cholesterol esterification in impulsive patients causing self-harming. A possible explanation of subjects having a comparatively higher level of serum cholesterol and having depressive symptoms can be that an elevated cholesterol level may cause a decrease in 5-HT receptor sensitivity or in 5-HT transporter activity by direct binding to membrane receptors or transporter molecules. Cholesterol can also be responsible indirectly by altering fluidity of the neuronal membrane and thus causing an imbalance of neurotransmitters. Thus more evidence points to the fact that serum cholesterol profile plays a prominent role in controlling the balance of brain neurotransmitters, which in turn have been responsible for the precipitation of some psychiatric symptoms. A study found an increased risk of suicide in patients with a low cholesterol level (<4.0 mmol/L) and in contrast, the presence of comorbid anxiety disorder and treatment resistance in patients with an elevated cholesterol level (>5.6 mmol/L).[22] As we have noted in our clinic, clinicians have to be aware of the confounders, such as diet and medication, affecting the lipid profile status in depressive patients coming for treatment. Ghaemi et al.[9] have reported that medication is not the only contributor to changes in the lipid profile. No significant difference had been found in lipid concentrations based on the types of antidepressants used for treatment purposes.

Conclusion

Finding biological correlates in psychiatric disorders always pose a challenge and the present study has thrown some light in using physiological markers as lipid profile components, namely serum cholesterol- and LDL-cholesterol concentrations as well as cholesterol/HDL-cholesterol- and LDL-cholesterol/HDL-cholesterol ratios to differentiate between clinical subtypes of the depressive disorder. Furthermore, assessing cardiovascular risks in those groups can be possible besides psychiatric diagnosis, as indicated in our findings. Since depressive groups may sometimes present with similar symptoms, using above markers can help in diagnosis and preventive health risk can also be ascertained.

The study has limitations of a comparatively smaller sample size of patients in assigned groups. It could be better if all treatment interventions could be done earlier keeping the difference minimum between groups, but that could not be maintained uniformly between the groups. Inclusion of a healthy control group could supplement the findings, which we plan to do in our next study. The whole picture of the pathophysiology of depressive disorders can be clearer with the investigations on biological markers such as cholesterol. The modern trend of a frequent use of lipid-lowering agents to cut down cardiovascular risks can be questioned in the context of the present study. A further study aiming to link the lipid profile status with impulse control disorder and a risky behavior in depressive subgroups comprising a bigger sample size should be proposed. Furthermore, the role of low serum cholesterol in the course of recovery from depressive disorder needs further investigation.

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ORIGINAL ARTICLE

Coinfection of HBV and HCV in HIV-positive Injecting Drug Users

Sunanda Joshi[1], Nalini Mittal[2]

Abstract

Introduction: Drug addicts represent a high-risk group for acquiring parenterally transmitted viral infections. It is very likely that an injecting drug user (IDU) infected with HIV will be infected with either HBV or HCV or both because of common high-risk behaviors.

Materials and methods: A cross-sectional study was carried out in which a total of 229 blood samples were collected from IDUs. They were screened for HIV.

Results and discussion: All HIV-positive patients were tested to observe whether a HBV or HCV infection (or both) is also present in the patients. A total of 22 patients were HIV-positive (9.6%). Of the 22 HIV-positive patients, 10 were positive for HCV (45.45%), 7 were positive for HBV (31.81%), and 2 (9%) were positive for all three.

Conclusion: Prevention efforts such as vaccination of IDUs and maximum syringe distribution should be taken to avoid sharing of syringes. Screening of all HIV-positive IDUs for HBV and HCV should be made mandatory.

Keywords: Hepatitis B virus, Hepatitis C virus, Human immunodeficiency virus, Injecting drug users.

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Introduction

Drug addicts represent a high-risk group for acquiring parenterally transmitted viral infections such as human immunodeficiency virus (HIV), hepatitis C virus (HCV), and hepatitis B virus (HBV). It is very likely that an injecting drug user (IDU) infected with HIV will also be infected with either HBV or HCV or both because of common high-risk behaviors.[1] HBV and HCV coinfection in HIV-positive individuals are of utmost importance owing to the underlying consequences such as the hepatological problems associated with these viruses, which have been shown to decrease life expectancy in the HIV-infected patients.[2] According to Centers for Disease Control and Prevention (CDC), treatment with antiretroviral therapy has improved the health and extended the life expectancy of people with HIV and liver disease—much of which is related to HBV, and HCV causes non-AIDS-related deaths in this population.[3]

Injecting drug users (IDUs) have the second highest HIV prevalence in our country (7.14%).[4] India has an estimated 177,000 IDUs.[4] The IDU population has been largely studied in the high HIV prevalence states in north-eastern and southern parts of the country, where prevalence of HIV (25.4–59.6%), HBV (10%), and HCV (54.5–90.4%) has been reported.[5–7] The hospital where the study was carried out is situated in a part of Delhi where there is low-income slum and a state vegetable market, accounting for a high percentage of IV drug users. The aim of the study was to find the coinfection of HBV and HCV in HIV-infected IDUs, as the coinfection of viruses increases the morbidity and mortality of each other.[8]

Materials and Methods

A cross-sectional study was carried in a secondary healthcare centre of Delhi over a period of 6 months in the year 2015. IDUs attending the integrated counseling and testing centre (ICTC) of our hospital were referred to the microbiology department. Consent was taken and counseling was given to explain the purpose of the study to each one of them. A total of 229 blood samples were collected from IDUs. Whole blood (4–5 mL) was collected and serum was obtained. The serum samples were tested for the presence of HIV antibodies according to National AIDS Control Organization (NACO) guidelines. HIV-positive samples were tested for HBsAg by Meri Screen (Meril Diagnostics). All positive samples were confirmed by SD bioloine kits. Anti-HCV antibodies were detected in the serum using Qualpro rapid diagnostic kits.

Results

Of a total of 229 IV drug users, 218 were male and 11 were females. There were 22 male patients who tested positive for HIV, whereas none of the females were tested positive. Of these 22 patients, 21 were positive for HIV 1 and 1 was positive for both HIV 1 and 2. In these patients, it was noted that 10 were positive for HCV (45.45%), 7 were positive for HBV (31.81%). Of these 17 positive patients for HCV and HBV, 2 (9%) were positive for all three. The prevalence of HIV in this study is 9.6%, and the prevalence of HIV 1 and HIV 2 is 0.43%.

HIV positive	*HIV plus HCV*	*HIV plus HBV*	*HIV plus HCV plus HBV*
22/229 (9.60%)	10 (45.5%)	7 (31.81%)	2 (9%)

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Statistical calculations using Chi-square test revealed that the difference in the prevalence of other infections' markers such as HBsAg and HCV with HIV was not statistically significant ($p > 0.05$).

Discussion

Nearly 75% of people with HIV who report a history of injection drug use are also infected with hepatitis C virus (HCV). HIV/HCV co-infection more than triples the risk for liver disease, liver failure, and liver-related death. People with HIV infection in the West are often affected by chronic viral hepatitis; about one-third are co-infected with either HBV or HCV. More people living with HIV are infected with HCV than with HBV (CDC).

Our study showed male predominance (100%), which is in accordance with the study conducted in Iran (98%). This could indicate a higher prevalence of high-risk behaviors among men compared to women (IRAN study). However, some studies have suggested that there has been a rising number of female drug users over the past two decades.[9]

In our study the prevalence of HIV infection was 9.60%; in other studies carried out in Delhi, the prevalence of HIV infection was 25.9 %,[10] 37%,[1] and 13.8%.[5] Though the HIV prevalence was less when compared to that in other studies in Delhi, it was similar to a study from Amritsar in IDUs.[11] The low prevalence in our study may be attributed to the National AIDS Control Programme Phase-IV (2012–17). The program included-targeted interventions (TI) for high-risk groups and needle-syringe exchange programme (NSEP) opioid substitution therapy (OST) for IDUs, which could have influenced the results of our study.

HIV–HCV coinfection was 45.5%, while HIV–HBV coinfection was 31.81% in our study. Earlier quoted studies from Delhi reported HIV HCV coinfection of 19.6%),[10] 9.6 %,[1] and 14.5%[5] while HIV–HBV coinfection was 3.4 % among IDUs in 2012. HIV–HCV and HIV–HBV coinfection were found in 9.09% of patients, which is in accordance with the study, which showed 11.17%.[1] HIV–HCV coinfection was high compared to HIV–HBV coinfection, which is similar to the findings of other studies.

The mixed infection of HIV-1 and HIV-2 viruses has been reported from the northeastern states of India among the drug abusers by many workers.[12] But, in our study, mostly HIV-1 infection was detected from the drug addicts and only one HIV-1 and HIV-2 mixed infection was detected, which indicates that HIV-2 has not made it into this population.

Conclusion

The problem of injecting drug use (IDU) along with the a high prevalence of associated infections is rapidly spreading in some developing countries, including India.[13,14] The infectious consequences of drug injection poses a global problem with more than 60 countries documenting HIV infection among persons practicing illicit drug injections today.[15] We observed that coinfection of HIV is higher with HCV when compared that with HBV. All HIV-positive IDUs should be screened for HBV and HCV infection and treated accordingly. Prevention efforts should include vaccination of IDUs who are non-immune to HBV and to implement target interventions, syringe sharing with efforts such as maximum syringe distribution cover. Hepatitis B and C should be included in HIV prevention messages and counseling.

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ORIGINAL ARTICLE

Blood Donor Retention: Role of a Donor Satisfaction Survey

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Abstract

Introduction: Efforts are needed to strengthen blood donor management at all levels, including educating and motivating more individuals to be involved in voluntary blood donation and converting them to retention donors. Donor retention is influenced by many factors, including the quality of blood donation experience, environment, services, wait time, and the type of interactions with the staff. It is important to develop donor feedback and a follow-up mechanism to encourage more future donations assessing the current donor management strategy.

Materials and methods: This study was planned to observe the current blood donation practice at the blood bank of a tertiary-care teaching hospital in order to assess the blood donation experience and reasons and barriers for blood donation. A trained counselor interviewed a total of two hundred consecutive donors and the responses were noted on a predesigned and validated questionnaire form after taking informed consent.

Results: Altruism was the most common reason for donating blood $n = 107$ (53.5%), while other reasons included helping a known person or an interest in gifts provided by the blood bank after blood donation (e.g., mugs, bags, stationery). The donors reported news, college motivation programs, and family discussions as the most common areas where they had heard first about blood donation, with others being workplace, camp, or public discourses. The common reasons for not donating till now were "fear of needles" $n = 58$ (29%), "not demanded or unrequested for" $n = 40$ (20%) and "fear of weakness post-donation" or asthenophobia $n = 30$ (15%).

Conclusion: Donor satisfaction surveys and analysis helps in increased donor retention, self-confidence, and feedback for suggesting an improvement.

Keywords: Blood donor retention, Feedback from blood donors, Motivation for blood donation.

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Introduction

Blood transfusion is an indispensable component of healthcare. It contributes to saving millions of lives each year in both routine and emergency situations, permits increasingly complex medical and surgical interventions, and markedly improves the life expectancy and quality-of-life of patients with a variety of acute and chronic conditions.[1]

The rise in human life-expectancy and improvements in medical technology have led to a constant increase in the demand for blood transfusions. However, the aging of the donor population resulting in higher morbidity and new donor screening deferral criteria to increase safety against transfusion-transmitted diseases have decreased the availability of eligible blood donors. Worldwide, the current challenge that blood banks are facing is to recruit and retain qualified blood donors to fulfill the rising transfusion needs.[2] A well-functioning blood transfusion service is dependent on forthcoming blood donors who are willing to donate voluntarily without being mandated.[3]

Even well-established donor programs have to work constantly to bring in new donors while maintaining contact with existing donors and encouraging them to donate again. As in any organization, an effective blood donor program requires effective management in a way that it ensures both blood safety and donor retention.[1] Retention of blood donors, preventing donors from lapsing and eventually becoming inactive, has benefits over the recruitment of new blood donors.[4]

Motivation to donate blood can vary broadly from altruistic reasons to strictly personal reasons, such as getting a day off work or having blood tested for transmitted diseases. The decision to donate blood and return for further donations also depends on social responsibility, personal credit, social pressure, satisfaction and, mainly, a positive donation experience. Therefore, blood banks must develop strategies and incentives to retain donors and special attention must be paid to the impact of donor deferral on donor availability.[2]

Protecting the health and safety of donors and staff and the efficacy of donated units of blood is a central responsibility of the blood donor program. This requires the provision of a suitable, clean, safe environment for each stage of the blood donation process.[1]

Volunteers can play a variety of roles in the blood donor program, either in community-based activities organized by organizations to which they belong, or by working directly with the blood service in donor recruitment or blood donor sessions. Volunteers are usually enthusiastic and may be highly effective in motivating others to donate blood.[1]

Well-defined quality systems should be in place for all activities and procedures to ensure the safety and efficacy of the blood supply

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and to contribute to the sustainability and cost-effectiveness of the program.[1] The blood donation experience, therefore, needs to be carefully planned and evaluated periodically in all centers. This effort should include ensuring eligibility through rational and evidence-based donor selection criteria and at the same time educating and motivating the donors to stay involved in blood donation. It is therefore important to develop donor feedback and a follow-up mechanism to encourage more future donations assessing the current donor management strategy.

This study was planned to observe the current blood donation practice at the blood bank of a tertiary-care teaching hospital in order to assess the blood donation experience and reasons and barriers for blood donation.

Materials and Methods

An observational, descriptive cross-sectional study was carried out among blood donors visiting the blood bank of a tertiary-care teaching hospital. Those donors who fulfilled the criteria for blood donation were included in the study. A trained counselor interviewed a total of two hundred consecutive donors and the responses were noted on a predesigned and validated questionnaire form after taking informed consent. The questionnaire included their views on reasons for motivation to donate blood and also those factors that contributed to satisfaction during a blood donation experience. The factors that would influence their decision to donate again were also enquired. The demographical details were recorded. The responses were later analyzed and presented using tables in the form of numbers and percentages using a microsoft excel sheet.

Observation

A total of 200 donors were included in this study. Of the donors included in the study, maximum numbers ($n = 144$ (72%)) belonged to 21- to 40-year age group. Males were more than females; male:female ratio was 7.3:1. Only 4 (2%) donors were illiterate. Among the educated donors, 90 (45%) were graduates and 34 (17.5%) were postgraduates.

A total of 107 (53.5%) donors were married. The number of donors who smoked was 56 (28%). Those who consumed alcohol were 70 (35%).

Altruism was the most common reason for donating blood ($n = 107$ (53.5%)), while other reasons included helping a known person or an interest in gifts provided (e.g., mugs, bags, and stationery). The donors reported news, college motivation programs, and family discussions as the most common areas where they had heard first about blood donation, with others being workplace, camp, or public discourses. The common reasons for not donating till now were "fear of needles" $n = 58$ (29%), "not asked by anyone to donate/ not demanded or unrequested for" $n = 40$ (20%) and "fear of weakness post-donation," also known as asthenophobia $n = 30$ (15%).

Among these 200 donors, 119 (59.5%) were repeat donors and among these 117 (58.5%) reported a good past blood-donation experience. They ranked the importance of various factors that contribute to a good donation experience. The attitude of staff at reception and phlebotomy was perceived as good in 96 (48%) and 84 (42%) cases, respectively. They reported that 117 (58.5%) were appreciated for blood donation by the staff. The refreshment area was reported as clean and inviting in 126 (63%) cases. When asked to rate their experience at our blood bank 196 (98%) donors reported a good overall experience.

When asked about their intentions to donate in future, 173 (86.5%) donors wanted to donate again and 99% were ready to donate when asked in case of an emergency. However, only 169 (84.5%) wanted to be informed about upcoming camps. They wanted to be informed for subsequent camps through e-Mail $n = 14$ (7%), SMS $n = 76$ (38%), and phone calls $n = 110$ (55%). The suggestion for promoting voluntary blood donation included road shows, media, pamphlets, camps, and motivational talks.

Discussion

Donor characteristics have been studied previously and found to result in the improvement of services and a high level of satisfaction among blood donors who are a precious commodity to maintain the supply of this life-saving resource. In this study, we analyzed donor's views and their satisfaction levels in an attempt to provide an insight into the reasons for inadequate donor retention in current donor management strategy. Blood donation is a noble and altruistic act. It is thought that altruistic behavior increases as age progress, with older donors having higher scores. But our study is an exception to this fact since there is evidence that altruism is established early on in life. Social responsibility appears to be another important motivation for donation.

The most active participation (72%) by the young age group (21–40 years) among blood donors should be noted, which was similar to the findings of the studies done by Allain et al.[4] and Hinrich et al.[5] A major chunk of these donors are educated (98%), which reflects the fact that it is illiteracy that contributes to ignorance. It indicates the importance of voluntary blood donation awareness among college students so that it becomes a part of their regular habits and values.

The under-presentation of females, which was similar to the findings of a study done by Van Dongen[6] (M:F = 7.3:1), maybe explained by the temporary cause of deferral (e.g., menstruation, lactation, pregnancy, low-weight) and a high prevalence of anemia among females in India. In a study done by Hollingsworth, female donors constituted only 1% of the donor population.[7] More than half (59.9%) of the donors were repeated donors. A donor may stop donating because of practical reasons such as lack of a comfortable environment to donate or because of a bad experience when donating last. However, this does not hold true in our study, as 98% of donors perceived a good past experience at our center, including friendly attitude of staff at the reception, the phlebotomists with interactive skills which is supposed to be a major factor to allay the fear and anxiety, particularly amongst the first-time donors, that may precipitate vasovagal attacks.

The importance of social networks as a recruitment channel for blood donation is noteworthy. Among our subjects, 55% of the donors wished to be informed via phone calls regarding upcoming subsequent blood donation camps. 86.5% of the donors enthusiastically expressed their willingness to keep up their participation in this endeavor. This indicates that the commitment to donate blood is high among donors.

In our study, 40% were first-time donors. This was similar to the findings of the study, which was done by Olaiya et al.,[8] whereas the study by Zaller et al.[9] showed that only 17.5% of the donors were first-time donors. The predominant reason among the first-time donors for not presenting before was fear of needles, which were similar to the findings of a study done by Olaiya et al.,[8] followed by a lack of motivation and, to some extent, a prevalence of the notion of post-donation weakness. The increasing demand for blood

donation has encouraged health authorities to convert first-time blood donors to become regular blood donors. The satisfaction of donors with the current donation experience influences their intent to donate blood in the future.

Regular feedback regarding our services helps the Blood transfusion services in many ways. If the results indicate a satisfactory service and donor satisfaction, it increases self-confidence and motivates to perform better. However, adverse reporting and relatively negative feedback indicate which area needs improvement and thus also enable the blood transfusion services to perform better in the future.

As an example, the satisfactory donor experience with regard to the behavior of staff and infrastructure calls for the appreciation of concerned personnel. However, the fact that only 58.5% of donors were thanked for the noble act shows a need to train the staff regarding their role towards converting a first-time donor to a retention donor. Hence, to understand better about what motivates donors to give blood, we need to explore their behavior at intervals and get their constant feedback.

A major shortcoming of the study was that it had a very small sample size. More such studies need to be carried out to improve the standard of blood donor services. Similar feedback sessions should be conducted at campsites also so as to make camp services better. It was also found to be a time-intensive activity that demands logistics in terms of stationary and staff. However, it must be planned and executed, as it is an important measure to improve donor safety and retention.

Conclusion

Donor satisfaction surveys and analysis results in increased donor retention, self-confidence, and feedback for suggesting an improvement. Without a coordinated and adequately resourced voluntary blood donor program, achieving safe and sufficient blood supply will remain an aspiration rather than a realistic goal.

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ORIGINAL ARTICLE

Gum Chewing: A Novel Method for Improving Gut Motility after Cesarean Section

Mayuri More[1], Sushil Kumar[2], Sunil Sharma[3]

Abstract

Background: The presence of bowel movements after any abdominal surgery is an important event and indication for switching the patient from intravenous fluids to oral feeding. Gum chewing has been reported to help in the early return of bowel sounds in patients who have undergone abdominal surgery. The present study evaluates the efficacy of gum chewing on bowel movements in postcesarean patients.

Materials and methods: A total of 200 women delivered by lower segment cesarean section, under spinal anesthesia were included in the study. The patients were randomly allotted to two groups. Group I—chewing gum group and group II—control group. Two hours after cesarean section, the women in the study group received one stick of gum every four hours to be chewed for 30 minutes until regaining their bowel function. The women in the control group followed the standard postoperative care. Each woman in both groups was examined abdominally using a stethoscope to detect the intestinal sound every one hour. The following outcome parameters were noted: the time to hear the first bowel sound, time to mobilization, time to first passage of flatus, time to first feeling of hunger, the time to first defecation, and length of the hospital stay.

Results: The two groups were well matched in terms of age of the patients, parity, ANC registration, gestational age, and the history of previous abdominal surgery. Outcome parameters connected with bowel movements were significantly shorter in group I (chewing gum). However, the duration of hospital stay in both groups was the same.

Conclusion: The study confirms the effectiveness of gum chewing on peristaltic activity after a primary lower segment cesarean section. It is a harmless and inexpensive method for stimulating early bowel movements. Early bowel movements also mean less use of IV fluids in the post-operative period, thus early ambulation.

Keywords: Bowel movements after cesarean section, Effect of gum chewing on bowel movements, Postoperative Ileus.

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Introduction

Cesarean section is the most common surgery that could result in postoperative changes in the autonomic nervous system, leading to reduced bowel motility and associated problems.[1] The delay lasting for 3–5 days, in return of regular bowel movements following an abdominal surgery is referred to as paralytic ileus.[2] It is also one of the major problems encountered by patients who have undergone a cesarean section, leading to an increased hospital stay, postoperative pain, abdominal distension, an inability to breastfeed the baby, and eventually delays in recovery.[3] Ileus occurs in cases with the use of opioids and excessive handling of intestines in abdominal surgeries that temporarily contribute to stoppage of the bowel movements; the mechanism related is probably a dysfunction in parasympathetic system activity (inhibitory neurons).[4]

Withholding postoperative oral intake to cesarean patients until the return of bowel function is a general practice. Clinically, the return of the bowel function is diagnosed by the passage of flatus or stools, feeling of hunger, or the presence of bowel sounds.[5] Studies have shown that early postoperative feeding could be safe prior to the return of flatus or stool;[6] a delay in the initiation of feeding leads to delayed wound healing, increased cell breakdown, elevated risk of infection, and the need for more intravenous fluids. This leads to additional costs on the healthcare system and on the family.[7]

There is no particular treatment for postoperative ileus although certain methods such as nasogastric suctioning, early feeding, IV fluid,[7,8] local analgesia, minimal surgical manipulation, use of non-steroidal anti-inflammatory drugs, and high carbohydrate content drinks[8,9] have been reported to decrease the incidence of postoperative ileus.

Gum chewing causes a person to feel good owing to stimulation of stomach and secretion of digestive and gastric juices. It increases the appetite and peristaltic bowel movements and also hastens ileus recovery[10–13] and it has also been recently reported as a method to reduce ileus.[14] Gumchewing is a form of sham feeding to stimulate bowel motility after surgery. The presumed mechanism of action is parasympathetic stimulation of the gastrointestinal tract, which is similar to oral intake but with theoretically less risk of vomiting and aspiration. Gumchewing is a cheap and harmless strategy to reduce postoperative ileus when used immediately after surgery. The present study was thus conducted to investigate the effect of gum chewing on the return of postoperative bowel motility in patients undergoing a cesarean section.

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Aim and Objective

The aim of this study was to investigate the effect of gum chewing on the return of postoperative bowel activity in women undergoing a cesarean section.

Materials and Methods

Study Area

MGM Medical College and Hospital, Kalamboli, Mumbai. A tertiary care hospital.

Study Population

Women delivered by a lower segment cesarean section under spinal anesthesia.

Study Design

A case-control study. A total of 200 women delivered by a lower segment cesarean section fulfilling eligibility criteria were included in the study after taking informed consent. These cases were randomly divided into one of the following two groups (100 each) using computer-generated random numbers:

Group I—chewing gum group

Group II—control group (undergoing standard management)

Study Duration

Dec 2016—May 2018

Inclusion Criteria

- All women delivered by lower segment cesarean section under spinal anesthesia.

Exclusion Criteria

- Women undergoing cesarean section under general anesthesia.
- Patient's refusal to participate in the trial.

Methodology

Written informed consent was obtained from each participant. The demographic and obstetric data were collected. After two hours of cesarean section, the women in the study group received one stick of sugarless gum every four hours to be chewed for 30 minutes until regaining bowel function. The women in the control group followed the standard post-operative care. Each woman in both groups was examined abdominally using a stethoscope to detect the intestinal sound every one hour and was asked to report the time of first-time feeling of bowel movement, passing flatus or stool, or feeling hunger. The following outcome parameters were noted: the time to first bowel sound, time to mobilization, time to first passage of flatus, time to first feeling of hunger, time to first defecation, and the length of the hospital stay.

Statistical Analysis

The quantitative data were represented as their mean ± SD. Categorical and nominal data were expressed in percentage. The *t* test was used for analyzing quantitative data, the nonparametric data were analyzed by Mann–Whitney test, and categorical data were analyzed using the Chi-square test. The significance threshold of *p* value was set at <0.05. All analysis was carried out by using SPSS software, version 21.

Results

A total of 200 women delivered by a lower segment cesarean section fulfilling the eligibility criteria were included in the study after taking informed consent. These patients were randomly divided into one of the following two groups (100 each) using computer-generated random numbers:

Group I—chewing gum group and group II—control group undergoing standard management (Tables 1 and 2).

Mean age of group I was 27.13 years while in group II it was 26.42 years with no difference between the groups (*p* 0.54).

Out of the total 200 study cases, 52.5% were primi and 47.5% were multigravida with no significant difference between study the groups (*p* 0.77) (Tables 3 to 6).

Out of the total 200 study cases, 97.5% were registered cases, while 2.5% were unregistered cases with no significant difference between study groups (*p* 1.0).

Mean gestation age of study groups I and II was 38.67 and 38.91 weeks with no significant difference between study groups (*p* 0.71).

Histories of previous abdominal surgeries were given by 14% of cases in the study with no significant difference between study groups (*p* 0.83) (Tables 7 to 10).

Table 1: Group distribution of study subjects

Group	*N*	*(%)*
I (chewing gum)	100	50.0
II (control)	100	50.0
Total	200	100.0

Table 2: Mean age comparison of study groups

Variables	*Group*	*N*	*Mean*	*SD*	*p value*
Age	I	100	27.13	4.59	0.54
	II	100	26.42	4.05	

Table 3: Distribution of cases as per obstetric history

	Group			
Obstetric history	*I*	*II*	*Total*	*p value*
Primi	54	51	105	0.77
	54.0%	51.0%	52.5%	
Multi	46	49	95	
	46.0%	49.0%	47.5%	
Total	100	100	200	
	100.0%	100.0%	100.0%	

Table 4: Distribution of cases as per ANC history

	Group			
ANC history	*I*	*II*	*Total*	*p value*
Registered	97	98	195	1.0
	97.0%	98.0%	97.5%	
Unregistered	3	2	5	
	3.0%	2.0%	2.5%	
Total	100	100	200	
	100.0%	100.0%	100.0%	

Table 5: Mean comparison of gestation age among study groups

Variables	*Group*	*N*	*Mean*	*SD*	*p value*
Gestation age (weeks)	I	100	38.67	1.14	0.71
	II	100	38.91	1.09	

Table 6: Distribution of cases as per the history of previous abdominal surgeries

History of previous abdominal surgeries	*Group*			
	I	*II*	*Total*	*p value*
Yes	15	13	28	0.83
	15.0%	13.0%	14.0%	
No	85	87	172	
	85.0%	87.0%	86.0%	
Total	100	100	200	
	100.0%	100.0%	100.0%	

Table 7: Mean comparison of time to hear first bowel sound, first flatus, and defecation

Variables	*Group*	*N*	*Mean*	*SD*	*p value*
Time to hear first bowel sounds (hours)	I	100	10.76	0.34	<0.01
	II	100	18.01	0.43	
Time of first flatus (hours)	I	100	16.54	0.46	<0.01
	II	100	25.87	0.33	
Time to defecation (hours)	I	100	26.11	1.09	<0.01
	II	100	36.89	0.89	

Table 8: Mean time for feeling hunger and time for the first diet

Variables	*Group*	*N*	*Mean*	*SD*	*p value*
Time of feeling hunger (hours)	I	100	7.01	0.51	<0.01
	II	100	11.68	0.64	
Time to first diet (hours)	I	100	28.76	2.01	<0.01
	II	100	38.90	3.21	

Table 9: A comparison of mean IV fluids' requirement among study groups

Variables	*Group*	*N*	*Mean*	*SD*	*p value*
IV Fluids (500 mL)	I	100	4.17	1.12	<0.01
	II	100	7.01	2.13	

Table 10: A comparison of mean hospital stay among study groups

Variables	*Group*	*N*	*Mean*	*SD*	*p value*
Hospital stay (days)	I	100	4.04	1.12	0.44
	II	100	4.89	1.78	

Meantime to hear first bowel sound (10.76 vs 18.01 hours), time for first flatus (16.54 vs 25.87 hours), and time for defecation (26.11 vs 36.89 hours) were significantly less in the chewing gum group with respect to controls ($p < 0.05$).

Meantime of feeling hunger (7.01 vs 11.68 hours) and time for first diet (28.76 vs 38.9 hours) were significantly lower in the chewing gum group with respect to controls ($p < 0.05$).

Mean IV fluids administered were significantly lower in the chewing gum group with respect to controls (4.17 vs 7.01 pints; $p < 0.01$).

Most of the patients were discharged on 4th or 5th day post-cesarean section. Mean hospital stay was comparable between the chewing gum and control groups (4.04 days vs 4.89 days; p 0.44).

Discussion

Postoperative malfunctioning of the gastrointestinal tract is associated with high morbidity and regarded as a significant factor in determining the hospital stay of the patient. Multiple factors can cause a postoperative malfunctioning of the gastrointestinal tract (e.g. response to stress, interventions applied during operation, manipulation of the bowel, adhesions in case of repeat C-sections, and duration of surgery).

Oral feeding is customarily allowed for cesarean-section patients after confirming the initiation of gut sounds. Several studies have reported that oral feeding prior to gut motility may lead to an increase in the tissue injury, delayed wound healing, and high rates of postoperative infection. It has been observed that bowel motility and function are enhanced by gum chewing.[10–13]

The present study was aimed to investigate the effect of gum chewing on the postoperative bowel motility in women undergoing a cesarean section. A total of 200 women delivered by a lower segment cesarean section at our hospital fulfilling eligibility criteria were included in the study. These cases were randomly divided into one of the following two groups (100 each) using computer-generated random numbers. Group I—chewing gum group (study group), and group II—control group. The results are discussed in the upcoming paragraphs.

Demography

Mean age of group I was 27.13 years while in group II it was 26.42 years with no difference between the study groups (p 0.54). Both the groups were comparable with respect to obstetric history, ANC registration, and gestation age.

Intestinal Motility

In the present study, the mean time to hear first bowel sound (10.76 vs 18.01 hours), time for first flatus (16.54 vs 25.87 hours), and time for defecation (26.11 vs 36.89 hours) were significantly less in the chewing gum group with respect to controls ($p < 0.05$). The mean time of feeling hunger (7.01 vs 11.68 hours) and time for the first diet (28.76 vs 38.9 hours) was also significantly lower in the chewing gum group with respect to controls ($p < 0.05$).

Similar findings were also noted by various other authors.[1–16] In their study observed that mean postoperative time interval to first hearing of normal intestinal sounds (10.9 ± 2.7 vs 15.6 ± 3.7 hours), passage of flatus (17.9 ± 4.6 vs 24.4 ± 7.1 hours), defecation (21.1 ± 4.7 vs 30 ± 8.2 hours), and discharge from the hospital (40.8 ± 10.6 vs 50.5 ± 8.9 hours) were significantly shorter in the chewing gum group ($p < 0.001$). Ledari et al.[2] observed that the mean average postoperative interval of the first bowel sounds (21.9 vs 26.1 hours, $p < 0.01$), the first feeling of hunger (11.8 vs 14.5 hours, p 0.05), the first passage of flatus (24.8 vs 30.0 hours, p 0.0002), and the first defecation (30.6 vs 38.4 hours, $p = 0.001$) were significantly shorter in the chewing gum group when compared to the control group. Ajuzieogu et al.[3] observed that the mean time to first bowel sounds (21.9 ± 8.0 vs 26.1 ± 10.0), the mean time to first flatus (24.8 ± 6.4 vs 30.0 ± 10.0), and the mean time to defecation (30.7 ± 5.9

vs 40.0 ± 9.0) were significantly reduced in patients who chewed gum compared with controls. Wajid et al.[5] observed that the mean duration of the feeling of hunger was 11.38 ± 3.14 hours in the chewing gum group and 16.84 ± 0.49 hours in the control group. The mean duration of first bowel sound was 21.39 ± 0.68 hours in the chewing gum group and in the control group were 28.27 ± 0.60 hours. The mean duration for the first passage of flatus was 25.94 ± 0.71 hours in the chewing gum group and 32.00 ± 0.77 hours in the control group. The mean duration of the first defecation was 31.56 ± 0.81 hours in the chewing gum group and 41.28 ± 0.80 hours in the control group. Mansour et al.[10] in their study observed the following findings in chewing gum and control group: first time of hearing intestinal sound was 3.93 ± 1.02 vs 4.87 ± 1.96, $p = 0.008$, the first passage of gas was 6.54 ± 1.37 vs 7.65 ± 2.42, $p = 0.013$, the first hungry feeling was 7.63 ± 2.24 vs 8.83 ± 3.18, $p = 0.024$, the first defecation was 10.25 ± 2.15 vs 11.58 ± 1.96, $p = 0.031$, the first eat was 11.60 ± 2.03 vs 14.08 ± 3.58, $p = 0.000$, respectively. Deshpande et al.[14] observed a significant difference in the return of bowel movement (8.8 vs 17.5 hours), first feeling of hunger (7.2 vs 12.5 hours), first passage of flatus (17.5 vs 26.4 hours), and first defecation (27.1 vs 37.2 hours) respectively in the study (chewing gum) and control groups. Sajid et al.[15] in their study had following observations: In group I (chewing gum), the duration of passing first flatus was 7.39 ± 1.98 hours and in group II (control group), the duration was 12.80 ± 4.26 hours, the average duration to passing flatus was significantly lower in the chewing gum group when compared with controls (p value < 0.01). In group I (chewing gum), the duration of defecation was 10.93 ± 2.78 hours and in the group II (control), it was 18.82 ± 5.46 hours; the average duration to defecation was also significantly lower in the chewing gum group when compared with the controls (p value < 0.01). In group I (chewing gum), the duration to defecation was 10.93 ± 2.78 hours and in the group II (control) it was 18.82 ± 5.46 hours; the average duration to defecation was significantly lower in the chewing gum group when compared with controls (p value < 0.01).

Short et al.,[4] Zhu et al.,[6] Huang et al.,[8] Morais et al.[9] and Ciarduli et al.[12] in their respective reviews also observed that gum chewing is associated with early recovery of bowel motility in women after a cesarean section.

Hospital Stay

Most of the patients were discharged on the 4th or 5th day post-cesarean section. Mean hospital stay in the present study was comparable between chewing gum and control group (4.04 days vs 4.89 days; p 0.44).

Similar to the present study, Esfehani et al.[16] in their study also observed no difference in the duration of hospital stay between study groups. Huang et al.[8] in a systemic review observed that length of hospital stay (SMD: 0.59; 95% CI: 1.18–0.00; $p > 0.05$; I^2: 93%) was reduced in the chewing gum group; however, these results were not statistically significant. However, Maeboud et al.[1] in their study observed that mean days for discharge from the hospital (40.8 ± 10.6 vs 50.5 ± 8.9 hours) were significantly shorter in the chewing gum group ($p < 0.01$). Short et al.,[4] Zhu et al.,[6] Morais et al.,[9] and Ciarduli et al.[12] in their respective reviews also observed that gum chewing is associated with a decreased length of hospital stay (LOHS).

Thus, to summarize, our study depicted that gum chewing is very beneficial and effective in the early return of bowel motility and quick recovery after cesarean section. Gum chewing after CS is safe, well-tolerated, and associated with rapid resumption of intestinal motility and a shorter hospital stay, with a potential impact on reducing the overall healthcare costs in the case of routine implementation. Hence, the routine use of chewing gum is strongly recommended after a cesarean section.

Conclusion

The conclusion has been drawn on the basis of the results and observations of the present study indicating the effectiveness of gum chewing on the peristaltic activity after a primary lower segment cesarean section. It is an acceptable and inexpensive method for decreasing the time of regaining bowel movements and earlier passage of flatus and stool. It is found to be effective in reducing the use of intravenous fluids in the immediate postoperative period in a cesarean patient. In short, the chewing gum method is a simple, acceptable, well-tolerated, and cost-effective way to promote bowel movements in patients who have undergone a cesarean section.

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MINI REVIEW

Galactorrhea

Alaka Deshpande

Abstract

An inappropriate secretion of a milk-like substance from breasts is called galactorrhea. The commonest cause is over-secretion of the hormone Prolactin. Causes and management of prolactinemia are discussed in this paper. A protocol to investigate these cases has been given. The advent of dopamine agonists, which inhibit secretion of prolactin, has made the management of these cases simple and safe. All patients of hyperprolactinemia may have associated tumors in the pituitary (prolactinomas). If these are less than 3 cm in size, as seen on neuroimaging, medical management may be enough. Tumors exceeding 3 cm in size may need a surgical resection because they may produce compressive effects. Hypothyroidism must be excluded and, if present, treated appropriately.

Keywords: Bromocriptine, Cabergoline, Dopamine agonists, Galactorrhea, Prolactin, Prolactinoma.

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Introduction

Galactorrhea is defined as an inappropriate secretion of a milk-like substance from the nipples of either women or men and may be unilateral or bilateral. It may be watery, milky, or bloody. If bloody, one has to investigate the case for neoplasms such as duct papilloma or carcinoma. Conversely, the absence of blood does not rule out an underlying tumor.

The Talmud (a religious text of Judaism termed by Christians as Hebrew bible) describes a man who nursed his baby after the untimely demise of his wife. This may be the first recorded case of male galactorrhea.

Breast milk is normally secreted from the mother's breast after the delivery of a child, which is essential to feed the baby. It may persist for about six months after cessation of breastfeeding. It was in the 1930s that a hormone was detected by Riddle[1,2] and his associates in animals, which stimulated the secretion of breast milk in animals. It was also associated with milk crop gland development in birds. As it could stimulate lactation, the hormone was named as prolactin.

Later it was found that it is secreted by lactotroph cells of the anterior pituitary, which comprise about 15–25% of cells of the anterior pituitary. Therefore, it is also called a leuteotropic hormone (LTH). Prolactin (PRL) acts by binding to the PRL receptors located on the extracellular surface of the target tissue. On the evolutionary scale, prolactin is an ancient hormone serving multiple roles in mediating the care of progeny (sometimes called the "parenting" hormone).

Isolation of PRL in humans remained elusive till 1970[3] because bioassays that were then used could not differentiate PRL from the growth hormone (GH), which also had lactogenic properties. Development of radioimmunoassay (RIA) in 1970 made it possible to identify prolactin distinctly from GH, leading to an undeniable discovery of these two as separate hormones.

Extra-pituitary PRL[4]

PRL has also been detected in the extra-pituitary tissues (ePRL),[4] which include thymus, lymph glands, skin, mammary glands, ovaries, and prostate among others. Regulation of ePRL is different from that of the regular PRL.

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Physiology

Prolactin (PRL) is a polypeptide[5] composed of 199 amino acids and secreted by lactotroph cells of the anterior pituitary. In circulation, it is found in three sizes:

- Monomeric little PRL—23 kD—most bioactive
- Dimeric PRL—Big PRL—48–56 kD
- Polymeric form Big PRL >100 kD.

The human PRL gene is located on chromosome 6 and apparently arose from a single common ancestral gene giving rise to the relatively homologous PRL, GH, and placental-lactogen-related proteins. Hypothalamic regulation of the pituitary occurs through neuropeptidases such as GnRH and TRF. But PRL is regulated by neuroendocrine neurons via a neurotransmitter dopamine. The neuropeptidases have a stimulatory role, while dopamine inhibits the secretion of PRL. If the anterior pituitary is separated from the hypothalamus, the secretion of PRL increases, whereas the secretion of other pituitary hormones decreases. The secretory phase of the menstrual cycle is due to the release of progesterone from the corpus luteum. PRL acts to maintain the corpus luteum.

During conception, PRL helps in sustaining the pregnancy by the maintenance of corpus lutea function, leading to progesterone secretion. High levels of PRL during pregnancy inhibit gonadotropin-releasing hormone (GnRH) from the hypothalamus, thereby decreasing the secretion of FSH and LH and thus protecting a lactating mother from a premature pregnancy.

Functions of PRL

Reproductive Functions

- Maintenance of corpora lutea function
- Progesterone secretion
- Stimulation of lactation through its actions on the mammary gland. PRL along with insulin and corticoids stimulate the development of the mammary gland during pregnancy so as to prepare it for lactation at parturition.
- Regulation of maternal behavior,[6] relieving anxiety, and facilitating breastfeeding

Other Functions

- Hepatic function—bile transport and metabolism
- Pancreatic function—it has been shown in experimental animals that elevated PRL leads to expansion of beta cells and shifts in insulin and glucose.
- Immune-related functions—it has been observed that multiple sclerosis patients show remission during pregnancy. Role of prolactin in autoimmunity awaits further research.
- Clevenger and Reynolds[7] have reported a possible role of PRL in the human breast and liver cancer. They reported PRL and expression of PRL receptors in human breast cancer.

PRL in mouse cell line has been shown to inhibit the tumor suppressor activity of BRCA1.[8]

It also stimulates the proliferation of lymphocytes and reduces macrophage activity.

Causes of Galactorrhea

- *Idiopathic Galactorrhea with regular menses:* This is the commonest cause seen after parturition, which persists despite the resumption of menses. Normal prolactin levels may permit milk production as the treatment of these cases with dopamine agonists alleviates galactorrhea. It does not represent a pathologic entity.
- *Chiari-Frommel Syndrome*:[9] It is postpartum galactorrhea, amenorrhea, and utero-ovarian atrophy in non-nursing patients.
- *Hyperprolactinemia*: This is the commonest cause of Galactorrhea

Causes of Hyperprolactinemia

The fasting serum PRL level in an adult woman in reproductive age is 5–20 ng/mL.

Physiological

- Coitus, exercise, sleep, stress
- Pregnancy
- Lactation, suckling response
- Depression

Pregnancy

PRL increases throughout pregnancy. The levels are variable (35–600 ng/mL). The cause of raised PRL is increasing levels of serum estradiol during pregnancy.

Lactation and suckling

During gestation, there is lactotroph hyperplasia due to estrogen. Breastfeeding causes nipple stimulation, which releases milk probably via the neural pathway.

Table 1 shows other causes of hyperprolactinemia.

Hypothyroidism

Primary hypothyroidism predisposes to raised PRL levels. It is probably due to hypersensitivity of lactotrophs to raised levels of TRF. PRL levels in hypothyroidism rise by up to 60 ng/mL.

Drugs

Various mechanisms are described by which drugs raise PRL levels. Cessation or modification of drug therapy normalizes the PRL levels within 3–4 days.

Prolactinomas

Tumors arising from lactotroph cells are common pituitary tumors. They arise from the monoclonal expansion of a single cell, which probably has undergone a somatic mutation. In most of the lactotroph adenomas, the pituitary tumor transforming gene is over-expressed. Prolactinomas are the commonest cause of hyperprolactinemia. About 10% of tumors are composed of both lactotroph and somatotroph cells and, therefore, secrete both PRL and GH. Clinical manifestations depend on the hormone profile and patients can have acromegalic features.

Microprolactinomas—less than 1cm in diameter
Macroprolactinomas—more than 1 cm in diameter
Adenoma less than 1 cm is associated with serum PRL below 200 ng/mL
Adenomas between 1 cm and 2 cm, PRL is between 200 and 1000 ng/mL
Adenomas more than 2 cm, PRL is more than 1000 ng/mL

Clinical Features

Due to Hormonal Dysfunction

In Premenopausal women: Hypogonadism, scanty menses, secondary amenorrhea, anovulatory cycles, infertility, decreased libido, dryness of vagina, painful sex, hot flushes, and galactorrhea

In Men: Hypogonadotropic hypogonadism, decreased libido, erectile dysfunction, infertility, gynecomastia, and galactorrhea

Due to the Effects of Compression

Headache, restriction of the field of vision, visual impairment, invasion of the cavernous sinus, and/or sphenoidal sinus with corresponding neurological effects.

Investigations

- Urine pregnancy test
- Serum free T3, free T4, and TSH
- Serum prolactin
- Serum growth hormone
- Serum insulin-like growth factor 1
- Serum cortisol
- Serum testosterone in males
- Perimetry and brain MRI for the size of the prolactinoma and its extension in patients presenting with compressive features

Table 1: Causes of hyperprolactinemia

Drugs	*Systemic disorder*	*Hypothalamic dysfunction*	*Pituitary*
Estrogen, OC	Chr. renal failure	Damage to stalk	Prolactinoma
Neuroleptics	Hypothyroidism	Granuloma	Acromegaly
Antipsychotics	Cirrhosis	Infiltrations	
Dopamine receptor blockers	Polycystic ovarian disease	Trauma/surgery stalk resection	Macroadenoma
Dopamine synth. inhibitors	Cranial radiation	Craniopharyngioma	Plurihumoral adenomas
Opiates	Epilepsy, chest wall trauma	Rathake's cyst	

Management[10,11]

With the advent of dopamine agonists, management of galactorrhea with hyperprolactinemia has become a lot simpler. Dopamine and its agonists inhibit prolactin synthesis and its secretion. Bromocriptine was the first dopamine agonist introduced; subsequently, another drug cabergoline (which is more effective and better tolerated than bromocriptine) was introduced. After cabergoline was available, it became the drug of choice. Treatment with cabergoline is started at 0.25 mg once or twice a week. Usually within 2–3 weeks, PRL levels are normalized. It is continued in the same dose for about 2 years. Serum PRL levels are monitored at regular intervals. If PRL levels did not normalize within 2–3 weeks, the dose is increased gradually up to a maximum dose of 1.5 mg twice or thrice weekly. Once PRL level gets normalized, the same dose is continued for 2 years. Not only does cabergoline normalize PRL levels but it also reduces the size of both micro and macro-prolactinomas without surgery. Before cabergoline was available, bromocriptine was used. It is less effective and has more side effects than cabergoline. Bromocriptine was given at a dose of 1.25–2.5 mg orally once or twice a day.

Patients with hypothyroidism should be examined for galactorrhea and their prolactin levels must be measured. In my own study,[12] I found 30% of hypothyroid patients had hyperprolactinemia and 18% of them had PRL levels between 24 and 60 ng/mL. They responded to thyroxine replacement alone. The rise in PRL levels up to 60 ng/mL can be due to hypersensitivity of lactotrophs to raised levels of TRF. Remaining 12% of cases had PRL levels between 61 and 300 ng/mL. Of these, 8 patients were found to have prolactinomas on neuro-imaging. These patients needed treatment with both thyroxine replacement and cabergoline.

Surgical removal or debulking of prolactinomas is indicated if their size is more than 3 cm. It is done through the trans-sphenoidal route. Another indication of surgery is in women who want to conceive because conception will increase the size of the tumor.

Conclusion

Most of the cases of galactorrhea are idiopathic; however, each case should be subjected to an estimation of serum TSH and PRL levels. Cases with gynecomastia without any apparent cause should also have PRL levels measured. If PRL level exceeds 60 ng/mL, neuroimaging should be carried out to evaluate the possibility of a prolactinoma. All cases of prolactinomas can be managed with the dopamine agonist cabergoline, which is a safe drug with acceptable side effects. Patients with evidence of compressive symptoms due to giant prolactinomas will need to undergo surgery. If prolactinoma is associated with hypothyroidism, thyroxine replacement must be given.

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REVIEW ARTICLE

Technological Challenges for Management of Genetic Complexities of Myelodysplastic Syndromes

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Abstract

Background: Chromosomal abnormalities (CA), including del(3q, 5q, 7q, 11q, 12p, 17p, 20q); loss of 5, 7, and Y; trisomy(8,19); i(17q); and balanced and unbalanced translocations have been demonstrated as prognostic markers in 5-tier risk-grouping and WHO-2016 classification of myelodysplastic syndromes (MDS). However, monosomal karyotype (MK) in the presence or absence of a complex karyotype (CK) has not been considered in the WHO classification. Additionally, a plethora of somatic mutations of MDS-specific and elderly populations collected through a-CGH, SNP-array, next-generation, and targeted sequencing has led to understanding of their impact on MDS-phenotype, initiation and progression of the disease, and treatment outcome in single or cooperating effects of comutations of several pathway-mechanisms.

Methods: The present review on technological challenges has been raised on the information available through Google-search using MDS-genetics, mutations of MDS, diagnosis and prognosis of MDS, etc. with a view to understanding the possibilities in low-resource settings.

Results: Mutual exclusivity and cross-talk of such mutations help in self-renewal of leukemic stem cells. However, molecular screening is not only time-consuming but also expensive in poor-economic settings. Nevertheless, the significance of unspecific and uncalled mutations is yet to be understood. In contrast, conventional cytogenetic assays have specific aberrations of prognostic and therapeutic values, which cover the whole genome in a cost-effective manner. However, since somatic mutations of clonal hematopoiesis of indeterminate potential (CHIP) in asymptomatic and/or patients with idiopathic cytopenia of undetermined significance (ICUS) have the potential for favoring the leukemic onset to progression, molecular screening has inherent importance within the disease-mechanism.

Conclusion: The WHO-2016 risk-classification has considered mutations of *SF3B1*, *TP53*, and *MLL* for management of MDS, and also powered conventional cytogenetics for diagnosis and risk-stratification of MDS.

Keywords: Chromosomal rearrangements, Mutational complexities, Myelodysplastic syndrome, Somatic mutations, Technological challenges.

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Introduction

Myelodysplastic syndromes (MDS) are characterized as heterogeneous diseases having premalignant clonal changes of the hematopoietic system. The disease is typically presented with blood cytopenia, ineffective hematopoiesis, and a higher propensity of transformation to acute myeloid leukemia (AML). The conventional cytogenetic study, which is chosen as the first line of diagnosis, has frequently demonstrated chromosomal abnormalities (CA), including deletions (del) of 3q, 5q, 7q, 11q, 12p, and 20q, monosomy 5/7, trisomy 8/19, i(17q), and loss of Y of "very good" to "very poor" prognostic implications in IPSS-R.[1–6] Independent impact of monosomal karyotypes (MK) has not gained importance in IPSS-R stratification because the missing chromosome can be rearranged on normal chromosomes and appear as a marker; however, MK alone or in association with structural aberrations result in genomic instability.[5,6] Normal karyotypes of over 30% *de novo* and 50% therapy-related MDS leads to silent progression and transformation of the disease. Therefore, utilization of advanced techniques for understanding the mutational spectrum in hematopoietic stem cells (HSC) and its clonal and sub-clonal developments facilitated risk-estimation of MDS and its evolution.[3,7,8]

Molecular techniques such as comparative genomic hybridization (CGH), single nucleotide polymorphism (SNP), and sequencing of the whole genome or exome have identified a plethora of somatic mutations.[9,10] Such random mutations are described as 'passengers' in HSC, which on the acquisition of non-random 'founder' mutations lead to the initiation of the disease mechanism.[11,12] Somatic mutations of signal transduction kinases: *FLT3-ITD/*MPL/*GNAS/JAK2/KIT* (15%), transcription factors: *RUNX1/TP53/ETV6/GATA2* (15%), tumor suppressors: *TP53/WT1*, epigenetic modifiers: *TET2/ASXL1/IDH1/IDH2/EZH2/DNMT3A* (45%), RNA splicing: *SF3B1/U2AF1/SRSF2/ZRSR2* (64%), RAS-pathway: *KRAS/NRAS/CBL/NF1/PTPN11*(12%), cohesin complex: *STAG2/RAD21/SMC3/SMC1A* (13%), and many other mutations such as *SETBP1/mi-RNA/ABCB7* (10%) have led to re-defining MDS-pathogenesis.[9,10,13–17] Direct association of MDS-status has been demonstrated with some of the mutations such as mutations of *PRPF8* and *SF3B1* and ring sideroblasts; reduced *TET2* activity and increased DNA-methylation; mutations of *DNMT3A* and reduced overall survival (OS) with faster AML-transformation; *TET2*-mutations and response to hypomethylating drugs; del5q and response to lenalidomide; and so on.[18–20]

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TET2-like epigenetic mutations in asymptomatic older individuals guided to understand that the MDS is an age-related disease,[8,21–24] and also contributes to clonal hematopoiesis of indeterminate potential (CHIP) for disease-initiation.[25] Mutagenic events of RNA-splicing and epigenetic machineries are frequently reported in MDS. *DNMT3A* was frequent over *ASXL1* and *TET2* mutations in apparently healthy elderly population.[25,26] CHIP and MDS-specific mutations have postulated that a single and dormant mutant clone could progress through a pre-leukemia to an overt leukemia with accumulation and cooperation of driver mutations.

In view of the above facts, it is understood that age-related pre-leukemic MDS is an acquired the disease of HSC, which could be characterized by a conventional cytogenetic study, and a wide range of molecular techniques for recognition of clonal and sub-clonal aberrations of chromosomes and path-way genes, which are important for risk-classification and outcome-analysis of MDS. However, availability and affordability for the screening of mutations of MDS patients of low-resource settings is a matter of concerns. Therefore, the present review has addressed the disease-specific CA, somatic mutations, and cross-talk among them for initiation to transformation of the disease and technologies available for risk-assessment and clinical management of MDS patients.

Mutations of MDS and Complexities

Chromosomal alterations, including loss/gains of chromosomes/segments, balanced/unbalanced translocations (t(1;3)/t(2;11)/t(3;21)/t(6;9)/t(11;16)/etc.), CK with ≥3 aberrations, MK with at least one structural rearrangement along with monosomy of one autosome, etc. have been reported in 7–8% *de novo* MDS with an unfavorable outcome.[27,28] MK indicates a poor prognosis and that worsens when combined with CK and advancing age; however, it has lost its distinction as an independent prognostic factor when associated with ≥5 aberrations.[28–30] Deletions indicate haploinsufficiency wherein del(7q)/−7 is associated with a poor prognosis. Del (17p)/i(17q) results in loss of tumor suppressor *TP53* and is associated with an unfavorable clinical outcome, whereas inv/t(3)(q21–q26) leads to increased blasts and a rapid transformation to AML. There are several abnormalities such as trisomy 8, del(20q), -Y, del(9q), −13/del(13q), del(11q)/t(11q), del(12p)/t(12p), ±19/t(19), idic(Xq13), etc. which are not MDS-specific but globally present in myeloid neoplasia. Del(5q) has been classified as a distinct 5q-syndrome with refractory anemia (RA).[31] *RPS14*-haploinsufficiency in del5q-patients perturbs P53-signaling and ribosomal biogenesis, block erythroid differentiation and that results in severe macrocytic anemia in MDS.[32] Del(5q) is a good prognosticator; however, in association with TP53 mutations, this disease progresses to AML and develops resistance to the immune-modulating agent lenalidomide.[33,34]

Besides landscapes of mutations detected in MDS patients, at least one mutation has been reported by sequencing with a median of 10 mutations/patient in >90% patients, which includes non-pathogenic 'passengers' as well as non-random 'founder' and 'driver' mutations, wherein mutations of RNA-splicing and DNA-methylation systems are reported as 'founders'.[8–10,35] Mutations in ~40 genes have been demonstrated as 'drivers', which are involved in clonal evolution in ~80% of MDS, where mutations of chromatin modification and signaling systems occurred later as 'sub-clonal'. Targeted deep-sequencing has reported mutations in *TP53*, *EZH2, ETV6, RUNX1,* and *ASXL1,* and that conferred a poor prognosis collectively in 439 patients;[18] while mutations in *SF3B1, TET2, SRSF2,* and *ASXL1*;[35] and *TET2, SF3B1, ASXL1, SRSF2, DNMT3A* and *RUNX1* were reported in ~10% MDS in each of the two separate studies.[10]

Mutual exclusivity has been reported in a number of mutations such as *TET2* and *IDH1/2* was mutually exclusive within the same functional pathway; *SF3B1* was mutually exclusive when co-occurred with *ASXL1* and *IDH1;* while co-occurrence of splicing-mutations was rare. Interestingly, *SF3B1* confers a good prognosis; in contrast, *ASXL1* and *IDH1* render poor prognosis. Co-operating effect of *TET2* and *SRSF2* caused monocytosis, resulting in progression to a chronic myelomonocytic leukemia (CMML).[36,37] Collectively, biological interactions of concomitant mutations and their mutual exclusivity has led to understanding that a higher quantum of mutations contributes to a higher degree of clonal expansion in high-risk subtypes (RAEB1 and RAEB2), and also, shorten the disease-free OS.[10,38–40] It is further hypothesized that multiple RNA-splicing mutations drive MDS to AML-transformation through the acquisition of multiple clonal cytogenetic and molecular alterations of chromatin modulation and signaling, and dictates the phenotype of MDS-disease.[13,15] Occurrence of recurrent CA has been implicated as secondary events and outcome of genomic instability, where CK has demonstrated a very poor outcome.[41–43] Therefore, the independent expression of single mutation and accumulation and concomitant occurrence with others have negative effects on the clinical significance for risk-classification and targeted therapeutic outcome.

It is noteworthy that healthy individuals, especially the elderly population, harbor some of the mutations and chromosomal aberrations of leukemic reference such as *BCL2* and *BCR-ABL* rearrangements; CNVs at 5q/11q/17p/20q in individuals of >70 years age; altered expression of >40 point-mutations; non-pathogenic 'passenger' mutations without clonal expansion; and mutations of DNA-methylation system, particularly *DNMT3A* and *TET2,* which are detected in both patients with MDS/AML as well as in the healthy individuals in an average of >2% and ~6% of >70 years.[8,24,25,44–46] Intensely treated AML patients had demonstrated the presence of *DNMT3A* mutation in complete remission state.[24] Somatic mutations of *DNMT3A*, *TET2*, and *ASXL1* were also reported in diabetes mellitus, coronary heart disease, and ischemic stroke.[26,27] Furthermore, MDS-specific clonal mutations increased from 9.6% (70–79 years) to 18.4% (≥90 years) in line of the aging process.[22] Thus, the question was raised on the age-related clonal CHIP-mutations in apparently healthy population and risk of malignancy owing to acquisition and cooperation of further mutations, and contribution of co-morbidities leading to disarrayed erythropoiesis.[26,47] There was evidence of hematologic neoplasia-specific CHIP mutations in the elderly population with an allele frequency of ≥2% and 0.5–1% annual risk of hematologic neoplasia; however, these mutations do not meet the diagnostic criteria of MGUS/PNH/MBL though indicate cytopenia or normal blood count and leads to disease-progression.[26,48] Spontaneous CHIP-mutations may occur many years before initiation of clonal expansion, remain dormant in the sub-clinical state, and develop frank/overt malignancies in association with other accumulated mutations coupled with CK.[8,21,22,27,49] Thus, CHIP-mutations have been designated as 'seeds' of leukemia, which also facilitates self-renewal of leukemic HSCs and deregulation of cellular differentiation and maturation.[49,50]

The reported studies have indicated the need for further studies on a different population of the different morbid condition with a view to preventing the onset and malignant transformation of MDS, and also to designing meaningful targeted drugs.[27,51] However,

the employment of technologies and the endpoints are matters of serious concerns as it depends on the economic condition of the country and its patients. The low- to middle-income countries are truly not equipped, mainly because of financial constraints, for supporting screening of disease-specific mutations and management of diseases. Otherwise, opportunistic screening of CHIP mutations could have prevented neoplastic development, especially age-related pre-leukemic conditions. Therefore, the present review has discussed technological sensitivities and specificities for risk-classification and therapeutic management of MDS.

Technologies for Understanding MDS Disease-state

Conventional Cytogenetics

Conventional bone marrow cell culture and chromosomal analysis in a karyotypic form following the traditional 'G-banding' is useful for investigation of all chromosomes on one screen. It facilitates recognition of balanced/unbalanced rearrangements, including translocation, inversion, deletion, ring, dicentric and marker chromosomes, and also numerical alterations, including hypodiploid/hyperdiploid conditions and aneuploidies. In addition to disease-specific aberrations, conventional cytogenetics allows detection of additional chromosomal abnormalities, including the expansion of clonal and sub-clonal developments. In MDS, del(3q/5q/7q/11q/12p/20q), monosomy 5/7, trisomy 8/19, i(17q), –Y, etc. have been frequently reported as single exclusive or complex aberrations (CK), wherein monosomal karyotypes (MK) with loss of whole/partial chromosome occurred owing to complete monosomy and/or deletion of chromosomal segments. Thus, the efficiency of a comprehensive chromosomal investigation by conventional the cytogenetic technique has bagged the certificate as the "gold standard" technique for understanding and management of hematologic malignancies.[1]

Therefore, the conventional cytogenetic study is important for every new MDS-diagnosis and also for patients having differential diagnosis with persistent unexplained cytopenias. Such patients may represent the incipient stage of MDS even in the absence of morphologically identifiable dysplasia. Thus, a baseline cytogenetic profile is of immense importance for all suspected MDS. Chromosomal rearrangements are not static in MDS; however, accumulation of abnormalities results in genetic instability, indicating an adverse prognosis and disease progression. Hence, conventional cytogenetic monitoring is recommended in the revised WHO 2016 classification.[32]

Fluorescence *In Situ* Hybridization (FISH)

The use of sequence-specific probes in FISH facilitates detection of gains/losses and cryptic rearrangements on interphase nuclei. However, several studies have experienced that FISH can detect 70% of the abnormalities detected by conventional cytogenetics.[52] Furthermore, FISH is unable to pick up complex rearrangements, and thus, FISH alone fall short of being considered in IPSS-R for risk-stratification. In several studies, FISH has detected abnormalities in otherwise normal cytogenetics in fewer than 3% of cases and had 90% agreement with metaphase-cytogenetics. The false-negative rate of conventional cytogenetics appeared to be zero,[53] or ≤2.8%.[34,54] FISH would be useful in an unsuccessful cytogenetic setting of no metaphase-yield (<20 metaphases) or inadequate number, and poor chromosome-morphology. On the basis of the fact of high concordance between FISH and conventional cytogenetics, parallel FISH testing involves an unnecessary additional cost and thus, is not justified. Detection of unbalanced translocations and recognition of very small numbers of abnormal cells by FISH due to high background and inherent lower precision is of limited clinical value. FISH extracts information on the probes used for hybridization and multiplex FISH is not available in a low-resource setting and also it requires a precise signal analysis for describing the chromosomal rearrangements.

Molecular Karyotyping

The advent of technological refinement has enabled the detection of unbalanced changes on DNA-microchips; however, that does not allow the distinction between multiple large clones (clonal mosaicism, compound lesions, etc.). Molecular karyotyping by CGH, array-CGH (aCGH), and SNP arrays (SNP-array) have a superior resolution over conventional metaphase analysis, and thus, aCGH and SNP-array eliminate the use of metaphases in malignant samples. In addition to diagnosis, array-based karyotyping tools for molecular chromosome mapping beyond the boundaries of mono-/trisomies and deletion/duplication are of significant prognostic and pharmaceutical importance.

Comparative Genomic Hybridization (CGH) and aCGH

Conventional CGH uses FISH technique on metaphase chromosomes and detects CNVs across the whole genome. However, it has a low resolution (3–10 MB). Also, CGH cannot detect mosaicism, inversions and balanced translocations, and thus, demonstrated no additional advantages compared to conventional cytogenetics.[55] Therefore, refinement of CGH technology based on the microarray using bacterial artificial chromosome (BAC), oligonucleotide, and SNPs has significantly improved the resolution (BAC: 75–200 kb; oligonucleotide: 25–85 mers; smaller insert clones, cosmids: 30–40 kb; fosmids: 40–50 kb).[56] The genomic resolution of different aCGH platforms is defined by spacing and length of the DNA probes. Array-CGH is a combination of conventional CGH and FISH; however, it does not require metaphase chromosomes. Thus, it is a useful tool in cases with a low or poor metaphase yield and also powerful in the normal cytogenetic scenario.

In MDS, aCGH reported 39% more cryptic alterations compared to conventional cytogenetics.[57] Application of aCGH facilitates a genome-wide simultaneous detection of CNVs at multiple loci and analysis of hundreds to thousands of genes considered on the microarray in one single experiment. Commercially available aCGH platforms reproduce a 50-fold higher resolution with chromosomal rearrangements in 15–20% more cases compared to conventional cytogenetics. However, low-degree mosaicism, inversion, balanced translocations, polyploidy, etc. cannot be detected by this technique.[58] In general, DNA from patient and control reference DNA are labeled with fluorochrome dyes and co-hybridized to the chip containing arrayed genomic clones or oligonucleotide probes and the arrays are scanned using a fluorescent imaging scanner. The fluorescent signal ratio (excess or gain in red, under-representation of tumor DNA; excess of green, over-representation of tumor DNA) of patient and control DNA indicates CNVs along the genome and the results are analyzed using bio-statistical algorithms.[59] Targeted aCGH focuses only on specific regions of a genome or specific genes.

Genome-wide BAC-aCGH has detected novel CNVs in 47% of MDS patients, including deletion of *RUNX1* (344 kb) gene in three MDS patients at the time of AML transformation, and also *EVI1* (3q26.2), *APC* (5q22), *TCERG1* (5q32), *EMP1* (12p13.1), *KITLG* (12q21.3),

and *NF1* (17q11.2).[59] Although all CNVs are not of direct clinical significance pertaining to a patient with normal chromosomes, the finding of cryptic rearrangements (deletions and duplications) are definitely informative for risk-stratification, defining disease subtypes, designing rational therapy, prediction of treatment outcome and identification of genes and pathways linked to pathogenesis, and thus, guiding for targeted drug development. Therefore, aCGH has been considered important in MDS and also considered as a complementary tool to conventional cytogenetics in the adverse situation.

SNP-array

SNP-based oligonucleotide array enables detection of loss of heterozygosity (LOH), microdeletions, and uniparental disomy (UPD) with a higher resolution. The advent of high-density SNP-array has changed the level of molecular understanding of MDS-pathogenesis with a facility of genome-wide-association-studies (GWAS). Frequent detection of cryptic alterations with a high prevalence of UPD using SNP-array has been reported in low-risk MDS.[60,61] A combined approach of SNP-array and conventional cytogenetics showed convincing results of SNP-array as an independent predictor of overall survival (OS), event-free survival (EFS), and progression-free survival (PFS). Thus, SNP-array appeared reliable for MDS diagnosis, classification, prognostication, and therapeutic monitoring.[60] The discovery of MDS-specific homozygous mutations in *TET2* and *EZH2* through SNP-array has tremendously contributed to the development of DNA-methyltransferase inhibitors such as azacytidine and decitabine.[9,62,63] Employment of SNP-array studies of del(5q) and abnormalities of 17(p) dictated the severity of disease phenotype in hematologic malignancies.[15,48,49,64]

Microarray-based gene expression profiling on bone marrow CD34+ cells of 55 MDS patients revealed deregulation of mitochondrial genes in RARS-MDS, and down-regulation of multiple ribosomal genes, and genes involved in the initiation of translation in 5q-syndrome.[65] In another study on 183 patients, deregulation of immunodeficiency, apoptosis, and chemokine signaling pathways were described on CD34+ cells at the early MDS stage, whereas deregulation of DNA-damage response and checkpoint pathways were evidenced in advanced MDS.[66] A significant association of gene expression profiles and deregulated pathways were also demonstrated in patients with del(5q), trisomy 8, or -7/del(7q). Clinical accuracy of gene-expression profiling was found to be 93% accurate in sub-typing of leukemias; however, only 50% of MDS was correctly classified owing mainly to marked heterogeneity of MDS.[10] A signature-expression of 20 genes on CD34+ cells from a large group of MDS patients help segregated a good from poor prognosis. Investigation of the effect of mutations and gene expression demonstrated the power of transcriptome on prognostic scoring and prediction of treatment outcome.[67]

The advantages of high-resolution, genome-wide coverage and minimal DNA requirement in SNP-array and yield of quality-result have widened its application. In MDS, SNP-array investigation is expected to detect novel clonal changes with a promising direction towards understanding its pathogenesis, transformation, and response to treatment. However, challenging potential of SNP-array needs validation on a large database of genomic CNVs, association with disease onset and progression, and outcome of treatment. Also, variation in genomic CNVs largely rests on different platforms and the methodology used, though the use of the bone marrow and peripheral blood presented no difference.

Sequencing

The incredible advantage of next generation sequencing (NGS) technology for detection of mutations in MDS through global sequencing has implicated several specific and unspecific mutant genes, which will certainly be of clinical significance. NGS is able to detect fusion rearrangements in balanced translocations, deletions, duplications, CNVs and UPD, and also numerical changes of cytogenetic failure.[8,10,13,15,21,22,68] Therefore, NGS stands as a judicial combination of conventional cytogenetics, aCGH and SNP-array, and a comprehensive platform for a genome-wide investigation of as precise as the low frequency of mutations.

Analysis of sequencing data with low-frequency or non-coding mutations, and cost and time required for NGS are the limiting factors for a routine clinical workup. Moreover, cytogenetic anomalies detectable by conventional karyotyping could be underestimated by NGS, and thus, NGS cannot replace conventional karyotyping in the clinical setting. Nevertheless, detection of key mutations could be accomplished through targeted sequencing of small groups of genes of diagnostic and therapeutic interest. NGS is an important tool for diagnosis of otherwise diagnostically challenged cases. In MDS, rapid screening of identified genes of prognostic and diagnostic importance in large cohorts could be undertaken for understanding actual implications of mutations on treatment outcome following homogeneous treatment with disease-modifying agents. Sequencing of clinically relevant mutations in a standardized manner within affordable time-frame could guide clinical validation and acceptance of the technique.

Mutation analysis has increasingly become important for MDS-management and thus, molecular assay-platforms are being incorporated into diagnostic algorithms for patients suspected with hematologic neoplasia. Academic hemato-pathology groups, commercial pathology laboratories, and bioinformatics groups are in the process of refining data-filtration for calling disease-causing mutations and drawing an interpretation of findings. Targeted deep-sequencing appears important for extending translational opportunities for a further dissection of clonal myelodysplasia, non-clonal cytopenia, and clonal hematopoiesis arising upon aging or in the context of acquired aplastic anemia.[10,68] Therefore, large-scale genetic and molecular profiling of multiple targeted genes by combining molecular karyotyping and sequencing would be invaluable for sub-classification and prognostication of MDS and further guide to design an individualized therapeutic program. Further focus on developing simple methods for detection of mutations would be important, since establishing sequencing facilities and use of the technology for identification of driver mutations at bedside is difficult in the far future, especially for low- and middle-income countries.

New WHO Recommendation on Technological Application

It has been recommended in the WHO 2016 classification that chromosome abnormalities (CA) will continue to be classified as MDS-specific and carry its clinical significance. WHO-2016 has exclusively recommended conventional cytogenetics for detection of CA.[32] In the absence of dysplasia and other diagnostic morphology, CAs, including trisomy 8, del(20q), and loss of Y, are not considered MDS-specific. Del(5q) as single or in combination with one additional abnormality of the low-risk group has been re-classified to indicate a similar prognosis.[32,68] MK has not been considered in the new risk-classification to avoid disputes on its risk

when present with CK.[5,8–10] Thus, conventional G-banding study has been powered by WHO-2016 classification amidst technical advancements for CA-based risk-grouping of MDS,[32,48] though a concomitant use of SNP-array and conventional cytogenetics has a significant outcome of clinical prediction of OS, EFS, and PFS.[32]

Although landscapes of point mutations have been identified in MDS, mutations of *SF3B1, MLL,* and *TP53* have been recommended by WHO for prognostication of MDS with ring sideroblast, del5q, and other categories. However, CHIP mutations, though developed bonafide MDS in some individuals, have not been considered for risk-stratification in the new classification owing mainly to a lack of clear understanding of their expression and interaction with other co-operating mutations. Therefore, molecular screening of somatic mutations, CNVs, UPD, CHIPs, ICUS (idiopathic cytopenia of undetermined significance), etc. have not attracted much interest in the new classification system of MDS. However, further studies might lead to the incorporation of more mutations of clinical significance in MDS-classification and therapeutic development, especially that of epigenetic mechanism.[10,48,49,51] Clonal cytopenias with *ASXL1, RUNX1,* and *TP53* mutations did not present features of MDS or specific CA; however, clonal CA might increase the risk of MDS in patients with persistent ICUS.[26] Thus, mutation analysis would be important to refine the MDS-cases from ICUS for clinical management, though molecular screening of mutations is still far to reach in low-economic settings. Nevertheless, molecular aCGH, SNP array, and sequencing techniques extract genome-wide information on mutations at a better resolution, irrespective of the karyotype status, and most importantly in interphase cells in the absence of, or inadequate chromosome morphology. Thus, dynamic opportunistic screening of CHIP-mutations in ICUS or asymptomatic healthy elderly individuals could prevent hematopoietic malignancies. However, conventional cytogenetics facilitates a genome-wide screening of balanced and complex rearrangements, which are not recognized by molecular techniques.[32,48] Therefore, it is clear that WHO-2016 has recommended a conventional cytogenetic study mandatory for MDS-diagnosis and risk-grouping.

Conclusion

MDS has been characterized by CA and categorized in different risk-groups. The conventional cytogenetic study relies on metaphase chromosomes of a good morphology and covers the whole genome for detection of inter- and intra-chromosomal rearrangements. Advancement of technological innovation and development of bioinformatics tools have facilitated the collection of a wide spectrum of somatic point mutations in MDS and AML patients; however, many of these are uncalled for clinical understanding. However, mutations of *SF3B1* of RNA-spicing and epigenetic factors are demonstrated as founders and drivers of MDS-pathogenesis, and also targeted for therapeutic development. Some of the MDS/AML-specific mutations have been detected as CHIP in apparently healthy elderly individuals, which might favor leukemogenesis and disease progression. Screening of such mutational spectrum has an immense value of prediction of disease-development and management; however, clinical or laboratory facilities of low-resource setting have yet to establish such facilities for molecular screening of mutations. On the basis of the knowledge gained on the clinical impact of somatic mutations, CA, and hematopoietic phenotypes, WHO has revised risk-stratification of MDS where conventional cytogenetics has been powered for MDS-management, while mutations of *SF3B1, MLL,* and *TP53* have been recommended for understanding MDS-phenotype and therapeutic outcome. Therefore, conventional cytogenetic characterization of bone marrow cells could enable disease management in the absence of information on point-mutations.

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SHORT COMMUNICATION

An Excerpt of Geriatric Diseases in India

Bani B Ganguly[1,2], Nitin N Kadam[2]

Abstract

Background: Aging is a consequence of accumulated effects of living conditions, acquired mutations, and an inefficient regenerative mechanism of the progenitor cells. Chronologic aging is linearly linked to an increase in health-complexities of noncommunicable types. In contrast, medical advancements is enhancing the life-expectancy—certainly at a higher cost; however, the trend could outnumber the young workforce subsequently. Hence, understanding of disease-prevalence is essential with a view to making necessary arrangements for offering appropriate care to the geriatric population.

Materials and methods: Records of over 47,000 outpatient medical consultancies were retrieved from the hospital management system and considered for investigating the disease-prevalence in the older population.

Results: Older population was largely affected with diseases related to the cardiovascular system followed by general medical complications. In general, men were more affected with geriatric diseases, which could largely be due to a lack of financial and other preparedness of the retirees.

Conclusion: A significant osteoarthritis problem in females is undoubtedly associated with aging of ovaries. An intense look at geriatric diseases may guide for building age-friendly and dedicated accommodation at home and healthcare centers. The knowledge may be helpful for handling geriatric disease-burden of low- and middle-income countries.

Keywords: Aging, Cardiovascular diseases, Geriatric diseases, Life-expectancy, Noncommunicable diseases.

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Background

Human aging is not merely a consequence of wear and tear, but it is the inefficient mechanism of replacement of the spare parts as reflected in hair-color, tooth-decay, skin-wrinkles, etc. as marks of aging. Every organ is maintained by the self-generating stem cells. However, environmental stress, epigenetic manipulation, intrinsic micro-environment, DNA-damage, and error-prone or lack of repair diminish the regenerating power of the stem cells, promoting the aging of organisms.[1] Additional contribution from economic and societal stress aggravates human aging with tons of diseases, which is worst for low- or middle-income countries.[2] Besides proneness to infections, a wide spectrum of noncommunicable diseases (NCDs) frequently confines elderly people either to a hospital and/or to a wheel chair for a lifetime. World-wide cardiovascular diseases (CVDs) dominate over all NCDs (50%), being the leading cause of death and disability, which is majorly influenced by life-style/unhealthy diets/lack of physical activities.[3] Uncontrolled behavioral risk factors increase blood-pressure, blood-glucose, and blood-lipid and set a threat for death. In contrast, advancement of medical management and awareness of healthcare influence the life-expectancy, which has become a global issue of health-management and health-insurance of aging.

Materials and Methods

To take a stock of disease-spectrum with a view to measuring healthcare arrangement in a hospital setting, we have analyzed the incidence of NCDs from the outpatient data of 60+ aged males and females ($n = 47,350$). Fourteen systemic disorders were correlated with eight age-groups of five-year age-gap.

Results

The CVD stood first followed by miscellaneous complications for which men and women visited our medicine department. The ailments of endocrine, neurologic, nephrologic, general surgery, gastro-enteric, and ophthalmic problems appeared more or less uniform in both genders; however, musculoskeleton/orthopedic and urologic problems were strikingly higher in women and men, respectively (Fig. 1). Other NCDs were not so actively captured in this hospital, especially cancer due mainly to the apex (ACTREC) facility located in the vicinity.

Discussion and Conclusion

Indian life-expectancy of 69.09 years has a skewed death rate of 7.3 vs a birth rate of 19 per 1,000.[4] Indians retire from work at 60 years, leading to a financial crunch for many. If retirees do not own accommodation, not secured with pension and have children unsettled, they fall prey to CVD, and succumb to death within the first five years post-retirement. Malnutrition and unhealthy diets contribute to orthopedic (osteoporosis/osteoarthritis) and urologic (kidney stone) problems in the two genders. A lack of health-insurance and social/family securities underlie a long stay

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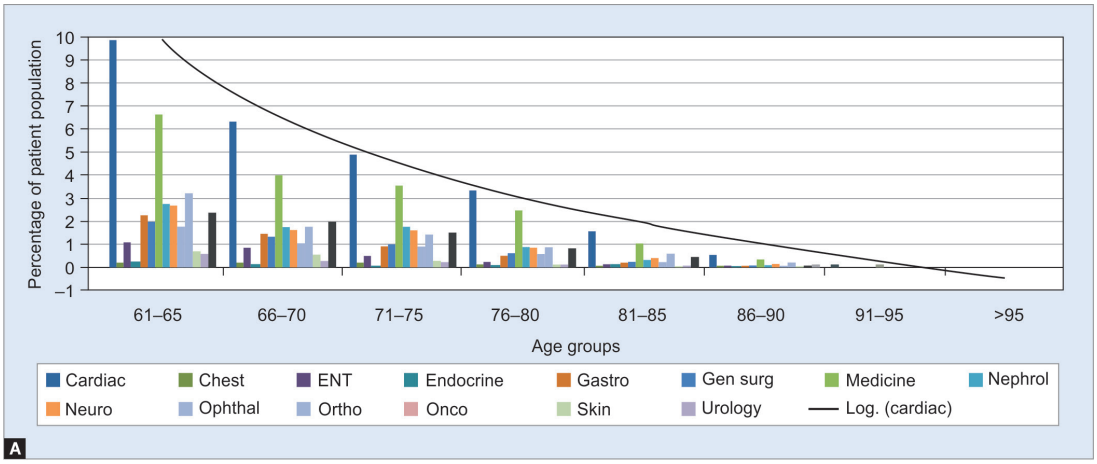

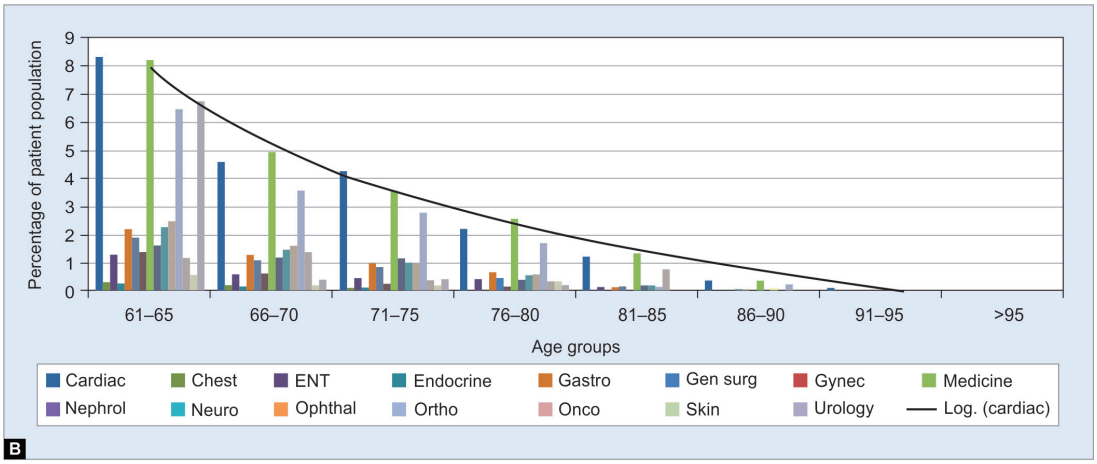

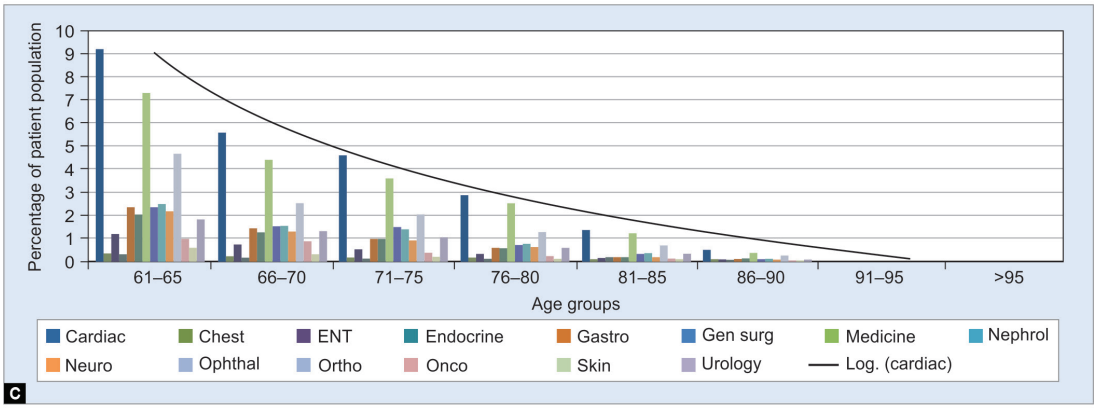

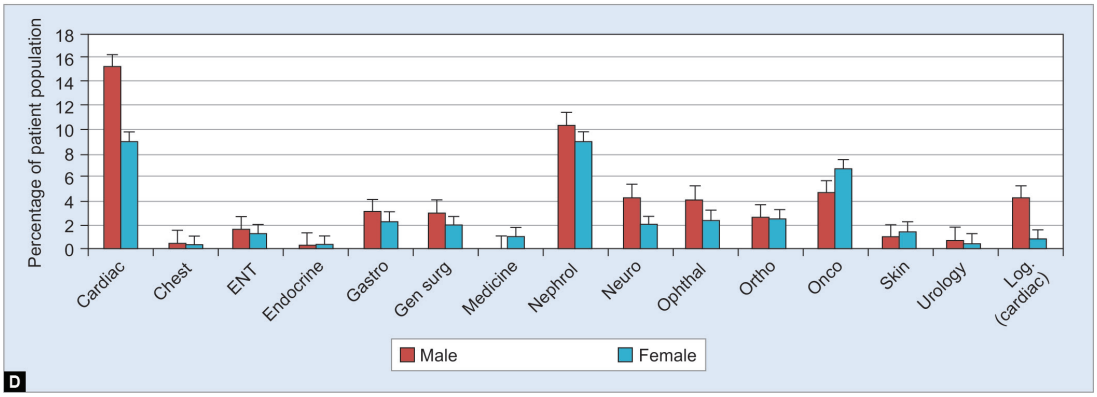

Figs 1A to D: Age-related disease burden; (A) Male; (B) Female; (C) Combined; (D) Male vs female

in hospitals. Altogether, enhanced life-expectancy jeopardizes the lives of elderly people in the Indian scenario. India's mega health reform scheme,[5] which was set as the flagship agenda of the recent election, would not benefit the elderly population. Therefore, Indian public-health and health-insurance policies need to be redefined for 1.35 billion population; especially age-friendly accommodation, social security, and dedicated long-term healthcare arrangement in hospitals would not only protect the elderly population but also their family members and other hospital-patients from financial burden and infection, respectively. Analysis of age-related morbidity and mortality is underway on a larger population to understand the 'cause and effect' accurately.

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CASE REPORT

Dilemma in Managing Carcinoid Crisis Secondary to a Metastatic Well-differentiated Neuroendocrine Tumor of the Lung

NC Diong[1], Narasimman S[2], Subashini R[3], Cindy TJ[4]

Abstract

Background: Well-differentiated neuroendocrine tumors (NET) of the lung account for 2% of all primary lung neoplasms. Less than 2% of the lung NET present with the carcinoid syndrome manifested as facial flushing, diarrhea, palpitation, and bronchospasm, as a result of a hypersecretion of hormones and peptides from the tumor. Carcinoid crisis is a life-threatening complication of the carcinoid syndrome and its manifestation as coronary vasospasm is rare. Octreotide is a gold-standard treatment to control the symptoms; however, octreotide as a triggering factor for coronary vasospasm has never been reported.

Case description: A 62-year-old man presented with multiple episodes of carcinoid symptoms is referred to our hospital. A series of investigations were carried out and he was diagnosed with the lung NET with a liver and bone metastasis. He developed coronary vasospasm, which could be due to the carcinoid crisis itself or the treating agent octreotide, after initiation of octreotide for carcinoid syndromes. After intense perioperative management by multidisciplinary teams, he underwent successful symptom control by perioperative octreotide and surgery.

Conclusion: Surgery is the mainstay treatment to control carcinoid syndromes or crisis. Multidisciplinary therapy in perioperative care is paramount to ensure an optimal surgical outcome.

Keywords: Carcinoid syndromes, Carcinoid tumors, Neuroendocrine tumors.

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Background

Well-differentiated lung NET or lung carcinoid account for 2% of primary lung neoplasms.[1] Only less than 2% of lung carcinoids are functional, exhibiting the carcinoid syndrome: facial flushing, diarrhea, palpitation, and bronchospasm due to a hyper secretion of hormones and peptides, such as serotonin from the tumor.[2] Carcinoid crisis is a life-threatening complication of the carcinoid syndrome causing a severe hypertension or hypotension, which can be precipitated by general anesthesia, tumor manipulation, and diagnostic or therapeutic intervention. Coronary vasospasm is a rare manifestation of the carcinoid crisis.[3]

Octreotide is a somatostatin analog (SSA) that binds to a somatostatin receptor, inhibiting the release of peptides and amines and thus help controlling symptoms.[4] Octreotide is a gold-standard treatment to control both the carcinoid syndrome and crisis, and is also recommended as prophylaxis against the carcinoid crisis when these patients undergo a surgery.[5] The side effects of octreotide are minimal,[5] and octreotide as a trigger to coronary vasospasm has never been reported.

Lung NET with the carcinoid syndrome or crisis is a rare tumor with limited published literature to date. There is no standard treatment available especially for metastatic lung carcinoids, but primary tumor removal is recommended with multidisciplinary team involvement.[6] Optimum perioperative management to minimize the risk of crisis is imperative to improve surgical outcomes.

Case Description

A 62-year-old man presented with multiple episodes of carcinoid syndrome manifested as profuse diarrhea, vomiting, and facial flushing for 3 months is referred to our hospital. A series of investigations did revealed raised urine 5-HIAA (3677 mg, normal range 2–7) and serum chromogranin (67,320 ng/mL, normal range 27–94). Contrast enhanced computerized tomography (CECT) showed a left lung mass with multiple metastatic bilobar lesions in the liver and bone. An ultrasound-guided biopsy of the liver lesion showed a well-differentiated neuroendocrine tumor positive for TTF-1, which indicated a lung or thyroid origin. A Ga-68 DOTANOC PET scan showed a somatostatin receptor (SSRT) expressed in the left lung mass, liver, and bones (Fig. 1). He was treated for lung NET with a liver and bone metastasis.

He received the first subcutaneous dose of 30-mg long-acting octreotide after the diagnosis. He developed the carcinoid

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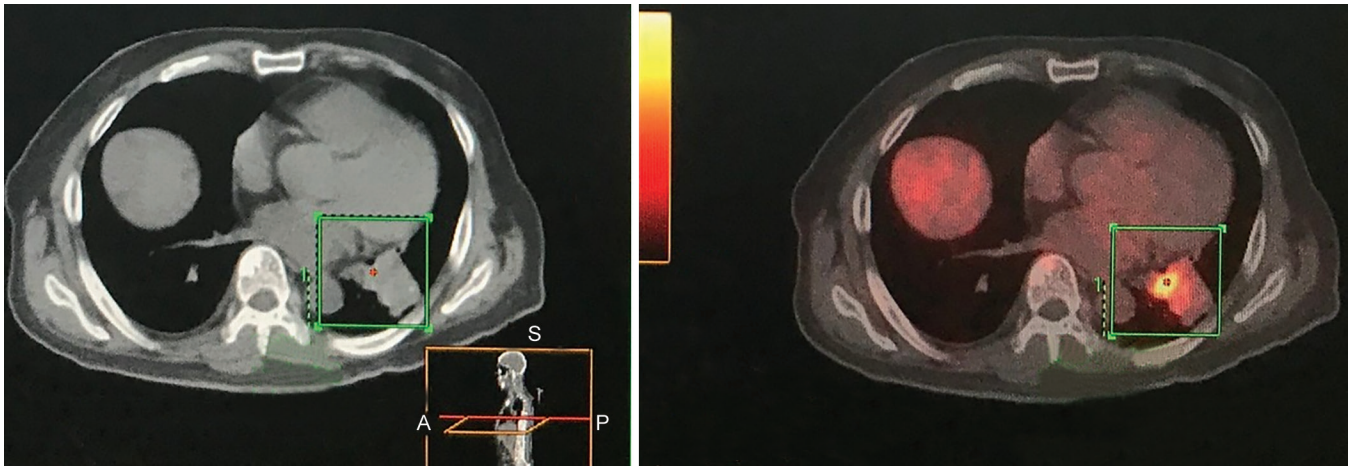

Fig. 1: CT/PET Ga-68 showing an irregular mass at the left lower lobe of the lung with Ga-68 DOTANOC uptake

syndrome one week later and was started intravenous (IV) octreotide infusion for the first time and this was when he first experienced chest pain. The symptoms resolved with the cessation of the infusion. A series of echocardiogram showed transient ST elevation. The ECHO revealed ejection fraction (55%) and mild tricuspid regurgitation. Coronary angiography revealed mild disease (50%) at the distal left anterior descending coronary artery. We treated him for coronary vasospasm secondary to the octreotide or carcinoid crisis.

He underwent a left uniportal video-assisted thoracoscopic surgery (VATS), a lower lobectomy, and a lymph node dissection within one month from the last episode of the crisis. For medical control, an IV octreotide infusion was initiated 12 hours before surgery at a slow tapering dose: 25 mcg/hour for the first 2 hours, then 50 mcg/hour for 2 hours, and subsequently maintained at 100 mcg/hour till surgery. The aim was to keep the intensity of an anticipated crisis to the minimum during surgery and watch out for coronary vasospasm complication. Despite continuous octreotide infusion (100 mcg/hour) and a frequent intermittent high dose of bolus octreotide (50–100 mcg) intraoperatively, he developed a carcinoid crisis evident by a persistent hypotension, which was supported by vasopressin and phenylepinephrine without evidence of an acute coronary event. The surgical aim to control the crisis was by first identifying and ligating the left inferior pulmonary vein, followed by the common basal and superior segmental artery, then bronchus of the lower lobe, and finally lymph node dissection (Fig. 2). Postoperatively he was infused with octreotide at a tapering dose for a day. His postoperative recovery was uneventful and was discharged home on day 7.

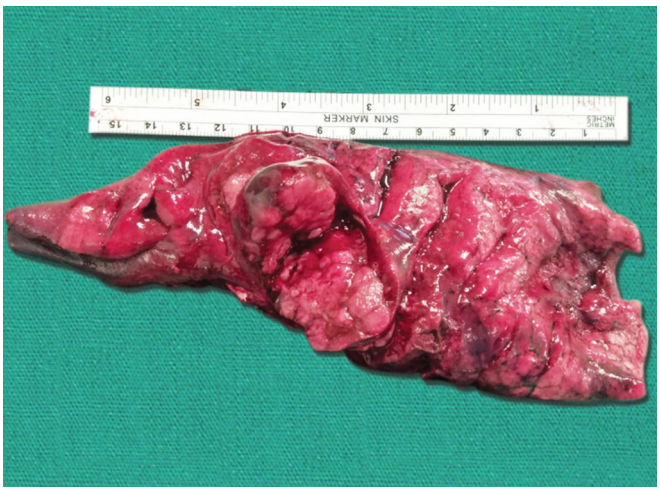

Fig. 2: A centrally located solid tumor measuring 3 × 4 cm

Discussion

The patient was subjected for a left lower lobectomy to reduce the tumor burden and his frequency of developing the carcinoid syndrome and crisis. The dilemma was whether to initiate octreotide preoperatively in consideration of his previous history of developing coronary vasospasm possible secondary to either the octreotide or carcinoid crisis. About 40% of patients with the carcinoid syndrome have the manifestation of cardiac complications where 95% of the cases showed a right valvular dysfunction.[3] The phenomenon of coronary vasospasm secondary to the carcinoid crisis has only scarcely been reported.[3] Mediators secreted by the carcinoid tumor such as serotonin and histamine have been suggested to be involved in the pathogenesis of coronary vasospasm.[7] In contrast, coronary vasospasm complicated by octreotide has never been reported. Fenning reported a case of coronary vasospasm, after the first peptide receptor radionuclide therapy (PRRT) treatment for the carcinoid syndrome secondary to a metastatic NET.[3] This shows that the treating modality can be an iatrogenic trigger for coronary vasospasm, as in this case, octreotide. The demonstrated spasm was temporary and reversible, and the same treatment was resumed without complication subsequently.

Though most literature agreed to pre-medicate patient undergoing a procedure or surgery with octreotide to reduce the risk of carcinoid crisis,[8] there is no standard guideline describing the dose and duration for the administration of octreotide. The ENET consensus guidelines recommended IV octreotide infusion at a starting dose of 50–100 mcg/hour as prophylaxis 12 hours before surgery and continued 48 hours after surgery with dose titration as required.[9] Owing to previous coronary vasospasm, in which octreotide could be one of the possible causes, we started octreotide pre-operatively at a lower dose of 25 mcg/hour and titrate accordingly with a close cardiac monitor. We tapered

off his octreotide one day after surgery, all without any acute cardiac event.

Surgical resection is the treatment of choice for the lung NET.[2] The National Comprehensive Cancer Network (NCCN) guidelines advocate a minimally invasive surgery to be considered for all patients requiring a lung resection for malignancy.[10] VATS lobectomy has gained international acceptance and popularity because of benefits such as shorter hospital stay, less tissue trauma, and less postoperative pain.[10] Nodal involvement affects survival[11] and it is present in up to 25% of well-differentiated lung NET.[6] Therefore, a complete lymph node dissection should be carried out at the time of resection.

Conclusion

Lung NET with the carcinoid syndrome or crisis are a unique and heterogeneous group of tumors requiring a multidisciplinary team approach for optimal care. The carcinoid syndrome needs to be controlled by octreotide prior to a surgical intervention, and the management can be challenging when dealing with a life-threatening coronary vasospasm when its root cause is not well-established. Surgery is the mainstay of treatment and the minimally-invasive approach is favored.

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CASE REPORT

Double Pouch Colon

Vidyanand Deshpande[1], Gaurav Chamle[2]

Abstract

Congenital pouch colon (CPC) is a rare type of anorectal malformation found mainly in North Indian states. A 2-day-old male neonate with type V CPC (i.e., double pouch colon) has been reported. This is 6th such case reported in the world literature.

Keywords: Anorectal malformation, Congenital pouch colon, Double pouch colon.

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Introduction

Congenital pouch colon (CPC) is defined as a condition where a part or whole of the colon is replaced by a pouch-like dilatation, which usually has communication with the urogenital tract in the form of fistula.[1] Double pouch colon is a type of CPC when a colon is replaced by two pouches with a normal interposition colon segment.[2]

Case Description

A 2-day-old, 2.7-kilogram male full-term neonate, born out of a non-consanguineous marriage was referred to us with a complaint of absent anal opening since birth and abdominal distension and meconuria since day 1. On examination, the patient had a distended abdomen and absent anal opening with a flat perineum. The fantogram showed two large air-fluid levels in the abdomen (Fig. 1). Echocardiogram was suggestive of patent ductus arteriosus with severe pulmonary artery hypertension.

At laparotomy Saxena–Mathur classification, a type V pouch colon was seen with the intervening segment of only 2 centimeters. This dumb-bell-shaped pouch colon was ischemic, thinned out at places, and had blood supply only from marginal branches (Fig. 2). The poucho-vesical fistula was divided and closed, pouch excised, and terminal ileostomy was done (Fig. 3). The patient was discharged uneventfully on 8th postoperative day.

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We had planned a second-stage surgery after 3 months. However, the patient, unfortunately, succumbed to lower respiratory tract infection at 2 months of age.

Discussion

In 1912, Spriggs described a congenital-pouch-colon-like condition while he was working with a specimen from London Hospital Museum, where the left half of the large gut was absent.[3] CPC is now included in International Krickenbeck classification in rare variants category of anorectal malformations.[4] In 1984, Narsimharao et al. coined the term "pouch colon syndrome."[5] Saxena–Mathur classification divides the CPC into five types:

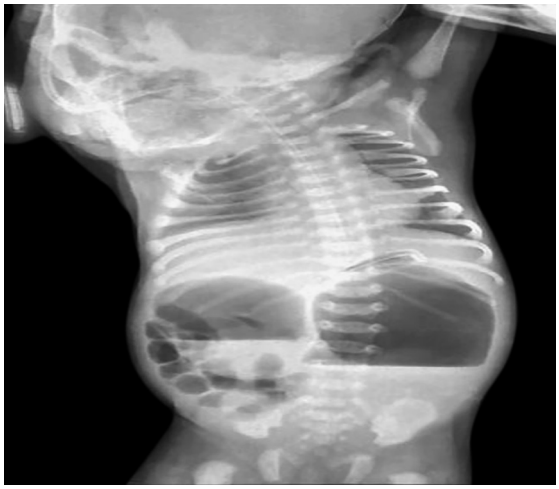

Fig. 1: X-ray showing two large-air-fluid levels

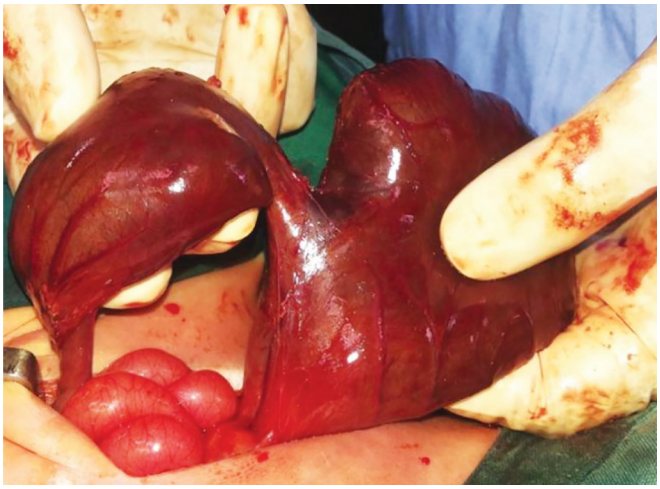

Fig. 2: A thinned out double pouch colon

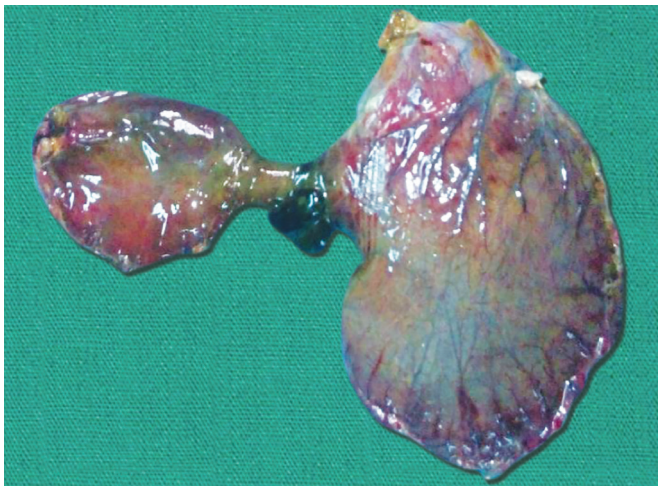

Fig. 3: Specimen with areas of perforations

Type I: Normal colon is absent, and ileum opens into a pouch colon.

Type II: Ileum opens into a normal cecum that opens into a pouch colon.

Type III: Normal ascending colon and transverse colon open into a pouch colon.

Type IV: Normal colon with a rectosigmoid pouch.

Type V: Double pouch colon with a normal interposition colon segment.[2]

In a large study at a center in North India done by Mathur et al., the CPC constituted 17.2% of all anorectal malformations and amongst all CPCs, type V variant is seen in 1.5%.[2] There are only 5 reported cases of CPC type-V in the world literature and this is the 6th case.[6,7]

The etiology of the double pouch is vascular insult due to the obliteration of the ileocolic branch of the superior mesenteric artery along with the obliteration of inferior mesenteric artery, leading to the formation of the double pouch. However, the middle portion remains normal as a result of its supply from the middle colic branch of the superior mesenteric artery.

For type V CPC, the procedure described is excision of the distal pouch with coloplast of the proximal pouch under the cover of ileostomy. However, in our case, both the pouches were ischemic and had areas of impending perforation, hence excision and end ileostomy was done.

Conclusion

In conclusion, we can say that the treatment needs to be individualized according to the peroperative findings. The outcome depends on the associated anomalies.

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CASE REPORT

Anesthetic Management in a Parturient with Complete Heart Block Posted for Emergency Uterine Evacuation: A Case Report

Aaditya A Prabhudesai[1], Kasturi H Bandyopadhyay[2], Chumki A Datta[3], Shilpita Banerjee[4]

Abstract

A 34-year-old lady in the 19th week of gestation was referred for emergency evacuation of products of conception, following intrauterine fetal death and persistent vaginal bleeding. She was suffering from complete heart block with a heart rate of 42 beats per minute. A temporary pacemaker was implanted and she was taken up for surgery. She developed an acute bronchospasm just before induction of anesthesia, which was successfully managed, without delaying the operative procedure. Her anesthetic management is discussed in detail in this paper. She was discharged on the 8th postoperative day after implanting a permanent pacemaker. Cause of her complete heart block was found to be systemic lupus erythematosus.

Keywords: Bronchospasm, Complete heart block, IUFD, Pregnancy.

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Background

Complete heart block (CHB) in pregnancy is uncommon.[1] Recurrent mid-trimester abortions are common owing to immunologic factors associated with diseases such as systemic lupus erythematosus (SLE), Sjögren's syndrome, systemic infections, placental pathologies, thrombophilia, and diabetes.[2] Our case was complicated by a sudden, unexpected preoperative bronchospasm that dictated a prompt management of the respiratory emergency, making the management of general anesthesia more challenging.

Case Description

A 34-year-old fourth gravida at the 19th week of gestation presented with chest pain and dizziness for four days and vaginal bleeding for two days. Chest pain was non-anginal and intermittent. Dizziness was concurrent with chest discomfort and non-postural. She gave no history of fever, loss of consciousness, headache, and swelling of legs or face. There was no past history of asthma and allergy to any medication. Family history had nil relevance.

She had a full-term vaginal delivery 6 years back followed by two mid-trimester spontaneous abortions and had not undergone any antenatal checkup for the present pregnancy till date.

On examination, the patient was conscious, cooperative, oriented, afebrile, pale with a heart rate (HR) of 42 beats/minute, a blood pressure of 130/70 mm Hg, and a respiratory rate of 20/minute. Auscultation of lungs revealed bilaterally equal air entry without adventitious sounds. Cardiovascular examination was normal apart from bradycardia. Airway examination showed adequate mouth opening, neck extension, Mallampati Grade II. She had taken her last meal four hours earlier. Obstetrical examination revealed the 18th-week uterus with blood clots and prolapsed cord in the vagina.

Investigation showed Hb 9.7 g/dL; total leukocyte count (TLC) 19,280/mm^3; differential count neutrophils 90, lymphocytes 7, and eosinophils 3; platelets 3.2 lakhs; trothrombin time 14.09 seconds with international normalized ratio (INR) 1.05. aPTT was 33.5 and D-dimer 3259.30 ng/mL. Serum electrolytes, blood glucose, cardiac enzymes, and thyroid function test were within normal limits. Arterial blood gas analysis revealed pH 7.42, pCO_2 16 mm Hg, pO_2 77 mm Hg, and serum lactate 4.7 mmol/L. ECG showed CHB, while 2D echocardiography and chest radiography were within normal limits (Fig. 1). Ultrasonography and Doppler study documented an absence of fetal cardiac activity with reversal of flow in the uteroplacental bed, implying intrauterine fetal death. Bilateral lower limb Doppler showed normal flow in deep veins. After counseling and obtaining written informed consent, she was accepted as ASA IIIE. Intra-arterial cannulation for hemodynamic monitoring in addition to intravenous cannulation with a 16 G cannula for maintenance of the administration of fluids was carried out. Two units of packed red blood cells were cross-matched. Temporary pacemaker implantation (TPI) was done in the cath lab and set at VVI mode with a rate of 70 bpm, an output of 5 mA, and a sensitivity of 5 mV (Fig. 2). She was premedicated with Inj. metoclopramide 10 mg IM and Inj. ranitidine 50 mg IV.

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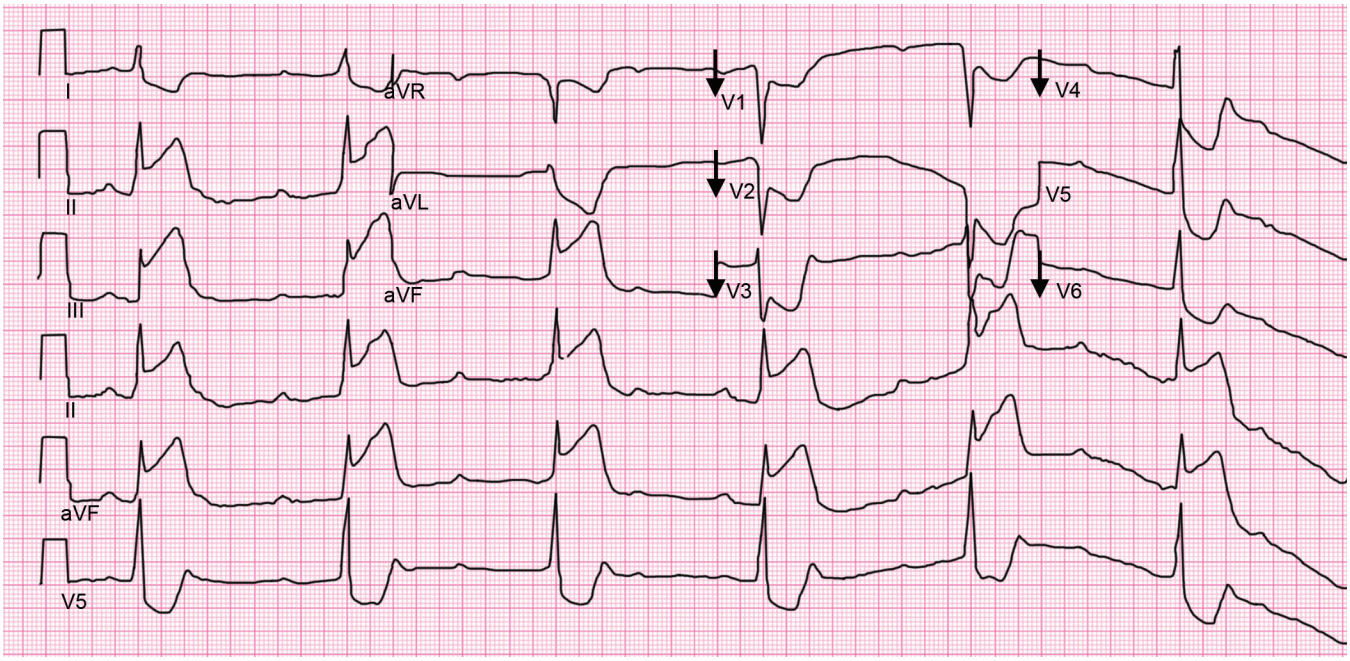

Fig. 1: ECG showing complete heart block in the patient

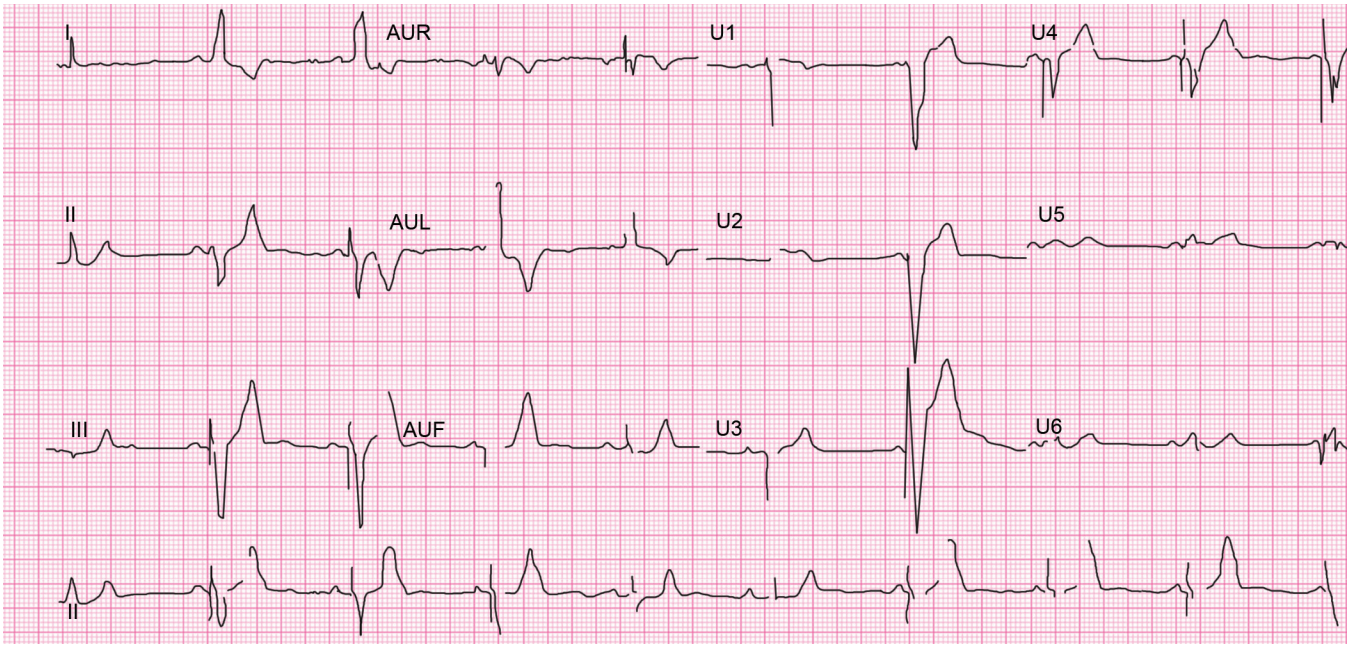

Fig. 2: ECG of the patient after permanent pacemaker

After attaching standard ASA monitors in OT, she suddenly developed tachypnea and air hunger with RR 44 per minute, HR 148 bpm, BP 170/90 mm Hg, inadequate air entry with bilateral wheeze and rhonchi, desaturated to 73–68% even with a non-rebreathing oxygen mask delivering 10 L/minute. Bronchospasm was diagnosed and the procedure was withheld till the patient stabilized. She was propped up to 60°, administered humidified O_2, nebulized with 2.5 mg salbutamol every 15 minutes and injected with hydrocortisone 200 mg IV. After 45 minutes, HR settled down to 96/minute, RR 28/minute, BP 130/90 mm Hg with SpO_2 93% on 6 L/minute oxygen supplementation by a face mask.

General anesthesia (GA) was administered by a rapid sequence induction with an injection of ketamine (2 mg/kg) and an injection of succinylcholine (1.5 mg/kg). Endotracheal intubation is followed with 7 mm ID cuffed ET Tube and anesthesia is maintained using sevoflurane (2%) with oxygen:air (50:50) and titrated the dose of injection vecuronium and injection fentanyl. She was ventilated in intermittent positive pressure ventilation (PCV mode, peak airway pressure 30 cm H_2O and I:E 1:2). Intraoperatively patient remained hemodynamically stable and ABG showed pH 7.45, pCO_2 16 mm Hg, pO_2 87 mm Hg with *c*Lactate 2.8 mmol/L; however, there were bilateral scattered rhonchi and basal crepitations. She underwent

elective postoperative ventilation and was extubated 36 hours later. A permanent pacemaker was implanted before discharge on 8th postoperative day. Follow-up investigation after 6 weeks reported raised Anti-ds DNA antibody titre 1:320 (significant > 1:80) and Anti-Sm antibody titre 1:160 (significant > 1:40).

Discussion

The positive findings in our patient were the history of two mid-trimester abortions, symptomatic CHB, IUFD, anemia, raised total leukocyte count, and D-dimers levels complicated with an immediate preoperative bronchospasm.

CHB associated with pregnancy is rare.[3] Our patient did not manifest similar symptoms in her previous three pregnancies, which included one full-term delivery of a healthy baby and two mid-trimester spontaneous abortions, thus confirming that a CHB was acquired. The common causes of an acquired CHB are coronary artery disease, dyselectrolytemia, autoimmune disorders, and infections such as viral myocarditis and physiological changes of pregnancy themselves. Normal cardiac enzyme levels and echocardiography ruled out an acute coronary event and infective myocarditis.

The cause of anemia, neutrophilia, and raised serum lactates can be attributed to the pregnancy state itself and also to degenerated circulating fetal products as a sequelae of IUFD. D-Dimer concentration increases above normal (500 ng/L) in pregnancy owing to increased fibrinogen levels, with the mean values being 409 ng/L and 690 ng/L in the second and third trimester respectively.[4] A significantly raised value of D-dimer (3259.60 ng/L) in our patient implied that the underlying hypercoagulable state is related to a reason other than pregnancy. American College of Cardiology (ACC) and American Heart Association (AHA) guidelines advise Temporary Pacemaker Implantation (TPI) in CHB associated with symptomatic bradycardia,[5] which we carried out in this case and took her up for uterine evacuation in view of active vaginal bleeding as ASA IIIE.

The patient experienced an episode of bronchospasm in the immediate preoperative period. We deferred the procedure and treated the bronchospasm. The cause of spasm could be due to the circulating products of the two-day-old IUFD, pre-operative administration of prostaglandin E_2 vaginal suppository or some other cause. Hyper-reactive airway as a cause of bronchospasm was unlikely, as there was no past history of asthma, atopy, allergy, or hypersensitivity reactions.

Since our patient had a full stomach, a rapid sequence induction was done and elective postoperative ventilation was planned due to persisting bronchospasm.

CHB was persistent as was evident in the Holter monitoring postoperatively. A dual-chamber permanent pacemaker was implanted prior to discharge on the 8th postoperative day.[6] At follow-up, six weeks after surgery, serum levels of Anti ds DNA antibodies and Anti Sm Antibodies 1:120 were tested. Both were significantly raised: Anti ds DNA 1:320 (significant > 1:160) and Anti Sm 1:120 (significant > 1:80), favoring the diagnosis of systemic lupus erythematosus (SLE), which explained the presence of CHB and recurrent mid-trimester abortions.

Conclusion

Our case (a 34-year-old lady) is presented in the fourth gestation with CHB, IUFD, and active vaginal bleeding. She was posted for emergency uterine evacuation. TPI was carried out on her for CHB. Before induction, she developed a severe bronchospasm, which was treated with intravenous bronchodilators and hydrocortisone. Surgery was carried out under GA. Postoperatively she required ventilatory support for 36 hours. She was discharged on the 8th postoperative day after implantation of a permanent pacemaker. The cause of her CHB and recurrent trimester abortions was later found to be due to SLE.

Clinical Significance

CHB, though rare in pregnancy, should be investigated appropriately and more so when associated with IUFD, bad obstetric history, hypercoagulable state, and a perioperative bronchospasm, all of which suggest the presence of an underlying disease with multisystem involvement. A multidisciplinary team approach is always required to obtain a positive patient outcome.

Acknowledgment

We acknowledge Dr Sumanto Mukhopadhyay, Consultant Cardiologist, for prompt guidance and TPI followed by PPI support and his pivotal role in optimization of the patient.

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CASE REPORT

Spectrum of Depression in Children and Adolescents with Type 1 Diabetes—Report of Three Cases

Darpan Kaur[1], Nilay Patel[2], Rakesh Ghildiyal[3]

Abstract

Sparse literature is available on mental health in the context of diabetes in children and adolescents of developing countries, such as India. We report three cases of depression in children and adolescents who are suffering from type 1 diabetes mellitus (T1DM). We found a spectrum of depression ranging from double depression to depression with somatic syndrome to severe depression with psychosis in diabetics of these age groups. We suggest that further original research may be directed in the arena of mental health in children and adolescents.

Keywords: Child and adolescent, Depression spectrum, Diabetes mellitus.

MGM Journal of Medical Sciences (2019): 10.5005/jp-journals-10036-1244

Introduction

Type 1 diabetes is a disorder of impaired insulin secretion and glucose metabolism. The initial diagnosis is most commonly made in children and adolescents who often present with an acute illness followed by several weeks of polyuria, polyphagia, polydipsia, and weight loss. Sometimes, the diagnosis is incidental during a routine blood sugar test. Diagnosis of type 1 diabetes and its management is a significant stressor for children and parents.[1] In 2007, the total child population of the world (0–14 years) was estimated to be 1.8 billion, of whom 0.02% had diabetes. Approximately, 440,000 children around the world have diabetes at any given time and 70,000 new cases are diagnosed each year.[2] The estimated prevalence of a psychiatric disorder was 47.6% in one longitudinal investigation of 92 children (ages 8–13 at the time of diagnosis) followed for 10 years with major depression being the most frequent diagnosis at 27.5%, followed by conduct and anxiety disorders. The highest incidence of depression was in the 1st year after diagnosis.[3] Mood disorders, such as major depressive disorder and dysthymia, are the most frequently reported diagnoses in youth with type 1 diabetes, with a cumulative probability of 27.5% by the 10th year of type 1 diabetes duration.[4] Sparse literature is available on mental health in the context of diabetes in children and adolescents of developing countries, such as India.

Aim

To describe rare cases of depression in type 1 diabetes in childhood and adolescents.

Objectives

- To understand depression in children and adolescents with chronic medical conditions, such as diabetes.
- To appreciate challenges in the assessment, diagnosis, and management of depression in pediatric diabetes.

Case Description

Case 1

Master Abc, a 15-year-old boy with type 1 diabetes in pediatrics ward who was under evaluation for fever and abdominal pain, was referred to the child and adolescent psychiatry clinic in view of sadness of mood, anger outburst, crying spells, and behavior problems. The patient reported that for the past 1 year he was sad, feeling hopeless, helpless, crying, not getting good sleep, and feeling that he is a burden to his family. There was no family history of psychiatric illness and developmental delays. His medical history revealed that he had raised blood glucose level and his HbA1C was 11.40% and was on daily insulin injections since 1 year. His mental status examination confirmed that he had depressed mood and affect and depressive cognitions of hopelessness, helplessness, worthlessness, and schemas of loneliness. He was diagnosed with depressive disorder, current episode moderate with somatic syndrome with diabetes mellitus and stressors related to coping with illness, and perceived financial burden to parents. He was started with tablet escitalopram 5 mg titrated to 10 mg once a day (OD) along with cognitive behavioral therapy. He showed good improvement in his depressive symptoms.

Case 2

Miss Xyz, a 12-year-old girl, a known case of type 1 diabetes since 4 years, admitted in the pediatrics ward for fever, vomiting, and loose stools, was referred to the child and adolescent psychiatry clinic in view of sadness of mood, refusal to eat food, not talking with family members, and irritability. She was complaining of feeling depressed since the past 4 years but not that severe and was able to carry on with her daily activities. She had feelings of sadness and hopelessness since the past few years on a daily basis, but since the past 6 months she had become more depressed and was crying a lot. She felt that she was a burden to her family and was finding it difficult to cope with her repeated medical

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admissions. She was not able to go to school regularly and missed her friends. There was no family history of psychiatric illness and developmental delays. Her medical history revealed raised blood glucose level and her HbA1C was 10.30% and was on daily insulin injections. Her serum creatinine was high, probably due to diabetic nephropathy. Her mental status examination confirmed that she had depressed mood and affect and hopelessness, worthlessness, and rumination of thought. She was diagnosed with dysthymia with depressive disorder (double depression) and diabetes mellitus, and stressors related to coping with illness. She was started with tablet escitalopram 5 mg OD and titrated to 10 mg OD over 2 weeks with regular counseling and cognitive behavioral therapy. The patient showed improvement in depressive features and her adherence to her diabetes treatment also improved and she is on regular follow-up in liaison with pediatrics.

Case 3

Master Abc, a 13-year-old boy, a known case of type 1 diabetes since 5 years, was referred from the pediatric ward to the child and adolescent psychiatry clinic in view of behavioral problems, namely, irritability, not cooperating properly with treatment, getting angry, refusing to eat food, and being quarrelsome. Caregivers reported that there was history of sadness of mood, ideas of hopelessness, and helplessness and that he had lately become suspicious towards others, feeling that others are talking about him and laughing at him. He was feeling guilty and asked for repeated forgiveness from his parents for being a burden to them. He had started expressing ideas that he does not want to live any longer and was not cooperating with treatment properly. There was no family history of psychiatry illness or any developmental problems. His medical history revealed raised blood glucose level and his HbA1C was 9.70%. He was on daily insulin injections. His mental status examination showed that he had depressed mood and affect and depressive cognitions. His thought examination showed delusion of guilt and persecution secondary to his mood state. He was diagnosed with depressive disorder and severe episode with psychotic features with diabetes mellitus. He was started with tablet fluoxetine 10 mg and risperidone 2 mg along with cognitive behavioral therapy. He showed improvement in depression.

Discussion

It is important to highlight that depression may be underdiagnosed in children with diabetes because of the overlap of symptoms, such as fatigue, weight loss, and impaired memory, which are common in both mood disorder and fluctuations in blood glucose levels, such as hypoglycemic episodes and chronic hyperglycemia may directly contribute to alterations in behavior and mood.[5,6] Patients with poor metabolic control were three times more likely to be depressed than those with good control and that for each 1% rise in HbA1C, there was a 27% increased probability of depression.[7] Depression may affect adherence to diabetes treatment due to decreased interest, energy, and motivation, which subsequently cause poor diabetic control and may worsen symptoms of guilt or hopelessness.[8] Depression in young people with T1DM has a variety of consequences including poor glucose control due to nonadherence to medication, which can negatively impact long-term health outcomes. Depression can lower the quality of life and increases suicide rates. Suicidal thoughts in the 1st year after T1DM diagnosis are related to poor compliance with diabetes care. Adolescents are already a high-risk group for suicide due to the challenges of puberty, peer pressures, and independence from parental control.[9] Diagnostic criteria for depression are the same for children and adults, with the exception that children and adolescents may express irritability rather than sad or depressed mood, and weight loss may be viewed in terms of failure to reach appropriate weight milestones. Treatment of childhood and adolescent depression consists of psychotherapy, pharmacotherapy, or a combination of these.[10]

Conclusion

Depression can exist in children and adolescents with type 1 diabetes. We found a spectrum of depression in the case series ranging from double depression to depression with somatic syndrome to severe depression with psychosis in children and adolescents with diabetes. Further studies are required in the arena of mental health problems in children and adolescents who suffering from T1DM.

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