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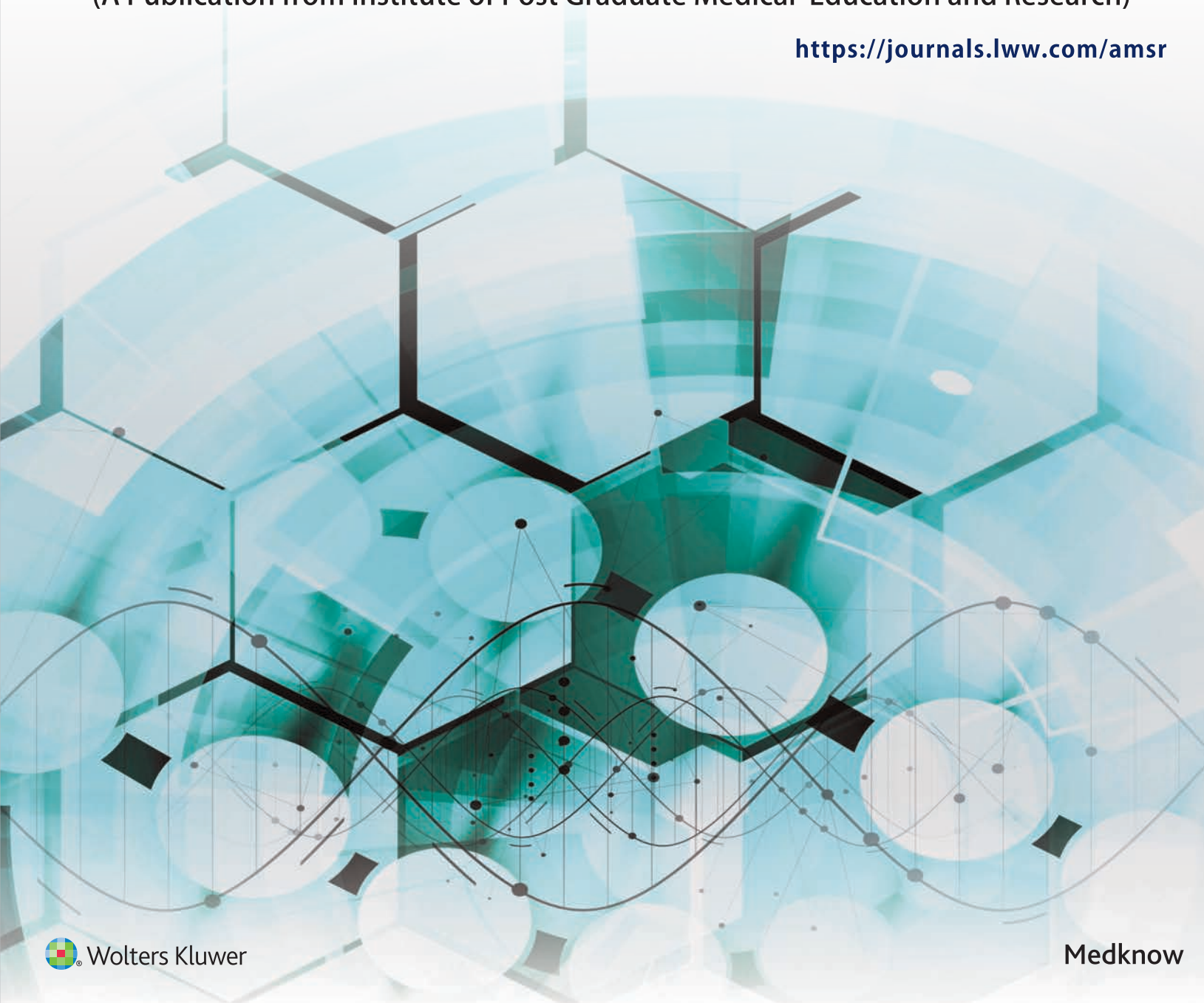

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# Annals of Medical Science and Research

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# Annals of Medical Science and Research

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## Letter to the Editor

# District clinical specialist teams: a major change agent in South African health system

South African public sector health system was fragmented and characterized by geographical inequalities, racial inequalities, and poor access to health care under apartheid. In 1990, the African National Congress (ANC) established a health commission aimed at transforming the health sector into a single system with an equitable distribution of resources and expanded service delivery. In 1994, the new National Department of health adopted the primary health care (PHC) approach as the structural orientation of the South African health care system. Equitable resource distribution, expanded access, decentralized services aimed at promoting local health needs, community involvement through the district health service (DHS), and preventive and promotive health care were the main focus of the national health system.[1]

Adequate information on maternal and women's health was lacking under apartheid. Proper monitoring was initiated under new government and maternal mortality ratio (MMR) was reported to be very high at 150 per 100 000 live births in 1994–1996.[2] The literacy rate of the female was 81% in 1996 which was fair which might not have any influence on mortality and morbidity as there is no published data to relate female literacy to mortality and morbidity of the country in the context of DCST.[3] Currently, MMR in South Africa is 88 per 100,000 live births.[4] The common causes of maternal deaths are attributed to hypertension, HIV, and post-partum hemorrhage.[4]

South Africa has incorporated the sustainable development goal (SDG) and it aims to achieve maternal mortality to less than 70 per 100,000 live births by 2030.[5] Achieving this target will need improvement in the quality of antenatal care, effective management of high-risk pregnancies, and the strengthening of referral systems and adequate provision of emergency patient transport among other services.

In the context of high maternal mortality, maternal health was looked at with utmost priority. Numerous initiatives were then introduced by the National Department of Health (NDoH) to address these challenges. These initiatives did not produce desired results on maternal mortality and other maternal health indicators. A national committee to conduct confidential enquiry into maternal deaths (NCCEMD) was developed who identified that maternal mortality could be attributed to (a) administrative factors, (b) patient-treated factors, and (c) health workers related factors.[6] In addition, a policy document on PHC re-engineering (2011) was published. Based on these observations, the NDoH decided to address these factors by appointment of a District Clinical Specialist Team (DCST) in each of the 52 districts in South Africa[7,8] as a part of PHC re-engineering.[7,9] This intervention was probably the most important health intervention introduced during the last decade in South Africa.

The DCST comprised of an obstetrician and gynecologist, a pediatrician, a family physician, an advanced midwife, an advanced pediatric nurse, an advanced PHC nurse and anesthesiologist.[10] The primary role of this team is to reduce maternal and child mortality and morbidity in each district, to reduce HIV related illness by clinical governance, to provide supervision, mentoring and support services throughout a district.[11,12] As every district in South Africa has all level of health care facilities including tertiary hospital, regional hospital, district hospital, community health centers and PHC clinics, DCST was expected to be an interface between all levels of health care which then would lead to improvement at the country level.

In each district, a DCST was expected to be responsible for the following areas of work, which would form the basis of their annual performance assessments: (a) quality of clinical services; (b) clinical training; (c) monitoring, evaluation and improving clinical services; (d)supporting district level organizational activities; (e)supporting health systems and logistics; (f) collaboration, communication, and reporting; and (g) teaching and research activities. Their work would be judged based on changes in maternal and pediatric indicators in a district.[10] Implementation of DCST into the district health system has broadened the availability of specialist doctors and nurses at a PHC level and it was also meant to redirect specialists from a hospital-based model to an *inclusive PHC model* as a part of PHC re-engineering. This new and innovative role of the DCST was expected to

offer an opportunity for internal system diagnosis and the potential to support realization of global goals such as the MDGs and SDGs.[13] It was expected that the new clinical governance role of the DCST at the district level could help in ensuring quality in service delivery for South Africa to move its human resource strength towards universal health coverage.[14]

A decade has passed since implementation of DCST. As it was advocated by NDOH, in each district in South Africa, DCST activities were based on four pillars, namely clinical effectiveness, clinical risk management, professional development and management and finally improve accountability of maternal and child health. These four pillars of activities covered a broad range of activities under each of them. Clinical effectiveness aimed to improve the clinical work standards at all health facilities and regularize clinical auditing in order to improve the performance of indicators. Clinical risk management entailed Identification of the risks, assessment of the credentials of staff qualifications and quality of their training, analysis of the adverse incidents, developing plan of action from the morbidity and mortality meetings, recommending improvement plans to prevent the recurrence of maternal deaths due to the avoidable factors and strengthen inter-facility referral system. Professional development and management was focused on in-service training, onsite staff mentoring, identify opportunities and needs for formal education, monitoring the coverage on mandatory trainings and arrange appropriate trainings and also to motivate and coordinate operational research within the facilities. Improvement on accountability for maternal and child health included team work with Ward Based Outreach Team on health preventative and promotional activities, teamwork with health communication officers and health promoters on dissemination of health education to the community and organizing community events.

There was a general improvement in record keeping and reporting of maternal health indicators at all health institutions which resulted from regular monitoring by DCST. There was a significant improvement in access to health care. Maternal health indicators such as antenatal first visit before 20 weeks rate, ANC patients initiated on ARV rate, postnatal visit within 3–6 days rate and stillbirth rate showed slow improvement over the years. Maternal mortality showed significant reduction in South Africa. It is presumed that various activities of DCST played an important role in overall improvement in maternal and child health indicators in South Africa.[15] DCST have played a role as an important change agent in South African health system and can further contribute to the achievement of SDG in South Africa.

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## Conflicts of interest

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Review Article

# Competency-based medical education: An overview

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**Abstract**

Competency-based medical education (CBME) has emerged as a transformative approach to medical training, revolutionizing traditional models of education. This comprehensive review article provides an in-depth overview of CBME, encompassing its underlying principles, implementation strategies, and impact on medical education. By synthesizing current research and literature, this article highlights the strengths and challenges of CBME while also identifying potential future directions for advancement. The review emphasizes CBME's learner-centered approach and focuses on outcomes and performance, integration of clinical practice and theory, and continuous assessment and feedback. It explores various implementation strategies, including competency framework development, curriculum design, program assessment, and technology integration. The impact of CBME on medical education is discussed, emphasizing enhanced learner outcomes, improved patient care, alignment with evolving healthcare needs, flexibility in training, and the development of lifelong learning skills. The strengths of CBME, such as its emphasis on outcomes, tailored learning experiences, and assessment-driven feedback, are examined, along with the challenges of faculty development, resource allocation, standardization, and resistance to change. Furthermore, the review suggests future directions for CBME, including continued research, technology integration, interprofessional education, global adoption, and longitudinal assessment. In conclusion, this comprehensive review underscores the transformative potential of CBME in medical education, calling for further exploration, research, and collaborative efforts to shape its future.

**Keywords:** CBME principles, challenges, impact, implementation

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## INTRODUCTION

Competency-based medical education (CBME) is an approach to medical training and assessment that focuses on the achievement of specific competencies or observable abilities required for the practice of medicine. These competencies are defined based on the needs of patients, society, and the healthcare system. They may include clinical skills, communication skills, professionalism, ethical decision-making, teamwork, leadership, and lifelong learning.

Assessment in CBME is ongoing and integrated throughout the learning process, providing learners with timely feedback to guide their development. Milestones, entrustable professional activities, and workplace-based assessments are commonly used to evaluate learners' progress and readiness for independent practice.

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The ultimate goal of CBME is to produce competent physicians who are able to meet the evolving healthcare needs of the population they serve. By aligning education with the desired outcomes of medical practice, CBME aims to improve the quality of healthcare delivery, patient safety, and overall healthcare system performance.[1,2]

### Early influences

#### *Outcome-based education*

The shift toward outcome-based education in the 1970s and 1980s, which emphasized defining clear learning outcomes and aligning educational activities to achieve those outcomes, laid the foundation for CBME.[1]

#### *Competency movement*

The competency movement in various professions, including medicine, gained momentum in the 1990s. This movement emphasized defining specific competencies required for practice and developing educational programs to ensure learners achieve those competencies.[2]

### The Flexner report and competencies

The Flexner Report, published in 1910, played a significant role in transforming medical education in the USA. While the report focused primarily on curriculum and standards, it also highlighted the importance of defining competencies for medical practice.

The idea of identifying specific competencies for physicians was further reinforced by subsequent reports and initiatives, such as the General Professional Education of the Physician and Surgeon report in 1984 and the Outcome Project by the Accreditation Council for Graduate Medical Education (ACGME) in the early 2000s.[1,3]

### The outcome project and competency frameworks

The ACGME's Outcome Project, launched in 1999, aimed to shift medical education from a time-based model to an outcomes-based model. The outcome project led to the development of competency frameworks, such as the ACGME's six core competencies (patient care, medical knowledge, practice-based learning and improvement, interpersonal and communication skills, professionalism, and systems-based practice). These frameworks provided a foundation for CBME implementation.[1,4]

### International adoption and milestones

CBME principles and competency frameworks began to be adopted and adapted by medical education programs worldwide. This led to the development of various competency-based frameworks and assessment tools in different countries.[2,4]

### Contemporary developments

Ongoing research and evaluation of CBME programs have provided insights into its effectiveness, challenges, and opportunities for improvement, informing further advancements in the field.[4]

## KEY PRINCIPLES OF CBME

CBME is built on a set of key principles that guide its design, implementation, and assessment. These principles ensure that learners develop the necessary competencies for effective medical practice. The key principles of CBME are as follows.

### Competency framework

In the current CBME curriculum of medical graduates, the competence classification is leveled as know-know how-show how-perform that indicates an apparent goal of performing ability and skill acquisition of the students. At the lowest level of the pyramid is knowledge (knows), followed by competence (knows how), performance (shows how), and action (performs). Miller's (1990) work-based assessment model for clinical competence is practically generalized as the basic model of UG medical education. This is in contradistinction to Bloom's taxonomy model of cognitive levels, which emphasizes the creative and innovative aspects of the learners. Thus, a relative overemphasis on the component of skill and competence over the knowledge component becomes the hallmark of the new CBME. In the absence of meaningful and significant works in this area of education research, it is not really a prudent proposition.

#### *Integration of theory and practice*

In CBME, there is the introduction of multiple objectivity in the student evaluation system. For example, the proposition of objectively structured practical examination, objectively structured clinical examination, and simulated experimentation in virtual platforms is said to substantially replace the conventional pattern of practical and clinical examinations. Knowledge is gained through a cycle of hands-on experience with reflection guided to the conceptualization and then returning to the application. When complemented by self-assessment, the students' understanding and skills are further enhanced.

### Emphasis on assessment and feedback

Multiple assessment methods, such as workplace-based assessments, direct observation, and simulations, are used to evaluate learners' progress. Feedback from faculty, peers, and patients is provided to learners to guide their learning, identify areas for improvement, and reinforce positive behaviors.[3]

### Individualized learning pathways

CBME recognizes that learners have unique educational needs and progress at different rates. Individualized learning plans are developed to address these varying needs. Learners are actively involved in their learning and collaborate with educators to set learning goals, select learning activities, and monitor their progress. This individualization promotes learner autonomy and enhances engagement and motivation.[4]

### Lifelong learning and continuous professional development

CBME instills a culture of lifelong learning in physicians. It recognizes that medical knowledge and healthcare practices evolve over time, and physicians must continuously update their competencies to provide high-quality care.[5]

These principles collectively promote learner-centered education, focusing on the achievement of specific competencies and ensuring that learners are well-prepared for the complexities of medical practice.[6]

## ADVANTAGES OF CBME

The traditional teaching method has the following.

### Time-based progression

Traditional medical education follows a structured timeline, with students progressing through predefined courses and clinical rotations based on time spent in each phase.

### Knowledge-centered

The primary emphasis is on acquiring and retaining a broad range of medical knowledge across various disciplines. The curriculum covers extensive content within subjects such as anatomy, physiology, pharmacology, and pathology.

### Assessment

Traditional medical education relies on summative assessments, such as exams and standardized tests, to evaluate students' knowledge. Performance in these assessments determines progression and achievement.

### Teacher-directed

Faculty members play a central role in delivering didactic lectures, leading clinical rotations, and assessing students. The curriculum is primarily driven by the expertise and guidance of faculty members.

CBME offers several advantages over traditional time-based models of medical training. Some key advantages of CBME are as follows.

#### *Enhanced focus on outcomes and performance*

CBME shifts the focus from time spent in training to the achievement of specific competencies. Learners are explicitly guided toward desired outcomes, ensuring that they develop the essential knowledge, skills, attitudes, and behaviors needed for effective medical practice. This outcomes-based approach promotes a higher level of accountability and ensures that graduates are competent and practice-ready.[7]

#### *Individualized learning and flexibility*

CBME recognizes that learners have unique educational needs and progress at different rates. Individualized learning plans are tailored to the strengths and weaknesses of each learner, allowing them to focus on areas that require more attention. Learners have the flexibility to advance at their own pace, ensuring a more personalized and effective learning experience.[8]

#### *Improved assessment and feedback*

CBME provides a robust and comprehensive assessment system. It utilizes multiple assessment methods, including workplace-based assessments, direct observation, and simulations, which offer a more accurate and holistic evaluation of learners' competencies. Timely and specific feedback is provided to learners, guiding their learning, identifying areas for improvement, and reinforcing positive behaviors.[8,9]

#### *Alignment with evolving healthcare needs and patient-centered care*

CBME ensures that the competencies developed by learners are aligned with the changing healthcare landscape and evolving patient needs. By integrating competencies related to patient-centered care, communication, teamwork, professionalism, and systems-based practice, CBME promotes the delivery of high-quality, patient-centered healthcare.[7,9]

#### *Promotion of lifelong learning and professional development*

CBME fosters a culture of lifelong learning and continuous professional development. Learners are encouraged to engage in ongoing learning activities and stay updated with the latest advancements in medical knowledge and practices. This commitment to lifelong learning ensures that physicians adapt to new challenges and provide up-to-date care throughout their careers.[9]

#### *Improved patient care and safety*

CBME aimed to produce competent and skilled physicians who are better equipped to provide safe and effective patient care. By focusing on specific competencies related to clinical skills, critical thinking, and patient management,

CBME enhances the quality of healthcare delivery, reduces medical errors, and improves patient outcomes.[8]

*Promotion of self-reflection and self-regulation*

CBME encourages learners to reflect on their performance and take responsibility for their own learning and professional development. Through ongoing assessment and feedback, learners gain insight into their strengths and areas for improvement, enabling them to identify and address their learning needs. This promotes self-regulation and empowers learners to continuously improve their competencies.[10]

Overall, CBME offers advantages such as outcome-focused education, individualized learning, improved assessment and feedback, alignment with evolving healthcare needs, promotion of lifelong learning, and enhanced patient care and safety. By adopting CBME, medical education programs can better prepare learners to meet the demands of modern healthcare and ensure the delivery of high-quality, patient-centered care.

## SOME IMPORTANT FACETS OF CBME

### AETCOM

Designated Module and Implications in Community Practice AETCOM (Attitude, Ethics, and Communication) is a designated module within CBME that focuses on developing essential nontechnical skills in medical professionals. This module emphasizes the importance of cultivating attitudes, ethics, and effective communication skills in the context of community practice. AETCOM acknowledges that medical professionals not only need clinical expertise but also need to be compassionate, ethical, and skilled in effective communication to provide patient-centered care. Within the AETCOM module, medical learners are exposed to various scenarios and case studies that simulate real-world situations they may encounter in community practice. They are trained to navigate complex ethical dilemmas, develop empathetic attitudes, and master communication skills required for effective doctor-patient interactions. This module provides opportunities for learners to reflect on their own attitudes, values, and biases and how these can impact patient care in diverse community settings. AETCOM enables learners to understand the importance of cultural competence, patient autonomy, and shared decision-making. It helps them develop skills to effectively communicate with patients from different backgrounds, build trust, and establish therapeutic relationships. Ultimately, AETCOM contributes to the delivery of patient-centered care and the development of well-rounded, empathetic physicians.[11]

### Early clinical exposure

Early clinical exposure (ECE) is a foundational component of CBME that provides learners with early exposure to clinical environments, patient interactions, and healthcare teams. ECE aims to bridge the gap between theoretical knowledge and clinical application, offering learners a first-hand experience of the healthcare setting from the early stages of their medical education. ECE promotes early professional identity formation, fostering a sense of responsibility, and motivation among learners. ECE also allows learners to develop important skills such as history-taking, physical examination, and basic procedural competencies. It helps them contextualize their theoretical knowledge, reinforcing their understanding of medical concepts and their relevance to patient care. In addition, ECE provides learners with opportunities to observe healthcare professionals' ethical conduct, communication skills, and professionalism, serving as role models for their own development.[12]

### Self-directed learning

Self-directed learning (SDL) recognizes that medical professionals must be lifelong learners, capable of adapting to advancements in medical knowledge and evolving patient needs. The need for SDL stems from the ever-expanding body of medical knowledge and the rapid pace of advancements in healthcare. SDL equips learners with the ability to identify their learning needs, set goals, and independently acquire knowledge through various resources, including textbooks, online platforms, research articles, and educational workshops. In practice, SDL encourages learners to engage in critical thinking, problem-solving, and self-assessment. Learners are encouraged to identify their strengths and areas for improvement, develop learning plans, and seek out opportunities for continuous professional growth. The integration of technology, such as online learning platforms and educational apps, can also support SDL by providing learners with easily accessible and up-to-date resources.[13]

### Foundation course

This course typically takes place at the beginning of medical education and provides learners with a solid foundation in basic sciences, clinical skills, and professionalism. In addition, the foundation course emphasizes professionalism, ethics, and the development of a patient-centered approach. By establishing a strong foundation, the course ensures that learners have a comprehensive understanding of the basic sciences and essential clinical skills before proceeding to more advanced clinical rotations. It creates a common knowledge base among learners, promoting consistency in education and assessment. The foundation course

also offers an opportunity for learners to acclimate to the learning environment, develop study skills, and establish a professional identity. It helps learners transition from a primarily theoretical focus to practical application and clinical reasoning.[14]

### Other important facets of CBME

i) Leadership qualities such as effective communication, decision-making, collaboration, and advocacy are integrated into the competency framework. Learners are encouraged to develop leadership skills to lead healthcare teams, influence healthcare policy, and promote patient advocacy.[15]
ii) Learners are exposed to team-based care models, where they work alongside professionals from various disciplines to provide comprehensive patient care. This approach promotes effective communication, shared decision-making, and mutual respect among healthcare team members.[16]
iii) CBME acknowledges the value of mentorship program in supporting learners' personal and professional growth. Mentorship programs connect learners with experienced practitioners who guide, inspire, and provide valuable feedback. Mentors help learners navigate their educational journey, offer career guidance, and provide role modeling to shape learners' professional identities.[17]
iv) Family adoption is an integral aspect of CBME that recognizes the importance of the patient's social context. Learners are encouraged to understand and acknowledge the impact of a patient's family, cultural background, and social support systems on their healthcare experience. By adopting a family-centered approach, medical professionals can provide holistic and patient-centered care.[18]

## CHALLENGES AND CONSIDERATIONS

### Resistance to change and faculty buy-in

Implementing CBME often requires a significant shift in educational philosophy, curriculum design, and assessment methods. Faculty members and stakeholders may resist change due to concerns about increased workload, unfamiliarity with new approaches, and the need for faculty development. Gaining faculty buy-in and addressing their concerns through effective communication and faculty development programs is crucial for successful CBME implementation.[19]

### Standardization versus individualization

Balancing the need for standardization and consistency in competencies while accommodating individual learner differences can be challenging. CBME aims to develop core competencies, but learners may have diverse educational backgrounds and learning styles. Striking a balance between standardization and individualization requires careful curriculum design, personalized learning plans, and assessment strategies that account for individual learner needs.[19]

### Assessment methods and validity

CBME relies on a variety of assessment methods to evaluate learners' competencies. Ensuring the validity, reliability, and fairness of these assessments can be complex. Developing robust assessment tools, training assessors, and maintaining consistency in the application of assessment criteria are essential to ensure accurate evaluations of learners' progress and readiness for independent practice.[20]

### Resource implications and workload

Implementing CBME may require additional resources, including faculty time, educational infrastructure, and technology support. The transition to CBME can increase the workload for educators due to the need for more frequent assessments, individualized learning plans, and feedback provision. Adequate allocation of resources and careful planning can help mitigate these challenges.[21]

### Integration into existing educational systems

Embedding CBME within existing educational systems and accreditation frameworks can be challenging. CBME may require modifications to existing curricula, assessment methods, and accreditation standards. Collaboration with regulatory bodies, accreditation agencies, and educational institutions is necessary to ensure alignment with existing structures and promote the recognition of CBME programs.[22]

### Learner and faculty training

CBME requires appropriate training for learners and faculty members to understand the principles, competencies, assessment methods, and learning processes associated with CBME. Providing comprehensive training programs and ongoing support is crucial to equip learners and faculty with the necessary knowledge and skills to navigate CBME effectively.[21]

### Equity and inclusivity

It is important to ensure that CBME implementation does not inadvertently exacerbate existing disparities and inequities. Attention should be given to equity, fairness, and inclusivity in assessment practices, support for underrepresented learners, and addressing potential biases that may arise during the assessment and evaluation processes.[22,23]

## FUTURE DIRECTIONS

### Continuous refinement of competency frameworks

Regular review and updates of competencies will ensure that learners are equipped with the knowledge, skills, and attitudes required for contemporary medical practice.[24]

### Integration of technology and innovative assessment methods

Virtual reality simulations, online platforms, and mobile applications can enhance assessment accuracy and efficiency. Technology-driven tools will support competency tracking, feedback provision, and personalized learning experiences for learners.[25]

### Collaboration and sharing best practices

Collaboration can facilitate the development of standardized assessment tools, promote faculty development initiatives and foster the exchange of successful strategies for curriculum design and learner support.[7]

### Research and evaluation of CBME effectiveness

Ongoing research and evaluation will be vital to assess the effectiveness and impact of CBME on learner outcomes, patient care, and healthcare systems.[25]

### Ensuring equity and inclusivity in CBME implementation

Efforts should be made to address potential biases and disparities in assessment and support systems. Strategies should be developed to ensure equal opportunities for learners from diverse backgrounds and to promote inclusivity in competency development and assessment processes.[18]

## CONCLUSION

CBME is a learner-centered approach that has gained recognition and adoption worldwide. It offers numerous advantages, including outcome-focused education, individualized learning, improved assessment and feedback, alignment with evolving healthcare needs, promotion of lifelong learning, and enhanced patient care and safety. CBME is built on key principles such as competency frameworks, integration of theory and practice, assessment and feedback emphasis, individualized learning pathways, and promotion of lifelong learning. The impact of CBME is far-reaching, benefiting learners, patients, and the healthcare system. Learners experience clear expectations, personalized learning plans, and increased engagement. Improved patient care and safety result from the production of competent physicians. Advancements in assessment and feedback methods provide comprehensive evaluations. CBME supports professional identity formation and fosters consistency and collaboration in medical education. Future directions for CBME include refining competency frameworks, integrating technology and innovative assessment methods, promoting collaboration among institutions, conducting research and evaluation, and ensuring equity and inclusivity in implementation. With ongoing research, collaboration, and evaluation, CBME can continue to evolve and effectively prepare healthcare professionals to meet the evolving needs of patients and healthcare systems.

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There are no conflicts of interest.

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Review Article

# An insight on chronopharmacology and its application in pharmacotherapy

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## Abstract

Numerous pathophysiological conditions change over the course of a day. The biological rhythms that many physiological processes go through include the sleep-wake rhythm and metabolism. Chronopharmacology is a branch of science that studies the effects of various treatments on internal balance and biological timings. Chronopharmacology can aid with drug dose optimization problems, such as enhancing effectiveness or minimizing side effects. The metabolic fate of a pharmaceutical substance in a human is not stable throughout time. Thus, there is growing interest in chronotherapeutics in the fields of experimental biology, medicine, pharmacy, and medication delivery. Utilizing the timing of medicine consumption, this knowledge and the abundance of data should be used wisely to maximize the drug's safety and efficacy. The goal of optimizing pharmacotherapy in accordance with the fundamental principles of clinical pharmacology is to maximize methodological individualism, assuring the highest level of efficacy and security for the patient's treatment. This essay provides a succinct review of chronopharmacology, including its several subfields, the effects it has on the body's various systems, and a general explanation of chronopharmacotherapeutics.

**Keywords:** Chronopharmacology, chronopharmacotherapeutics, chronotherapy, circadian rhythm

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## INTRODUCTION

The field of chronobiology known as chronopharmacology studies how medications affect the timing of biological processes, phases associated with biological scheduling, and innate periodicities that affect pharmacological effects. The body's circadian rhythm can be used to forecast a drug's pharmacological effects when it is given. It is conceivable to associate with both time and bodily activities. The maximum efficacy and least amount of toxic effects of a drug can be accomplished if it is given at the proper time, hat is, the correct medication in the correct form at the correct dose at the correct time. This is similar to how sleep - awake, feed appetite, happiness, and depression are controlled by biological clocks. Therefore, the medication works in concert with the biological clock.[1]

Circadian Rhythm: Because of the fact that the primary supply of sunlight and energy on Earth is sporadic, animals quickly evolved physiological functions to take advantage of these changes. These clocks are referred to as "circadian"

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collectively (Latin circa Diem—about a day). A creature's circadian rhythm, often known as a natural mood, is defined as movements that occur on a 24-hour cycle in its instinctual, physiologic, and social functions. Circadian rhythms are spontaneous in origin and have been shown to persist in unrestrained settings. All of the key organ systems in mammals are influenced by circadian clocks, and this influence directly affects disease pathology, which also fluctuates with the time of day.[2]

## Chronopharmacology-related fields of study

- Chronotherapeutics
- Chronokinetics
- Chronesthesy
- Chronergy[3]

## Chronotherapeutics

The finding that every metabolic event experiences rhythmic fluctuations in time is essentially what this refers to. It is predicated on the discovery that many medications' pharmacokinetics and pharmacologic sensitivities have an important association with the peak-to-trough periodic action in clinical manifestations and co morbidities. It is becoming abundantly evident that the precise moment that patients take their prescription may be much more important than was previously thought as more is discovered about chronobiology and chronotherapeutics. Studies discovered that some therapies may perform effectively if their administration is synchronized with day-night trends and circadian rhythm. Traditionally, medications have been prescribed at regular intervals across the day in an attempt to keep consistent drug concentration over the course of a 24-hour cycle.[4]

## Chronopharmacokinetics

Chronopharmacokinetics is the study of how drugs are absorbed, distributed, metabolized, and excreted over time. Circadian variations in liver enzyme activity, gastrointestinal blood flow, gastrointestinal motility, and drug protein binding. Over the past 20 years, many chronopharmacokinetic investigations have been carried out. These studies' findings show that medication kinetics is influenced by the timing of administration. There have been studies conducted on humans, especially in the areas of cardiovascular pharmaceuticals, nonsteroidal anti-inflammatory drugs (NSAIDs), local anesthetics, anticancer treatments, psychiatric drugs, antibiotics, and anti-asthmatic drugs. The majority of medications appear to have a greater rate or degree of bioavailability in the morning than in the evening.

## Chronotoxicology

It is a feature of chronodynamics; it specifically relates to the timing of dosing, that is, rhythm dependent variations in the symptoms and intensity of side effects and therefore hypersensitivity of patients to treatment. Circadian is derived from the Latin words circa, which means "around," and dian, which means "day." The most significant biological rhythms for both humans and animals are circadian rhythms. They are crucial for regulating the levels of neurotransmitters, hormones, enzymes, electrolytes, and glucose as well as for maintaining the body's temperature, heart rate, blood pressure, organ blood flow, lung, and kidney functioning. Pharmacotherapy benefits from studying rhythms.[5]

## Chronesthesy

The cyclic "changes in the vulnerability or sensitivity of a target system" are explained by chronesthesy. In that it deals with the physiological and biochemical changes brought on by a medicine based on the time of administration, chronesthesy is in many respects comparable to the area of pharmacodynamics. Ultimately, the discipline of chronesthesy believes that modifications that take place at the molecular level frequently cause differences in how well a medicine works. For instance, modifications in the degree of membrane permeability or modifications in how the cell membrane reacts to chemicals used in cellular communication (i.e., receptors on the surface of brain cells) occur over generally anticipated time periods.[6-11]

## Chronergy

This field of research considers both how the time of day may affect a drug's effects as well as how the drug themselves may affect an organ's biological rhythm. In order to evaluate how a drug affects a person as a whole, chronergy, then, synthesizes data from chronopharmacokinetics and chronesthesy. Although it receives relatively lesser attention in the literature currently in circulation, this subject is gradually becoming one of the more well-liked subspecialties of chronopharmacology.[12-15]

## Diseases displaying circadian rhythm

### *Allergic rhinitis*

The symptoms of allergic rhinitis include weariness, daytime drowsiness, and sleep problems. The quality of sleep may be hampered by these symptoms. The nasal obstruction that results in sleep-disordered breathing is to blame for the sleep disturbances associated with rhinitis. It is believed that nighttime and early morning hours are the worst for the harshness of nasal decongestion.[16]

### *Bronchial asthma*

A relatively well-known illness where a significant amount of circadian variation occurs is asthma. Early in the

morning, asthma cases are more prevalent. In the evening, asthma symptoms can occur 50 to several times more frequently.[17]

Exaggerated lung dysfunction and hyper responsiveness of the airways occur at night and in the early hours of the morning. This is because nighttime bronchoconstriction is supported by circadian shifts in the neurotransmitters epinephrine, AMP (adenosine monophosphate), histamine, and other inflammatory mediators, cortisol, vagal tone, body temperature, and lower airway secretions.[18]

### *Peptic ulcer disease*

Numerous components of the digestive system are subject to diurnal cycles; erosive gastric discharge is more prevalent in the evening. Around dusk, stomach motility, little inner motility, and gastric exhaustion all slowdown.[19] Between 22:00 and 02:00, stomach acid output is 2–3 times higher than during the day. additionally, eating and drinking trigger the creation of stomach acid right away. Heartburn symptoms during the day occur from acid secretion driven by meals, whereas those during the night are brought on by the circadian rhythm of gastric acid secretion, which peaks at night. The 24-hour cycle of the peptic ulcer illness is present, as are once a week and yearly cycles.

### *Stroke*

Comparable to other cardiovascular events, the incidence of stroke is highest right after rising in the early morning and lowest during midnight sleep. Since a major number of these can have fatal or serious effects, the prevalence of cardiovascular disorders such as severe myocardial localized necrosis, strokes, and arrhythmia also exhibits a definite diurnal movement.[20]

### *Rheumatoid arthritis*

Arthritis symptoms and clinical indications change throughout time. Early in the morning is when arthritis symptoms such as stiffness and discomfort in the joints are most noticeable. This is caused by the circadian rhythmicity of proinflammatory cytokine production, which peaks at night and early in the morning when cortisol (an anti-inflammatory hormone) is lowest and melatonin (a proinflammatory hormone) is highest. additionally, sex hormones influence the circadian rhythms of arthritis. The luteal phase, when estrogen and progesterone production is greater than in the follicular phase, is when the symptoms are most prevalent.[21]

### *Diabetes mellitus*

Diabetes is a condition where insulin's circadian timing and evolution are of physiologic relevance and clinical significance. In this method, insulin is released in a pulsatile fashion; occasionally, though, it is periodic. Insulin's circadian cycle, which lasts 8–30 min, can show off its ideal action. In a circadian example, the modulators of insulin release and activity are released and draw the insulin release mechanism. Therefore, the differential between the highest and lowest levels of plasma insulin fixation has a temporary rhythmicity, and complicated alternative circadian harmony is variable insulin obstruction in the early morning and late at night.[22]

### *Cancer*

When tumors are small and growing most swiftly as well as when they are larger and growing more slowly, the rhythm circadian variations in the tumor circulation and malignant growth development are crucial. Tumor cells may be particularly vulnerable to the drug's pharmacologic and pharmacokinetic features, rhythmic variations in DNA and RNA synthesis, RNA translational activity, and mitotic migration. It has been found that the illness chronogenetic therapy is effective at hiding tumors *in vivo*. for example, it has been proven that CLOCK characteristics influence how the anticancer drug cyclophosphamide acts.[23,24]

### *Significance of chronopharmacotherapy*

Chronopharmacology is necessary to evaluate the course of treatment in order to shorten the duration, especially when patients have already compromised the kidneys, heart, liver, or other organs. Any kind of medicine accumulation in these organs results in more significant injury, which could lead to an organ's functioning being reduced. In this way, chronopharmacotherapy becomes a crucial component of the treatment of some infections, particularly those that target specific body areas.[25]

## Applications of chronopharmacotherapy

### *Allergic rhinitis*

Non-sedative anti-histaminic medications are taken before night to control the worsening during sleep because rhinitis is most severe in the morning and evening. For severe allergic rhinitis, oral corticosteroid therapy can be administered in the morning.

### *Bronchial asthma*

Asthma risk is greater at night and in the early morning hours. Consequently, a formulation for sustained release of:

- Theophylline is administered at night as it improves the drug's effectiveness, lessens its toxicity, and aids in avoiding repeated doses.
- Use of cholinergic antagonists such as Ipratropium bromide during the night can reduce high nocturnal cholinergic activity caused by vagus nerve hyperactivity.

- To enhance their effectiveness, corticosteroids should be taken during the day, around 5:30 pm
- Zileuton, a leukotriene receptor antagonist, should be used at night because it was discovered that LTB4 (Leukotriene B4) concentration was at its highest then.

*Peptic ulcer disease*

H2 receptor blockers such as ranitidine and famotidine are preferentially administered in the evening since nighttime is when peptic ulcer disease pain, acid secretion, and ulcer perforation are at their peak.

*Arthritis*

Rheumatoid arthritis symptoms are stronger in the morning, but osteoarthritis symptoms are much worse at night and less severe in the morning. As a result, NSAIDs such as ibuprofen, ketoprofen, and indomethacin are administered at night to people with rheumatoid arthritis while they are given in the morning to people with osteoarthritis.[26]

*Cardio vascular disorders*

Because of more physical activities, higher catecholamine action, enhanced platelet aggregation, elevated vascular tone, and greater thrombolytic activity, the blood pressure is often 20% higher right after awakening.[27] In order to treat hypertension, new COER Verapamil (controlled onset extended release) is used. It is designed precisely that when taken before bed, it dissolves gradually and works best between the hours of 5 and midday. additionally, there is no drop in blood pressure during nighttime. ACEIs (Angiotensin Converting Enzyme Inhibiters), such as doxazosin and ramipril, are used before bedtime instead of using in the morning.

*Diabetes mellitus*

Patients with diabetes mellitus frequently have morning hyperglycemia. These two phenomena can be used to explain this

- Dawn phenomenon and,
- The Somogyi phenomenon.
  a) Dawn phenomenon: This is characterized by persistently elevated glucose levels preceding breakfast in the morning. Usually, it happens between 3 and 5 O' clock in the morning. This is brought on by an upsurge in growth hormone production, which has hyperglycemic effects while patients sleep.[28]
  b) The Somogyi effect: The syndrome is also known as rebound hyperglycemia. It refers to hypoglycemia, which is low blood sugar at night followed by high blood sugar in the morning. Because of some hormones' insulin-antagonistic effects, particularly those from the hypothalamic-pituitary-adrenal axis, hypoglycemia is followed by hyperglycemia. Long acting or too much insulin is the main cause. During the evening or at bedtime, glucose levels will be relatively low to insulin, but later, as growth hormone, cortisol, and catecholamine levels rise, hyperglycemia will result. As a result, regulated release insulin (insulin pumps) should be chosen or used when there is a higher risk of hyperglycemia. It is important to take precautions to prevent insulin from peaking at the inappropriate time or in the midst of the night.[29]

*Cancer*

Cancer cells have different biological cycles than normal cells. At roughly 2 am, the tumor cells develop quickly, and by 10, they grow slowly. Drugs are recommended based on:

- The length of the cell cycle phase
- Cell proliferation rate
- Colorectal cancer: Oxaliplatin is given for colorectal cancer during the day, whereas 5-Floruracil is given at night.
- Breast cancer: The later part of the menstrual cycle is chosen for the treatment of these solid tumors because it has a higher success rate than the earlier half. The cancer-spreading enzymes are inhibited by progesterone, which is secreted in the second half of the cycle. At night, cyclophosphamide toxicity was lower and cure rates were higher. This means that by carefully choosing the time of administration, the therapeutic index can be maximized.[30]

## Advantages of chronopharmacotherapy

1. It prevents an overdose from occurring with any kind of medication.
2. By guaranteeing that drug use is appropriate, it raises the value of a medication.
3. It minimizes the drug's side effects and aids in the patients' short-term adherence to therapy.[31]

## Disadvantages of chronopharmacotherapy

1. As the individual dosages are given for more than 24 h during the treatment, it develops a non-24 h rest wake disorder following the treatment. It is not precisely typical; rather, it is unknown how dangerous it is.
2. A person could occasionally be denied sleep as well.
3. The person seems to be less effective throughout chronotherapy, and it may be challenging to maintain attention until the other schedule.
4. The patient must have a break from their hectic schedule because their treatment will take some time.

5. This treatment requires therapeutic monitoring, and usual rest professional counselling is advised.
6. The person must continue to keep themselves awake until the subsequent rest plan, thus he needs to occupy himself with anything to ensure that he stays awake until the subsequent calendar.
7. Patients may occasionally experience oddly hot or cold sensations.
8. To avoid responses, the patient must regularly consult the specialist.[32,33]

## CONCLUSION

The practice of medicine requires an understanding of circadian rhythms (24-hour cycles). Most medical illnesses appear and worsen in predictable ways depending on the timing and intensity of major physiologic and biochemical circadian rhythms. The basis for chronotherapeutics is rhythmicity in the pathogenesis of diseases. The steadily expanding discipline of chronopharmacology has provided several openings for creative work that will help to structure better systems for adjusting and managing the treatment of numerous disorders. The major goal of this article is to promote chronopharmacology research for better medical care using already known active medications, as well as chronopharmacotherapy as a practical need for treating various diseases.

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Original Article

# Cutaneous manifestations of diabetes mellitus: Correlation with HbA1C level—A cross-sectional observational study from a tertiary care center in Eastern India

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## Abstract

**Background:** Diabetes mellitus (DM) is a common and debilitating endocrinological disease that affects a variety of organs, including the skin. Between 30% and 70% of patients with DM, both type 1 and type 2, will present with a cutaneous complication at some point during their lifetime. A variety of dermatologic manifestations have been linked with DM; these conditions vary in severity and can be benign, deforming, and even life-threatening. Such skin changes can offer insight into patients' glycemic control and, indirectly, their HbA1C levels. It may be the first sign of metabolic derangement in undiagnosed patients with diabetes.

**Objectives:** Statistically correlate HbA1C value with glycemic control using cutaneous manifestations of DM. To classify the severity of DM by taking into account certain cutaneous manifestations.

**Materials and Methods:** Consecutive 103 diabetic patients attending dermatology outpatient department of a tertiary care hospital in Kolkata were included in the study. History regarding duration and type of DM, control of diabetes, and drug history were taken. Patients underwent thorough dermatological examinations to evaluate the skin disorder. Appropriate routine and laboratory investigations were done. Relevant microbiological and histopathological examinations were carried out in atypical and doubtful cases to confirm the diagnosis. Data were recorded and analyzed.

**Results:** Out of 103 diabetic patients included in the study, 59 (57.3%) were male, and 44 (42.7%) were female, of which 89 patients had cutaneous manifestations associated with DM. We have noticed a significant correlation between certain types of skin manifestations and HbA1c values. The fungal infections were seen among mid (8.0–9.5) and low (6.5–8.0) HbA1c ranges. Most of the cases of xerosis and associated pruritus had HbA1c levels in the mid range. Vitiligo, nail changes, and systemic complications were mostly seen among HbA1c values in the mid and high range (9.5–11). In our study, there was a strong association of HbA1c value with the duration of diabetes ($P = 0.001$), diabetic dermopathy ($P = 0.012$), and systemic complications of DM ($P = 0.027$). Acanthosis nigricans ($P = 0.016$), nail changes ($P = 0.041$), and fungal infection ($P = 0.032$) also showed a significant association with HbA1c values. A statistically weak association was observed with bacterial infection ($P = 0.362$), xerosis ($P = 0.487$), lichen planus ($P = 0.066$), and vitiligo ($P = 0.778$).

**Conclusion:** DM is the commonest endocrine disorder that frequently accompanies skin manifestation. Recognition of clinical features of DM is important as delayed detection is associated with comorbidities like coronary artery disease, hypertension, and dyslipidemia; until recently, dermatologists were of the opinion that diabetic ulcers were the only skin manifestation that predated its development but studies have shown that there are many more cutaneous manifestations specific to DM. These manifestations appear earlier than the systemic manifestations and, if recognized, can help in the early diagnosis of DM. Cutaneous manifestations can serve as a predictor for the long-term glycemic control of patients and help endocrinologists in preventing the grave complications of a silent killer like diabetes.

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**Limitations:** A small sample size compromised the external validity of the study. The study was conducted in a tertiary care center and was thus not representative of the situation in the field.

**Keywords:** Cutaneous, diabetes, glycemic, HbA1C, patients

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## INTRODUCTION

Diabetes mellitus (DM) is one of the most common endocrine disorders that pose a significant burden on patients, health care system, and society.[1] At least 30% of the patients suffering from diabetes are affected by different types of cutaneous disorders throughout the course of the disease.[2] Individuals with type 2 diabetes are more likely to acquire cutaneous manifestations compared to type 1 diabetes.[3] Cutaneous features can present as the first sign of diabetes or can manifest at any time during the course of the disease. Long-term duration of DM causes permanent and irreversible functional changes and cause damage to body cells. It can lead to problems arising from biochemical, structural, and functional irregularities.[2] Cutaneous complications of diabetes can provide a clue to the current and past metabolic status of the patient.[4] At times, evaluation of skin disorder leads to a diagnosis of underlying diabetes. In a known patient with diabetes, cutaneous manifestations can also provide warning signals regarding possible systemic involvement. Moreover, certain skin changes might appear in a certain degree of severity of diabetes. Common skin infections like staphylococcal and streptococcal infections tend to be more severe in diabetic patients.

The cutaneous manifestations of DM can be classified into four subtypes: (a) cutaneous disease with weak to strong association with DM, (b) cutaneous infections, (c) cutaneous manifestations due to DM complications, and (d) cutaneous reactions due to DM treatment.[4] The exact pathogenesis of most of the dermatoses is unknown. It is assumed that vascular and connective tissue alterations, immune system impairment, and associated metabolic alterations play an important role in pathogenesis.

## AIMS AND OBJECTIVES

- Statistically correlate HbA1C value using cutaneous manifestations of DM.
- To classify the severity of DM using its cutaneous manifestations

## MATERIALS AND METHODS

Consecutive 103 diabetic patients attending dermatology outpatient department (OPD) of a tertiary care hospital in Kolkata were included in the study. The data was collected for a duration of 1 year, from May 2021 to June 2022. All diabetic patients of either sex who have expressed willingness to participate in the study through written informed consent were included. Patients suffering from acquired immunodeficiency deficiency Syndrome, who have congenital/acquired immunodeficiency syndromes and receiving immunosuppressive medications, nondiabetic, or patients with gestational diabetes or with impaired glucose tolerance were excluded from the study. History regarding duration and type of DM, control of diabetes, and drug history were taken. Patients underwent through a dermatological examination to evaluate the skin disorder. Assessment of diabetic retinopathy was done by an ophthalmologist. Diabetic neuropathy was assessed using Foster criteria.[5] Appropriate routine and laboratory investigations were done. Relevant microbiological and histopathological examinations were carried out in atypical and doubtful cases to confirm the diagnosis. Digital photographs were taken of all patients willing to be photographed. Data regarding fasting, postprandial blood glucose levels, and HbA1C levels were recorded. The data were tabulated, and statistical analysis was done by MedCalc for Windows software, version 20.009 (MedCalc Software, Ostend, Belgium).

## RESULTS AND ANALYSIS

### Demographic profile

Out of 103 diabetic patients included in the study, 59 (57.3%) were male and 44 (42.7%) were female, of which 89 patients had cutaneous manifestations associated with DM [Table 1].

The age of the patients range from 11 years to 84 years, with a mean age of 48.97 and a standard deviation of 17.50. Most of the cases are between 41 and 60 years ($n = 43$) [Table 2].

**Table 1: Relationship between the number of diabetic patients with gender**

| Sex | Number of diabetic patients ($n$ = 103) as per cutoff value HbA1c 6.5% or above | Number of patients with diabetic dermatoses | Percentage of diabetic patients ($n$ = 103) |
|---|---|---|---|
| Male | 59 | 51 | 57.3 |
| Female | 44 | 38 | 42.7 |

**Table 2: Relationship between the number of cases with age of patients (years)**

| Minimum | Maximum | Mean | Standard deviation |
|---|---|---|---|
| 11 | 84 | 48.97 | 17.50 |

**Table 3: Relationship between the number of diabetic patients with duration of disease (years)**

| Minimum | Maximum | Mean | Standard deviation |
|---|---|---|---|
| 1 | 26 | 12.07 | 7.08 |

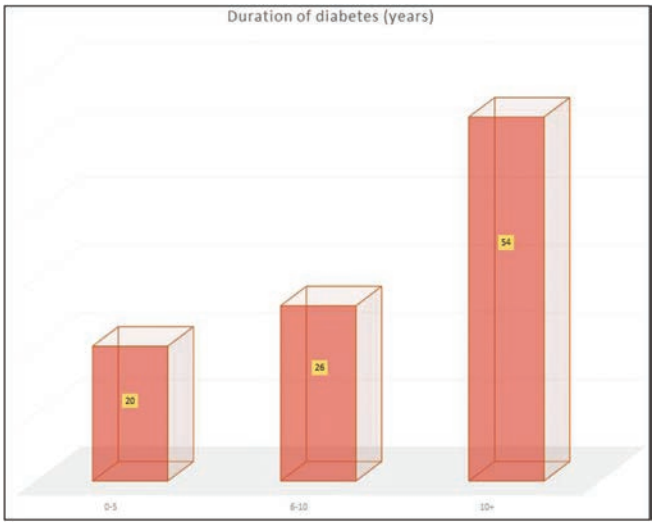


**Figure 1:** Bar Graph showing relation number of patients and duration of diabetes. Most of the cases (n=54) had diabetes from a longer duration (> 10 years).

Duration of diabetes range from 1 year to 26 years, with a mean duration of 12.07 years and a standard deviation of 7.08. Most of the cases ($n$ = 54) are of longer duration (10+ years) [Table 3, Figure 1].

## Range of cutaneous manifestations observed in study subjects

Amongst the myriad skin presentations that we have encountered in this study, the most common was fungal infections ($n$ = 43), seen in 41.73% cases. Tinea was the most common fungal infection encountered (23.3%), followed by candidal balanoposthitis and vulvovaginitis (14.56%). Xerosis and pruritus were the second most common presentation in our study samples ($n$ = 23; 22.33%). Bacterial infection was seen in 19 cases (18.44%); these cases were predominantly folliculitis, cellulitis, furunculosis, and impetigo. Acanthosis nigricans was seen in 16 cases (15.55%), and 11 cases (10.67%) had acrochordon. In most of the cases, these two conditions coexisted. Nine cases had nail changes like pitting, ridging, and onychoschizia. Diabetic dermopathy was observed in eight cases. Lichen planus was seen in four cases and vitiligo in nine cases. Overall, 72% patients had more than one cutaneous manifestations of diabetes. Among the systemic complications of DM, diabetic nephropathy was seen in three cases, retinopathy was seen in two cases, and two cases had diabetic neuropathy. Perforating dermatoses were seen in two cases. Among the treatment-related complications, insulin injection site lipoatrophy was observed in one case [Figure 2].

## Classification of diabetic skin manifestations according to the HbA1c value

The HbA1C values of all diabetic patients were recorded and classified according to their skin manifestations. This is to understand at which HbA1c value and what type of

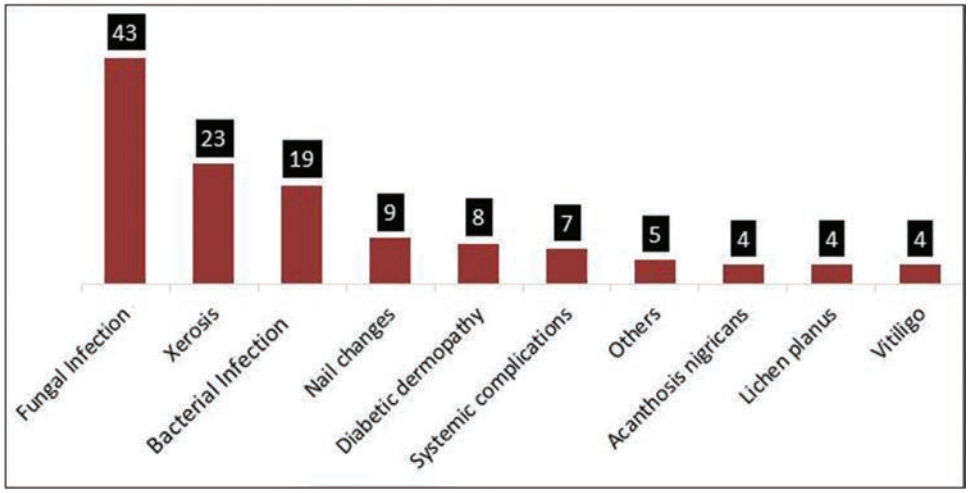


**Figure 2:** Bar Graph showing range of cutaneous manifestations observed in diabetic patients.

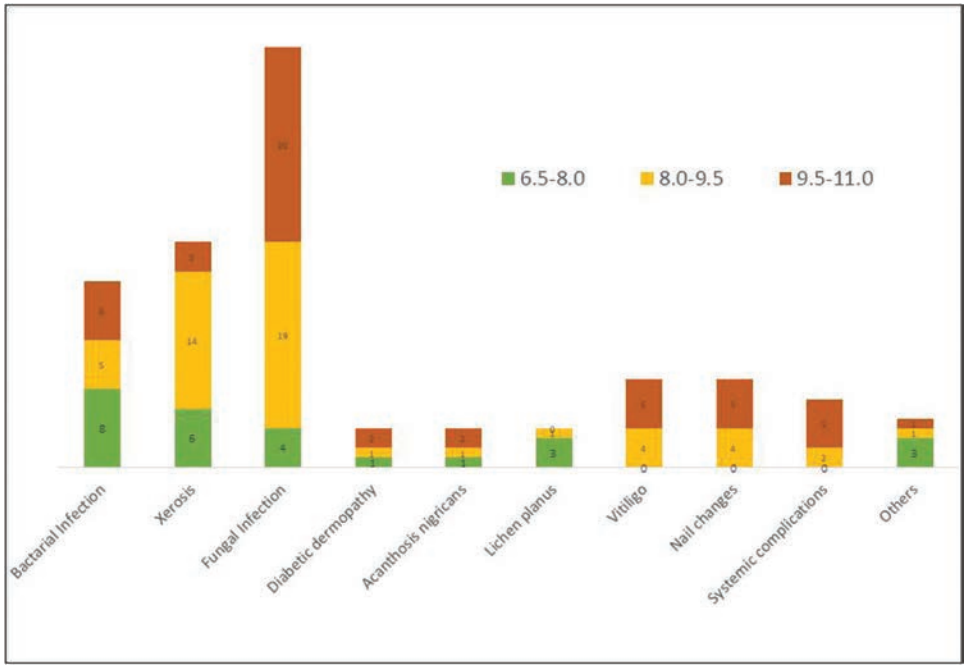


**Figure 3:** Bar Graph showing classification of diabetic skin manifestation according to HbA1C values.

cutaneous features are seen. For the classification, the entire range of HbA1c values was arbitrarily divided into a lower range of 6.5%–8.0%, a mid-range of 8.0%–9.5%, and a higher range of 9.5%–11.0%. We have noticed a significant correlation between certain types of diabetic skin manifestations and HbA1c values. The fungal infections were mostly seen among mid and low HbA1c range. Among the 43 cases with fungal infections, 20 cases had HbA1c values in the range of 9.5%–11.0% and 19 cases had HbA1c between 8.0% and 9.5%. Most of the cases of xerosis and associated pruritus ($n = 14$) had HbA1c levels between 8.0% and 9.5%. Vitiligo, nail changes, and systemic complications were mostly seen among HbA1c values in the mid and high range. Among the nine cases with vitiligo, five cases had HbA1c values between 9.5% and 11.0%, and in four cases in the range of 8.0%–9.5%. Systemic complications like diabetic neuropathy, retinopathy, and nephropathy were observed in seven cases. Among them, five cases had HbA1c values within 9.5%–11.0%, and two patients had in the range of 8.0%–9.5%. Nail changes were seen in nine cases, and among them, five cases had HbA1c values between 9.5% and 11.0%. Four cases had HbA1c within 8.0%–9.5% [Figure 3].

## Strength of association between HbA1c values and different diabetic skin manifestations

Using null-hypothesis significance testing, the strength of the association between different cutaneous manifestations of DM and HbA1c values was compared. The *P*-value was calculated for each parameter. A *P*-value of less than 0.05 was taken as statistically significant.

In our study, there was a strong association of HbA1c value with the duration of diabetes ($P = 0.001$), diabetic dermopathy ($P = 0.012$), and systemic complications of DM ($P = 0.027$). Acanthosis nigricans ($P = 0.016$), nail changes ($P = 0.041$), and fungal infection ($P = 0.032$) also showed a significant association with HbA1c values.

A statistically weak association was observed with bacterial infection ($P = 0.362$), xerosis ($P = 0.487$), lichen planus ($P = 0.066$), and vitiligo ($P = 0.778$).

## Relationship between severity of diabetes and duration of the disease

The severity of diabetes was estimated using HbA1c values and compared against the duration (in years) of patients are suffering from the disease. The plot shows as the duration of diabetes increases, and the HbA1c value also tends to increase [Figure 4]. This signifies the importance of early diagnosis and appropriate treatment to limit the multisystem involvement of DM.

## Prediction of severity of diabetes by clinical observation

HbA1c value can be predicted based on clinical observation of various parameters like duration of diabetes, different cutaneous manifestations, nail changes, etc. We have seen in *P*-value null-hypothesis significance testing there are strong associations between certain parameters that might predict the value of HbA1c before the laboratory testing. With a high *R*-square value, the HbA1c predicted value could be used as a tool for level 1 screening.

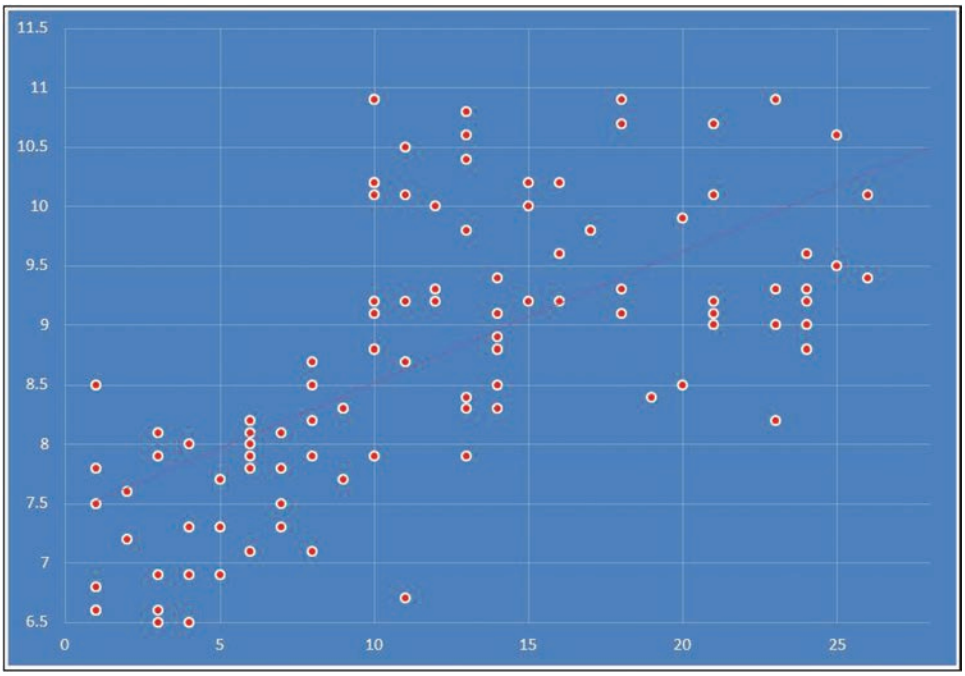


**Figure 4:** Scatter diagram showing relationship between severity and duration of diabetes. The plot shows as the duration of diabetes increases the HbA1c value also tends to increase.

| variables | Coefficients |
|---|---|
| Duration (d) | 0.09 |
| Fungal Infection (FI) | 0.56 |
| Diabetic dermopathy (di) | 0.30 |
| Acanthosis nigricans (An) | 0.65 |
| Nail changes (Nc) | 0.75 |
| Systemic complications (Sc) | 0.55 |
| Intercept (c) | 5.25 |
| **R – square value** | **0.83** |

**Figure 5:** The diagram shows the coefficient of the HbA1c predictive model.

The HbA1C value can be predicted with a linear regression modeling that could be built with statistically significant parameters. The diagram below shows the coefficient of the HbA1c predictive model [Figure 5].

$$HbA1c(H)(predicted) = 0.09 * d + 0.56 * FI + 0.30 * di + 0.65 * An + 0.75 * Nc + 0.55 * Sc + 5.25$$

The residual plot shows predicted HbA1c values determined by a linear regression model. The predicted HbA1C values show a close association with the actual observed values [Figure 6].

## DISCUSSION

The purpose of our study is to predict the severity of DM using HbA1C value from the cutaneous manifestations of the disease and to classify different skin manifestations of diabetes according to the severity of the disease. The result of our study confirmed our hypothesis that the severity of diabetes could be assessed in terms of HbA1C level just by observing cutaneous manifestations of the disease.

In our study sample, type 2 diabetes patients were far common as compared to type 1 patients, which is usually seen in most of the random diabetic patient sample.[6] The most common age group involved in our study was 41–60 years, similar to that seen in a study by Bhat *et al.*[7] Cutaneous manifestations associated with diabetes were seen in 86% of total diabetic study samples, and it is a relative consistency between our study and some other previous studies.[8,9] A review of various kinds of literature suggests a wide variety of prevalence for different skin manifestations of DM. In our study, cutaneous infections were the most common finding, which supports the finding of the study conducted by Furquan *et al.*[10] on 100 patients with type 1 and type 2 diabetes. Fungal infection was most common amongst our study patients, followed by bacterial infections. Raghu *et al.*, Timshina *et al.*, Bhat

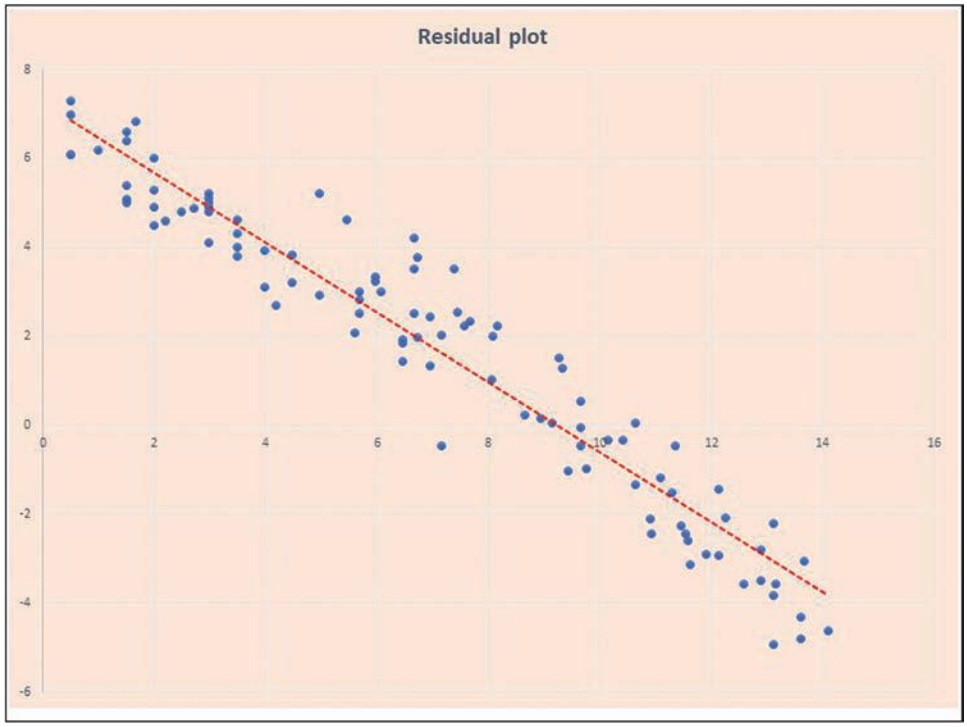


**Figure 6:** The residual plot shows predicted HbA1c values determined by linear regression model. The predicted HbA1C values show a close association with the actual observed values.

*et al.*, Raghunatha *et al.*, Al-Mutairi *et al.*, and Abhishek *et al.* showed that fungal infections were the commonest which was similar to this study.[11] A study conducted by Khurshid *et al.* and Rajendra *et al.* revealed bacterial infections more commonly than fungal infections, which were seen in 160 (64.5%) and in 67 (19%) patients.[12] Xerosis and pruritus were the second most common finding in our study, seen in 22% cases which is also similar to the study done by Rao and Pai.[6] In a study conducted by Chatterjee *et al.*,[13] 67% patients have more than one cutaneous manifestations of DM. In our study, 72% showed more than one skin manifestations linked to diabetes. In a descriptive study by researchers to investigate the effect of DM control on the occurrence of cutaneous manifestations among 500 diabetic patients, there was no statistically significant difference in patients in terms of age, gender, DM duration, and fasting plasma glucose.[14] However, in another study, a statistically significant association was observed between cutaneous manifestations and DM duration.[15] Also, according to the results of an observational study done by Shahzad *et al.* on 320 diabetic patients, in patients who had less than 5-year DM duration, the prevalence of cutaneous manifestations was 80%, whereas in patients with more than 5-year duration, the prevalence of skin manifestations rose to 98%, and this difference was statistically significant ($P < 0.001$).[16] A study was done by Bhat *et al.*, Raghunatha *et al.*, Mahajan S *et al.*, Al-Mutairi *et al.*, Neerja, Mahmood *et al.*, showed a lesser number of patients under the category of dermatoses which are commonly associated with diabetes.[17-19] Nail changes were seen in nine cases in our study, mostly pitting, ridging, and onychoschizia, and it had a strong association with HbA1c value. Dermatoses associated with increased risk of DM, like vitiligo, lichen planus, and perforating dermatoses, were observed in our study and have also been reported in the previous study.[19] Vitiligo in DM can occur as a result of multiple autoimmune dysfunctions. In our study, systemic complications of diabetes like diabetic neuropathy, retinopathy, and nephropathy were observed in seven patients, and a strong association was observed among these systemic complications with the severity of diabetes. Also, the severity of diabetes, as represented by HbA1c level, tends to be higher with a longer duration of the disease.

Interestingly, in our study, certain cutaneous manifestations like fungal infections, acanthosis nigricans, nail changes, and diabetic dermopathy showed a strong correlation with HbA1c values. The regression analysis using these parameters showed the statistically predicted HbA1c value correlating with the actual observed HbA1c values, thus enabling the physician to gauge the severity of DM from the evaluation of the cutaneous manifestations of the disease.

## CONCLUSION

DM is a common endocrine disorder that frequently presents with a wide variety of cutaneous manifestations.

Often these cutaneous manifestations present well before any systemic manifestations and are the only tell tale sign of an underlying diabetes. Hence, early recognition of the associated cutaneous manifestations and treatment is of paramount importance to limit the systemic complications of diabetes. Duration and severity of diabetes is equally important as long standing untreated or improperly treated patients can develop various macro and microvascular complications associated with DM. To assess the severity of the disease HbA1c measurement is an effective tool as it is an important indicator of long-term glycemic control with the ability to reflect cumulative glycemic history of the previous two to three months. Our study shows association of different types of diabetic dermatoses with severity of diabetes as represented by the HbA1C level. Also, we have observed that with regression analysis, the HbA1C value can be accessed just from the cutaneous manifestations of diabetes. The residual plot also showed close association of the predicted HbA1c values with actual measured value. This can be effectively used to screen diabetes as well as to gauge the severity of the disease.

## Limitation

The small sample size and single-center OPD-based assessment are the major limitations of our study. Further multicentre studies with larger sample sizes are needed for establishing our hypothesis.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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Original Article

# Acute effects of single-bout isometric handgrip exercise on selected cardiovascular parameters in young normotensive adults at a tertiary care center of West Bengal

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## Abstract

**Context:** Hypertension is currently prevalent along with other lifestyle disorders, which further adds up to cardiovascular morbidity. Young adults especially those of 18–25 years are also affected because of their sedentary lifestyle. Thus, a need for a compliable exercise that can be introduced in daily life is widely sought for.
**Aims:** To record changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR), before and after a single bout isometric handgrip (IHG) exercise.
**Settings and Design:** This interventional study has been conducted at I.P.G.M.E.&R., Kolkata.
**Materials and Methods:** Eighty-four young healthy individuals were selected based on predefined inclusion and exclusion criteria. After a fixed protocol for exercise, their pre and post (after 3 min and 3 h) IHG exercise values of blood pressure (BP) and HR were recorded and analyzed.
**Statistical Analysis Used:** Paired sample *t* test was done to compare the mean values of each of the parameters.
**Results:** Three-hour post-IHG values of SBP and MAP are reduced significantly ($P = 0.000$), whereas those of DBP and MAP are reduced but not significantly. The decrease in HR post 3 h of IHG is not statistically meaningful.
**Conclusions:** Single-bout IHG exercise elicits a significant reduction in BP when recorded after 3 h. Thus, if studied further, it promises to be a useful tool in the regular regimen of antihypertensive management with positive clinical outcomes.

**Keywords:** DBP, hypertension, IHG, MAP, SBP

**Key Messages:** Acute reduction in blood pressure can be seen with isometric exercise.

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## INTRODUCTION

Worldwide, hypertension or high blood pressure (BP) has caused around 7.5 million deaths, which accounts for 12.8% of global mortality. Around 57 million disability-adjusted life years (DALYS) or 3.7% of total DALYS have been attributed to hypertension.[1] The World Health Organization has estimated that hypertension is directly

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responsible for about 62% of stroke and 49% of coronary artery disease worldwide.[2] BP of young adult population is considered to be a prediction tool for the future incidence of cardiovascular events.[3] Approximately, 15%–20% of the young adult population have been diagnosed with hypertension, with an expected increase in the same due to high obesity rates.[4] Physical activity has been proven to be a beneficial intervention not only due to its effectiveness in preventing and treating hypertension. As aerobic exercise training, dynamic exercise training has been shown to elicit reductions in systolic BP (SBP) and diastolic BP (DBP). The mechanisms by which these improvements occur are believed to be cardiovascular structural adaptations with or without autonomic modulations.[5] Isometric handgrip (IHG) exercise is a form of static resistance exercise, which is characterized by a change in muscle tension, whereas the muscle length remains constant. As contrast to isotonic exercises, in isometric exercise, only small groups of muscles remain in a contracted state throughout the exercise, resulting in compression of blood vessels and occlusion of blood flow to the active muscle.[6]

Nowadays, people used with modern life have become dependent on electronic gadgets, machines, and automobiles, which have made them to lead a sedentary life. The lack of physical activity or exercise has resulted in a lot of chronic morbidities including coronary artery diseases and hypertension.[7]

On this background, the present study intends to have an idea about the pattern of immediate changes (if any) of certain cardiovascular parameters (SBP, DBP, mean arterial pressure [MAP], and heart rate [HR]) after a "standard protocol of single bout isometric exercise" in a population of young adults from the southern part of West Bengal, India.

## SUBJECTS AND METHODS

This study was an analytical cross-sectional one, which was carried out on 84 healthy undergraduate students who attended classes at the Department of Physiology, I.P.G.M.E.&R., Kolkata, after getting clearance from the Ethical Committee of I.P.G.M.E.&R, Kolkata, and the West Bengal University of Health Sciences from May 2020 to August 2021. The following predefined criteria were applied during the selection of study subjects.

### Inclusion criteria

1) BP <139/89 mmHg.
2) Healthy, well-nourished.
3) Male and Female.
4) Age group 18–25 years.

### Exclusion criteria

1) Any recent h/o illness.
2) Consumption of antihypertensive medicines.
3) Carpal tunnel syndrome.
4) Wrist/finger joint arthritis
5) C/o chest pain.
6) Vertigo, dizziness, or loss of consciousness during physical activity.
7) History of known cardiac disease, bronchial asthma, and epilepsy.

## MATERIALS AND METHODS

For all study subjects, pre and post (after 3 min and 3 h) exercise values of BP were recorded using a conventional mercurial sphygmomanometer (Diamond BPMR112 Regular Velcro Cuff), and HR was also recorded by electrocardiogram (ECG) (BPL Cardiart 108T Digi Manual ECG Machine). The subjects were instructed to compress the handle of handgrip spring dynamometer (INCO, Ambala, India) [Figure 1] keeping arm adducted, elbow flexed at 90°, and the forearm and wrist in a neutral position, with maximal effort for 5 s, and isometric contraction was recorded. Three attempts were given with a pause of 30 s between each attempt. The mean of these three readings was taken as maximal voluntary contraction (MVC) of the respective subject. After a resting period of 3 min, the subject was asked to perform the isometric contraction at 30% of his/her MVC with the dominant arm for 2 min. Such exercise was repeated for another three times with a resting interval of 1 min in between consecutive bouts of contractions.

## RESULTS

### Data analysis

Data are reported as mean ± standard deviation. Paired *t* test was used for the comparison of parameters in preexercise resting state to those of 3-min and 3-h values after a single bout of IHG exercise. $P \leq 0.05$ is considered statistically significant. Data were analyzed and represented using MS Excel 2010 software package for Windows (Microsoft Corp., USA) and with SPSS Statistical package for Windows, version 20.0 (IBM Corp., NY, USA), wherever applicable.

## DISCUSSION

Hypertension is a major risk factor for cardiovascular disease. Numerous studies have investigated the effects of aerobic training on BP, and because the studies on the effect of isometric training have been limited to date, it has not yet been accepted as BP lowering management strategy.

Hypothetically, if single handgrip exercise could help to lower BP even for a couple of hours, the patient could exercise several times a day, and regularly to get a more pronounced and longer lasting effect on BP, because such training takes only a few minutes and can be conveniently performed. This could potentially prevent the risk related to high BP.[8]

In this study, unilateral handgrip training protocol (4 × 2 min, 30% MVC, separated by 1 min of rest between sets) was used, similar to other studies (McGowan *et al.*,[9,10] Badrov *et al.*,[11] Carlson *et al.*,[12] Van Assche *et al.*,[13] Ash *et al.*,[14] and Goessler *et al.*[15]). The main consideration for the choice of this protocol was that a short-term statistically significant BP-lowering effect was observed in their study.

It is well known that BP increases while performing isometric exercise.[16] To find out how fast is the recovery of BP after isometric handgrip exercise, we first measured BP, 3 min after training. Van Assche *et al.*[14] demonstrated that 1 min after handgrip exercise, BP was still significantly increased compared with baseline. Olher *et al.*[17] reported that 5 min after training, BP had returned to pretraining values. Thus, it is not surprising that values of values of SBP [Table 1 and Figure 2], DBP [Table 1 and Figure 2], and MAP [Table 1 and Figure 2] were significantly raised when measured after 3 min of single bout isometric handgrip exercise.


**Figure 1:** Spring type handgrip dynamometer

Olher *et al.*[17] did not find any significant changes in BP after 1 h of the exercise, whereas significant reduction in BP was demonstrated by Van Assche *et al.*,[14] and Souza *et al.*[18] after 7 and 1 h of exercise, respectively.

In the present study where only normotensive subjects were included, it was seen that after 3 h of isometric exercise SBP and MAP, both were significantly reduced [Table 2 and Figure 2], whereas DBP did not show any significant variation [Table 2 and Figure 2]. The results of the present study were partly similar to that of Piikmann *et al.*,[8] who demonstrated in their study a statistically significant reduction in SBP and DBP in normotensive subjects post 3 h of single bout IHG exercise.

The reduction in SBP ≥2 mmHg and DBP ≥2 mmHg is considered clinically meaningful, because it is associated

**Table 1: Comparison of pre and post 3 min isometric handgrip exercise study parameters among all the participants**

| Study parameters | Pre IHGE (MEAN ± SD) *n* = 84 | Post 3 min IHGE (MEAN±SD) *n* = 84 | p- Value |
|---|---|---|---|
| SBP | 122.24 ± 10.48 | 129.07 ± 9.98 | 0 |
| DBP | 76.79 ± 5.39 | 82.21 ± 5.82 | 0 |
| MAP | 91.93 ± 5.63 | 97.43 ± 5.45 | 0.023 |
| HR | 77.50 ± 6.09 | 84.45 ± 7.84 | 0 |

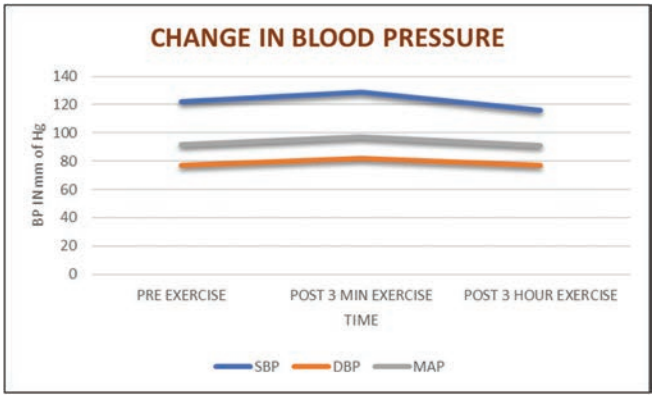


**Figure 2:** Change in blood pressure along with change in time

**Table 2: Comparison of pre and post 3 h isometric handgrip exercise study parameters among all the participants**

| Study parameters | Pre IHGE (MEAN±SD) *n*= 84 | Post 3 hour IHGE (MEAN±SD) *n* = 84 | p- value |
|---|---|---|---|
| SBP | 122.24 ± 10.48 | 115.88 ± 6.99 | 0 |
| DBP | 76.79 ± 5.39 | 76.93 ± 4.46 | 0.178 |
| MAP | 91.93 ± 5.63 | 90.91 ± 4.61 | 0 |
| HR | 77.50 ± 6.09 | 76.58 ± 6.57 | 0.115 |

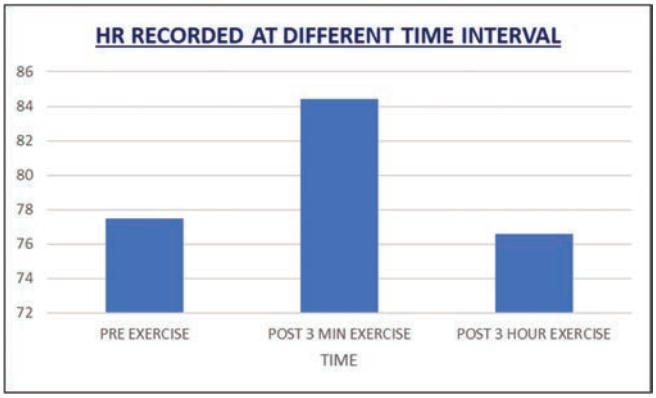


**Figure 3:** Recording of heart rate at different time interval

with significant risk reduction in the incidence of heart failure among normo- and hypertensive individuals. A total of 2 mmHg reduction in SBP decreases stroke and coronary artery disease-related death rates by 6% and 4%, respectively; a reduction of 5 mmHg will further cause reductions of 14% and 9%, respectively.[19]

Other researchers have shown that during isometric training, chemoreceptor reflex responsible for sympathetic nerve activity is reduced, thus causing attenuation of sympathetic nerve response to sympathetic nerve activity, which is responsible for the decrease in resting BP over a period of time.[20]

It has also been shown that exercise and training improve local, endothelium-dependent vasodilation in medicated hypertensives. It was found that the incidence of hypertension was lower in individuals engaged in occupations that had component of isometric effort.[21]

Although the mechanisms responsible for the reduction of BP remain to be fully clarified, improvements in conduit and resistance vessel endothelium-dependent dilation, oxidative stress, and autonomic regulation of HR and BP have been reported.[8]

In the current study, the HR of the subjects increased post 3 min of the exercise and decreased after 3 h from the preexercise value [Tables 1 and 2 and Figure 3], whereas the increase in HR from preexercise to post 3 min exercise is statistically significant, but the decrease in its post 3 h value from preexercise HR is not statistically significant [Tables 1 and 2].

Limited resources were available to show a statistically significant decrease in HR as an acute effect of IHG exercise. According to Devereux *et al.*,[22] following IHG exercise given HR reserve is deemed to be a valid representation of the effects of the autonomic nervous system on cardiac function, and parasympathetic reactivation was enhanced following IHG exercise. It is known that a rapid reduction in arterial distending pressure may follow an exercise-induced arterial constriction or compression. This suggested that during the postexercise period, any sustained sympathetic activation is overridden by potent vasodilator stimuli. Therefore, the present data suggest a heightened parasympathetic reactivation, following its withdrawal during exercise.[22]

Our study consisted of limited number of subjects with no control group, and the protocol was followed only to note down acute effects where the long-term training was not implemented.

## CONCLUSION

IHG exercise training involves a markedly lesser time commitment compared with traditional aerobic exercise training schedule and could serve as an alternative to any recommended aerobic training regimen. Based on the currently available research, IHG exercise seems to be a promising modality of physical activity, utilizing short session durations and cost-effective measures to elicit significant improvements in BP and autonomic regulation. Part of these improvements, although transient, is observed even after one session of a typical IHG training protocol. These results are often observed in older and/or hypertensive adults, but there is a paucity of studies investigating the acute effects of various IHG protocols on cardiovascular parameters in young adult population of India, especially the South Bengal region, where the study has been conducted.

We could only manage to take a sample size that is comparatively less in number than expected standards. We have not also measured NO level in the blood to further study the mechanism of reduction in BP following IHG protocol. To analyze the therapeutic application of these findings, the need for further studies on hypertensive participants is warranted.

IHG exercise training can be promising to be a simple, cost-effective, compliance-friendly, and nonpharmacological method in improving cardiovascular health, the scope of which can be explored with relevant further studies. Implementing IHG exercises with different grades can be of help to explore the relationship between isometric muscle tension and cardiovascular parameters (BP and heart rate variability).

### Financial support and sponsorship
Nil.

## Conflicts of interest

There are no conflicts of interest.

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Original Article

# KIBRA promoter methylation and association with clinical manifestation of renal cancer: A study in a tertiary institute in eastern India

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## Abstract

**Objective:** This study aims at detecting KIBRA promoter methylation and association with clinic-pathological manifestations in renal cancer.

**Materials and Methods:** In this study, we have studied the KIBRA promoter methylation in twenty cases of renal cell cancer and compared them to their stage, grade, and histopathology.

**Result:** We have found that significant amount of KIBRA promoter methylation is present in high grade tumors irrespective of the stage. 5 out of 6 grade III tumors and all 6 grade IV tumors were positive for significant KIBRA promoter methylation as compared to 1 out of 5 grade I tumor.

**Co BGJ_7_23 nclusion:** DNA methylation alterations participate in renal carcinogenesis which significantly correlated with the clinicopathological diversity of clear cell renal cell carcinomas and can be considered as potential targets for therapy.

**Keywords:** Clear cell cancer, DNA methylation, KIBRA promoter, renal cell cancer

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## INTRODUCTION

Renal cell carcinoma (RCC) is an adenocarcinoma of kidney, accounting for 3% of all adult malignancies. Patient prognosis depends on multiple clinico-pathological factors such as tumor node metastasis (TNM) stage, Fuhrman nuclear grade, tumor size, and other hematological indices. Several molecular markers appear to serve as independent prognostic factors for RCC and have provided important insights into tumor biology.

*KIBRA* is a WW and C2 domain-containing protein has been identified as an upstream regulatory component of the Hippo pathway (also known as Salvador-Warts-Hippo tumor suppressor network), which regulates cell number by modulating proliferation, apoptosis, and differentiation.[1-4] In humans, impaired Hippo signaling has been reported in a variety of different cancers, linking deregulated Hippo signaling to tumor initiation and progression.

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The present investigation was aimed to

i) study KIBRA promoter methylation status in renal cell tumor;
ii) to compare KIBRA promoter methylation according to stage, grade, histopathologic type of tumor.

## MATERIALS AND METHODS

### Recruitment of subjects

20 RCC patients of any age were admitted to the Department of Urology, IPGMER and SSKM, Kolkata for the treatment. Subject inclusion criteria includes renal tumor that do not receive any previous treatment such as immunotherapy. before operation. Subject exclusion criteria were renal cancer patients receiving immunotherapy or targeted therapy before operation and benign tumors of the kidney. The study protocol was approved by the Institutional ethical committee of IPGME&R, Kolkata.

### Collection of samples and data

All patients underwent radical nephrectomy. Part of freshly operated renal cancer tissues were collected. For control sample, adjacent normal renal tissue was taken. History, clinical examination, imaging, biochemical reports, and histopathology were collected. Peripheral blood was drawn from every individual in ethylene diamine tetraacetic acid (anti-coagulant) containing vials.

### Promoter methylation analysis

Promoter methylation analysis of KIBRA genes will be performed to study the epigenetic alterations. Promoter methylation status of KIBRA gene was analyzed in CpG-rich islands in the promoter region of the respective genes by polymerase chain reaction-based methylation sensitive restriction analysis using HpaII (Promega, Fitchburg, Wisconsin), Msp1 and Hha1 (Sibenzyme, Novosibirsk, Russia) enzymes. The $\beta$-3A adaptin gene (K1) and RARβ2 (K2) will be used as digestion and integrity controls, respectively.

## RESULTS

Out of 20 patients we had 19 clear cell carcinoma and one papillary cell carcinoma. KIBRA promoter methylation was analyzed, and Figures 1 and 2 show the gel diagram when methylation is present and absent, respectively. Table 1 shows the distribution of stage of tumors included in our study as per TNM. 40% of the tumors were stage I, 40% were stage II, and 20% were stage III. Table 2 shows the distribution of grade of tumor in the patients along with KIBRA promoter methylation status. 5 out of 6 grade III tumors and all 6 grade IV tumors were positive for significant KIBRA promoter methylation, whereas only 1 out of 5 grade I tumor is positive.

## DISCUSSION

In our limited study with 20 patients, we had 19 clear cell carcinoma and one papillary cell carcinoma [Table 1]. 40% of the tumors were stage I, 40% were stage II, and 20% were stage III [Table 2]. KIBRA promoter methylation was analyzed, and Figures 1 and 2 show the gel diagram when methylation is present and absent respectably. 11 out of 12 grade III & IV tumors were positive for significant KIBRA promoter methylation [Table 3]. This shows that significant amount of KIBRA promoter methylation is present in high grade tumors.

In study by Wozniak *et al.*[5] carried out in Czech Republic and the United States, alterations of *KIBRA* expression in clear cell renal cell carcinoma (ccRCC) have been analyzed. The gene expression profiles of 101 ccRCC and adjacent tissue sample pairs of the K2 series suggested *KIBRA* down-regulation. In this line, it is observed that inactivated *KIBRA* expression depends on promoter methylation in ccRCC.[6]

Epigenetic events appear to accumulate during carcinogenesis, and DNA methylation alterations are one of the most consistent epigenetic changes in human

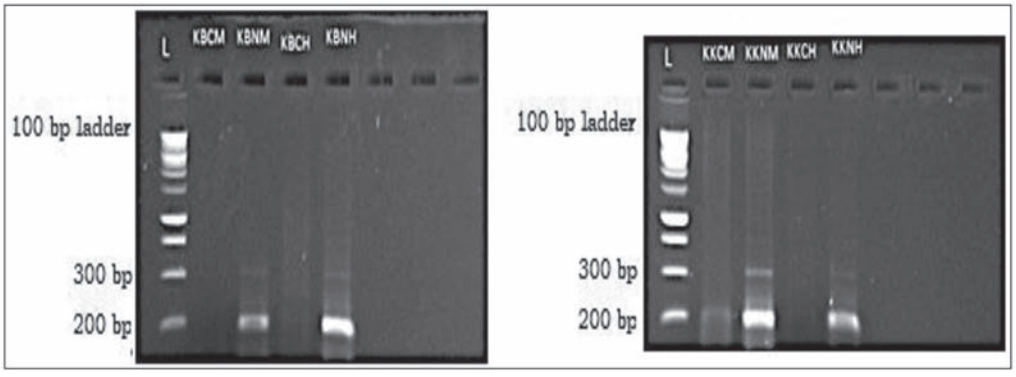


**Figure 1:** Result where when significant KIBRA methylation present. KB = KIBRA primer, C = cancer tissue, N = normal tissue, M = MspI (cut when methyl group present), H = Hha1 (cut irrespective of methyl group), KK = K1+K2 primer

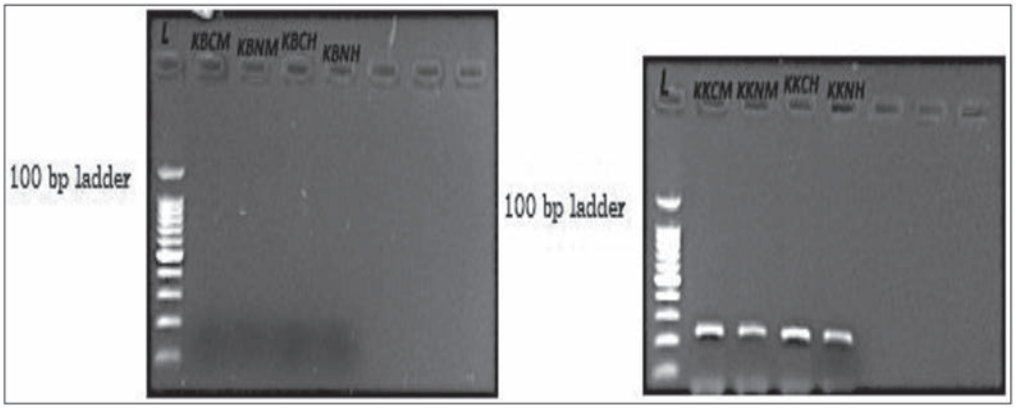


**Figure 2:** When significant KIBRA methylation absent. KB = KIBRA primer; C = cancer tissue; N = normal tissue; M = MspI (cut when methyl group present); H = Hha1 (cut irrespective of methyl group); KK = K1 + K2 primer

**Table 1: Distribution of subtypes of renal cancer in study population**

| Diagnosis | Frequency | Percent |
|---|---|---|
| Chromophobe | 0 | |
| Clear cell | 19 | 95% |
| Papillary | 1 | 5% |
| Total | 20 | |

**Table 2: Correlation of KIBRA promoter methylation with stage of tumor**

| | Methylation status | | Total |
|---|---|---|---|
| | Present | Absent | |
| Stage I | 5 (25%) | 3 | 8 (40%) |
| Stage II | 6 (30%) | 2 | 8 (40%) |
| Stage III | 3 (15%) | 1 | 4 (20%) |
| Total | 14 | 6 | |

**Table 3: Correlation of KIBRA promoter methylation with grade of tumor**

| | Methylation status | | Total |
|---|---|---|---|
| | Present | Absent | |
| Grade I | 1 | 4 | 5 |
| Grade II | 2 | 1 | 3 |
| Grade III | 5 | 1 | 6 |
| Grade IV | 6 | 0 | 6 |
| Total | 14 | 6 | |

cancers.[4,7-13] Accumulation of DNA methylation at CpG islands has been defined in well-studied cancers[14,15] such as those of the colorectum,[16] stomach,[17] and kidney[18,19] and has shown to be significantly correlated with clinico-pathological parameters.

Artificial transcription factor capable to activate the *KIBRA* core promoter, to significantly increase KIBRA mRNA as well as protein levels, thereby activating hippo signaling marked by elevated LATS1 and YAP phosphorylation are being studied. ZFP226 reduced the viability of breast cancer cells *in vitro*. It represents a molecular tool for the development of future applications in cancer treatment and needs further investigation.[20]

## Ethics committee approval

Obtained from the institutional ethics committee and research oversite committee. IPGME&R research over site committee—institutional ethics committee—memo no—IPGME&R/IEC/2019/454.

## Informed consent

Written informed consent was obtained from the patients for their anonymized information to be published in this article.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

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Case Report

# Rare case of primary neurofibroma involving urinary bladder without signs of neurofibromatosis: An "Oddball" to urologist

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**Abstract**

Literature related to neurofibroma involving the genitourinary system in a patient with systemic neurofibromatosis-1 (NF-1) is very few. The reported cases further decline in number when it comes to primary neurofibroma of the urinary bladder without signs of NF-1. Here, we report one such case of a 41-year-old gentleman with large bladder mass, presented to us with complaints of obstructive and voiding urinary symptoms with an episode of hematuria. Related imagines were done, and the patient underwent trans-urethral resection of bladder tumor. Histopathology and immunohistochemistry examinations were suggestive of neurofibroma. No recurrence in 6 months of follow-up.

**Keywords:** Primary neurofibroma bladder, neurofibromatosis-1, bladder tumor

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## INTRODUCTION

Neurofibroma in the genitourinary system is of very rare occurrence, and most of the time, it is secondary to systemic neurofibromatosis-1 (NF-1). Bladder is the most common site of involvement.[1] Vesicle, pelvic, and prostatic plexuses are the originating sites for the neurofibroma of the genitourinary tract. In bladder, it arises from nervous ganglia.[2] So far, literature has around 75 cases reported as bladder neurofibroma.[2,3] Most of them are associated with NF-1. Reported cases of neurofibroma involving bladder without NF-1 are very few. Whenever diagnosed, it poses a different challenge to urologist in terms of counseling the patient about treatment, genetic work-up (for NF-1), and follow-up protocol.

Most of reported primary bladder neurofibromas are of young age with different ways of presentation ranging from gross painless hematuria, irritative symptoms to incidental findings on images.[1-3] The diagnosis is based on clinical examination, imaging, and cystoscopic findings. Detailed family history and physical examination related to NF-1 become important.[3] Literature suggests different ways of management of neurofibroma involving bladder, but there

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are no definitive guidelines regarding that.[1] The patient's course, treatment, and review of literature regarding neurofibroma are discussed here.

## CASE DESCRIPTION

We, hereby, report a case of a 41-year-old male presented in the urology clinic with primary complaints of urinary frequency, urgency, intermittent urinary stream for 2 years, and history of single episode painless macroscopic hematuria 7 months back. Personal history including history of any addiction and smoking was absent. Past medical history relevant to the presenting complaints was not significant. The patient denied of any family history related to neurofibromatosis and any previous surgical intervention. He belongs to the central part of West Bengal. Physical examination was unremarkable. Digital rectal examination was suggestive of flat prostate with a firm consistency.

The patient came to us with a report of ultrasound (USG) done 2 years back for urinary complaints. USG was suggestive of urinary bladder mass of size 9 cm. The patient did not receive any treatment for the same. Computed tomography (CT) scan of abdomen was suggestive of smooth globular mass arising from the prostate and large enough to occupy the whole of urinary bladder (10 cm). Magnetic resonance imaging (MRI) pelvis was done to know the origin of the tumor, and it became evident that the mass is originating from the base of bladder on the right side and compressing the prostatic tissue [Figure 1].

Cystoscopy was suggestive of single broad base tumor originating from bladder wall with a smooth urothalial covering over it. Bladder mucosa over the rest of the bladder was normal. trans-urethral resection of bladder tumor was indicated, and done in two operative settings. Histopathological examination (HPE) of the tissue was suggestive of neoplastic lesion composed of spindle-shaped cells arranged in interlacing bundles and fascicles with no evidence of malignant transformation. Based on HPE findings, diagnosis of neurofibroma was made, and immunohistochemistry (IHC) examination for S-100 was

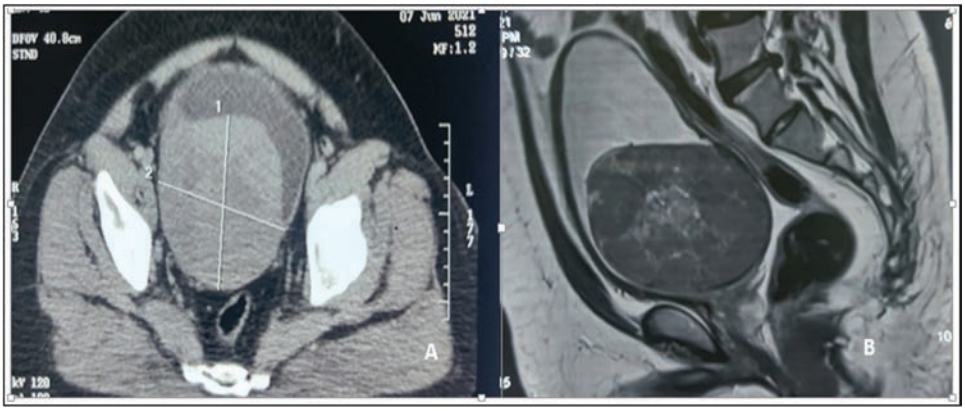


**Figure 1:** Imagine suggestive of urinary bladder mass. (A) CT scan pelvis suggestive of smooth large bladder mass originating from the prostate and occupying most of the urinary bladder. (B) MRI pelvis suggestive of large bladder mass compressing the prostatic tissue with 'Target sign' in T2-weighted image. CT: computed tomography, MRI: magnetic resonance imaging

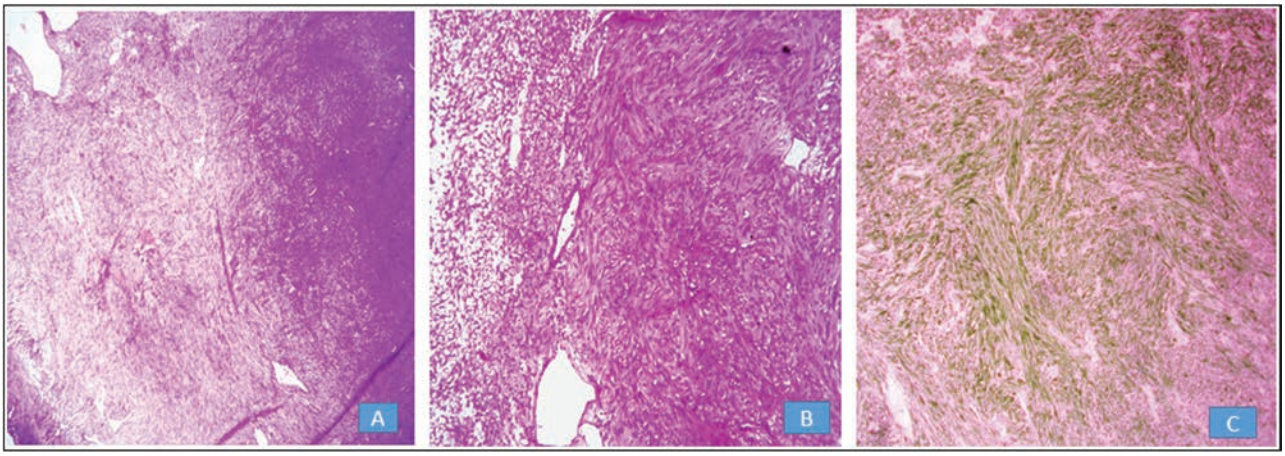


**Figure 2:** (A) Neoplastic lesion composed of spindle-shaped cells arranged in interlacing bundles and fascicles with no necrotic area or mitosis (H & E stain). (B) Higher magnification (100×) of the same image with myxoid area at the left upper part of the image. (C) 100× image with S-100 antibody stain. The spindle cells are strongly immunoreactive for S-100 protein antibody. H & E stain: hematoxylin and eosin stain

done. The tissue was immunoreactive to S-100 antibody, which confirmed our diagnosis of neurofibroma of bladder [Figure 2]. The patient was evaluated for signs of neurofibromatosis but there were no clinical relevant findings in favor of systemic diseases. The patient was advised for a regular follow-up by USG or cystoscopy. After 6 months of follow-up, now the patient is symptoms free, and there is no detectable reoccurrence on cystoscopy.

## DISCUSSION

NF-1 is a genetic disorder of peripheral nerve sheath transmitted in autosomal dominant pattern.[4] It is associated with the involvement of genitourinary organs such as bladder, penis, clitoris, prostate, urethra, testis, and ureter. Out of this, bladder is more commonly involved.[1] Neurofibroma of bladder associated with NF-1 has higher malignant potentials.[5] In contrast to that, primary bladder neurofibroma was found to have less chance of malignant transformation.[6] The patient with primary neurofibroma bladder should always be examined for other stigmata of NF-1.

Primary neurofibroma occurs in younger patients and one-third of cases are pediatric patients. It is three times more common in males.[1] In different case reports, the presentation is irritative urinary symptoms and sometimes asymptomatic. In contrast to the transitional cell carcinoma (TCC), this tumor rarely presents with history of hematuria.[1-3] The size of neurofibroma may vary but can be large enough to occupy the whole bladder. A tumor located near bladder neck may cause voiding symptoms as well. In our case, the patient is a 41-year-old male with irritative urinary symptoms with a single episode of hematuria 7 months back. The tumor was large in size. The base of the tumor was near the bladder neck, so the patient also had history of intermittent urinary stream.

USG and CT scan help in the diagnosis of bladder mass but cannot differentiate it from TCC. Mass with smooth margin, globular shape, and endophytic appearance in a young patient should point toward the benign nature of the condition. T2-weighted MRI image shows 'Target sign' in neurofibroma.[4] Cystoscopy may suggest a tumor with normal urothelial cover over it. The mainstay of diagnosis is HPE and is supported by IHC examination. The neuronal tissue seen on HPE can be stained using S-100 antibody. Mitosis and nuclear picture can point towards the malignant variety. All previous reported cases showed HPE findings of spindle cells with S-100 immunoreactivity.[1-3,5]

Many treatment options have been tried for neurofibroma bladder, but none have proven superior to others so far. Surgical resection options are trans-urethral resection of bladder tumor, partial cystectomy, or cystectomy. Other modalities such as serial observation, radiotherapy, chemotherapy, urinary diversion, and use of botulin toxin have been attempted with unproven effects.[1,6] Complete surgical resection is advised whenever possible. In our case, two-stage trans-urethral resection of bladder tumor was performed to achieve the complete tumor clearance.

Follow-up in this type of lesion becomes an important aspect of overall management. Literature suggests that genetic screening related to NF-1 should be carried out and should be followed up for the development of new lesion in other systems.[6] The tumor is associated with low recurrence rate and low malignant transformation. USG and cystoscopic follow-up for bladder neurofibroma should be done for the detection of recurrence or possible malignant transformation.[3] There is no established guideline for treatment and time interval for follow-up.

## CONCLUSION

Primary bladder neurofibroma without NF-1 needs special attention of a urologist as the diagnosis is rare and guidelines for the management are not yet established. Our patient is a 41 years old otherwise normal male presented with obstructive and voiding urinary symptoms and diagnosed as neurofibroma based on HPE and IHC. Complete tumor resection remains ideal choice at present. Close follow-up by USG and cystoscopy is utmost important for early diagnosis of recurrence and probable malignant transformation.[3] Genetic workup related to NF-1 should be considered in patient who does not present with other signs of the disease.

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Nil.

### Conflicts of interest
There are no conflicts of interest.

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Case Report

# Alveolar and interstitial disease in chronic smoker presenting as combined pulmonary fibrosis with emphysema: Double trouble!

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## Abstract

Tobacco smoke exposure causes diverse pulmonary manifestations with involvement of alveolar, interstitial, and vascular diseases due to inflammatory pathology apart from more lethal lung cancer. Combined pulmonary fibrosis and emphysema is a heterogenous lung disease documented in smokers, which includes emphysema in the upper lobes and pulmonary fibrosis in the lower lobes. In this case report, we have reported an 80-year-old male presented with progressive shortness of breath with fatigability and hypoxia treated as emphysema with inhaled bronchodilators. Response to medical treatment was not satisfactory with worsening of shortness of breath and fatigability. Clinical examination revealed that bilateral basal Velcro crepitation with resting oxygen saturation was 88% at room air. High-resolution computerized imaging documented emphysema in the upper lobes with honeycombing and the lower lobes with tractional bronchiectasis. Echocardiography documented pulmonary hypertension with dilated right atrium and ventricle. We have treated with oxygen supplementation during rest and ambulation, long-acting inhaled bronchodilator medicines, and antifibrotic nintedanib with strict counseling for the avoidance of tobacco exposure. Cardiopulmonary parameters' improvement including in 6-min walk distance was significant with bronchodilators and antifibrotics.

**Keywords:** CPFE, interstitial lung disease, nintedanib, smoker's lung, Velcro crept

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## INTRODUCTION

Combined pulmonary fibrosis and emphysema (CPFE) is an underrecognized syndrome characterized by chronic, progressive disease with a dismal prognosis. Frequent comorbidities with a higher incidence than in idiopathic pulmonary fibrosis or emphysema alone are pulmonary hypertension (World health organization group 3) in 47%–90% of the patients and lung cancer in 46.8% of the patients.[1] According to the definition of emphysema, the presence of excess fibrosis has been historically excluded from the diagnosis of emphysema.[2] However, there is an increasing recognition of the coexistence of emphysema and pulmonary fibrosis in individuals. Whether the combination of emphysema and pulmonary fibrosis is a distinct clinical entity or not remains unknown. Some

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consider it as a coincidence of two smoking-related diseases in one person, comparable with the coexistence of lung cancer and chronic obstructive pulmonary disease (COPD). However, previous data had suggested that interstitial lung abnormalities were inversely associated with emphysema in smokers.[3] In 2005, Cottin *et al*.[4] first time put forward a defined syndrome termed "combined pulmonary fibrosis and emphysema (CPFE)," which is characterized by heavy smoking history, exercise hypoxemia, upper lobe emphysema and lower lobe fibrosis, unexpected subnormal lung volumes, and severe reduction of carbon monoxide transfer. The CPFE syndrome comprises a heterogeneous population of patients, and a consistent definition of CPFE has not been put forward. High-resolution computed tomography (HRCT) is the mandatory tool to diagnose this syndrome. CPFE is frequently complicated by pulmonary hypertension, acute lung injury, and lung cancer, and the prognosis of it is poor.[5]

## CASE SUMMARY

An 80-year-old male, retired military professional, exchronic smoker, normotensive, nondiabetic, referred to our center by a family physician for progressively worsened shortness of breath from grade I to grade IV over a period of 2 years. He was having chronic dry cough and showed partial response to inhaled bronchodilators and inhaled corticosteroids. Family members said that he was treated with systemic steroids for recurrent and progressive respiratory symptoms with hospitalization for worsening in the last 2 years. He was a chronic cigarette smoker with a smoking index of 50 pack years. Past hospitalization records noted chest X-ray abnormalities as inhomogeneous parenchymal infiltrates [Figure 1, taken 2 years before] treated as COPD.

General physical examination documented as restless, thin built old aged male with normal body temperature and dry mucosa. Cyanosis and clubbing were noted. His heart rate was 118/min, respiratory rate was 30 breaths per minute and blood pressure was 110/60 mmhg. His oxygen saturation was 72% at room air during resting and 89%–96% during routine walk with oxygen supplementation at the rate 2L/min by nasal cannula.

Respiratory system examination revealed the following: bilateral breath sounds normal and adventitious sounds as bilateral Velcro crepitation's heard bilateral basal area.

Nervous system examination revealed the following: higher functions normal, no neurological abnormality, cranial nerves normal, and recent and past memory normal recall. Cardiovascular and gastrointestinal systems were normal.

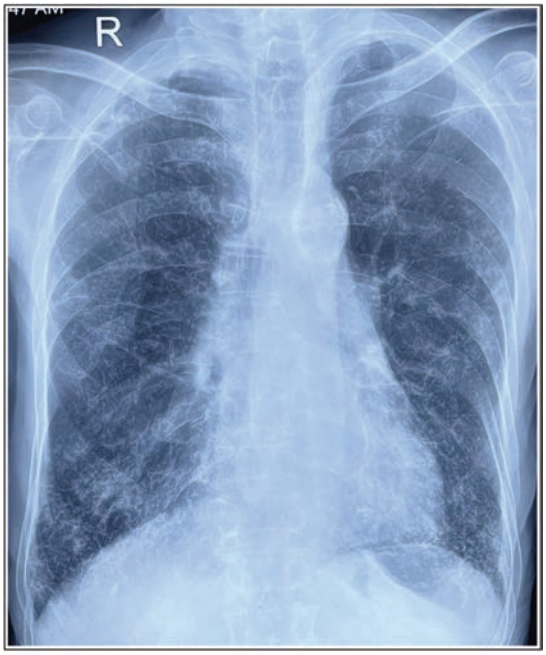


**Figure 1:** Chest X-ray posteroanterior view showing inhomogeneous parenchymal infiltrates

We have done HRCT thorax due to Velcro crepitations and signs of interstitial lung disease on chest X-ray. HRCT thorax documented emphysema in upper lobes and bilateral peripheral subpleural linear, reticular opacities with honeycombing and tractional bronchiectasis suggestive of usual interstitial pneumonia (UIP) pattern [Figures 2–5] and electrocardiogram suggestive of P-pulmonale.

Laboratory examination documented the following: hemoglobin: 11.0 gm%; total white blood cells: 21,000/mm$^3$; polymorphs: 85%; and platelet count: 490,000/uL.

Kidney function test revealed the following: serum creatinine: 1.1 mg/dL (0.6–1.2 mg/dL) and blood urea: 28 mg/dL (10–40 mg/dL).

Liver function tests revealed the following: Sr bilirubin: 14 mg/dL (6–1.2 mg/dL), indirect: 10.4, direct: 3.6; C-reactive protein: 281 mg/L (0–6 mg/L), random blood sugar level: 110 mg%; lactate dehydrogenase: 1080 IU/L (70–470 IU/L), uric acid: 3.4 mg (3.5–7.5 mg/dL); and N-terminal pro b-type natriuretic peptide: 598 pg/mL (<125 pg/mL).

Serum electrolytes are as follows: sodium: 138 meq/L (135–145 meq/L), potassium: 5.9 meq/L (3.5–5.5 meq/L), ionic calcium: 1.26 meq/L (1.09–1.36 meq/L); D-dimer: 450 ng/mL (<500 ng/mL); rheumatoid arthritis (RA) factor: 56 IU/L (0–20 IU/L); anticyclic citrullinated peptide: <7.0 U/mL (0–17 U/mL); and antinuclear antibody (ANA): negative (0–100).

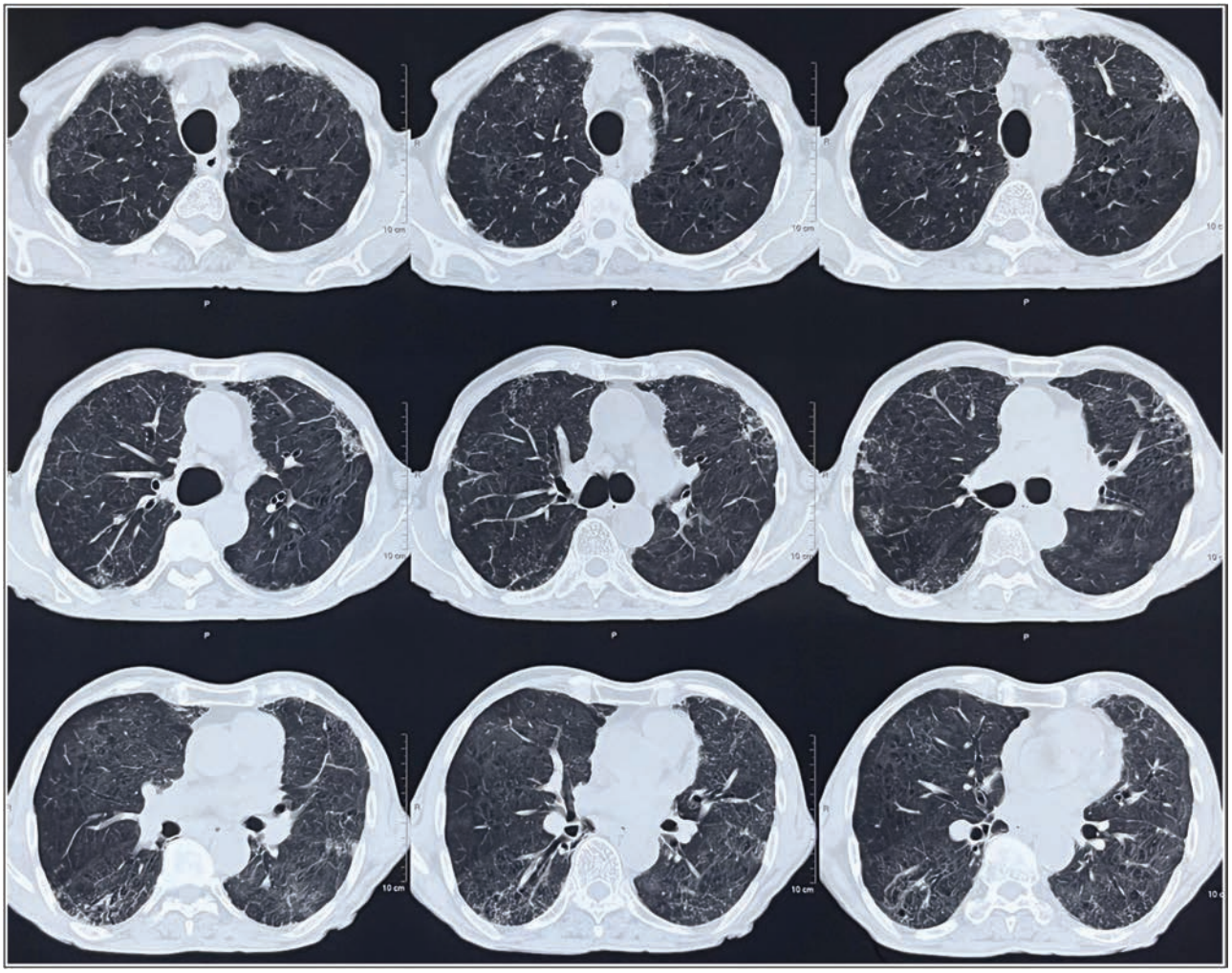

**Figure 2:** HRCT thorax showing bilateral peripheral subpleural interstitial reticular and linear opacities with emphysema in the upper and middle lobe. HRCT: high-resolution computed tomography

Myositis profile is as follows: PL-7 (anti-threonyl-tRNA synthetase antibody): positive; Anti-OJ (Isoleucyl-tRNA synthetase antibody): positive; and myositis panel suggestive of polymyositis in our patient as probable mechanism for CPFE other than smoking.

Spirometry analysis documented the following: forced vital capacity: 50.9% (1.66 L); forced expiratory volume in one second: 48.1% (1.36 L); and forced expiratory volume in one second/forced vital capacity: 105.82%.

Echocardiography reported as follows: evidence of severe PH RVSP by TR jet 100 mmHg, IVC dilated and noncollapsing, and no evidence of clot/vegetation or embolus and left ventricular ejection fraction was 60%.

Body plethysmography documented the following: residual volume: 2.08 L (77.2%); total lung capacity: 4.67 L (74.6%); functional residual capacity: 3.20 L (90.7%); and suggestive of restrictive pathology.

Diffusion single breath observed the following: Diffusing capacity of lung for carbon monoxide single breath: 23.3% (1.70 L); Carbon monoxide transfer coefficient: 44.3% (0.52 L); alveolar volume: 40.4% (1.34 L); and suggestive of parenchymal restrictive disorder with diffusion abnormality.

Six-minute walk test recorded after recovery in hospitalization at the time of discharge. The shuttle walk distance was recorded as 150 meters total walk distance with oxygen support. Oxygen saturation noted 93% with oxygen support pre-procedure and 90% with increase in oxygen support post-procedure with recovery time of 5 minutes. Heart rate was 96/min pre-procedure with oxygen support and 118/min post-procedure with increase in oxygen support & recovery time 5 min. Respiratory rate was 26/breath per minute with oxygen support and 36/breath per minute post-procedure with increase in oxygen support & recovery time 5 minutes.

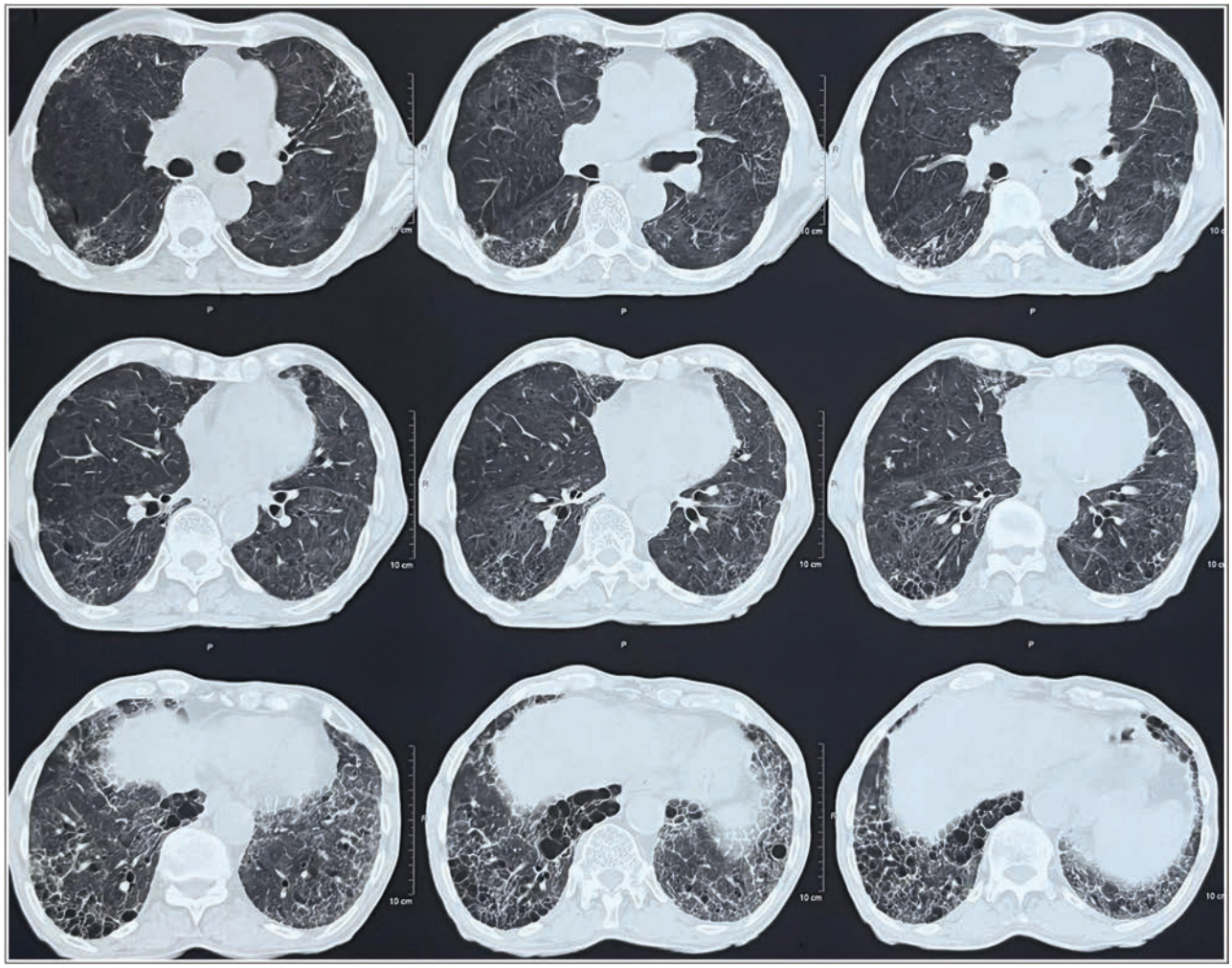

**Figure 3:** HRCT thorax showing bilateral peripheral subpleural interstitial linear, reticular opacities with tractional bronchiectasis and honeycombing in the lower lobes. HRCT: high-resolution computed tomography

Treatment started with oxygen supplementation with nasal cannula rate of 2 L/min and target oxygen saturation of more than 90% during rest and increased to 4 L during ambulation. Treatment given includes injection methylprednisolone 40 mg intravenously three times, antibiotic injection meropenem 1 g intravenous three times for exacerbation, nebulization with formoterol plus budesonide two times and glycopyrronium one time during hospitalization, rivaroxaban 2.5 mg as deep vein thrombosis prophylaxis, nintedanib 100 mg two times plus pirfenidone 400 mg three times daily for lung fibrosis, and tadalafil 20 mg one time daily for pulmonary hypertension. His health condition improved after 10 days of hospitalization and advised to continue oxygen supplementation at home during rest and ambulation. Discharged to home with esomeprazole 40 mg one time daily, dry powder inhaler glycopyrronium plus formoterol two times, tablet pirfenidone plus nintedanib, tadalafil, rivaroxaban and strict counseling for smoking cessation with subcutaneous injection of quadrivalent influenza and pneumococcal vaccine.

## DISCUSSION

CPFE is a clinical entity characterized by the combination of upper lobe emphysema and lower lobe fibrosis. The advent of computed tomography permitted recognition of the coexistence of pulmonary fibrosis and emphysema (CPFE). Although most cases of CPFE likely represent the common fibrotic pattern of UIP, a few cases have been reported as showing desquamative interstitial pneumonia or unclassified interstitial pneumonia.[6] Emphysema is defined as an enlargement of the air spaces distal to the terminal bronchioles due to the destruction of the tissues forming their walls. Emphysema secondary to smoking is typically centrilobular, which commonly manifests as small, localized areas of low attenuation within the central portion of the secondary pulmonary lobule on HRCT.[2] IPF is a chronic, progressive fibrosing interstitial pneumonia of unknown

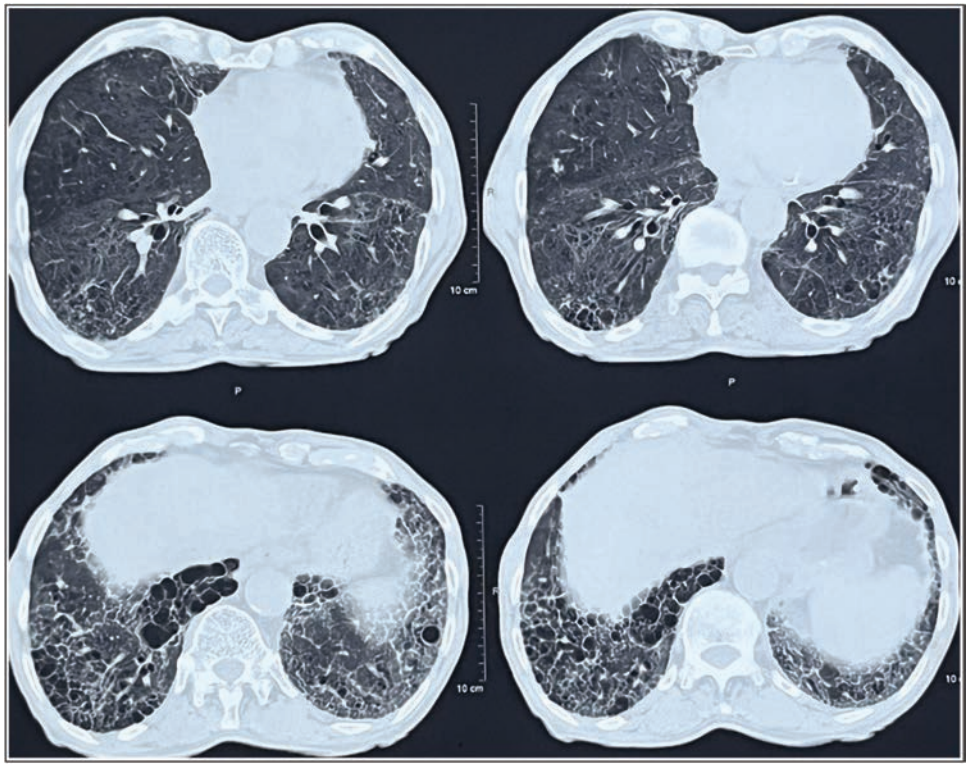

**Figure 4:** HRCT thorax showing bilateral peripheral subpleural tractional bronchiectasis and honeycombing. HRCT: high-resolution computed tomography

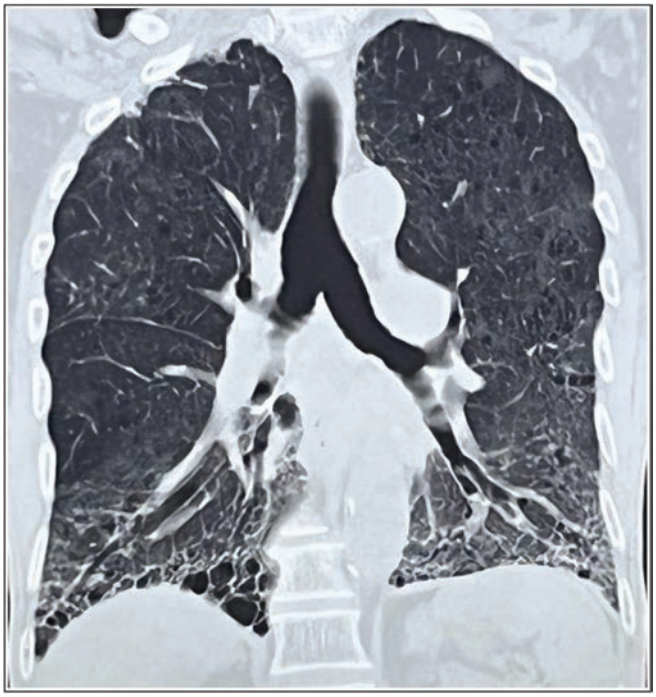

**Figure 5:** HRCT thorax sagittal section showing bilateral peripheral subpleural tractional bronchiectasis and honeycombing in the lower lobes with emphysema. HRCT: high-resolution computed tomography

cause, occurring primarily in older adults, characterized by progressive worsening of dyspnea and lung function, and associated with a poor prognosis. It is the most common ILD with a characteristic histologic pattern of UIP, which is characterized in HRCT by the presence of subpleural and basal predominance, reticular opacities, and honeycombing with or without traction bronchiectasis.[7]

In the present case report, we have documented progressively worsened shortness of breath treated as COPD with inhaled bronchodilators with corticosteroids. Clinical and radiological examination helped us to diagnose a case of CPFE in presence of bilateral Velcro crepitations on auscultation and honeycombing in HRCT imaging. We have treated with steroids, antifibrotics, and oxygen supplementation at home during rest and ambulation with pulmonary vasodilators documented satisfactory treatment outcomes as improvement in survival and quality of life.

## Key learning points from this case report

1. Progressive shortness of breath with partial response to inhaled bronchodilator and antimuscarinic needs prompt evaluation in COPD to rule out other causes of failure of treatment.
2. Chest X-ray gives definite clue for alternate diagnosis in cases with partial response to inhaled medicines in COPD.
3. Chest radiology showing blurred cardiac and diaphragmatic margins need interstitial disease to rule out. In fact, loss of demarcation of cardiac and

diaphragmatic margins in chest X-ray is "earliest marker" of interstitial lung disease.
4. Velcro crepitations on auscultation in COPD cases are "clinical clue" to suspect idiopathic pulmonary fibrosis in cases with chronic tobacco exposure.
5. HRCT is gold standard test to evaluate interstitial lung disease. Honeycombing, tractional bronchiectasis, and reticular opacities in bilateral lower lobes with peripheral, subpleural distribution suggestive of UIP pattern.
6. Combination of UIP pattern in the lower lobes with emphysema in the upper lobe is CPFE in cases with chronic smokers. With typical radiological pattern of CPFE, lung biopsy is not necessary for further confirmation.
7. Large number of CPFE cases with poor exercise tolerance (i.e., 6-min walk distance) necessitates echocardiography to rule out pulmonary hypertension, which is common but underestimated cause of persistent dyspnea in these cases.
8. Although DLCO is decreased in both emphysema and ILD independently, it can be assessed with lung volumes. Normal lung volumes with reduced DLCO are rare in CPFE.
9. Proportionately large number of CPFE cases are having rheumatological symptoms with positive RA factor. ANA blot needs strict evaluation in all cases of CPFE to rule out concurrent connective tissue disease (CTD). Myositis and undifferentiated CTDs are common in CPFE.
10. Bronchodilators, antifibrotics with or without pulmonary vasodilators, and oxygen supplementing as per oxygen saturation and echocardiography findings are the mainstay therapy for CPFE.

## CONCLUSION

CPFE is underestimated chronic lung disease presenting with emphysema plus interstitial lung disease. CPFE is common in smokers and a proportionate number of cases are having concurrent CTD. Pulmonary hypertension and lung cancer are two comorbidities associated with CPFE, which alters the final outcome. The combination of bronchodilators with antifibrotics has a "game changer" role in the management of CPFE.

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### Conflicts of interest
There are no conflicts of interest.

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Case Report

# Self-introduction of an electric wire into the urinary bladder

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**Abstract** The bladder is the most common site of foreign bodies in the urinary tract. We are presenting a case of a 39-year-old male who self-introduced an electrical wire into bladder. The wire was removed by suprapubic cystotomy after failed endoscopic retrieval. The case is presented for its rarity, along with a review of the literature.

**Keywords:** Bladder, electric wire, foreign bodies

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## INTRODUCTION

Self-insertion of foreign bodies in the urethra and bladder, usually for sexual gratification and autoeroticism, especially during male masturbation, is an unusual but important condition that urologists will encounter.[1]. People who insert foreign bodies for sexual gratification may avoid seeking medical help due to embarrassment and guilt.[2] A wide range of foreign bodies has been reported as self-introduction in the urinary bladder, including lead pencils, ballpoint pens, metallic wire, bullets, and wooden sticks. The usual presentation of such patients is generally urinary tract infection, pain, and hematuria.[3,4]

Radiopaque objects are detected by X-ray images, while others can be detected by ultrasonography. The primary treatment includes careful removal of the foreign body, causing minimal trauma to patients in order to avoid urethral injury and future erectile dysfunction in male patients. We present a case of self-insertion of an electric wire into the urethra for sexual pleasure during masturbation. With advances in endoscopic techniques, open surgery is not usually required, and the majority of cases can be treated using minimally invasive techniques.

## CASE PRESENTATION

A 39-year-old male was admitted to the Urology ward of a tertiary care center with a chief complaint of dysuria and hematuria. The patient inserted a tube-like foreign material into the bladder through the urethra. From his past discharge summary, the patient had a history of rectal perforation, following which exploratory laparotomy and colostomy were done, and colostomy closure was done after 1 month. The patient did not reveal his personal history regarding his relationship with his partner. He revealed this was the first time he had tried to insert an electric wire. An X-ray of the kidney, ureter, and bladder (KUB) region showed a coil-like structure inside the bladder [Figure 1]. Cystoscopy revealed a normal urethra with a coiled electric wire inside the bladder. He was planned for endoscopic removal of wire. Inside the bladder, a large coiled and knotted wire-like object with encrustations was seen. The

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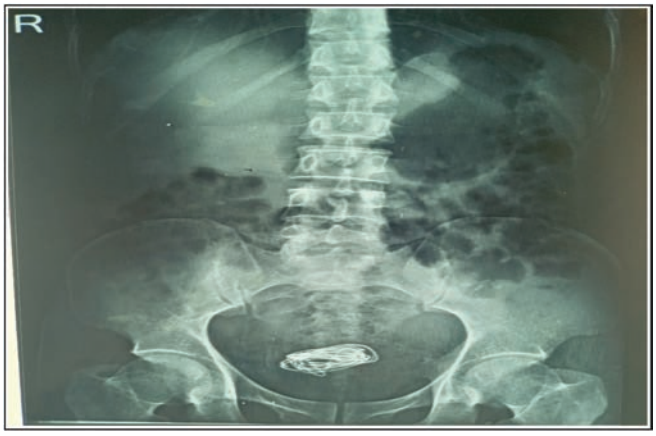


**Figure 1:** X-ray KUB showing a coil-like structure inside the bladder

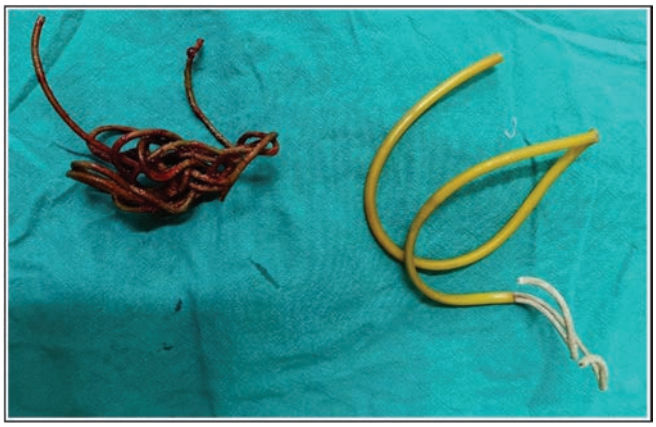

**Figure 2:** Electric wires after removal

wire could not be uncoiled, so cystoscopic retrieval failed. A 10 mm port was made in the suprapubic region, and percutaneous cystolithotripsy was attempted to remove the foreign body, but it failed. On suprapubic cystostomy, a long knotted encrusted electrical wire was found, which was removed intact.

After uncoiling, one wire was around 128 cm in length and another wire was 62 cm in length [Figure 2]. After the removal of the wires, the bladder and urethra were inspected for any injuries. The patient was discharged in stable condition and advised to attend psychiatric OPD.

## DISCUSSION

There are several cases in the literature that were used as intravesical or intraurethral masturbation instruments.[5] The urinary bladder is the most common site of foreign bodies in the genitourinary tract. A variety of conceivable items have been inserted into the bladder, including hairpins, hair clips, straws, matchsticks, lead pencils, ballpoint pens, metallic wire, plastic containers, bullets, copper intrauterine devices, broken parts of Foley catheters, forgotten JJ stents with calculus, wooden sticks, needles, pins, plastic toys, infant feeding tubes, ceramic sheaths of resectoscopes, prongs of endoscopic removal forceps, electrical wires, bullets, intrauterine contraceptive devices, encrusted sutures, surgical staples with stones, needles, household batteries, gauze, screws, pessaries, ribbon gauze, broken parts of endoscopic instruments, and knotted suprapubic catheters.[6] There are several reasons behind the insertion of this foreign body, such as psychiatric problems, drug abuse, misconduct, and sexual satisfaction. Most of the time, the reason for foreign body insertion was due to autoerotic manipulation. Aside from erotic stimulation, self-insertion can be done by psychotic patients, mentally retarded people, and children out of curiosity. The symptoms are due to the irritation of the object on the bladder's mucosa and the reduced capacity of the bladder. Trauma on the bladder wall causes hematuria.[7,8] If left untreated, serious complications such as stone formation, recurrent infection, and sepsis may occur. The small-sized object can be extracted directly without prior fragmentation, while the large-sized object needs to be fragmented first. If traumatic damage to the bladder was expected, an endoscopic approach is preferred. Most items can be removed transurethrally using cystoscopy grasping forceps. The cystoscopy procedure works both as a diagnostic tool and means of treatment. During the extraction, urethral injuries must be avoided. Knotting is also a possible complication. Treatment decision is based on the size and shape complexity of the foreign body to prevent iatrogenic injuries. LASER can be used to fragment large foreign bodies. Cystoscopy is recommended for small objects, whereas large impacted objects may require open removal via suprapubic cystostomy.[7,8] Suprapubic cystostomy increases the risk of urine leak and wound infection.

## CONCLUSION

Foreign bodies in the urinary bladder still remain a great challenge to urologists. A careful and proper evaluation of a patient's complete history combined with imaging modalities is necessary to assess a foreign body in the urinary tract. Total removal and complete clearance are the main principles in the management of this case to avoid the risk of further bladder injury. Cystoscopy is recommended for both diagnosing and extracting the foreign body. Further psychiatric evaluation is necessary to prevent reoccurrence.

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Nil.

### Conflicts of interest
There are no conflicts of interest.

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Case Report

# Pelvic lipomatosis: A rare case

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**Abstract** Pelvic lipomatosis (PL) is a benign condition characterized by excessive intrapelvic deposition of mature fatty tissue, resulting in compression of pelvic structures and causing a broad range of symptoms. As this condition is rare with limited cases, there are no standardized guidelines for its management. This case of PL was associated with bilateral hydroureteronephrosis and was managed with bilateral percutaneous nephrostomy insertion with long-term follow-up.

**Keywords:** Bilateral hydroureteronephrosis, fatty tissue, pelvic lipomatosis

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## INTRODUCTION

Pelvic lipomatosis is an uncommon disease that causes different symptoms due to intrapelvic overgrowth of fatty tissue compressing pelvic organs. It can be asymptomatic, but usually presents with dysuria, urinary incontinence, urgency and constipation

## CASE PRESENTATION

A 31-year-old male presented with dysuria, increased frequency of micturition, and a poor stream of urine for the last 2 years. He gives a history of smoking-seven pack years. No history of altered bowel habits or erectile dysfunction. No abnormality was found on a physical examination or digital rectal examination. The body mass index of the patient was 22 kg/m$^2$. An ultrasound of the whole abdomen was done, which showed bilateral gross hydroureteronephrosis with thinning of the renal parenchyma. Uroflowmetry showed a Qmax of 14 mL/s.

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A magnetic resonance imaging (MRI) of the kidney, ureter, and bladder, and pelvis was done, which showed circumferential wall thickening in the lower aspect of the urinary bladder with an inverted pear-shaped urinary bladder and diffuse fat deposits in the pelvis compressing the lower aspect of the urinary bladder and ureter [Figure 1]. A micturating cystourethrogram (MCU) was done, which showed a pear-shaped urinary bladder with a normal urethra [Figure 2].

A cystourethroscopy was done, which showed mucosal irregularities at the bladder neck. A biopsy from the bladder neck was taken, which was suggestive of normal transitional epithelium with some eosinophilic infiltrates, a solid nest of benign urothelial cells in the stroma, and no atypia in muscularis propria. All the features suggested a benign pathology.

Based on the above findings, a diagnosis of pelvic lipomatosis (PL) was made. A bilateral percutaneous nephrostomy was done in view of deranged kidney



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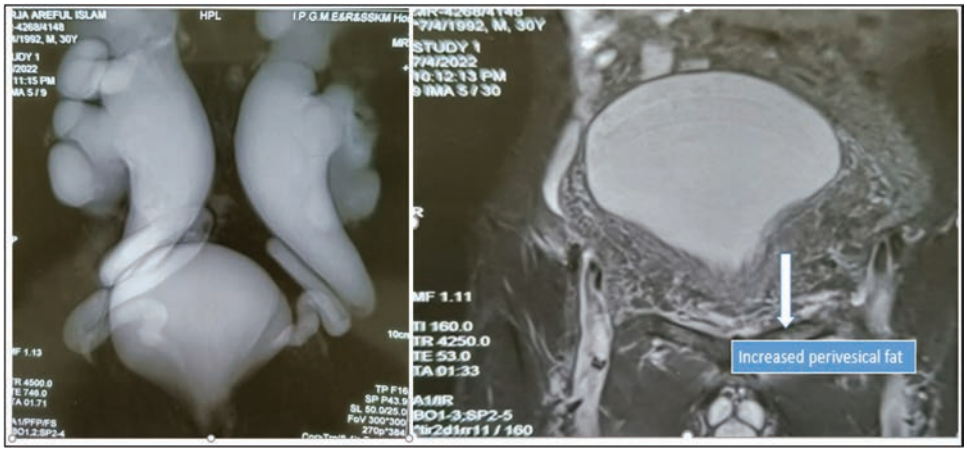


**Figure 1:** MRI KUB showing diffuse fat deposits in the pelvis with a "pear"-shaped urinary bladder. KUB = kidney, ureter, and bladder, MRI = magnetic resonance imaging

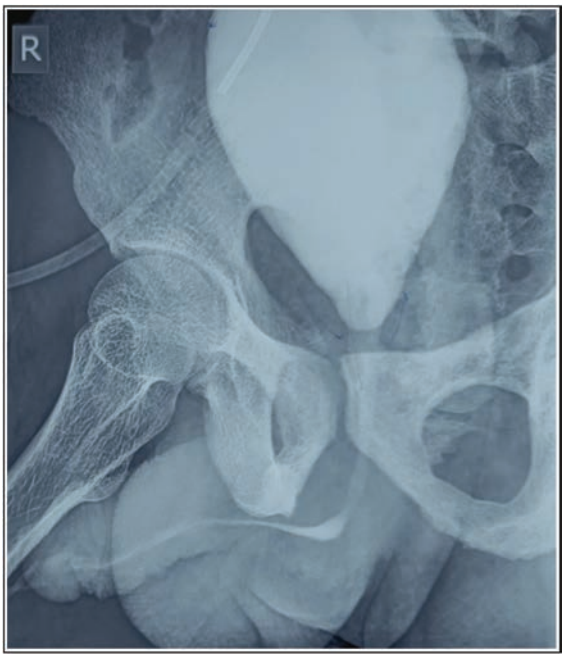


**Figure 2:** Micturating cystogram showing a "pear"-shaped urinary bladder

functions. A conservative approach to treatment was planned, with regular follow-ups. At 3 months of follow-up, ultrasonography (USG) showed mild hydronephrosis on the right side, and renal functions improved significantly. Hence, the left-sided nephrostomy was removed. At 5 months follow-up, USG showed no hydronephrosis on either side, and hence, the right-side nephrostomy tube was also removed. After 10 months of follow-up, the patient's symptoms are under control without a nephrostomy tube, with no hydronephrosis and normal renal functions.

## DISCUSSION

PL is a rare disease of benign proliferation. The term was coined in 1968 by Fogg and Smyth[1] after studying six cases of high fixation of the urinary bladder and colon with imaging appearances simulating a pelvic neoplasm but showing disproportionate amounts of fat in the pelvis on laparotomy. PL is more common in males, particularly African Americans.[2] The most common age of presentation is third or fourth decade of life. The etiology has not yet been established. However, it has been postulated that it might be associated with chronic pelvic inflammation secondary to a chronic urinary tract infection. Some authors have proposed that this disease is a manifestation of generalized obesity.[2] It may also be associated with diabetes mellitus, Cushing's disease, or hyperthyroidism.[3,4]

Due to compression of the pelvic structures, clinical symptoms vary from dysuria, hematuria, nocturia, tenesmus, constipation, and lower limb edema. Because of the subtle symptoms of early PL, some elderly male patients may be missed, and the incidence may be underestimated. Some patients present with severe hydronephrosis with impaired renal function at the time of diagnosis, with or without hypertension. Physical examination may reveal urinary retention, a palpable mass in the hypogastric region, elevation of the prostate on digital rectal examination, lower limb edema, or arterial hypertension.[2]

Imaging modalities are the first choice for the diagnosis of PL, as opposed to surgery or biopsy.[5] A characteristic "pear-shaped" urinary bladder is highly suggestive of PL. Previously, an intravenous pyelogram was useful in demonstrating this characteristic "pear-shaped" appearance of the urinary bladder, but, nowadays, computed tomography and MRI are central in diagnosing PL as they help in quantification and also demonstrate the extent of the disease. MRI and MCU suggested the characteristic "pear"-shaped urinary bladder in the present case. The possible complications related to PL as described in the

literature include hypertension, renal failure, portal vein thrombosis, and adenocarcinoma of the urinary bladder. The present case presented bilateral hydronephrosis with deranged renal parameters.

Studies have described both a conservative approach with regular monitoring of renal function and surgical modalities as treatments for PL, with varying results.[6,7] Antibiotics, steroids, and radiation therapy have been tried without much success. Surgical options such as ileal conduit with or without cystectomy, cutaneous urethrostomy, and bilateral percutaneous nephrostomy have been described in the literature. Our patient was managed with bilateral percutaneous nephrostomies. Complete surgical removal of the fatty tissue is challenging. Various surgical challenges, such as lack of surgical planes, presence of thick hypervascular, adherent fat that bleeds profusely, difficulty in separating the ureter from thick fat, and difficult anastomosis, have been reported.[7]

In our case, the patient was young and improved significantly with bilateral percutaneous nephrostomy, and the renal function remained normal without any further complications even after the removal of the nephrostomy tube with conservative treatment on follow-up. However, the patient was informed about the need for long-term follow-up for adenocarcinoma of the urinary bladder.

## CONCLUSION

The treatment of PL is still not standardized, but minimally invasive treatment such as bilateral percutaneous nephrostomy with long-term follow-up in cases such as ours can be a useful modality of treatment, provided the patient is willing to undergo long-term follow-up.

### Financial support and sponsorship
Nil.

### Conflicts of interest
There are no conflicts of interest.

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Case Report

# A giant Mullerian cyst in an adult male patient

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**Abstract** Mullerian duct cyst is a rare entity. We present such a rare case of Mullerian duct cyst in an adult male patient with its successful outcome.

**Keywords:** Mullerian duct cyst, Mullerian duct remnants, pelvic space occupying lesion

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## INTRODUCTION

Mullerian duct cyst is a remnant of the fused caudal end of the Mullerian ducts, which normally regresses *in utero*.[1] Mullerian duct cysts are difficult to diagnoses such, as they are rare in males, the present case is further complicated due to history of pelvic trauma. We herein present a case of an adult male patient with a large, palpable Mullerian duct cyst posing a diagnostic dilemma.

## CASE REPORT

A 33-year-old male patient presented to out-patient department with chief complaints of pain and swelling in suprapubic and perineal region for 2 months. He also had history of pelvic trauma 5 years back followed by poor urinary flow. Patient did not have old investigations or records of that event. Patient initially presented to peripheral hospital with acute urinary retention for which he was catheterized initially but later suprapubic catheterization (SPC) was done and referred to our hospital for further management. On examination abdomen was soft, non-tender and a smooth, firm swelling was palpable in suprapubic and perineal region, on evaluation patient was found to have a huge cystic pelvic space occupying lesion (SOL).

Ultrasound abdomen showed a peripherally hyperechoic complex septated collection noted in pelvis to postero-vesical region pushing the bladder antero-superiorly. Contrast enhanced computed tomography (CECT) of abdomen and pelvis showed a large multiseptated complex cystic SOL with peripheral enhancement, measuring about 18 cm × 12 cm × 10 cm in pelvis. The collection showed fluid/cystic content extending up to the root of scrotum [Figure 1]. The collection displaced the right ureter anteriorly, with left sided hydroureteronephrosis.

Magnetic resonance imaging (MRI) of abdomen and pelvis was suggestive of multiseptated complex cystic SOL noted in pelvis extending from perineum to postero-vesical region. Fat planes with urinary bladder and rectum appear intact. Catheter bulb noted at perineum at the base of penis. Other blood investigations were within normal limits.

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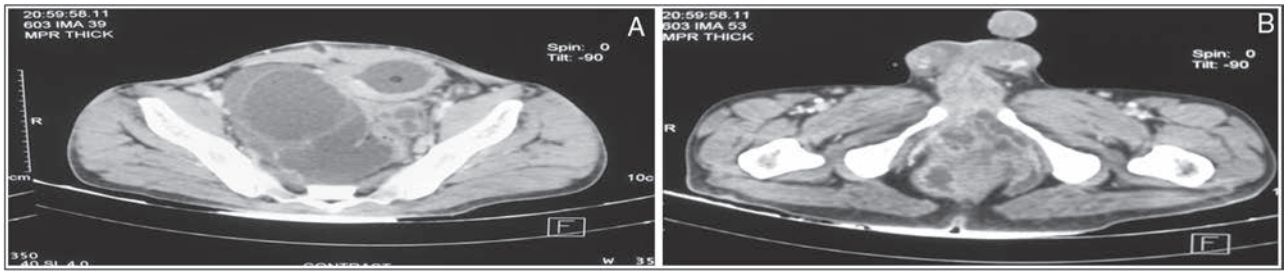


**Figure 1:** Contrast enhanced computed tomography (CECT) of abdomen and pelvis scan showed (A) large multiseptated complex cystic SOL measuring about 18 cm × 12 cm × 10 cm in pelvis. (B) It is extending up to the root of scrotum

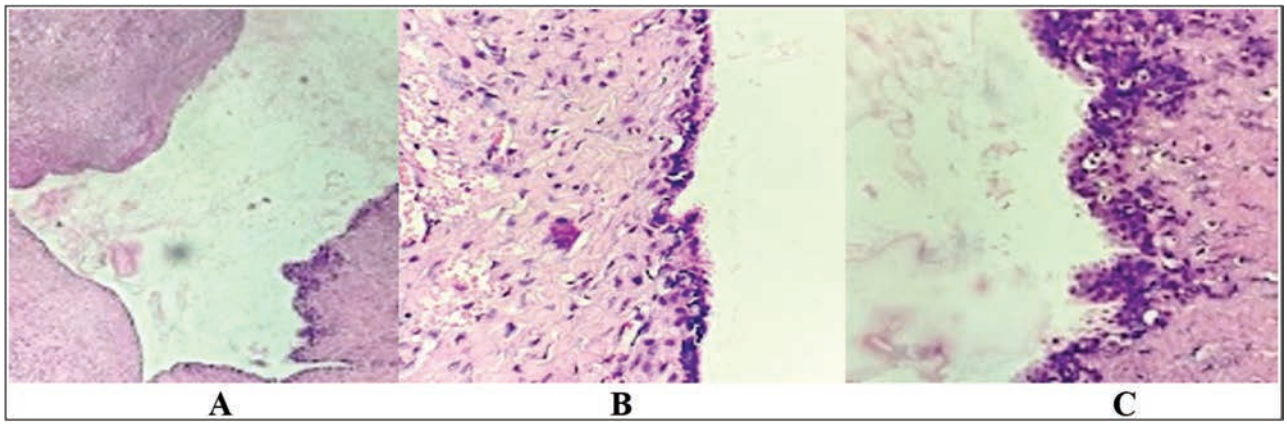


**Figure 2:** Hematoxylin and Eosin stain showing. (A) (HE ×10) Cystic structure with wall and underlying tissue. (B) (HE ×10) Blood vessels within fibrocollagenous tissue with lining cuboidal epithelium. (C) (HE ×40) Simple ciliated cuboidal epithelium resembling uterine tubal epithelium

As patient appeared under nourished and our country is endemic for tuberculosis, his cystic fluid aspirate was sent for gram staining, acid fast bacilli staining, and adenosine deaminase, which came out to be negative for tuberculosis.

Exploratory laparotomy followed by marsupialization of cyst wall and antegrade and retrograde urethroscopy with per-urethral catheterization done under general anesthesia. Intra-operative findings were multiloculated, multiseptated cyst in retroperitoneal space behind the urinary bladder with extension into the perineum. On cystopanendoscopy, the cyst was seen communicating with proximal bulbar urethra which was bypassed by per-urethral catheter (PUC) insertion over a guidewire under vision. Cyst wall was sent for HPE and straw-colored cyst fluid was sent for cytology and culture and sensitivity. PUC and SPC were removed after two weeks following peri catheter retrograde urethrogram and a good urinary flow was noted on uroflowmetry.

Histopathological examination of specimen showed features of a benign developmental cyst, favoring a Mullerian cyst [Figure 2]. The sections showed cystic structure lined by a single layer of ciliated cuboidal epithelium. Cystic fluid cytology was negative for malignant cells.

## DISCUSSION

Mullerian duct remnants, which include Mullerian duct cysts and enlarged prostatic utricles, are midline prostatic cystic lesions.[1] In the men, the Mullerian ducts regress under the effect of Mullerian inhibiting factor produced by the Sertoli cells of the testes at about the 10th week of fetal life.[1] Mullerian duct remnants result from incomplete Mullerian duct regression. Mullerian duct cysts tend to develop between the 3rd and 4th decades of life. The external genitourinary system is usually normal. Reported prevalence in older autopsy series in men is 1%.[2] They may be underreported as some authors found a prevalence of 5% in urologic patients.[3] These cysts are typically round and do not communicate with the urethra.[1,3] Our case was special as the cyst was communicating with proximal bulbar urethra which is an extremely rare presentation. They are commonly characterized by small retroperitoneal extensions in the midline. Variants occupying the entire pelvic region or extending into the perineum, as in our patient, are a rare clinical entity.[2] Different treatment options are available for Mullerian duct cysts. Transurethral resection and percutaneous aspiration are performed for small Mullerian duct cysts.[4]

Laparoscopic excision has been reported.[5] In large pelvic or abdominal cyst, open surgical excision is the treatment of choice.[1,6] Mullerian cysts are not so rare, and they are probably underreported.[3] As they are asymptomatic in most cases, treatment is indicated only in symptomatic cases.[3] But such a huge abdomino-pelvic and perineal multiple cysts are one of the rarest presentations.

## CONCLUSION

Because of the rare nature of these lesions, a high index of suspicion is necessary for diagnosis. Use of advanced imaging modalities like trans-rectal ultrasound and MRI are useful for aiding the identification of Mullerian duct cysts and prostatic utricles. Open surgical exploration remains the mainstay of diagnosis in case of confusion.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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Case Report

# Radiological "Triangle sign" in chest imaging in left lower lobe tuberculosis: A real puzzle

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## Abstract

Pulmonary tuberculosis is the most common etiology for lobar or multilobar atelectasis of the lung followed by foreign body and lung malignancy in the list. The left lower lobe atelectasis is underdiagnosed due to presentation as retrocardiac opacity, which is commonly missed by treating physicians. In this case report, a 46-year-old female presented with constitutional symptoms and retrocardiac triangular opacity in the chest cardiograph. High-resolution computed tomography thorax documented collapse with consolidation and necrosis in the posterior basal segment with loss of lung volume. Bronchoscopy documented purulent secretions coming out from the left lower lobe posterior basal segment without endobronchial abnormality. Bronchoscopy-guided bronchoalveolar lavage showed acid-fast bacilli, and nucleic acid amplification tests documented *Mycobacterium tuberculosis* genome without rifampicin resistance. She is treated with antituberculosis treatment for 6 months and observed good clinical, bacteriological, and radiological outcomes as "cure." We recommend basic regular training of family physicians for common radiological signs for early diagnosis and timely treatment with a successful outcome.

**Keywords:** High-resolution computed tomography thorax, left lower lobe collapse, pulmonary tuberculosis, triangle sign

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## INTRODUCTION

Lower lobe lung tuberculosis (TB) is defined as TB disease found below an imaginary line traced across the hila and including the parahilar regions on a standard posterior–anterior chest radiograph without concomitant involvement of the upper lobe. Anatomically, this includes the right middle lobe and lingular segments, in addition to the lower lobes. Lower lung TB is an atypical presentation of pulmonary TB, which often causes confusion in diagnosis. Obstructive atelectasis and overinflation are reported to occur in 9%–30% and 1%–5% of children with primary TB, respectively.[1,2] Consolidation of lower lung zones and normal findings are other atypical radiographic patterns associated with endobronchial TB.[3-4]

## CASE SUMMARY

A 46-year-old female, farmer by occupation, with no addiction history without any comorbidity referred to our center by a family physician for persistent fever and one episode of hemoptysis in recent onset.

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Clinical details are as follows:

1. Hemoptysis (minimal amount of blood), single episode associated with brisk coughing documented 1 day before hospitalization.
2. Shortness of breath on exertion in the last 1 month.
3. Fever: for 3 months, intermittent, low grade.
4. Cough: for 3 months, dry, intermittent, with minimal white sputum production.
5. Weight loss of 5 kg in the last 3 months.

General physical examination documented as restless, thin built young female with normal body temperature and dry mucosa. Her heart rate was 110 per minute, respiratory rate was 20 breaths per minute, blood pressure was 90/60 mmhg, and oxygen saturation 96% at room air resting & drops to 94% while walking at routine air.

Respiratory system examination revealed diminished breath sounds in the left intrascapular and lower axillary area, while breath sounds in rest of the lung areas are normal on both sides. Adventitious sounds as bilateral wheeze and crepitation's heard over the left intrascapular and lower axillary area.

Cardiovascular system, Nervous system, and gastrointestinal systems were normal.

We further asked attendants regarding the progression of disease over the last 3 months. They said that she was hospitalized for cough and fever in the recent past and treated as community-acquired pneumonia. Chest X-ray during hospitalization at the family physician's center showed the left lower lobe inhomogeneous opacification [Figure 1]. This typical triangular-shaped opacity in the left lower zone in retrocardiac region called Triangle sign. Triangle sign is an indicator of the left lower lobe basal segment collapse [Figure 2].

High-resolution computed tomography (HRCT) thorax was done for positive Triangle sign in the chest radiograph. HRCT thorax suggestive of the left lower lobe collapses with consolidations in the left lower lobe posterior basal segment. Collapse consolidation is associated with breakdown or cystic inhomogeneous opacities, which indicated underlying necrosis. The right lung and left upper lobe with lingular lobe lung parenchyma are normal [Figures 3 and 4].

Laboratory examination documented the following: complete hemogram, other hematological investigations, and liver and kidney functions were normal. Viral markers screen and tropical screen were negative. Sputum gram stain examination showed gram-positive cocci in pairs, and Ziehl Neelsen (ZN) stain examination was negative for acid-fast bacilli.

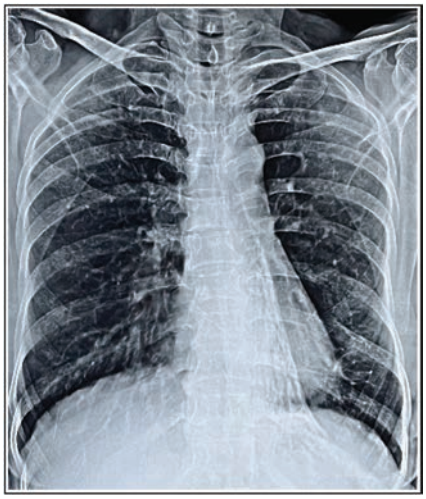

**Figure 1:** Chest X-ray PA with inhomogeneous opacity in the left lower zone

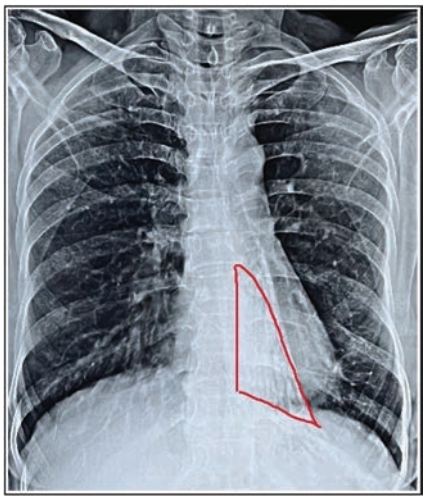

**Figure 2:** Chest X-ray PA with triangular-shaped opacity in the left lower zone retrocardiac region

We have performed bronchoscopy to rule out endobronchial cause and microbiological etiology for the left lower lobe collapse consolidation.

Bronchoalveolar lavage sampling reports were as follows: gram stain: few gram-positive cocci in pairs and chains; ZN stain: acid-fast bacilli documented; bacterial culture: no growth; and fungal culture: no growth.

Gene Xpert MTB/RIF documented *Mycobacterium tuberculosis* genome and negative for rifampicin resistance (rpo-b mutation).

We have started antituberculosis treatment (ATT) as per the National tuberculosis elimination program (NTEP) protocol according to weight band containing four drugs isoniazid (H), rifampicin (R), ethambutol (E), and pyrazinamide (Z). She was discharged to home

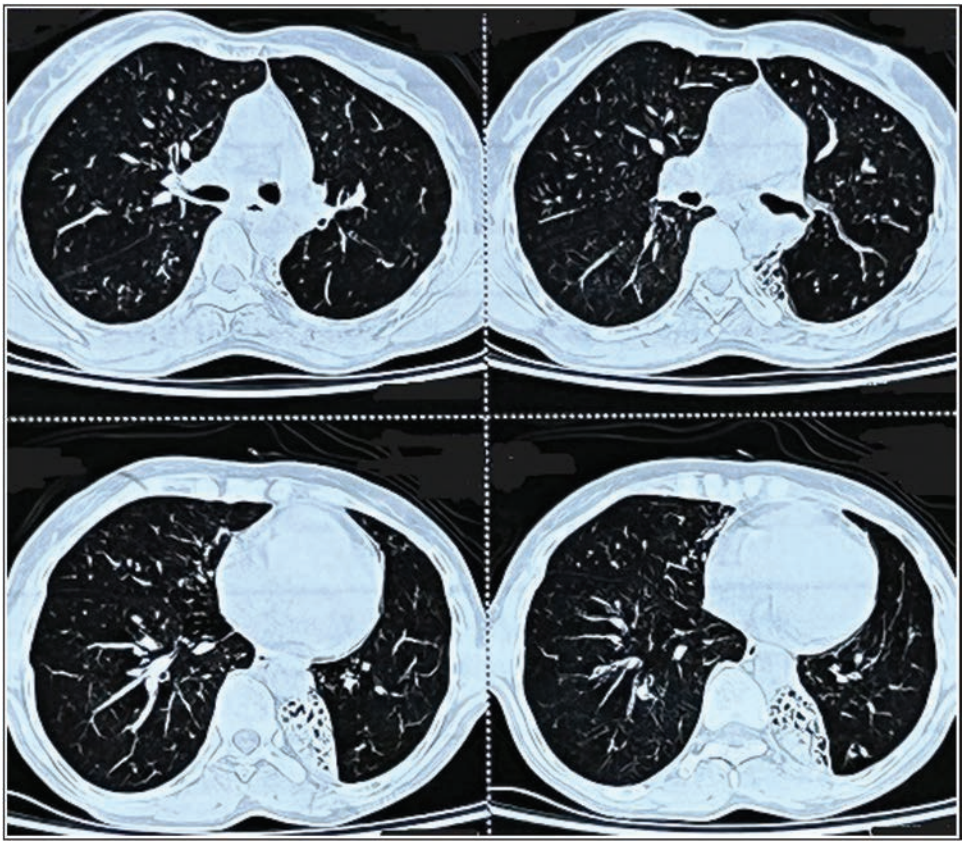

**Figure 3:** HRCT thorax showing the left lower lobe posterior basal segment consolidation

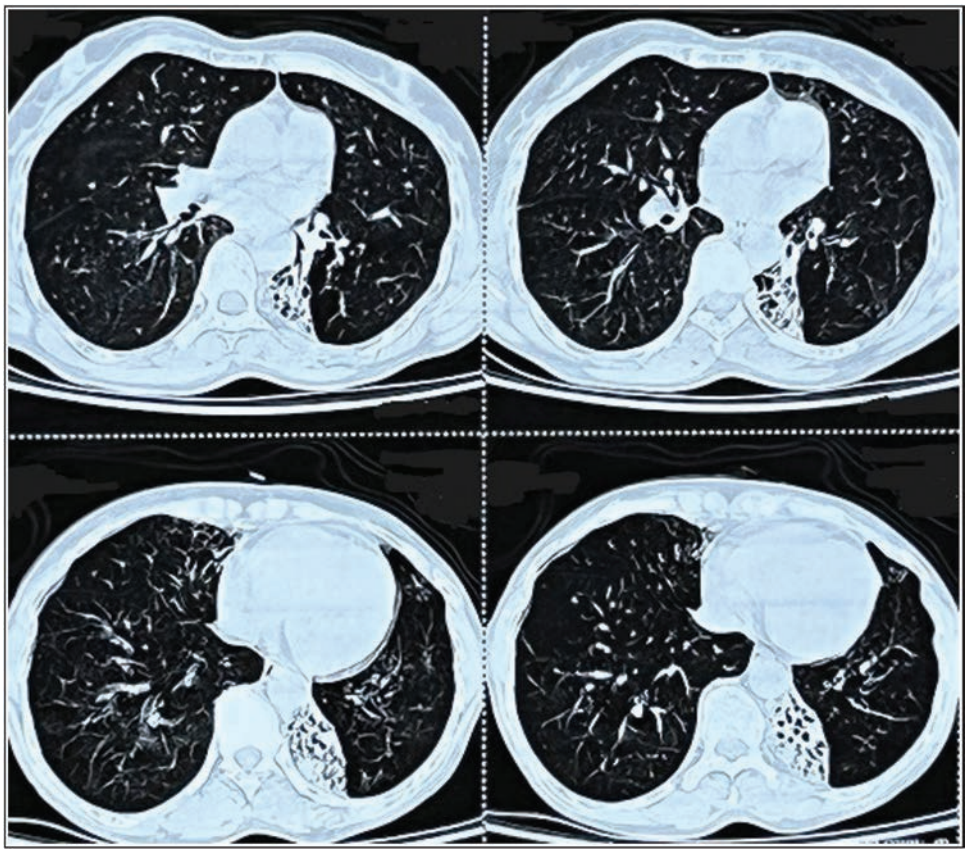

**Figure 4:** HRCT thorax showing the left lower lobe posterior basal segment collapse with consolidation

with advice for strict anti-TB treatment as four drugs in the first 2 months (HRZE) and three drugs in the next 4 months (HRE) as per the NTEP national guidelines for TB treatment. Microbiological examination documented negative *M. tuberculosis* genome in sputum at 2 months of treatment. We have documented weight gain and general health improvement with best compliance to anti-TB treatment and observed the importance of counseling.

## DISCUSSION

Lower lung field TB (LLF TB ) is defined as "TB disease found below an imaginary line traced across the hila and including the parahilar regions on a standard posterior–anterior chest roentgenogram." Ossen subdivided his cases into pure and impure groups: the pure group has no visible lesions in the upper lung fields and the impure group has nodular or fibrotic infiltrations in one or both apices. Other terms used for the same entity are "basal, lower lobe, hilar, parahilar, and perihilar tuberculosis."[5,6] The most likely explanation for the development of LLF TB is transbronchial perforation of a hilar lymph node, with spread to the adjacent lung. Thus, lower lung field disease occurs as a continuation of the primary TB infection or soon afterward in the postprimary period. This explanation is consistent with the high incidence of endobronchial involvement and with reported clinical and radiologic observations. A diagnosis of endobronchial disease is made when bronchoscopic evidence of stenosis or severe tracheobronchitis is detected or when there is roentgenographic evidence of atelectasis or tension cavities.[7] Other mechanisms postulated in the pathogenesis of LLF TB are restricted ventilation, costal breathing, and retrograde lymphatic flow from involved hilar nodes. It does not appear that patients with lower lung field disease have especially lowered resistance to TB. According to previous studies, the following conditions occur more frequently in patients with LLF TB than in general population with TB: diabetes mellitus, pregnancy, advanced age, malignancies, and advanced liver and renal diseases.[8-10] Kirtland and Winterbauer[11] had empirically defined slowly resolving pneumonia in immune-competent patients as either less than 50% clearing at 2 weeks or less than complete clearance at 4 weeks in a patient who has defervesced and symptomatically improved with antibiotic therapy. Normal resolution of pneumonia is not easily defined. It can vary depending on the infecting organism and the host's immune status. Patients typically note subjective improvement within 3–5 days of initiation of treatment. Nonresolving pneumonia (NRP) is defined as pneumonia with a slow resolution of radiographic infiltrates or clinical symptoms despite adequate antibiotic treatment (10–14 days). This can be due to defects in local or systemic immune defense mechanisms and due to the presence of unusual organism, resistant bacteria, or diseases that mimic pneumonia.[12]

"Triangle sign" and left lower lobe collapse: A Triangular opacity in the posteromedial aspect of the left lung in the retrocardiac region called "Sail sign, Triangle sign, or double left heart border sign." The second heart border is due to the dense edge of the collapsed the left lower lobe, which has been squashed into a triangle or sail shape as documented in our patient.[13] The left lower lobe collapse is readily identified on a well-penetrated radiograph of a patient with a normal-sized heart but can be challenging in the typical patient with collapse. Importantly, in Triangle sign left hemidiaphragm cannot be followed all the way to the spine. This is because the left lower lobe sits directly on top of the diaphragm, and as it no longer contains air, it is of the same soft tissue density as the diaphragm and, therefore, blends into it. Triangle sign may be documented due to collapse of left lower lobe due to endobronchial obstruction secondary to mucous plug, foreign body, bronchomalacia, endobronchial TB, benign or malignant lung process leading to endobronchial, submucosal or peribronchial growth.[7,14,15] A proportionate number of NRP cases are having LLF TB, and a high index of suspicion is a must while evaluating these cases.[16]

## CONCLUSION

In the present case report, we have documented constitutional symptoms with "Triangle sign" in chest radiograph which is underestimated due to lack of knowledge and finally diagnosed as left lower lung field Pulmonary TB. Sputum examinations were inconclusive, and bronchoscopy has documented a crucial role in diagnosing left LLF TB. We have documented improvement in clinical, microbiological, and radiological manifestations with ATT as per NTEP schedule. Triangle sign is usually underestimated and easily missed if not adequately trained in chest radiology.

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Nil.

### Conflicts of interest
There are no conflicts of interest.

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Case Report

# Burst suppression pattern on EEG in West syndrome in an infant with heterozygous variant in the CACNA1A gene

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**Abstract**

West syndrome is a severe epilepsy syndrome characterized by the classical triad of infantile spasms, hypsarrhythmia on electroencephalography (EEG) and psychomotor retardation. The classical hypsarrhythmia pattern on EEG consists of a high amplitude, arrhythmic, disorganized background with multifocal spikes and slow and sharp waves. The burst suppression (BS) pattern on EEG is a less commonly described pattern in West syndrome. Among the genetic causes of West syndrome, mutations in the CACNA1A gene are rarely reported. We hereby report a BS pattern on EEG in an infant with West syndrome with heterozygous variant in the CACNA1A gene.

**Keywords:** Burst suppression pattern on EEG, CACNA1A gene, modified hypsarrhythmia, west syndrome

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## INTRODUCTION

West syndrome is a severe, epileptic encephalopathy occurring in infancy and early childhood, characterized by infantile spasms (IS), developmental delay/regression, and a pathognomonic electroencephalography (EEG) pattern of hypsarrhythmia.[1] The classical hypsarrhythmia pattern is described as multifocal spike activity over a high voltage chaotic slow wave background. Various modified hypsarrhythmia patterns are described, of which burst suppression (BS) is an uncommon pattern.

## CASE REPORT

A 4.5-month-old baby girl was brought with complaints of multiple episodes of abnormal flexion of the head and flexion and adduction of all limbs, lasting a few seconds for the past 3 days. She was the firstborn child of a nonconsanguineous parentage with uneventful antenatal history; she was born term by cesarean section and had a birth weight of 3.1 kg. She had neonatal hyperbilirubinemia, for which phototherapy was given for 1 day. She had attained all developmental milestones normally till 4.5 months of age. For the past 3 days, the mother noticed that the baby was having recurrent episodes of flexor spasms with staring spells lasting for around 20 s; she had 4–5 episodes per day. After the onset of these episodes, the mother noted that the baby had a mild regression of the milestones attained. EEG was taken, which showed frequent bursts of multifocal spike and wave discharges followed by suppression of background, suggestive of a BS pattern indicating a modified hypsarrhythmia [Figure 1]. Magnetic resonance imaging brain with contrast was

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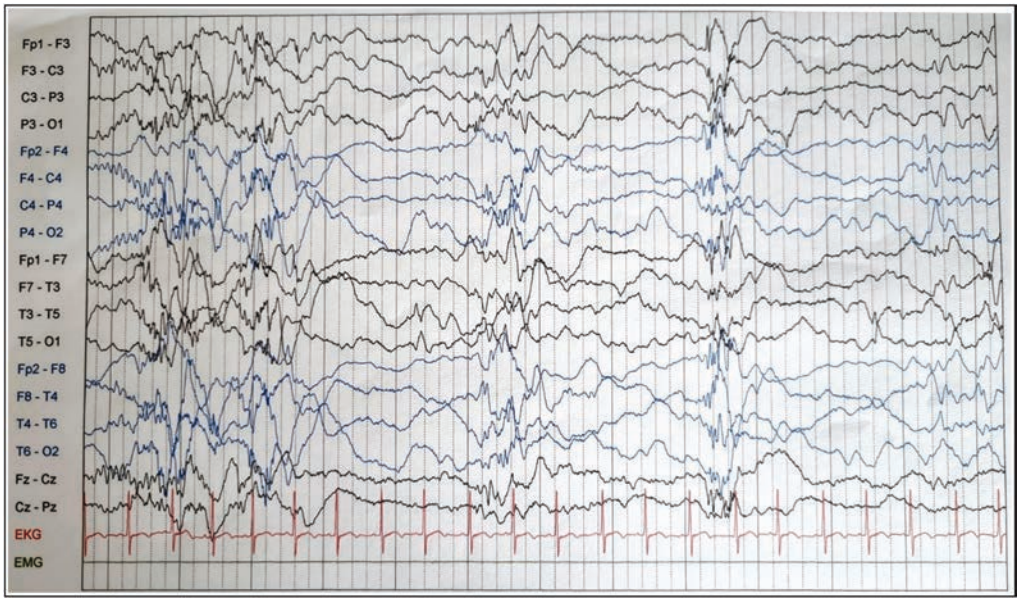


**Figure 1:** Electroencephalography showing frequent bursts of multifocal spike and wave discharges followed by suppression of background, suggestive of burst suppression pattern indicating a modified hypsarrhythmia

| Gene* (Transcript) | Location | Variant | Zygosity | Disease (OMIM) | Inheritance | Classification |
|---|---|---|---|---|---|---|
| ***TREX1* (+)** (ENST00000625293.3) | Exon 2 | c.340C>T **(p.Arg114Cys)** | Heterozygous** | Aicardi-Goutieres syndrome 1 (OMIM#225750) | Autosomal dominant; Autosomal recessive** | Uncertain Significance **(PM2,PP3)** |
| ***CACNA1A* (-)** (ENST00000360228.11) | Exon 23 | c.3844G>A **(p.Val1282Ile)** | Heterozygous | Developmental and epileptic encephalopathy 42 (OMIM#617106) | Autosomal dominant | Uncertain Significance **(PM2)** |

**Figure 2:** Whole exome sequencing report depicting two variants in two genes

normal. An inborn error of metabolism screening was done, which was also normal. Whole exome sequencing revealed two heterozygous variants in the CACNA1A gene (variant c.3844G>A) and TREX 1gene (variant c.340C>T); however, both variants were of uncertain significance related to the given phenotype [Figure 2]. The chromatogram is attached [Figures 3 and 4]. The diagnosis of West syndrome was made, and the baby was initiated on injection adrenocorticotropic hormone (ACTH), initially at a dose of 20 units/ day for 1 week; however, there was no decrease in the frequency of IS, so ACTH was increased to 40 units per day and was given for 3 weeks after which the frequency of the seizures reduced significantly. No other antiepileptic drugs were added. Repeat EEG taken after 2 weeks and 4 weeks of initiation of therapy showed persistence of BS pattern.

## DISCUSSION

West syndrome is characterized by the classical triad of IS, hypsarrhythmia on EEG and psychomotor retardation.[1] The IS in West syndrome usually appears by the age of 4–9 months, with a peak around 6 months of age. Developmental arrest or regression of already attained milestones usually develops with the occurrence of epileptic spasms. The classical hypsarrhythmia in EEG pattern in West syndrome is described as a chaotic and disorganized high amplitude slow background with multifocal epileptiform activity in the form of sharp waves and spike and wave discharges.[1,2] Modified hypsarrhythmia patterns include hemispheric synchronization, hypsarrhythmia with a consistent focus, hypsarrhythmia with voltage attenuation, or hypsarrhythmia with few spikes or sharp waves. Kramer *et al.*[3] studied the EEG features of 53 patients with epileptic spasms and analyzed for the severity of the following: disorganization of background, slowing, high amplitude, and spike activity. They also looked for the presence or absence of each of the following patterns and variants: electrodecremental discharges, relative normalization, absence of normal sleep activity, BS, hemihypsarrhythmia, occipital hypsarrhythmia, interhemispheric asymmetry, and interhemispheric synchronization; they observed that hypsarrhythmia variant patterns occurred frequently in up

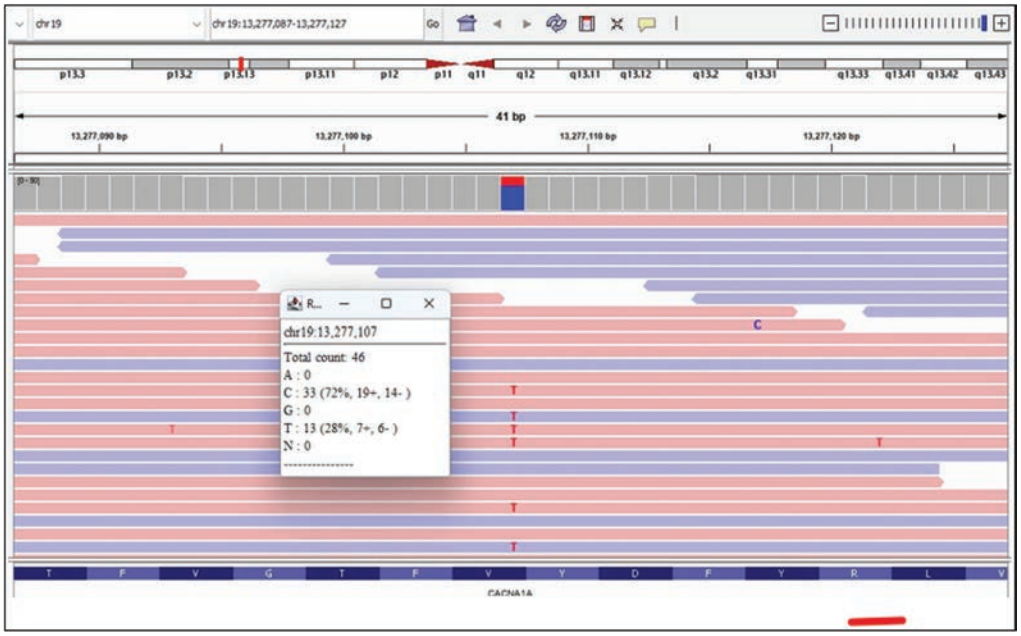


**Figure 3:** Chromatogram of the variant identified in the CACNA1A gene

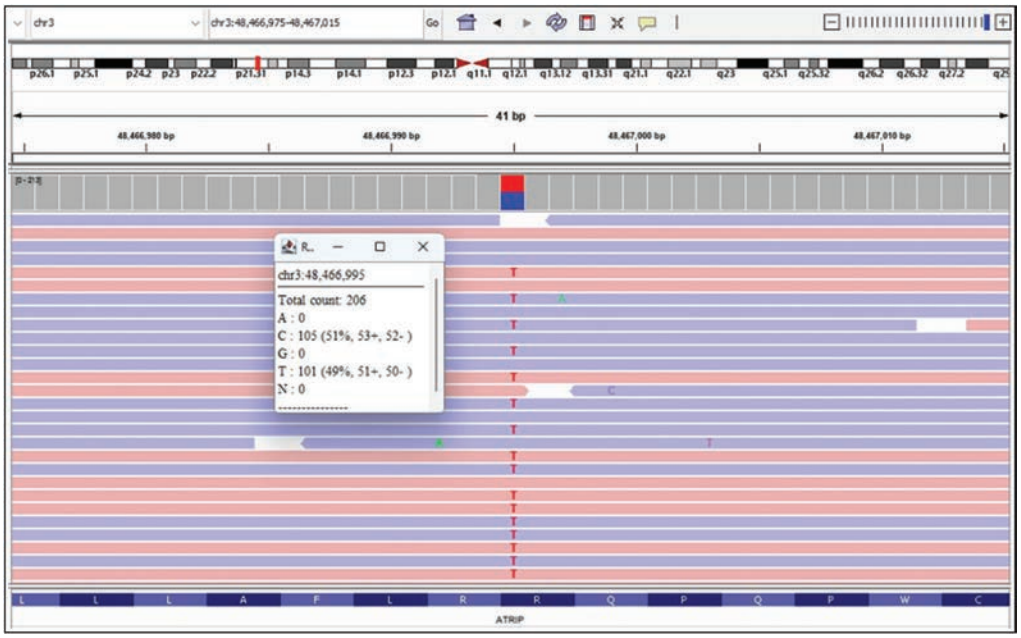


**Figure 4:** Chromatogram of the variant identified in the TREX1 gene

to 69% of the records. Kramer scoring system is one of the commonly used scoring systems used to define and assess the severity of hypsarrhythmia and in this scoring system, the presence of BS pattern indicates a severe type of presentation.[4] Our patient had a BS pattern, indicating a severe disease.

Many genes have been implicated in the pathogenesis of West syndrome and early infantile epileptic encephalopathies (EIEE); some of the candidate genes described are ATP2A2, CD99L2, CLCN6, CYFIP1, CYFIP2, GNB1, GPT2, HUWE1, KMT2D, MYO18A, NOS3, RYR1, RYR2, RYR3, TAF1, TECTA, and UBA1.[5] Several causal genes of EIEE are involved in the calcium-signaling pathway, including CACNA1A, which encodes the P/Q-type calcium channel alpha subunit; dysfunction in this pathway causes increased excitability of neurons leading to epileptiform discharges.[5] A 19p13.2 deletion disrupting CACNA1A was reported in a patient with West syndrome.[6] In a study by Li *et al.*[7] on more than 400 patients with epilepsy, whole exome sequencing was performed, and they observed that CACNA1A mutations were potentially associated with pure

epilepsy with phenotypes ranging from the mild form of epilepsies to the severe form of developmental epileptic encephalopathy. Another study on epileptic encephalopathies where whole exome sequencing was done also emphasized the importance of CACNA1A gene mutations.[8] In the study by Niu *et al.*[9] that aimed to explore the genotypes and phenotypes of *CACNA1A* variants in children with epilepsy, it was noted that CACNA1A variants had early seizure onset and developmental delay. Roux *et al.*[10] have concluded in their study that the phenotype of *CACNA1A*-associated epilepsy is very broad and usually severe, with most patients having refractory seizures and status epilepticus. Our patient had a heterozygous variant in the CACNA1A gene (variant c.3844G>A) and TREX 1gene. Mutations in the TREX1 gene have been reported in cases of Aicardi–Goutières syndrome, which is an early-onset encephalopathy characterized by intracranial calcification, leukoencephalopathy, and cerebral atrophy. However, there are no reports linking TREX 1 gene to West syndrome.

There are no previously published reports of BS pattern in West syndrome with a documented heterozygous variant in the CACNA1A gene. West syndrome is a severe epileptic encephalopathy syndrome that should be recognized early, and treatment should be initiated as soon as possible. Though less described, the BS pattern is a modified hypsarrhythmia pattern that should alert the treating physician to the diagnosis of West syndrome.

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## Conflicts of interest

There are no conflicts of interest.

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# Hurdles of neuropsychological testing and rehabilitation during COVID-19 pandemic

The COVID-19 pandemic has imposed a restriction on people, forcing them to adapt to an altered lifestyle. World Health Organization asked everyone to wear a facemask and maintain one meter of physical distance to prevent disease transmission. This new protocol has brzought in a huge alteration in healthcare facilities as well. Attending healthcare facilities physically sometimes is avoided and virtual medium is preferred. Face-to-face consultation is replaced with tele-consultation.[1] In low and low middle income countries (LMIC) like India a large part of the society has difficulty in accessing the virtual medium due to difficulties in finance, access to technology, and lack of technical literacy. Avoiding physical presence in healthcare facilities, often led to delay in medical examinations and diagnosis.[2]

Dementia sufferers and their care-givers have been experiencing tremendous difficulties in this pandemic.[3] For diagnostic purpose of cognitive impairment, it is necessary to conduct neuropsychological examinations which have a standard operating procedure on multiple occasions. But due to lack of public transportation many patients could not visit the hospital and individually reaching out to their home was not economic either. Neuropsychological examinations are mostly conducted in a face-to-face manner by the test administrator. There is generally exchange of testing materials between the test administrator and the patient. The COVID-19 protocols often hamper the successful neuropsychological assessment. Conducting test while wearing a facemask and maintaining physical distance becomes difficult. The time required for testing increases and thus, the process does not remain economic. Also sharing of test materials mandates frequent sanitization of materials, which is time-consuming and costly. Moreover, having separate sets of testing materials for each patient is not economic especially in LMIC.

Treatment of dementia encompasses not only pharmacotherapy but also cognitive rehabilitation which is often conducted by professionals in special care at day-care settings. Active social interactions and activities are essential for rehabilitation. Owing to the pandemic, social activities of elderly sufferers have jeopardized largely. Caregiving for them also becomes complicated. Following COVID-19-related lockdown most of the day-care centers are closed. The resultant change in the routine becomes difficult to adapt for the dementia sufferers.

New strategies need to be adapted for both neuropsychological testing and rehabilitation while not hampering the testing protocols and following COVID-19-related safety measures. Table 1 provides strategies which were employed to overcome some of these difficulties. Some other probable justified solutions to these problems are being discussed henceforth.

Communication is the act of exchanging information which can be done through verbal and non-verbal means. During neuropsychological testing generally an emphasis is put on both verbal communications, that is, emphasize on the words that are articulated; and also, the non-verbal communication which is mediated by various parts of the body, for example, facial expression, hand gesture etc. Facemask covers a greater part of the face and sometimes even makes verbal communication difficult. Use of transparent facemask can overcome the situation to some extent. Transparent facemask will help to see the lip movements and other facial expression.[4] Clear articulation of words and using a mini speaker may help the patient hear distinctly.

Alternate strategies may also encompass the usage of virtual medium.[5] The pandemic has brought in a drastic increase in usage of digital platform for work.[6] Conducting tests and cognitive rehabilitation programs through video conferencing can be an alternative in this pandemic. Distance administration of the tests through video calls can help in this regard. The test administrator and the patient may join over a video call, where the patient can answer to the questions asked over video call. Pencil and paper tests can also be administered in this format where the subject performs a test under video supervision and then share the performance with the test administrator. Aid from caregiver might be helpful in this situation, who can adjust the camera, supply the materials if required or also help with technical support for elderly people.

Digital divide is commonly experienced in this situation in LMIC where a section of the society is not accustomed with the virtual medium.[7] In contrast, applications or software can be developed to help in remote administration and scoring of these tests. This digitalization and virtual administration of the tests can continue even after the pandemic period. For this purpose, the interface needs to be simple so that clients and care-givers understand easily.

**Table 1: Hurdles that were commonly experienced and their solutions**

| Case vignette | How they were dealt with |
|---|---|
| 1)Mrs. M.D., a 55 years old illiterate lady with presenting complaint of forgetting, hallucination and irrelevant speech at times. She also had difficulty in hearing. She visited the hospital for neuropsychological testing. The difficulty faced for conducting the test was because of her hearing impairment, which became more evident by covering the face of the test administration with facemask and keeping 6 feet distance. | Family members of the client were asked to come in rescue. They sat near the client and repeated the verbatim said by the test administrator. |
| 2) Mr C.C, a 70 years old gentleman. Of late he is forgetting his daily chores. He talks in a feeble voice. He came to the hospital wearing double mask and a face shield. He is barely audible at the time of neuropsychological testing. | The neuropsychological testing was conducted in a room where there was minimum noise. No one except the test administrator and the client was allowed in the room. All electrical devices were temporarily turned off to minimise the noise produced out of them. |
| 3) Mr. D.B. is 60 years old gentleman. Of late he is forgetting any instruction given to him quite frequently. During the testing session he frequently removed his mask as he felt uncomfortable wearing it. | In addition to a surgical facemask, he was also made to wear a face shield. |
| 4) Mrs. A.B is 65 years old lady who was diagnosed with Alzheimer's disease 3 years ago. She used to visit a day-care facility thrice a week, where various neuropsychological rehabilitating activities took place. The day-care facility has been closed since lockdown. Mrs A.B. frequently forgets that the day-care is closed and ask her family members as to when can she go there again. | Group therapy was conducted through video calling facilities. |

Cognitive retraining pertaining to dementia can be digitalized too. Programed learning material in time-based modules can be developed to cater to the individualized rehabilitation needs. These modules can be designed and supervised by the cognitive therapist as per subject's requirement. Moreover, group therapy or group activities can be conducted through virtual medium. Interaction even if through online platform may help in socialization and other cognitive rehabilitation tasks that are usually practiced in day-care centers.

LMIC have the pressing need of adapting to the digital revolution and the pandemic has accelerated the process.

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## Conflicts of interest

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