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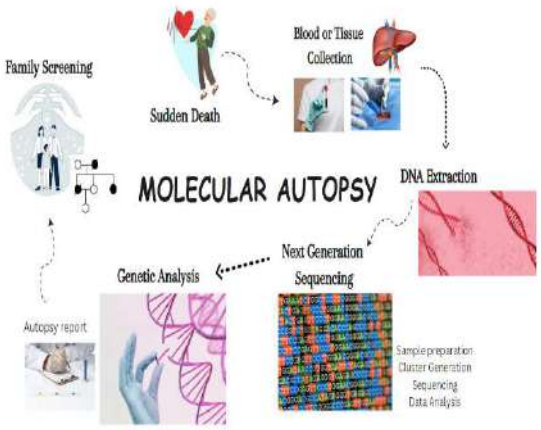

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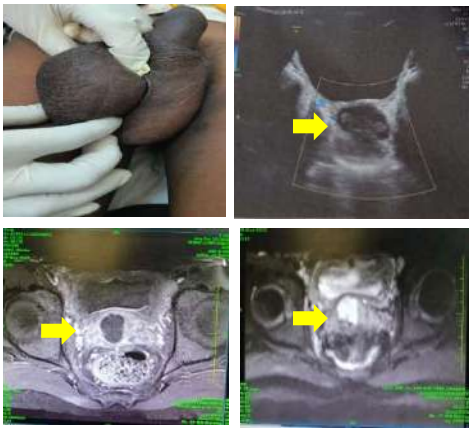
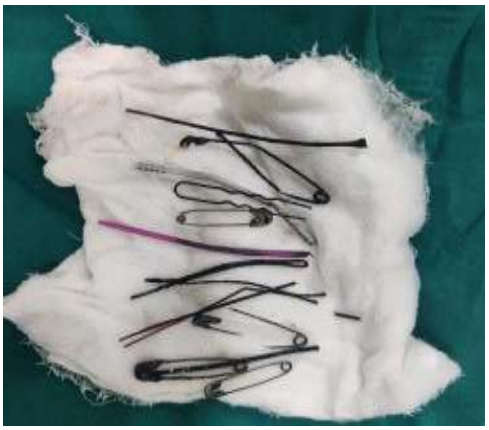
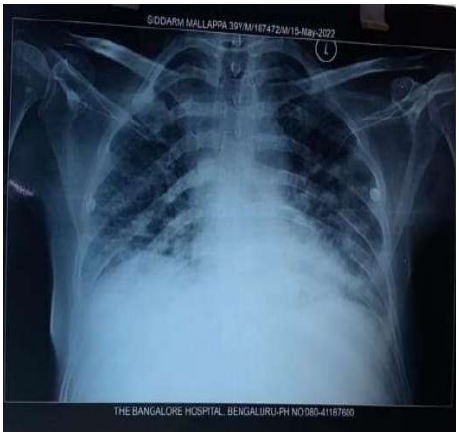


a. Right sided epididymo-orchitis; b. USG–Multiple hypoechoic; c. MRI–Hypointense collection in the prostate d. MRI–Prostatic abscess



Eighteen foreign bodies removed from the patient's penile urethra.



Lipiodol Embolism with Pneumonitis

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EDITORIAL

Present, Past and Future of 'Family Medicine' Practice in India

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There is an ever-increasing recognition of the importance of primary healthcare and the need for skilled family physicians in the Indian healthcare system. National Board of Examination in Medical Sciences (NBEMS) offers a post graduate Diplomate of the National Board (DNB) course in Family Medicine. Such a course would help bridge the gap between the demand for primary healthcare services and the availability of adequately trained family physicians. The delivery of holistic treatment and preventive medicine strongly counters the unnecessary burden on limited tertiary hospitals [1].

The DNB course in Family Medicine is focused to provide specialized training to medical graduates in comprehensive and continuing care for individuals and families. It would focus on equipping doctors with the necessary skills to address a wide range of medical conditions, preventive care, and health promotion. The course would emphasize the principles of holistic and patient-centered care, continuity of care, and community orientation.

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The concept of Family Medicine

Primary Healthcare

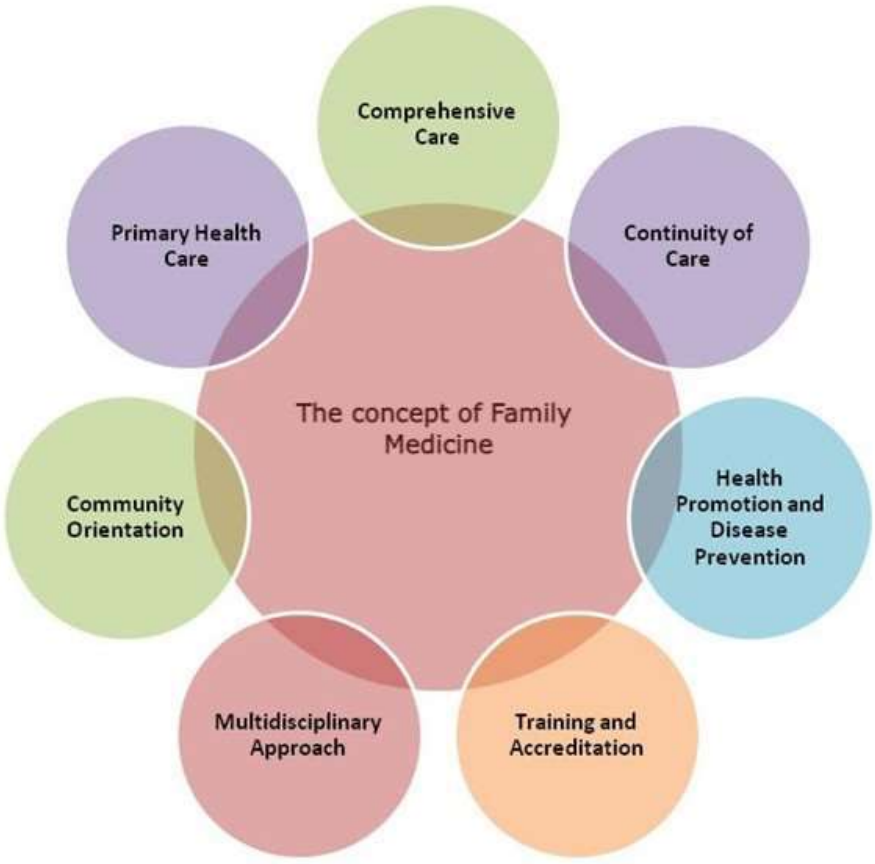
Family medicine serves as the first point of contact for individuals seeking medical care. Family physicians are trained to diagnose and treat a wide range of common illnesses and injuries. They are equipped to handle various medical conditions and offer preventive services such as vaccinations, health check-ups, and screening tests.

Continuity of Care

Family physicians in India emphasize building long-term relationships with their patients. They provide continuous care by managing chronic conditions, monitoring progress, and coordinating care with specialists when necessary. This continuity helps in better understanding the patient's health history, family dynamics, and individual needs.

Comprehensive Care

Family medicine aims to provide comprehensive care to patients of all ages and genders. Family physicians are trained in managing a broad spectrum of medical conditions across different organ systems. They address acute illnesses, chronic diseases, mental health concerns, and promote overall well-being.



Health Promotion and Disease Prevention

Family physicians play a crucial role in promoting health and preventing diseases. They provide counseling on lifestyle modifications, healthy eating habits, physical activity, and stress management. They also offer preventive services such as immunizations, screenings for various diseases, and early detection of risk factors.

Community Orientation

Family medicine in India recognizes the importance of community-oriented healthcare. Family physicians often work in primary healthcare centers, community health clinics, and private practices. They understand the local health needs, socioeconomic factors, and cultural influences that impact the health of individuals and families.

Multidisciplinary Approach

Family physicians collaborate with other healthcare professionals to ensure comprehensive care. They work closely with specialists, nurses, pharmacists, and allied health professionals to provide a holistic approach to healthcare delivery. This interdisciplinary collaboration enhances patient outcomes and promotes efficient healthcare utilization.

Training and Accreditation

In India, family medicine is gaining recognition as a distinct medical specialty. Several medical institutions and universities offer postgraduate programs in family medicine, providing specialized training to medical graduates. The National Medical Council (NMC) has also established guidelines and accreditation processes for family medicine training programs.

Family Medicine–Global Scenario

Family medicine in India shares many similarities with its counterparts around the world, as the principles and goals of providing comprehensive and primary healthcare remain consistent. However, there are also some notable differences influenced by factors such as healthcare systems, cultural contexts, and educational frameworks. In many countries, family medicine is recognized as a distinct medical specialty, with dedicated training programs and board certifications. This recognition allows family physicians to have a defined career path within the healthcare system. In India, while family medicine is gaining recognition, it is still in the process of being established as an independent specialty with standardized training and accreditation.

The healthcare systems across the world vary, and family medicine adapts to the specific needs of each country. In some countries, like the United States, family physicians often work in private practices, while in others, like the United Kingdom, they are integrated into the public healthcare system. In India, family physicians work in various settings, including private practices, primary healthcare centers, and community health clinics. The scope of practice for family physicians may vary across countries due to variations in healthcare systems and regulations. In some countries, family physicians are the primary healthcare providers, managing a wide range of medical conditions, performing minor procedures, and coordinating care with specialists. In

India, family physicians generally provide primary healthcare services, but the scope of practice may depend on the specific setting and the healthcare resources available.

Cultural factors can influence the practice of family medicine. In countries like India, where family and community play a significant role in healthcare decision-making, family physicians may need to consider the cultural beliefs, preferences, and dynamics of the patients and their families. This cultural context can impact the approach to healthcare delivery and patient management.

The training and education of family physicians can vary across different countries. Some countries have well-established residency programs and postgraduate courses specifically in family medicine. This program focuses on equipping physicians with the skills necessary for comprehensive and primary care. In India, while postgraduate programs in family medicine are being developed, the training pathways and standards are still evolving. Family medicine research and evidence-based practice contribute to the development and improvement of healthcare services. The focus and extent of research in family medicine may vary between countries. In countries with well-established family medicine programs, research is often conducted to address the specific healthcare needs and challenges of the population.

Initiative taken by the Govt. of India to promote and strengthen Family Medicine

The Government of India has taken several initiatives to promote family medicine and strengthen primary healthcare services in the country. Such as the following:

National Health Policy 2017

The National Health Policy emphasizes the need for strengthening primary healthcare services and promoting family medicine. It recognizes family medicine as a critical component of the healthcare system and highlights the importance of training and capacity building in this field.

National Health Mission (NHM)

The NHM, aims to provide accessible, affordable, and quality healthcare to all citizens, with a focus on rural and underserved areas. Under the NHM, initiatives have been taken to improve primary healthcare services, including the establishment of Primary Health Centers (PHCs) and Community Health Centers (CHCs) staffed by family physicians and other healthcare professionals.

National Board of Examinations (NBE)

The NBE, under the Ministry of Health and Family Welfare, is responsible for postgraduate medical education and training. It has been involved in the development of postgraduate programs in family medicine, such as the Diplomate of National Board (DNB) course in Family Medicine.

Collaboration with International Organizations

The government has collaborated with international organizations, such as the World Health Organization (WHO) and the World Organization of Family Doctors (WONCA), to promote family medicine.

These collaborations aim to enhance training programs, share best practices, and strengthen the role of family physicians in primary healthcare delivery.

Skill Development Programs

The government has launched skill development programs to enhance the capabilities of healthcare professionals, including family physicians. These programs focus on improving clinical skills, diagnostic abilities, and management of common medical conditions encountered in primary care settings.

The future of Family Medicine in India

The future of the family medicine course in India holds great potential for growth and development. While the field of family medicine is still in the process of gaining recognition and standardization in India, there are several factors that indicate a positive outlook for its future. As India continues to face healthcare challenges, there is a growing recognition of the importance of primary healthcare in addressing the healthcare needs of the population. Family medicine, with its focus on comprehensive and primary care, is well-suited to meet this demand. The Government of India has demonstrated its commitment to strengthening primary healthcare services and promoting family medicine through various initiatives. These initiatives include the National Health Policy, the National Health Mission, and collaborations with international organizations. Continued government support is likely to drive the development of family medicine in India.

Organizations like the IMA and AFPI have been actively advocating for the recognition and establishment of family medicine as a specialty in India. Their efforts,

along with the growing awareness among healthcare professionals and the public, are likely to contribute to the future growth of family medicine.

Postgraduate training programs in family medicine, such as the Diplomate of National Board (DNB) course in Family Medicine, are being developed and implemented in India. This program aims to provide specialized training to medical graduates and equip them with the necessary skills to practice family medicine effectively. Collaboration with international organizations and sharing of best practices in family medicine can contribute to the growth and development of the field in India. Learning from experiences and successful models from other countries can help in shaping the future direction of family medicine education, training, and practice in India. The development of a robust, research and evidence base, specific to family medicine in India can further support its growth. Research studies focusing on the effectiveness and outcomes of family medicine practice can provide valuable insights and guide policy decisions.

Family medicine, also known as general practice, is a medical specialty that focuses on comprehensive healthcare for individuals and families. In India, the concept of family medicine has gained recognition and importance due to its ability to provide primary healthcare services, preventive care, and continuity of care. Family medicine in India revolves around the principles of a holistic and patient-centered approach to healthcare

While the future of family medicine in India looks promising, it will require sustained efforts from all stakeholders, including healthcare professionals, educational institutions, regulatory bodies, and policymakers. Continued advocacy, standardization of training programs, and integration of family medicine into the healthcare system will be crucial in shaping the future landscape of family medicine in India.

Conflicts of interest

The authors declares that they do not have conflict of interest.

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ORIGINAL ARTICLE

Risk of hypospadias due to use of Pesticides among the rural families of Haryana, Uttar Pradesh and Bihar in India: An AIIMS-Delhi study highlighting the risk on agriculture produce in Pregnant Mothers & the importance of regulatory controls in the prevention of Birth Defects in Children

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Abstract:

Introduction: The potential risk of hypospadias in children born to mothers living close to agricultural area where pesticides are used has been a topic of interest in scientific research. The present study aimed to analyze the risk of hypospadias in families living under the direct exposure to pesticide and families living under no direct exposure of pesticides.

Material & Methods: The present study includes 129 patients with hypospadias who underwent reconstructive surgery by a single surgeon single institution. The odds ratio (OR) of hypospadias risk has been calculated with common controls. All the patients divided in two groups one with direct exposure to pesticide i.e. farmers and other is no direct exposure i.e. profession other than farming.

Results: The ORs were consistently greater in group 1, indicating an increased risk of hypospadias. Patients with direct exposure to pesticides showed a significantly higher OR when compared to patients without direct exposure to pesticides and common controls.

Conclusion: The study found a significant association between hypospadias occurrence and pregnant mothers' with direct exposure to the pesticide. The OR was greater than 1 with highly significant p value of <0.001. The fall out of this study has serious implication on agriculture produce, particularly of interest would be designing further studies on tea plantations, vineyards & beer manufacturing units.

Keywords: Hypospadias, Pesticide, Agriculture, Environmental factors, Endocrine disruptors

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Introduction

Hypospadias is a congenital condition where the urethral opening (meatus) is abnormally located on the ventral (underside) of the penis, rather than at the tip. It is a defect in the development of the urethra during fetal development, typically occurring between the 8th and 16th week of pregnancy. In a normal male urinary tract development, the urethral groove in the developing penis closes from the tip to the base, forming a tube that eventually becomes the urethra. In hypospadias, this closure process is disrupted, resulting in an opening that may be located anywhere along the underside of the penis, such as the head (glans), shaft, or even near the scrotum. Hypospadias is classified based on the location of the meatus, with different degrees of severity ranging from mild to severe. It is one of the most common birth defects affecting the male genitalia, occurring in approximately 1 in 200 to 300 live male births. Surgical correction is the main treatment for hypospadias, typically performed in early childhood. The aim of the surgery is to reposition the urethral opening to the tip of the penis and create a normal-looking and functional penis. The specific surgical technique used depends on the severity and location of the hypospadias. Regular follow-up care is also necessary to monitor the long-term outcomes and address any potential complications.

Epidemiology of hypospadias

The epidemiology of hypospadias has shown significant variation and remains imprecise. Incidence rates have differed across populations and time periods. According to the study conducted by Xiao Yu et al. estimated an incidence of 8 per 10,000 live male births in United States [1], while another study conducted by Bergman JE et al. an incidence of 18.6 per 10,000 births by 23 European national registries. It is worth noting that these estimates are not current and may have changed since then [2].

While a small percentage of hypospadias cases are associated with rare monogenic syndromes, the majority of cases are considered "idiopathic," meaning the cause is unknown. It is believed that a complex interplay between genetic variants and environmental factors during development may contribute to the development of hypospadias. There is evidence of a genetic predisposition, as first-degree relatives of individuals with hypospadias have a significantly increased risk of the condition (12 to 20-fold higher). Genome-wide studies have identified a few low-risk genetic variants associated with hypospadias, but the understanding of the genetic factors involved is still limited. Additionally, research into epigenetic factors, such as DNA methylation, is ongoing and may provide further insights into the development of hypospadias [3].

The contribution of environmental factors to hypospadias is presumed to be significant but has been challenging to assess. Some studies have suggested a possible link between hypospadias and decreasing male fertility, indicating the existence of a “testicular dysgenetic syndrome” in developed countries. However, further research is needed to understand the exact role of environmental factors, including exposure to agricultural pesticides and other suspected endocrine-disrupting substances [4].

Use of pesticides and risk of hypospadias

There has been scientific interest in investigating the potential association between pesticide exposure and the risk of hypospadias. Pesticides are chemicals used in agriculture, and some studies have suggested that certain pesticides may have endocrine-disrupting properties, meaning they can interfere with hormonal regulation and development [5]. Several epidemiological studies have explored the possible link between pesticide exposure and the risk of hypospadias, but the findings have

been mixed, and more research is needed to establish a clearer understanding of the relationship. Some studies have reported positive associations, while others have found no significant association or inconsistent results [6-8]. A meta-analysis published by Rocheleau CM examined the association between pesticide exposure and hypospadias risk. The analysis included 19 studies and concluded that there was a weak positive association between pesticide exposure and hypospadias risk. However, the authors noted limitations in the available data, including variations in study designs, exposure assessment methods, and potential confounding factors [9].

It's important to note that assessing the specific impact of pesticides on these conditions is challenging due to various factors, including the complexity of pesticide mixtures, differences in exposure levels, variations in study designs, and potential confounding factors. Furthermore, studies often rely on self-reported or indirect measures of pesticide exposure, which can introduce measurement errors.

The use of hazardous pesticides in agriculture

In India, several hazardous pesticides, insecticides, and fertilizers are commonly used in agricultural practices. While the use of pesticides and insecticides is intended to protect crops from pests and diseases, improper handling or excessive use can pose risks to human health and the environment. It's important to note that specific pesticide use may vary depending on the region, crop, and farming practices. The commonly used hazardous pesticides, insecticides, and fertilizers in India are organophosphates, pyrethroids, neonicotinoids, carbamates, glyphosate, and urea.

The risk of living close to agriculture area

The potential risk of hypospadias in children born to mothers living close to agricultural area where pesticides are used has been a topic of interest in scientific research. Pesticides used in agriculture have raised concerns due to their potential endocrine-disrupting properties and potential adverse effects on human health. Several studies have examined the association between maternal residential proximity to agricultural areas and the risk of hypospadias in offspring. However, it's important to note that findings from these studies have been inconsistent, and more research is needed to establish a clear link [9].

To gain a comprehensive understanding of the potential risk, it is essential to consider multiple factors such as the specific types of pesticides used, application methods, timing of exposure, and individual susceptibility. Additionally, regulations, pesticide management practices, and safety precautions in agricultural areas can vary across regions and countries, affecting the potential risk.

Methodology

The present study includes patients with hypospadias who underwent reconstructive surgery by a single surgeon (MB) at Department of Paediatric Surgery, All India Institute of Medical Sciences, New Delhi (India). The clinically significant cases that required surgical intervention were included in the study, while minimal glandular hypospadias cases that did not undergo surgery were excluded. The demographic data collection was conducted at Wednesday Paediatric Urology Clinic (WPUC), All India Institute of Medical Sciences, New Delhi (India) at the time of registration.

Inclusion and exclusion criteria

The study excluded cases resulting from genetic disorders of sex differentiation or hypogonadotropic hypogonadism. The children included in the study had undergone careful examination by pediatric surgeon.

A total of 129 hypospadias cases were included from three Indian states, Bihar, Haryana and Uttar Pradesh forms the study group. The patient's characteristics have been shown in Table 1. The study aimed to analyze the risk of hypospadias in families living under the direct exposure to pesticide and families living under no direct exposure of pesticides.

Statistical analysis

The statistical analysis has been performed to assess the risk of hypospadias in relation to families with direct exposure to pesticides and families without direct exposure. We compared incidence and severity of hypospadias and cryptorchidism cases. The odds ratio (OR) of hypospadias risk has been calculated between both the groups and compared with common controls attending the WPUC.

Results

In group 1 (direct exposure) 17 (18.5%) patients belongs to anterior site of hypospadias in which 6 (35.3%) are sub-coronal and 11 (64.7%) were glandular, the midline site were in 31 (33.7%) patients in which 10 (32.3%) were distal penile, 16 (51.6%) were proximal penile and 5 (16.1%) were mid-shaft. The posterior site belongs to 43 (46.7%) patients in which 18 (41.9%) were scrotal, 13 (30.2%) were peno-scrotal and 12 (27.9%) were perineal. On the other hand, in group 2 (without direct exposure) 3 (8.1%) were anterior and all were glandular, 21 (56.8%) were midline in which 6 (28.6%) were distal penile, 10 (47.6%) were proximal penile and 5 (23.8%) were mid-shaft. Posterior site belongs to 13 (35.1%) patients in which 4 (30.8%) were scrotal, 4 (30.8%) were peno-scrotal and 5 (35.5%) were perineal. Both groups, with and without direct exposure of pesticide were examined, and odds ratios (OR) were calculated. The ORs were consistently greater than 1 in group 1, indicating an increased risk of hypospadias. Patients with direct exposure to pesticides showed a significantly higher odds ratio when compared to patients without direct exposure to pesticides (Table 2).

Our findings suggest an increased risk of hypospadias associated with direct exposure to pesticide. The odds ratios were consistently higher in this group, indicating a potential association between direct exposure and hypospadias risk.

Table 1. General characteristics of the study population

S. No.	Characteristics	Numbers (%) / Mean±SD (Range)
1.	Total number of patients	*n*=129 (100%)
2.	Mean age (at presentation)	34.4±18.2 (12–72 months)
3.	Site of hypospadias (*n*=129)	
	1. Anterior	20 (15.5%)
	a) Sub–coronal	6 (30%)
	b) Glandular	14 (70%)
	2. Midline	53 (41.1%)
	a) Distal penile	17 (32.1%)
	b) Proximal penile	26 (49.1%)
	c) Midshaft	10 (18.8%)
	3. Posterior	56 (43.4%)
	a) Scrotal	22 (39.2%)
	b) Penoscrotal	17 (30.4%)
	c) Perineal	17 (30.4%)

5.	State wise participant	
	Bihar	36 (23.5%)
	Haryana	49 (32.0%)
	Uttar Pradesh	68 (44.5%)

Table 2. Odds ratios, with 95% confidence interval, of the risk of hypospadias by groups.

	Anterior site	**Midline**	**Posterior**	**Controls**
Odds ratio	32.1	2.2	10.9	1.1
95% confidence interval	5.66, 82.2	1.08, 4.8	4.55, 26.3	0.49, 2.39
z statistic	3.917	1.949	5.345	0.202
p value	<0.001	0.051	<0.001	0.839

Discussion

The present study acknowledges that the observed increased prevalence of hypospadias to the rural families with direct exposure of pesticide is an indirect indication supporting the possibility of a harmful effect of pesticides. However, the study did not specifically quantify or qualify the types and quantities of pesticides used in the agriculture land due lack of awareness about the pesticides. The complexity, variety, and dynamic nature of chemicals used in agriculture land, including pesticides (such as fungicides, insecticides, herbicides, bactericides, rodenticides, and fumigants), fertilizers, and other toxic chemicals, make it challenging to precisely assess their impact.

Additionally, during the study period, there was no available database to accurately quantify the nature and load of the chemicals used by the families. Therefore, the association between direct exposure to pesticide and hypospadias risk could be influenced by various environmental factors present in the vicinity of the agriculture land, and not solely pesticides. The study recognizes that agriculture land are a prominent location for pesticide spraying and play a significant role in Indian agriculture. A limitation of the study is that it did not gather occupational data for the mothers of the cases. It is plausible to expect that a higher percentage of mothers in group 1 may be occupationally involved in crop, fruits and vegetable production activities, potentially increasing their exposure to pesticides,

Evidence from Vineyard Study

A study published by Bougnères et al. explored a significant statistical link between the occurrence of hypospadias and the residence of pregnant mothers close to vineyards, it suggests a potential association between vineyard proximity and the development of hypospadias. The study also highlighted the need for future research to account for the changing nature and loads of pesticides in modern viticulture. This indicates that pesticides used in vineyards may be a potential environmental factor contributing to the observed association. Additionally, the study suggests that identifying precise hormone-disrupting chemicals would require a deep, systematic, and specific chemical investigation of vineyards and their immediate surroundings. This type of investigation would help in understanding the potential mechanisms by which vineyard-related factors could influence the development of hypospadias [11].

Use of Pesticides in Tea Farming

Pesticides used in tea farming can pose health hazards if not properly managed or used in accordance with safety guidelines. While pesticides are employed to protect tea crops from pests, diseases, and weeds, their misuse or overuse can lead to negative effects on human health and the environment such as acute

toxicity, chronic health effects, residue contamination and environmental impact. To mitigate these hazards, it is crucial for tea farmers to follow proper pesticide application techniques, adhere to recommended dosage and safety guidelines, and employ integrated pest management practices. Integrated pest management focuses on minimizing pesticide use by implementing a combination of preventive measures, biological controls, and targeted pesticide application when necessary [12-15].

Use of Pesticides in Beer Brewing

In beer production, pesticides can potentially pose health hazards if not used and managed properly throughout the brewing process. While beer itself does not typically contain high levels of pesticide residues, the ingredients used in brewing, such as barley, hops, and other adjuncts, may be treated with pesticides during cultivation can pose health hazards by agricultural use of pesticides like barley and hops, pesticide residue transfer etc. It's important to note that the overall risk of pesticide exposure through beer consumption is considered low. However, individuals with specific concerns or health conditions may choose to seek out information about the specific brewing practices and ingredient sourcing of the beers they consume [16, 17].

Further evidences from the previous work done by Author

In our previous study, we have establish polymorphisms in genes involved in xenobiotic metabolism, such as CYP1A1, GSTM1, and GSTT1, in relation to the etiology of hypospadias and their potential interaction with organochlorine pesticides. Organochlorine pesticides are a class of persistent environmental pollutants that have been implicated in various health effects, including endocrine disruption. They have been suggested as potential risk factors for hypospadias due to their ability to interfere with hormone signaling and disrupt normal development of the male reproductive system. In another study conducted by author (MB) [18]. In another study conducted by the author explored the polymorphisms in the P450 c17 gene, specifically the 17-Hydroxylase/17,20-Lyase enzyme, in relation to estradiol and testosterone concentrations in individuals with hypospadias. The P450 c17 enzyme is involved in the synthesis of sex hormones, including estradiol and testosterone. We have established that the hormone concentrations are influenced by various factors, including genetic, environmental, and developmental factors, in addition to P450 c17 gene polymorphisms. The interplay between genetic factors, hormone metabolism, and hypospadias is complex and still not fully understood [19].

A case-control study has been conducted by the author (MB) investigating the association between polymorphisms in the SRD5A2 and CYP17 genes and hypospadias risk among Indian children provided valuable insights into the genetic factors involved in hypospadias development. The SRD5A2 gene encodes the enzyme 5α-reductase type 2, which is responsible for the conversion of testosterone into its more potent form, dihydrotestosterone (DHT). Mutations or polymorphisms in the SRD5A2 gene can affect the activity or stability of the enzyme, leading to altered DHT levels. It is important to note that the relationship between SRD5A2 and CYP17 gene polymorphisms and hypospadias risk may vary among different populations. Genetic and environmental factors, as well as the interplay between multiple genes, may contribute to the development of hypospadias [20].

The Anupam Verma Committee

The government of India constituted the Anupam Verma Committee in 2013 to review 66

insecticides that were banned or restricted in other countries but still registered for domestic use in India. The committee's objective was to assess the safety and efficacy of these insecticides and make recommendations based on their findings. The committee recommended the ban on 27 pesticides as mentioned in the report. The reasons for the ban varied, but one of the key factors was the non-submission of required data for these pesticides. Without the necessary data, it becomes challenging to evaluate the safety and potential risks associated with their use. In 2016, the Anupam Verma Committee made a similar move and recommended a ban on 18 additional pesticides. These recommendations were implemented, and the ban came into effect from 2018. The committee's recommendations and subsequent bans aim to ensure the use of pesticides that have been thoroughly evaluated for their safety and efficacy, protecting human health and the environment in India [21].

The proposed ban on 27 pesticides by the Anupam Verma Committee has faced opposition from the Pesticides Manufacturers & Formulators Association of India (PMFAI). According to PMFAI, the ban would lead to a significant financial loss of up to Rs. 6000 crores. They argue that these pesticides are commonly used by farmers and are available at an affordable price, ranging from Rs. 350 to Rs. 450 per litre. In contrast, they claim that the alternatives suggested by the ban could be much more expensive, with prices ranging from Rs. 1,200 to Rs. 2,000 per litre [22].

On the other hand, environmentalists and civil society organizations have generally supported the ban on these pesticides. Their concerns focus on the potential risks associated with the use of these chemicals, including environmental pollution, human health hazards, and the adverse impacts on biodiversity and ecosystem balance. They advocate for the adoption of safer and more sustainable alternatives to protect the environment and promote sustainable agricultural practices.

Insecticides Act, 1968

The Insecticides Act governs the use, sale, manufacture, import, export, transportation, and distribution of insecticides or pesticides in India. It provides regulations and guidelines for the safe and responsible use of these chemicals.

Consumer Protection Act, 1986

Under the Consumer Protection Act, farmers can claim compensation for losses caused by the use of insecticides or pesticides. This allows farmers to seek redress for any damages or harm resulting from the use of these chemicals.

Registered Pesticides

As of June 30, 2020, there were 273 pesticides registered for use in India, with some having restrictions on their use. These registered pesticides have undergone evaluation and approval processes to ensure their safety and efficacy. India has banned the use, manufacture, and import of certain pesticides. For example, Endosulfan, which was used in cashew plantations, is banned due to its alleged health and environmental risks. Other pesticides, such as Captafol 80% Powder and Nicotine Sulfate, are banned for domestic use but can be manufactured for export purposes. Pesticides like Monocrotophos and DDT have restrictions on their domestic use, with specific limitations or prohibitions on certain applications.

Promotion of bio-pesticides

The promotion of bio-pesticides is an important strategy to reduce the reliance on chemical pesticides and encourage sustainable agriculture practices. The central and state governments in India have taken several initiatives to promote the use of biopesticides and check the increased usage of chemical

pesticides. Both central and state governments conduct regular inspections to ensure the quality and safety of pesticides available in the market. This helps to regulate the use of chemical pesticides and maintain quality standards by organic farming schemes, farmer education, research and development etc.

The Government of India has taken several steps to promote the reduced and safe use of pesticides in agriculture. Such as integrated pest management (IPM), pesticide management, pesticide quality control, promotion of biopesticides, rarmer education and training, research and development, monitoring and Surveillance etc.

These initiatives and regulatory measures aim to promote the judicious and safe use of pesticides in agriculture while minimizing their environmental and health impacts. The government continues to work towards strengthening these efforts and promoting sustainable pest management practices across the country.

Conclusion

It's important to note that specific pesticide products may have different toxicity profiles, and the classification can vary depending on the regulatory authority and the specific assessment criteria used. It's always recommended to follow the instructions and safety precautions provided by manufacturers and regulatory agencies when handling and using pesticides.

In conclusion, our study found a significant association between hypospadias occurrence in the offsprings and pregnant mothers, with direct exposure to the pesticide (OR consistently greater than 1 with p value <0.050). However, it is important to consider a more comprehensive perspective that incorporates null findings and study limitations, particularly in the context of commonly consumed agriculture produce, including Wineyards in the regions of Maharashtra & Kerala. Future environmental research should account for the evolving nature and loads of pesticides in agriculture.

Conflicts of interest

The author declares that they do not have conflict of interest.

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ORIGINAL ARTICLE

Correlation of admission S. Na+ and S. Cl- with severity and hospital stay in ADHF patients

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Abstract

Background: Electrolyte imbalances, particularly hyponatremia and hypochloremia, are common in ADHF patients and can influence disease severity and outcomes. Understanding the correlation between admission S. Na^+ and S. Cl^- levels with ADHF severity and hospital stay is crucial for optimizing patient management.

Aim: This study aimed to investigate the correlation between admission S. Na^+ and S. Cl^- levels with disease severity and length of hospital stay in ADHF patients.

Discussion: Diagnostic studies based on sodium and chloride are not only widely available but also, practicable and relatively inexpensive in comparison to other modalities. A total of 150 ADHF patients were included in the study. The mean admission S. Na^+ and S. Cl^- levels were assessed in relation to NYHA functional class and EF. Statistical analysis revealed significant correlations between admission S. Na^+ and S. Cl^- levels and NYHA class, as well as EF.

Conclusion: The correlation of admission S. Na^+ and S. Cl^- levels with disease severity and hospital stay in ADHF patients provides important insights. Monitoring and managing electrolyte imbalances, particularly S. Na^+ and S. Cl^- may have implications for optimizing patient care and improving outcomes in ADHF.

Keywords: Hyponatremia, hypochloremia, ADHF, Ejection Fraction, NYHA.

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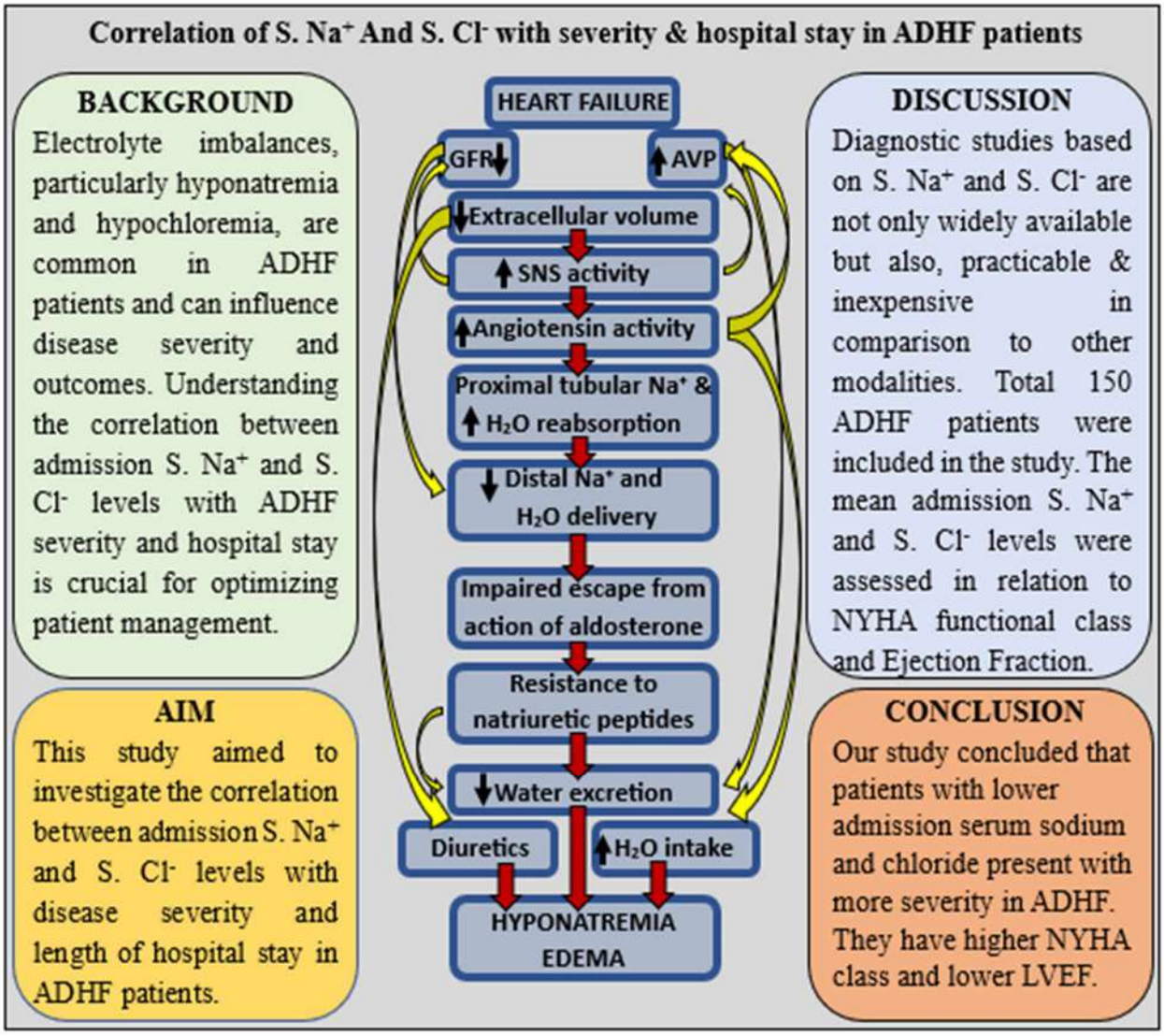
Graphical Abstract



Abbreviations-

ADHF	:	Acute Decompensated Heart Failure
LV	:	Left Ventricle
LVEF	:	Left Ventricular Ejection Fraction
2D-ECHO	:	2-Dimensional Echocardiography
NYHA	:	New York Heart Association
HFpEF	:	Heart Failure with preserved Ejection Fraction
S. Na^+	:	Serum Sodium
S. Cl^-	:	Serum Chloride
HFrEF	:	Heart Failure with reduced Ejection Fraction

Introduction

Heart failure is an evolving non-communicable epidemic in India, but the burden can be felt all over the world since it has been labelled as the new pandemic of the 21st century. During the protracted course of heart failure, it is common for patients to develop electrolyte imbalances, the most common of which are hyponatremia and hypochloremia [1].

Upregulation of maladaptive neurohormonal systems is associated with ventricular dysfunction in patients with heart failure. In heart failure, an imbalance of either of these electrolytes is a contributing factor in morbidity [2].

When a patient is admitted to the hospital with acute decompensated heart failure, hyponatremia is a known reason for the patient to have a prolonged hospital stay [3].

Pathophysiology of Heart Failure

Heart failure may be considered as an advancing condition that usually begins when a key event occurs destroying myocardium, resulting in the insufficiency of cardiac myocytes' ability to generate force required for normal supply of blood [4]. This is triggered by a key incident, frequently acute onset like MI, or sometimes of insidious onset like hypertension. Sometimes, it has an inherited onset, like several genetic cardiomyopathies. Myocardial disease is typically the most frequent cause of heart failure; however, heart rate or rhythm disorders, endocardial disorders, valvular pathologies, or pericardial abnormalities can also lead to cardiac dysfunction [5]. HFrEF pathogenesis involves a few pathogenetic mechanisms, including ischemia-related damage, abnormal myocyte calcium cycling, dysregulated neurohumoral stimulation, immunological stimulation, increased hemodynamic overload, extracellular matrix anomalies, ventricular remodeling, genetic mutations, and accelerated apoptosis. Pathogenesis of HFpEF is diastolic dysfunction, etiology of which has been substantially attributed to accumulation of extracellular matrix (i.e., myocardial fibrosis) due to activation of renin angiotensin aldosterone system [6].

Consequently,

- Increase in peripheral resistance leads to elevated LV after-load which further decreases cardiac function.
- Enhanced contractility, Heart rate, and LV afterload can aggravate or provoke coronary ischemia.
- Angiotensin II, aldosterone and catecholamines cause myocyte loss by apoptosis and myocardial hypertrophy and fibrosis [7].

Classification of Heart Failure

American College of Cardiology/American Heart Association 2022 guidelines define heart failure as a complex clinical syndrome with symptoms and signs that result from any structural and functional impairment of ventricular filling or ejection of blood [8]. ADHF term is defined for both, patients coming with de novo and those with worsening of previously chronic stable Heart failure [9]. Heart failure is classified according to New York Heart Association and patients are placed in four categories, based on limitation in physical activity or ejection fraction as shown in Tables 1 and 2 [8, 10].

Table 1. NYHA Functional Classification.

Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea (shortness of breath).
Class II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea (shortness of breath).
Class III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnoea.
Class IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Table 2. Classification of HF by LVEF

Type of HF according to LVEF	Criteria
HFrEF (HF with reduced EF)	LVEF ≤40%
HFimpEF (HF with improved EF)	Previous LVEF ≤40% and a follow-up measurement of LVEF >40%
HFmrEF (HF with mildly reduced EF)	LVEF 41%-49% Evidence of spontaneous or provokable increased LV filling pressures (e.g., elevated natriuretic peptide, non-invasive and invasive hemodynamic measurement)
HFpEF (HF with preserved EF)	LVEF ≥50% Evidence of spontaneous or provokable increased LV filling pressures (e.g., elevated natriuretic peptide, non-invasive and invasive hemodynamic measurement)

Hyponatremia in ADHF

Hyponatremia is defined as S. $Na^+ \leq 135$ mEq/L representing an excess water relative to total body solute. Severity of hyponatremia is divided as follows:

1. Mild: S. Na^+ = 130-135 mmol/L
2. Moderate: S. Na^+ = 125-129 mmol/L
3. Severe: S. Na^+ = 125 mmol/L [11]

Hyponatremia in heart failure is a multifaceted process. It involves the increased release of arginine vasopressin and inadequate tubular flow in the distal regions of the nephron, leading to excessive water retention and the progression of

hyponatremia in ADHF [12]. The severity of hyponatremia in ADHF is often proportional to the degree of cardiac dysfunction and serves as an indicator of advanced disease severity. Understanding the mechanisms and implications of hyponatremia in heart failure is crucial for improved patient outcomes [13].

Hypochloremia in ADHF

Chloride is a crucial anion found both in extracellular and intracellular compartments of the body. In patients with CHF, low blood chloride concentration is commonly observed and is associated with unfavorable outcomes [14]. Hypochloremia, regardless of sodium levels, has been found to carry a higher risk of death and hospitalization for heart failure compared to hyponatremia alone [15]. The occurrence of low chloride levels in ADHF can be attributed to similar mechanisms as hyponatremia, such as neurohormonal activation and the use of loop diuretics [16].

Nevertheless, there is a scarcity of studies and the potential of chloride as an independent prognostic marker is yet to be firmly established.

Methodology

All 150 eligible participants above the age of 18 years, admitted to the medicine wards and meeting the inclusion criteria, underwent a thorough evaluation. A detailed history was obtained, including information on symptom onset, precipitating factors, and use of diuretics, among other relevant factors. Comprehensive physical examinations were conducted, recording findings such as jugular venous pressure, chest auscultation, and the presence of peripheral edema. All participants underwent relevant investigations, including Complete Blood Count, Renal Function tests, Liver Function Test, and serum electrolyte analysis based on their presenting symptoms. Additional investigations, such as Chest X-Ray PA view, Electrocardiogram, and 2D ECHO, were performed as necessary.

Inclusion criteria

- The study enrolled individuals aged 18 years and above, who had a documented discharge diagnosis of ADHF resulting from diverse causes.
- It also encompassed patients who had previously been diagnosed with heart failure and presented to the emergency department in a decompensated state.

Exclusion criteria

- Age < 18 years.
- Additionally, patients who received chronic dialysis therapy, had sepsis, showed signs of acute coronary syndrome or myocarditis (based on their medical history, elevated troponin levels, and/or dynamic ECG changes), had incomplete hospital records, were pregnant, or had a malignancy were also excluded from the study.
- Furthermore, individuals who were unwilling to participate in the study were not included.

Measurement of S. Na^+ and S. Cl^- levels was carried out by collecting a venous sample in a plain vial, which was then processed using a biochemical analyzer (AU-480). In

our study, hyponatremia was defined as S. Na^+ levels ≤135 mmol/L, and hypochloremia was defined as S. Cl^- levels ≤96 mmol/L.

The duration of hospital stay was calculated as the number of days from admission to discharge of the patient in the inpatient department.

Results

This observational study was conducted among 150 patients at Government Multispecialty Hospital, Sector 16, Chandigarh. The study participants had a mean age of 60.71 ± 12.77 years, ranging from 36 to 89 years. Most participants (47, 31.3%) fell into the age group of 51-60 years, followed by (30, 20.0%) in the group of 41-50 years.

Among the 150 participants, (109, 72.7%) had diabetes mellitus, and (120, 80%) had hypertension. A history of heart failure was present in (62, 42.2%) of the enrolled patients, and (78, 52%) were on diuretics. Additionally, (17, 11.3%) had a history of alcohol intake, and (44, 29.3%) had a history of tobacco use. Other baseline investigations are documented as shown in Tables 4, 5 and 6.

Table 3. Distribution of study population according to NYHA

		Frequency	Percent
NYHA in class numbers	Class-III	27	18.0%
	Class-IV	123	82.0%
	Total	150	100.0%

Table 4. Baseline parameters and investigations of the participants

	N	Mean	Standard Deviation	Median	Minimum	Maximum
SBP (in mmHg)	150	163.09	26.27	167.00	90.00	230.00
DBP (in mmHg)	150	95.17	14.31	96.00	60.00	130.00
PR (in bpm)	150	112.61	10.54	112.00	94.00	140.00
Hb (in gm/dL)	150	10.86	2.35	11.00	5.70	16.10
TLC (per cubic mm)	150	9055.53	3629.26	8820.00	3800.00	31400.00

Table 5. Pattern of distribution of study population according to EF

		Frequency	Percent
EF	Preserved	45	30.0%
	Mild reduced	53	35.3%
	Reduced	52	34.7%
	Total	150	100.0%

Table 6. Correlation of admission S. Na^+ and S. Cl^- according to NYHA

		NYHA in class numbers		Mann-Whitney U (Z)	p-value
		Class-III	Class-IV		
Admission Serum Sodium (mEq/L)	N	27	123	2.884	.004
	Mean	133.15	128.31		
	SD	6.61	8.51		
	Median	133.00	130.00		
Admission Serum Chloride(mEq/L)	N	27	123	3.550	<.001
	Mean	102.96	97.10		
	SD	2.93	8.06		
	Median	103.00	101.00		

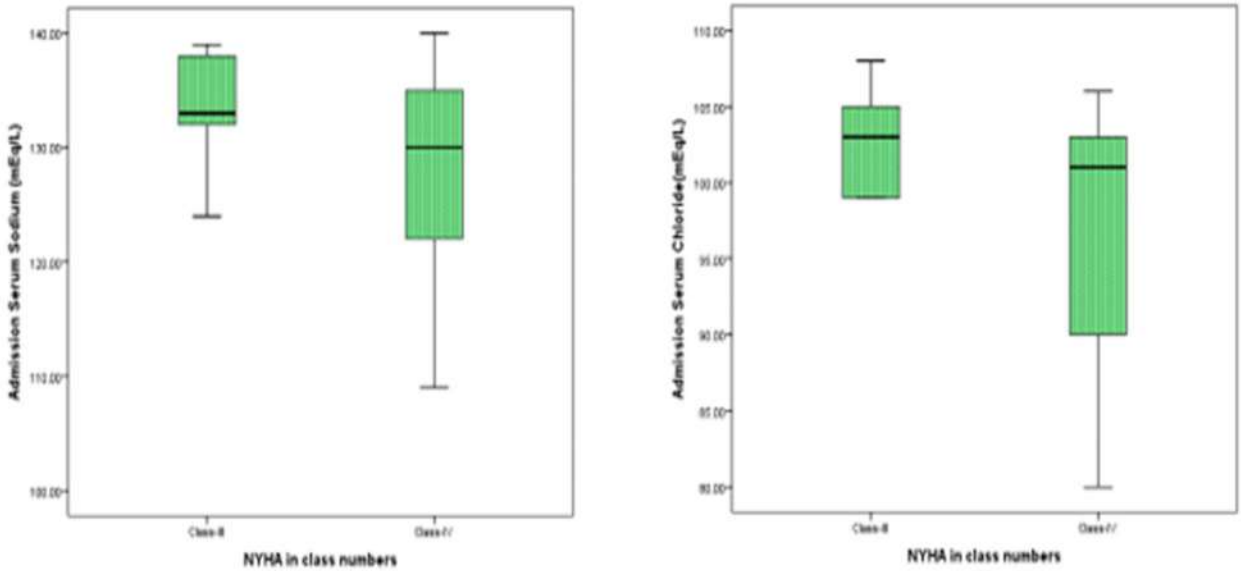


Figure 1. Box and whisker plot of admission S. Na^+ and S. Cl^- with NYHA class 3 and 4.

The mean admission S. Na^+ levels for patients classified as NYHA Class III were observed to be 133.15 ± 6.61 mEq/L, while for patients in NYHA Class IV, the mean admission S. Na^+ levels were 128.31 ± 8.51 mEq/L. Similarly, the mean admission S. Cl^- levels for NYHA Class III patients were 102.96 ± 2.93 mEq/L, and for NYHA Class IV patients, the mean admission S. Cl^- levels were 97.10 ± 8.06 mEq/L. These findings indicate a statistically significant correlation between NYHA classification and admission S. Na^+ and S. Cl^- levels as shown in Table 6 and Figure 1.

Table 7. Correlation of admission S. Na^+ and S. Cl^- according to Ejection Fraction

		EF			Kruskal Wallis (χ2)	p-value
		Preserved	Mild reduced	Reduced		
Admission Serum Sodium (mEq/L)	N	45	53	52	44.084	<.001
	Mean	132.53	131.00	124.42		
	SD	9.22	7.32	6.43		
	Median	137.00	134.00	126.00		
Admission Serum Chloride(mEq/L)	N	45	53	52	46.798	<.001
	Mean	101.31	101.66	91.85		
	SD	4.88	5.63	7.71		
	Median	102.00	103.00	90.00		

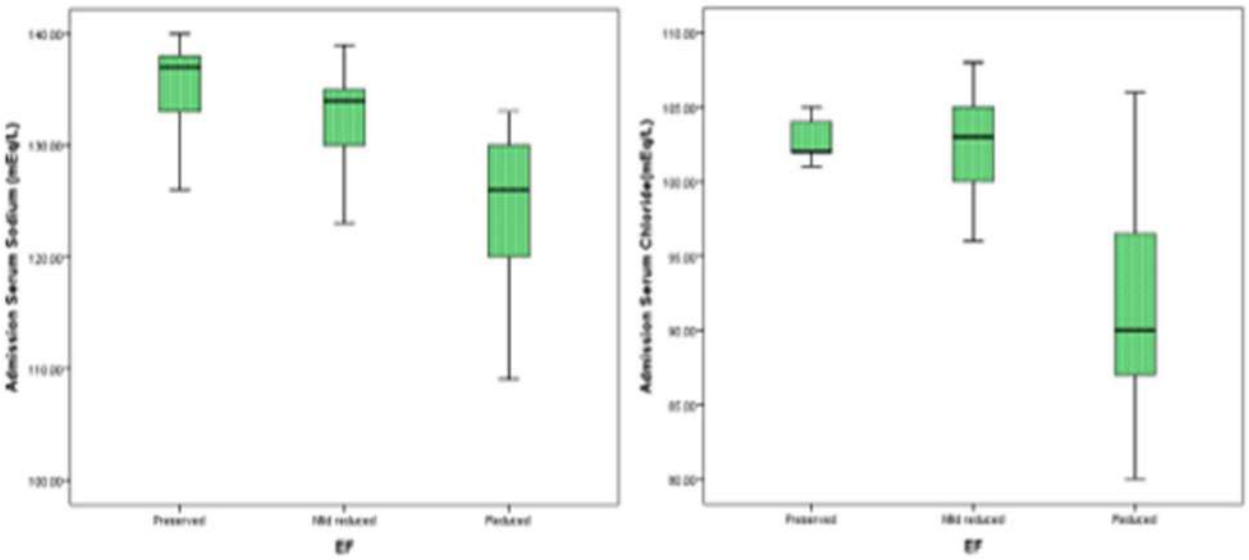


Figure 2. Box and whisker plot of admission S. Na^+ and S. Cl^- with Ejection Fraction

Furthermore, in relation to ejection fraction, the mean admission S. Na^+ levels were found to be 132.53 ± 9.22 mEq/L for preserved EF, 131.00 ± 7.32 mEq/L for mildly reduced EF, and 124.42 ± 6.43 mEq/L for reduced EF. Similarly, the mean admission S. Cl^- levels were 101.31 ± 4.88 mEq/L for preserved EF, 101.66 ± 5.63 mEq/L for mildly reduced EF, and 91.85 ± 7.71 mEq/L for reduced EF. These results establish a statistically significant association between admission S. Na^+, S. Cl^-, and EF as shown in Table 8 and Figure 2.

Table 8. Distribution of admission S. Na^+ and S. Cl^- with hospital stay duration

		Hospital Stay duration (in days)					Kruskal Wallis ($\chi 2$)	p-value
		3 days	4 days	5 days	6 days	7 days		
Admission Serum Sodium (mEq/L)	N	9	34	45	35	27	13.042	<.001
	Mean	132.44	133.35	130.44	125.74	125.19		
	SD	9.46	4.39	7.76	10.04	7.50		
	Median	139.00	135.00	133.00	129.00	124.00		
Admission Serum Chloride (mEq/L)	N	9	34	45	35	27	28.101	<.001
	Mean	104.11	103.06	99.22	93.69	94.00		
	SD	2.09	2.70	5.11	9.92	8.27		
	Median	103.00	104.50	101.00	96.00	90.00		

Moreover, it was observed that patients with lower admission S. Na^+ and S. Cl^- levels had a longer hospital stay duration. The mean admission S. Na^+ was lowest (125.19 ± 7.50 mEq/L) for a hospital stay duration of 7 days (p-value < 0.001). Similarly, the mean admission S. Cl^- was lowest (93.69 ± 9.92 mEq/L) for a hospital stay duration of 6 days (p-value < 0.001). This suggests that patients with lower S. Na^+ and S. Cl^- levels upon admission tend to have a prolonged hospital stay as shown in Table 8.

Furthermore, a positive linear correlation was observed between S. Cl^- and S. Na^+ levels, which was statistically significant (R2 linear = 0.325, p < 0.001). This finding highlights the relationship between these two electrolytes and their interplay in heart failure patients as shown in Figure 3.

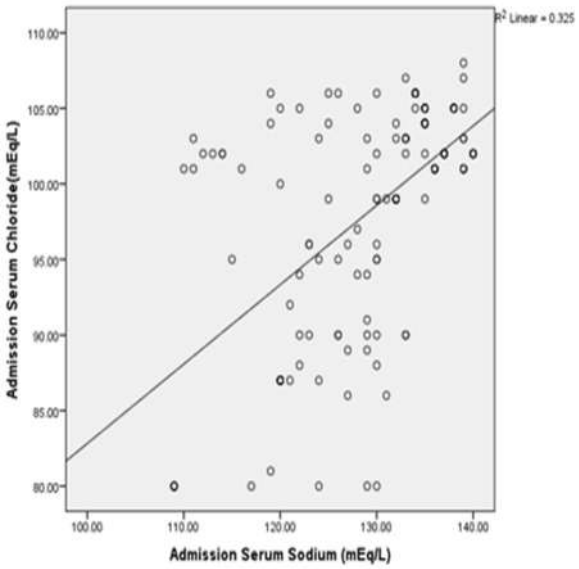


Figure 3. Scatter plot of correlation of admission serum sodium and chloride

Strengths

This study establishes a correlation between the values of admission S. Na^+ and S. Cl^- which has been found to be cost-effective and readily accessible, even at primary health care centers.

Limitations

• No follow-up of cases was conducted in this study.

• Additionally, logistic issues prevented the inclusion of prognostic markers such as BNP and NT-pro BNP for analysis.

Conclusion

Our study concluded that patients with lower admission serum sodium and chloride present with more severity in acute decompensated heart failure. They have higher NYHA functional class and lower LVEF. Also, there was a significant degree of negative correlation between hospital stay duration and admission serum sodium and chloride. Admission serum sodium was better marker for severity in ADHF. Admission serum chloride was better marker to predict hospital stay duration in ADHF. These results provide valuable insights into the association between electrolyte levels, NYHA classification, EF, and hospital stay duration in heart failure patients. Understanding these relationships can aid in better risk stratification and management strategies for improved patient outcomes.

Future Scope

The correlation study between admission serum sodium and serum chloride levels and their association with disease severity and hospital stay in ADHF patients provides valuable insights for future research. There is a need to further investigate the underlying mechanisms responsible for electrolyte imbalances in ADHF and their impact on the severity of the condition and hospitalization outcomes.

Prospective studies can be conducted to assess the potential of admission S. Na^+ and S. Cl^- as prognostic markers for predicting the duration of hospital stay and guiding treatment strategies for ADHF patients. Further research is needed to explore the role of chloride in predicting outcomes and its potential as a standalone prognostic indicator in heart failure.

With the advancements in the field of cardiology, there is an increasing need to explore and develop non-invasive techniques that can provide valuable prognostic information without resorting to invasive procedures.

Non-invasive approaches, such as echocardiography, utilization of cardiac biomarkers like BNP and NT-proBNP, as well as the use of wearable devices, show great potential in predicting the progression of heart failure, gauging response to treatment, and determining overall prognosis for patients. These non-invasive tools offer valuable insights into various aspects of cardiac function, hemodynamics, and fluid status, enabling timely interventions and personalized management strategies.

By incorporating these non-invasive techniques into future research and clinical practices, we can significantly improve risk stratification, enhance patient outcomes, and potentially reduce the duration of hospital stays specifically for individuals diagnosed with ADHF.

Ethics declarations

Funding This study did not receive any funding.

Conflict of interest

The authors declare that they have no competing interests.

Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability

Not applicable.

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ORIGINAL ARTICLE

Exploration of mentees' perception of mentoring among Undergraduate medical students: A Cross-sectional Study

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Abstract

Background: A successful mentorship program promotes personal and professional growth. Experienced mentors provide a nurturing relationship with the mentee. Lack of emotional support with highly expected competency pressurizes students' daily lives. A well-integrated mentorship program has enabled the psychosocial skills and humanistic attitudes among medical students. Mentor mentee pairing system and the knowledge of mentees' perception of mentoring were found to provide a satisfactory mentorship program. Though a number of studies on mentoring medical students were done elsewhere in India, the knowledge on mentee's perception of mentors, mentorship program and mentor-mentee expectations were lacking in south India, hence this study was chosen. **Objectives:** To analyze mentees' perception of mentors; To analyze the mentees' perception of the mentorship program; To analyze the mentees' perception of mentor-mentee relation. **Methodology:** This single-center, observational cross-sectional study was done with a sample size of 241. Undergraduate medical Students of all phases except the first year, who were willing to participate in the study, filled out the 15 items questionnaire. The questionnaire on an exploration of mentees' perception of mentors was validated with the internal consistency of 0.65 (Cronbach's alpha) after Principal compound analysis. The questionnaire was designed using google Forms and distributed through WhatsApp. **Results:** The response was tabulated and analyzed as frequency using Microsoft Excel. Most medicos prefer their mentor to be friendly and approachable to enhance their academic development. They expect the mentor to counsel, and coach them to improve their academic and social confidence. Mentees prefer to have specialist mentor. They do not prefer to have a mentor of same gender and the same mentor throughout the curriculum. Most of them feel that impractical expectations from the mentor as a disadvantage. They agree that mentoring is an everlasting relationship and prefer to have weekly, one-on-one meetings. They expect the mentor to help in developing strategies to solve a problem and agree to share their academic progress with their parents. Mentees agree that mentor expects mutual respect from their mentees. **Conclusion:** The knowledge of the perception of mentees on the mentors, mentorship program, and mentor-mentee expectations can enable the mentors to adapt to the mentee's needs and promote effective mentoring among undergraduate medical students.

Keywords: Mentor, Medical students, Perception, Questionnaire

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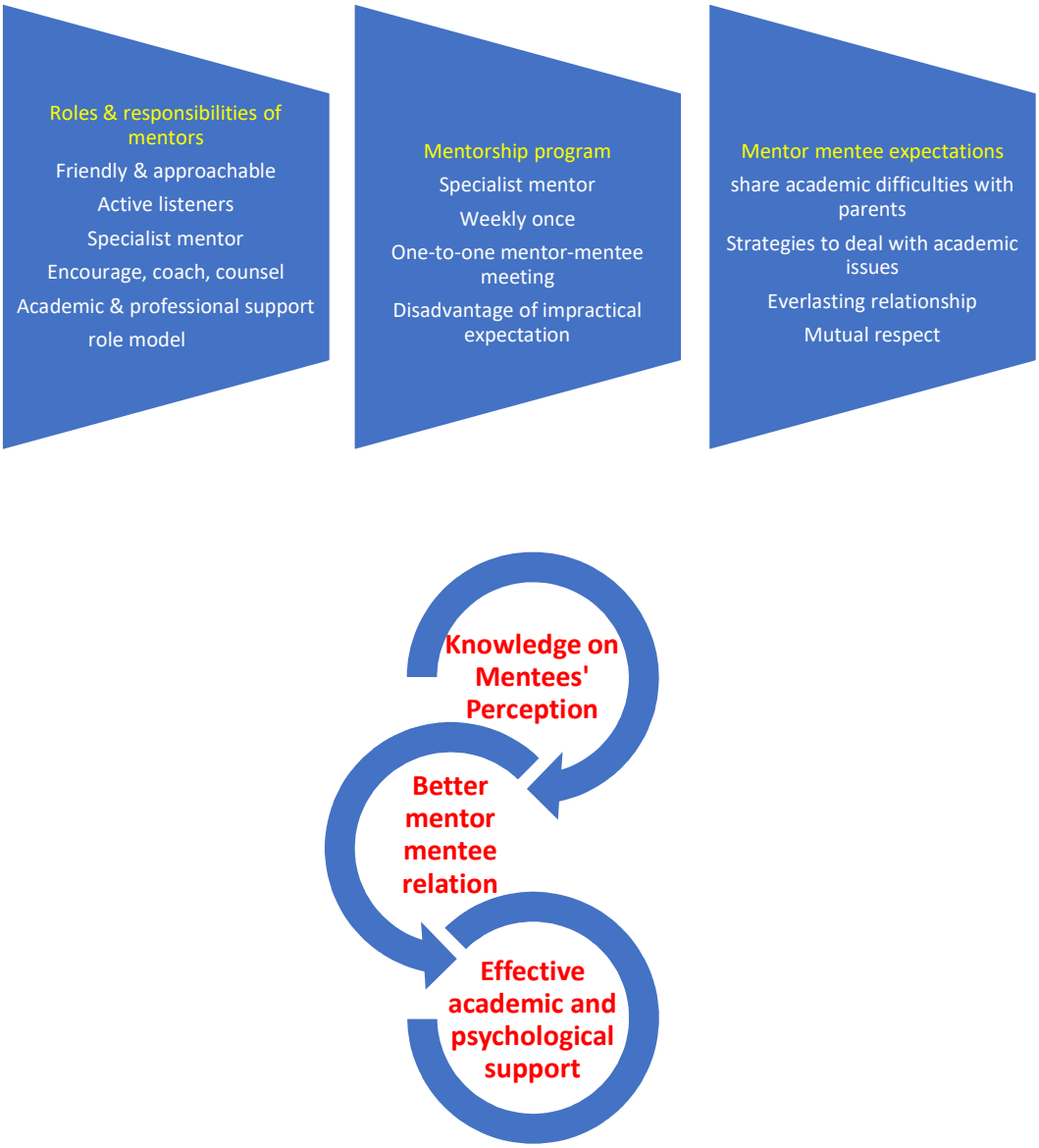
Graphical Abstract



Introduction

Mentoring enables medicos towards personal growth & development. It enhances their social and economic opportunity [1]. A successful mentorship program depends on the mentor-mentee relationship. The mentorship program fills the opportunity gap among the students and makes the students trust their parents. It promotes better communication [2]. It was observed that mentors enhance patient care by making the students professionally competent [3]. Clarity on the purpose and intention of mentoring is vital for an effective mentorship program [4]. Experienced mentors provide a nurturing relationship and serve as role models, teachers, and counselors to the mentee [5]. Want of competent medical graduates with a lack of emotional support pressurizes students' daily lives [6]. An integrated mentorship program has improved the psychosocial skills and humanistic attitudes among medical students even after completion of their undergraduate program [7]. Mentoring programs contribute to building and maintaining professional

identity among medical students and reaffirming the professional identity of mentors [8]. Limited faculty time due to commitments on clinical, teaching, research & guidance has led to involve peer or "near-peer" mentoring in various higher educational institutions [9]. Mentor mentee pairing system and the knowledge of mentees' perception of mentoring were found to provide a satisfactory mentorship program [10,11]. Lack of pairing between mentor and mentee and absence of a response by mentees to mentors were common problems encountered by mentors.

Though a number of studies on mentoring medical students were done worldwide and in the Northern part of India, the knowledge on mentees' perception of mentors, mentorship program and mentor-mentee expectations were lacking in south India, hence this study was chosen.

Methodology

This descriptive cross-sectional single-center study was conducted at a medical college in South India (from January 2022 to March 2022) after obtaining the Scientific Research Committee and Institutional Ethics Committee clearance. (No:132/SVMCH/IEC-Cert/Nov21). Self-selected non-probability sampling method was followed. The sample size was 241, calculated using the Epi info, Version 7.2.3.1, with a confidence interval of 95% and a margin of error of 5% expected frequency of 50% of the students who are submitting the form, as the known population of all the presently enrolled MBBS students is around 620 was 240. All the participants willing to fill out the questionnaire were included in the study and informed consent was obtained from them. Those do not compile with the study procedure were excluded from the study.

Data collection tool

The two-phased standardized methodology was implemented for validating the questionnaire. In phase 1 (qualitative phase), the questionnaire was developed through a literature review, focus group discussion, and expert evaluation (content validity). In phase 2(quantitative phase), the validity of the questionnaire was obtained by conducting a cross-sectional survey of 20 participants (however these participants were not included in the main survey). The internal consistency was assessed using Cronbach's alpha (0.65) after Principal compound analysis.

The final version of the questionnaire comprises 15 items (Annexure I). Section I comprises 4 questions on age, gender, the phase in which the participant is presently studying, and their consent to participate in the study. It does not include the mentee's identification to prevent bias and to enable the students to select the options without inhibition. Section II comprises Question no. 5, 6 & 7 which collects information on the roles and responsibilities of mentors, 8 to 15 questions that collect information on the mentorship program, and question number 16 to 19 on mentor & mentee expectations. For all the questions the mentees were allowed to choose more than one option except the 19th question (open-ended question) and the 11th, 12th & 13th questions. (5-point Likert scale where "1" - strongly agree "5"- strongly disagree) The survey was collected in the English language.

This web-based questionnaire was designed using Google forms and distributed via WhatsApp. The invitation letter explained the aim of the study and the approximate time required to complete the questionnaire. The nature of voluntary participation (consent), declaration of anonymity and confidentiality, and the

invigilator details were mentioned on the first page of the questionnaire. The name of the student was not collected to maintain anonymity.

Result

All the data were tabulated in Microsoft Excel. Mentees' perceptions of mentors, mentorship programs, and mentor-mentee expectations were analyzed as frequency using Microsoft Excel software.

Among the 241 participants, 32.8 % were male and 67.2% were female. Response from all phases of medical students was collected except the first year as they were new to the mentor-mentee program. 33 % of second-year students, 38% of final year part I, and 29% of final year part II responded. Responses to questions 5 to 18 are represented as a Bar diagram from Figures 1 to 14.

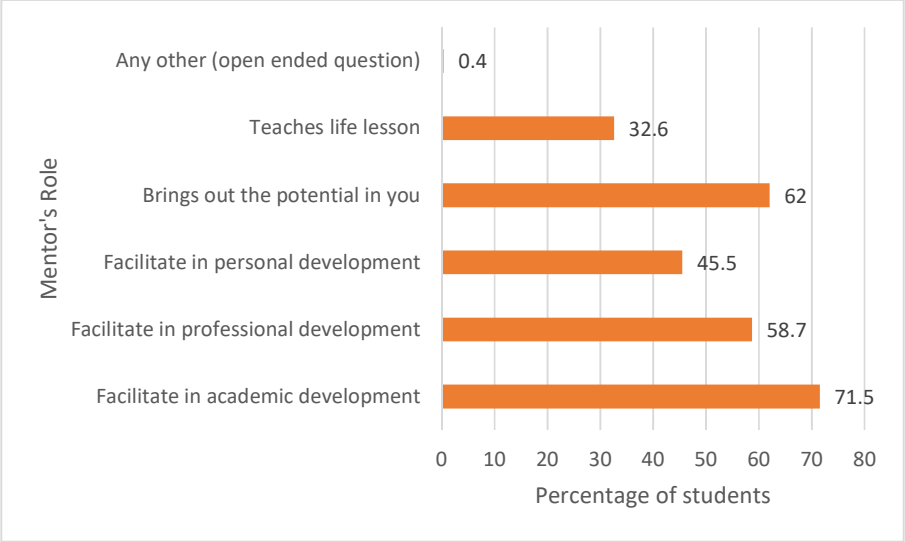


Figure 1. Frequency distribution on mentees perception on who the mentor is?

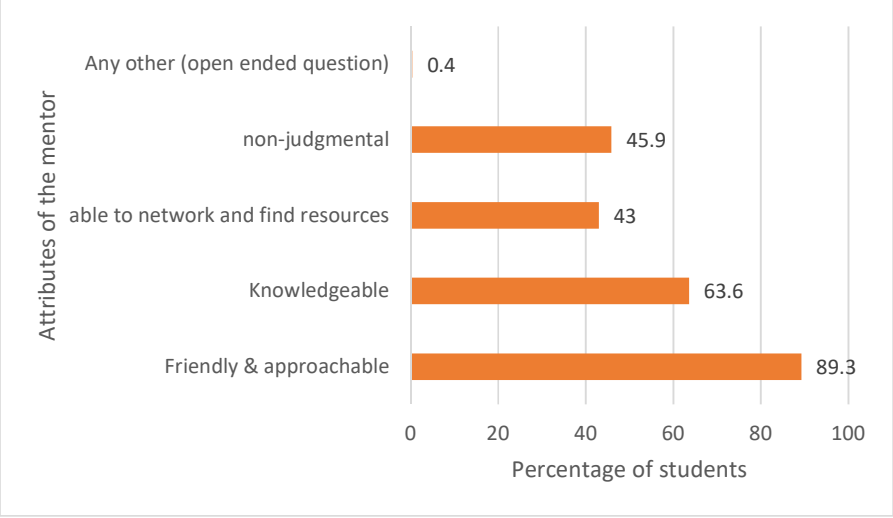


Figure 2. Frequency distribution on Attributes of the mentor

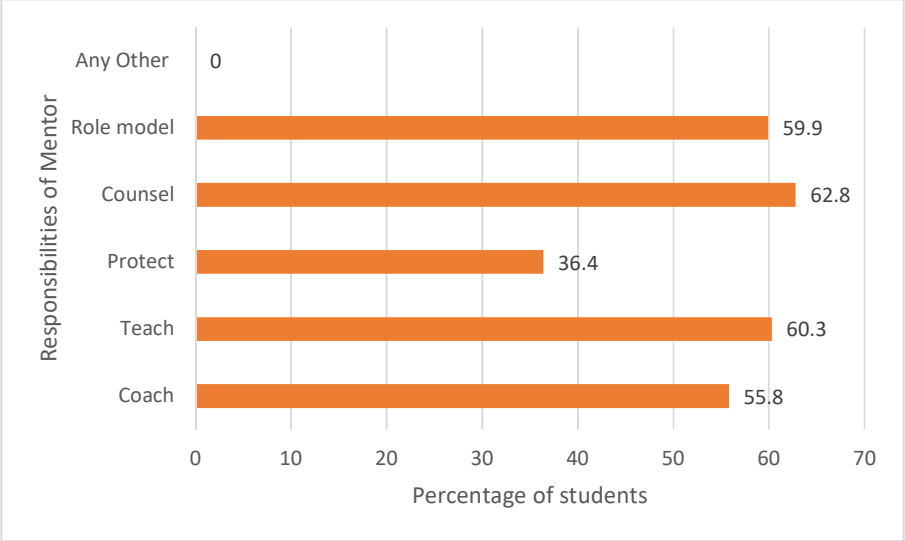


Figure 3. Frequency distribution of responsibility of the mentor

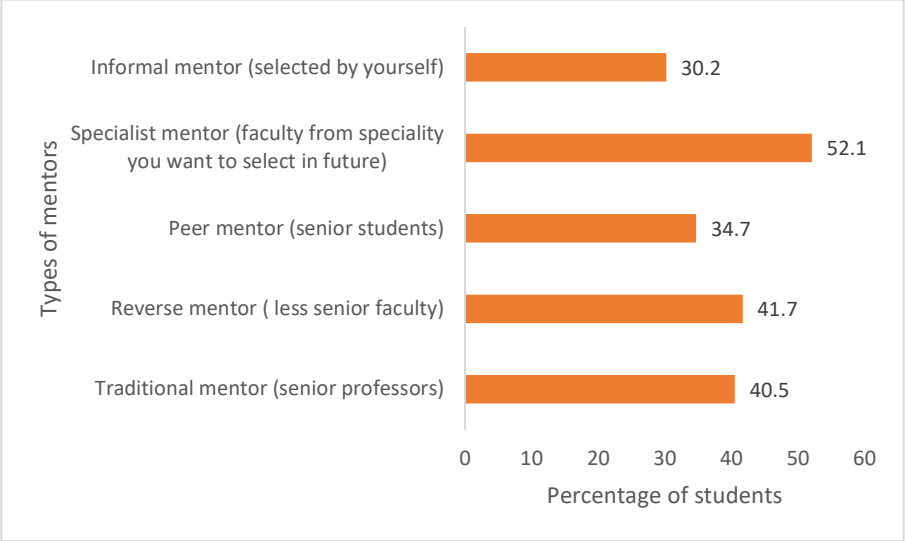


Figure4. Frequency distribution of students' preference towards the type of mentors

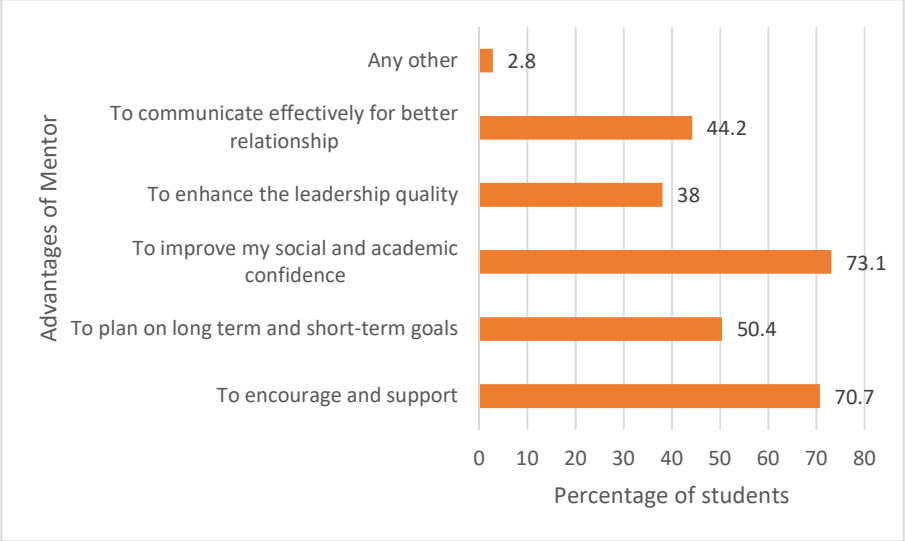


Figure 5. Frequency distribution on Advantages of having a mentor

In the open option, one student has responded that the mentor has to give Moral Support.

One student has suggested Innovative teaching to be an important attribute of the mentor in the open suggestion.

Additional advantage as suggested by some of the students was that the mentor developed their skill and attitude, enabled them to keep track of work based on the planned schedule, and helped to know their weaknesses. They have improved not only their academic growth but also their personal growth9.8% of the students have not committed any disadvantage of having a mentor..

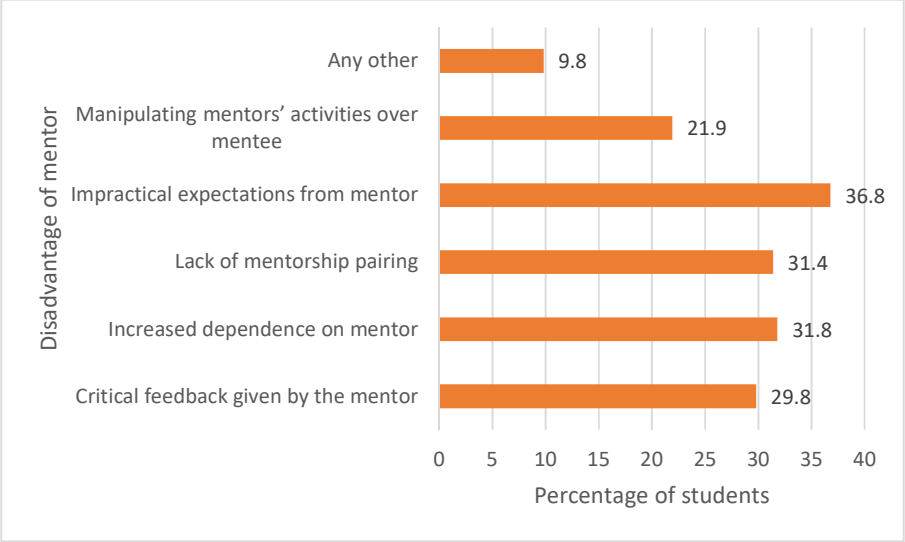


Figure 6. Frequency distribution on disadvantage of having a mentor.

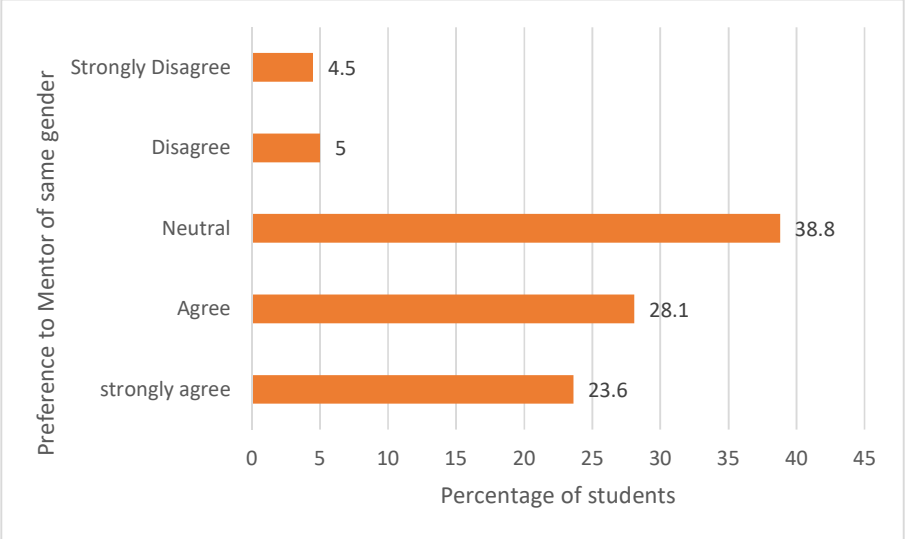


Figure 7. Likert scoring on preference to have mentor of same gender

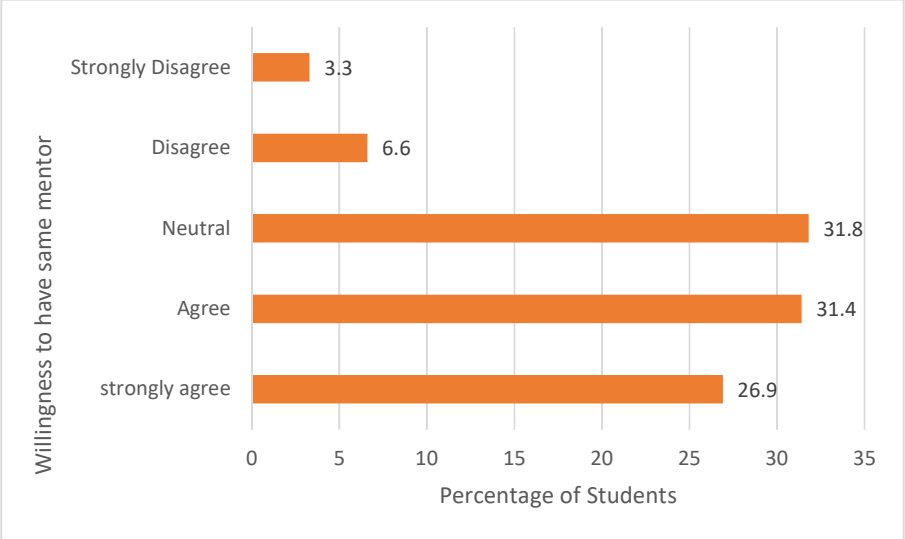


Figure 8. Likert scoring on willingness to have same mentor throughout the curriculum

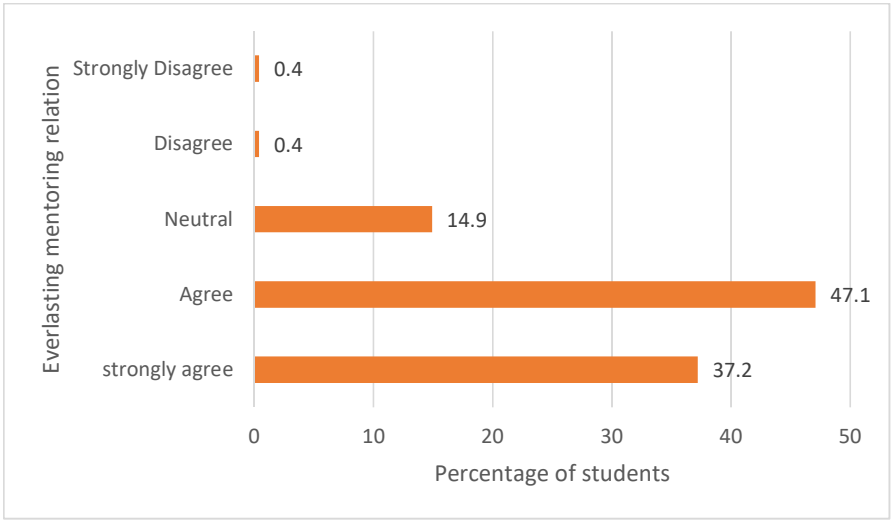


Figure 9. Likert scoring on "mentoring an everlasting relation"

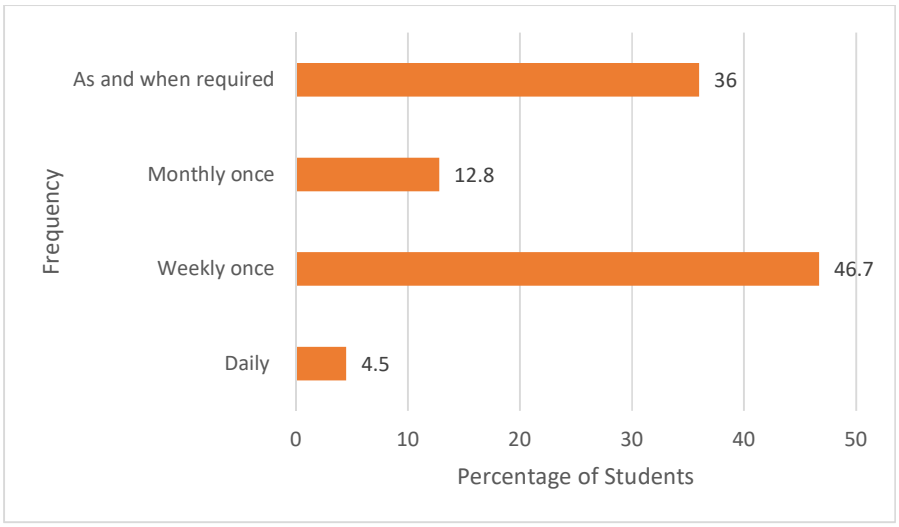


Figure 10. Percentage distribution on preference towards frequency of mentor mentee meeting

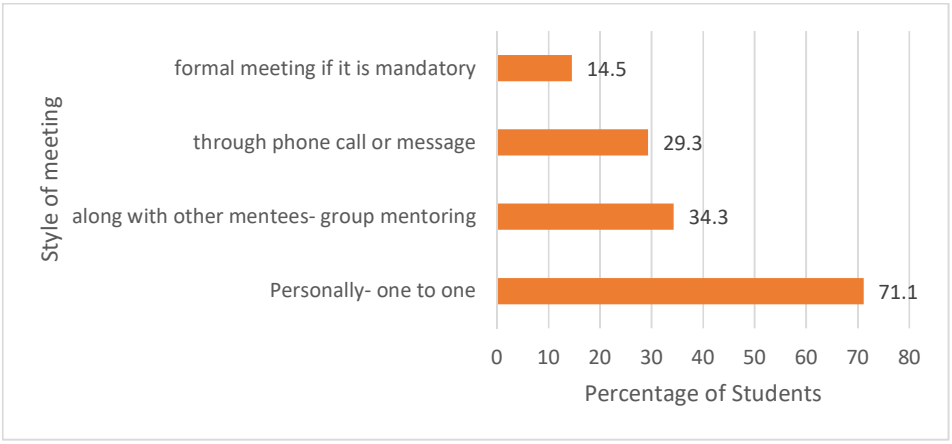


Figure 11. Frequency distribution on preferred style of mentor mentee meeting

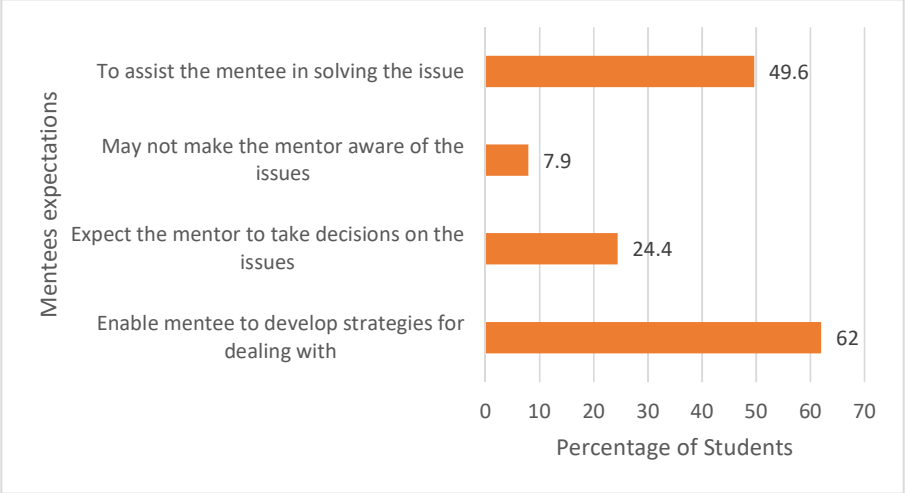


Figure 12. Students Response on Mentees expectations from mentors on personal and academic issues

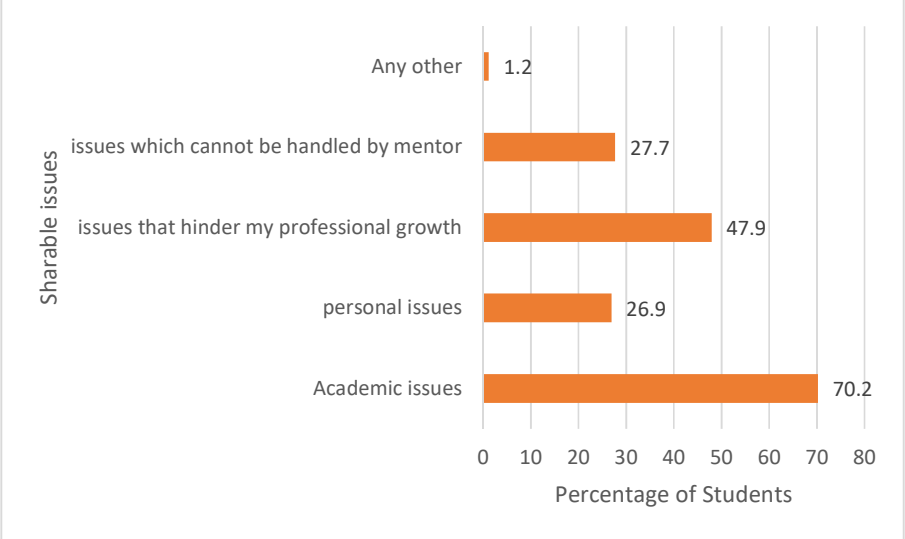


Figure 13. Percentage distribution on preference towards sharable issues with mentees parents

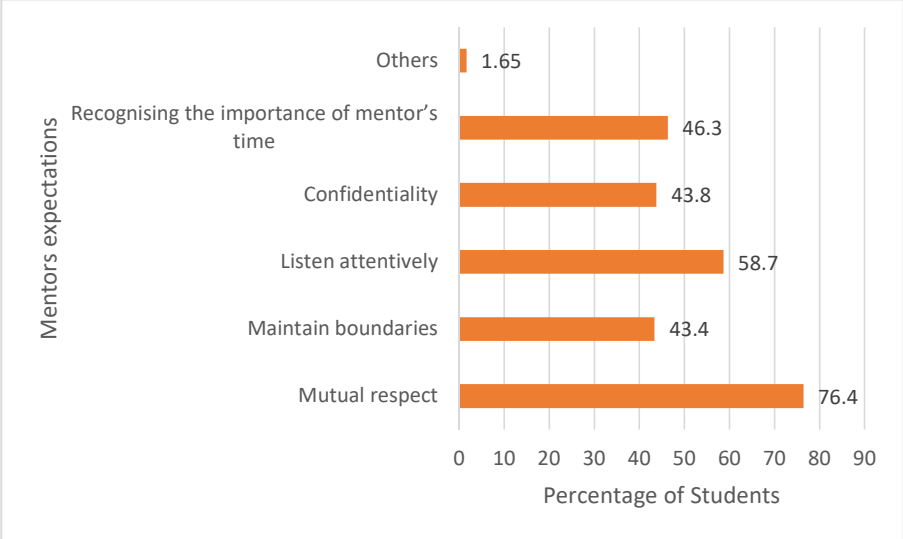


Figure 14. Frequency distribution on Mentors expectations from Mentee

0.8 % of the students have mentioned that a mentor has the right to share any type of problem with parents to solve. 0.4% of the students have responded that every issue should be solved at the mentor level in addition to the above options.

In addition to the above response, two students expressed that the mentor expects Openness from the mentee and two students responded that mentor needs recognition from the mentee.

The response to question number 15 (Open-ended question) was based on thematic analysis. It showed that 60% of the students were satisfied with the mentor-mentee program. 30% of students have mentioned no suggestions. 10% of students have mentioned the need for modification in assigning the mentors of their choice, to increase the frequency of mentor-mentee meetings, and asked for the mentor to be even more friendly and approachable.

Discussion

The study results shows that (Figures 1 to 14) the majority of the students expect the mentor to concentrate on their academic and professional development with a friendly and approachable attitude. They suppose the mentor not only to be knowledgeable and teach but also to counsel. Most of them prefer to have a specialist mentor who constantly encourages and supports them rather than having impractical expectations from the mentee. Majority of them do not show much interest in having mentors of the same gender or having the same mentor throughout the course. The majority expect to have weekly once, one to one meetings. Moreover, mentees expect the mentors to develop strategies to deal with academic or personal issues and expect to share academic issues, with their parents. They feel that mutually respectable mentor-mentee relations as long-lasting. More than half of the total participants were satisfied with the previous mentorship program.

More than 50% of the students have perceived that the mentor's role is to facilitate academic, and professional development and to bring out the potential in the students. This is similar to various other studies, where academic development and career guidance were the mentee's priority from mentors in addition to psychological support [12-14]. Most of the mentees prefer

to have a mentor with friendly, approachable, and knowledgeable attributes, similar to the expectation of mentees in a study done in Gujarat, where the students need their mentors to share their knowledge and experience in addition to emotional support [15]. However various other studies have made emphasis on interpersonal skills as an important attribute for mentors. [16,17]. Mentees expect that mentors are not only responsible to teach, and act as role models but also to coach and counsel the students. This is similar to the study findings of Kamarudin et al. [10]. Consistent support, guidance, and concrete help are the attributes of a positive role model [11]. Thus the goal of the mentor is to support personal and professional growth to promote mentees' progress.

The majority of the students prefer to have a specialist mentor (mentor from the specialization the student wants to select in the future) in addition to reverse mentoring. Similar to our study, various other studies have also reported the need for more than one mentor for the group of mentees [18,19]. In the study done by Dave et al. the mentees prefer to have subject-wise mentors [15]. However other studies made it flexible and the student can be made to switch mentors to make the mentee feel comfortable [10]. Maximum students perceive that having a mentor's advantage is improving social and academic confidence. Boosting the confidence level can help the students to face the exams without fear. This is similar to the study by Shapiro et al. where the mentoring program relieves exam-related stress [20].

Most of the mentees felt that impractical expectations from the mentor as a disadvantage of having the mentor. In contrast, as stated by Young et al. mentee was found to be responsible for planning and completing the stipulated task which could enhance the mentor-mentee relationship [21]. In this study, most of the mentees do not prefer to have a mentor of the same gender. Similarly, Kamarudin et al., found that though mentees were not interested to have the same mentor throughout the curriculum, the persistence of the same mentor-mentee group enables the mentees to have better interaction with the mentor and opportunity for bonding [10]. However, Dave et al reported that students prefer to have subject-wise mentors [15]. Some of the mentees perceive mentoring as an everlasting relationship. Similarly, Konstantinos D et al. have mentioned that voluntary mentoring and pairing can result in long-lasting relationships [22]. Mentoring is defined as a "long-term special relationship between the senior and the student" [23]. Majority of mentees prefer to have mentor-mentee meetings at least once a week or as and when required. Similar to the present study, various authors have suggested that students wish to have mentor meetings as per their needs [10,15]. However, the perception of students regarding the frequency of mentor-mentee meetings varies widely [12,24]. In this study majority of the students prefer to meet the mentor personally than as a group. This could enable them to share their problems which might hinder their academic development.

The students, in this study, prefer the mentor to develop strategies for dealing with academic/personal issues and to share only the academic issues with their parents or higher officials for further assistance. However, Attri S has mentioned that mentors could share psychological problems with mentees' parents [25]. In contrast, Freeman R has reported that mentoring should be confidential [26]. Most of the students, in this study perceive that the mentor expects mutual respect and active listening from the

mentee. Only 60% of the students were satisfied with the existing mentor-mentee program.

Students experiencing empathy and caring first-hand from their mentors develop into caring human beings and empathetic doctors. Being a challenging task, mentoring needs investment in time, energy, and emotional resources. Hence this study enables the mentors to adapt according to mentees' perceptions, to provide an effective mentoring program among undergraduate medical students despite the lack of pairing, choice of selecting the mentor by mentee, and volunteering of mentors in this program.

Strength of the study

Most of the studies have been done outside India with few studies published in North India, usage of the same questionnaire may not be fair in the present study setting in south India hence we have developed a questionnaire on mentees' expectations of mentors which have been tested for both internal and external validity.

Limitations

Perception of mentors about the mentees and their option to volunteer for the mentorship program was not obtained. The option to change the mentor or mentee whenever not satisfied by either the mentor or mentee was not considered. Being a single-center cross-sectional study – collective knowledge of the mentorship programs in other teaching medical institutions in south India was not known.

Conclusion

Formal mentoring of undergraduate medical students is of growing concern to forgo the heavy academic curriculum stress-free within the stipulated time. Hence from this study, we found that mentees are interested to have a more friendly and approachable specialist mentor, concerned mainly with academic progress, to encourage & support the mentee, to have at least weekly once, one to one mentor-mentee meetings, and share especially their academic difficulties with their parents. This knowledge can enable the mentors to adapt to the mentee's needs to make mentoring more effective among undergraduate medical students.

Ethics declarations

Funding This study did not receive any funding.

Conflict of interest

The authors declare that they have no competing interests.

Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability

Not applicable.

Author Contribution: Dr. U. Karthika contributed to designing the concept of the paper, manuscript preparation, and designing the questionnaire. Dr. A. Mangai contributed to the manuscript preparation and design of the questionnaire. Dr. K. Tamilselvan contributed to the statistical analysis, and preparing the manuscript.

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ANNEXURE I (QUESTIONNAIRE)

Exploration of mentee's perception of mentoring among undergraduate medical college students

This study is being done to enhance the mentor-mentee program in our college.

Fill out the questionnaire based on your own perception.

It will take 10-15 minutes to fill out the form.

Filling out the questionnaire and submitting ensures that you are volunteering & giving consent to participate in the study.

You have the right to withdraw from the study at any point in time.

You will not be affected in any way if you are not participating in the study. The name of the student is not collected to maintain anonymity and confidentiality. You can contact the investigator for queries.

Principal investigator: Dr. Karthika Priyadharshini

Co-investigator: Dr. Mangaiarkkarasi - Professor & Head of Pharmacology

Section 1

1. **I am volunteering to participate in the study**

Mark only one oval.

I am giving my consent to participate in the study

I am not willing or consenting to participate in study

Details of participant

2. **Age**

3. **Gender**
   Mark only one oval.
   Female Male

4. **Year/ Batch you belong**
   Mark only one oval.
   first year second year
   third/ prefinal year final year

Section 2

Answer the following questions based on your perception

5. **The mentor is one who? (you can choose one or more options)**
   Facilitate in academic development
   Facilitate in professional development
   Facilitate in personal development
   Brings out the potential in you
   Teaches life lesson
   Other:

6. **I like to have a mentor with the following attributes (you can choose one or more options)**
   Friendly & approachable
   knowledgeable
   able to network and find resources
   non-judgmental
   Other:

7. **The responsibility of the mentor shall be to (you can choose one or more options)**
   Coach
   Teach
   Protect
   Counsel
   Role model
   Other:

8. **Type of mentors you prefer (you can choose one or more options)**
   Traditional mentor (senior professors) Reverse mentor (less senior faculty) Peer mentor (senior students)
   Specialist mentor (faculty from specialties you want to select in future) Informal mentor (selected by yourself)

9. **What do you think is the advantage of having a mentor?**
   (you can choose one or more options)
   To encourage and support
   To plan on long term and short-term goals
   To improve my social and academic confidence to enhance the leadership quality
   To communicate effectively for better relationship
   Other:

10. **What do you think is the disadvantage of having a mentor?**
    (you can choose one or more options)
    Critical feedback given by the mentor Increased dependence on mentor
    Lack of mentorship pairing Impractical expectations from mentor
    Manipulating mentors' activities over mentee
    Other:

11. **Grade your preference to have a mentor of the same gender (Mark only one oval).**
    strongly agree
    agree
    neutral
    disagree
    strongly disagree

12. **Grade your willingness to have the same mentor throughout your MBBS course (Mark only one oval.)**
    strongly agree
    agree
    neutral
    disagree
    strongly disagree

13. **Mentoring is an everlasting relationship rather than short lasting (Mark only one oval)**.
    strongly agree
    agree
    neutral
    disagree
    strongly disagree

14. **How frequently do you like to meet your mentor? (give only one answer)**
    Daily
    Weekly once
    Monthly once
    As and when required
    Other:

15. **Preferred style of mentor-mentee meeting**
(you can choose one or more options)
Personally- one to one
along with other mentees- group mentoring
through phone call or message
formal meeting if it is mandatory
Other:

16. **What do you expect from a mentor when you face personal and academic issues? (you can choose one or more options)**
Enable mentee to develop strategies for dealing with
Expect the mentor to take decisions on the issues
May not make the mentor aware of the issues
To assist the mentee in solving the issue
Other:

17. **What type of mentees' issues do you feel the mentor can share with your parents or higher officials for further assistance?**
(you can choose one or more options)
Academic issues
personal issues
issues that hinder my professional growth
issues which cannot be handled by a mentor
Other:

18. **What do you think the mentor expects from the mentee?**
(you can choose one or more options)
Mutual respect
Maintain boundaries
Listen attentively
Confidentiality
Recognizing the importance of mentor's time
Other:

19. **Give your suggestions on the mentorship program**

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REVIEW ARTICLE

Molecular Forensic Medicine: An Overview

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Abstract

Molecular autopsy or Molecular Forensic Medicine is gaining importance across the globe in both developed and developing countries. This is relatively less thought-out or discussed in the Indian scenario. We are attempting to present a mini-review of ongoing developments in the field of Molecular Forensic Medicine and emphasize the need for starting Molecular autopsy programs in Medico-Legal Centres in our country. This cross-disciplinary branch requires concerted efforts from various stakeholders for successful implementation in day-to-day autopsy practice. In the post-pandemic era, it is worth noting that most of the leading teaching hospitals in India now possess the necessary infrastructure to carry out molecular studies. This presents a unique opportunity for us to initiate our national molecular autopsy program.

Keywords: Molecular Autopsy, Thanatotranscriptome, Thantomicrobiome, Sudden Death, Thantomarkers, Regenerative Medicine, Transplant Medicine, Forensic Pharmacogenomics, Toxicogenetics

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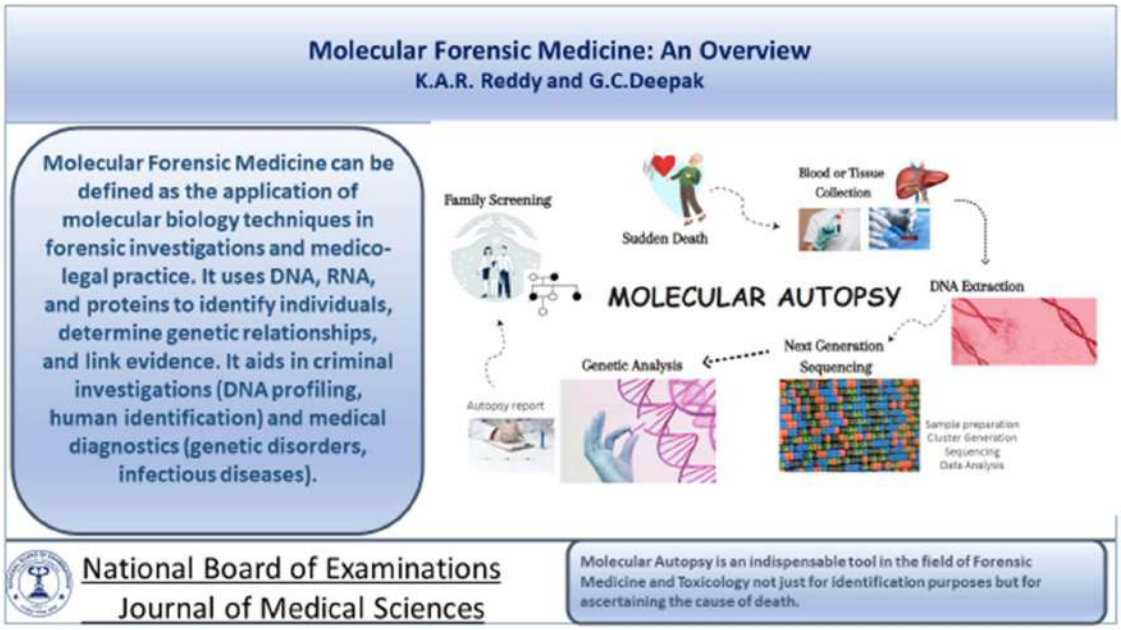
Graphical Abstract



Introduction

According to the National Cancer Institute, USA, Molecular Medicine is a branch of medicine that develops ways to diagnose and treat disease by understanding the way genes, proteins, and other cellular molecules work. Molecular medicine is based on research that shows how some genes, molecules, and cellular functions may become abnormal in diseases like cancer Molecular Forensic Medicine is defined as the application of knowledge of the field of Molecular Medicine in the aid and administration of justice.

Review of Literature

Molecular medicine is a hybrid branch with close collaboration between physicians and biologists. As we live in a promising world of personalized medicine, every medical practitioner needs to have a basic idea of recent trends in the field of molecular medicine. However, in this article, we are restricting ourselves only to the applications of this field towards Forensic Medicine and suggesting a few future directions of research.

Every forensic pathologist immediately thinks of DNA fingerprinting when someone mentions molecular techniques. A thorough assessment of the literature revealed numerous recent advancements in the area of molecular forensic medicine that go beyond the field's conventional uses for identification in resolving medico-legal cases. However, molecular testing is currently being considerably used and has far more potential in the field of autopsy. Today, the autopsy pathologist can analyze molecular data for inheritable thrombophilias, hereditary heart disorders, pharmaco-genetics, and infectious agent detection. The vital data gleaned from these genetic tests is frequently crucial to the immediate relatives of the dead as well as the community at large and may have significant medico-legal implications [1].

Molecular research has discovered mutations for structural cardiomyopathies

(myosin, troponin) and electrolyte channels (sodium, chloride, calcium) that have helped to understand these disorders. Molecular studies are of great help for the autopsy surgeon in cases of the sudden death of children and situations where structural alterations in the heart during autopsy are not obvious.[1] Six important cardiac ion channel genes (KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, and RyR2), for which disease-causing sequence variations have been previously described, are routinely included in the molecular analysis for cardiac channelopathies [2,3] (Table 1).

A rising number of inherited and congenital arrhythmia illnesses are brought on by gene mutations that produce faulty ionic channel proteins that control the transit of sodium, potassium, and calcium ions across cell membranes. Long QT syndrome (LQTS), short QT syndrome (SQTS), Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia (CPVT) are some of these ion channel diseases. The clinical and genetic characteristics of Brugada syndrome and the nocturnal sudden unexplained death syndrome in young Southeast Asian males are comparable [4]. Over-interpretation of excess epicardial fat in someone who is overweight or obese as evidence of arrhythmogenic cardiomyopathy and over-interpretation of hypertensive cardiac disease as hypertrophic cardiomyopathy are the two most typical cases we observe [5].

The full set of genes linked to various basic arrhythmia syndromes or cardiomyopathies is unknown. Thus, the absence of genetic variants at the time of genetic testing does not rule out the potential that a specific clinical trait has a genetic basis [5].

Table 1. Showing details of the genetic basis of sudden cardiac death in an Anato-morphologically normal heart [4].

S. No	Condition in which heart is Anato-morphologically normal	Type of disease and Genes implicated
1	Long QT Syndrome	SQTL1 KCNQ1/KVLQT1, SQTL2, KCNH2/HERG, SQTL3 SCN5A, SQTL4 ANKB, SQTL5 KCNE1/MinK, SQTL6 KCNE2/MiRP1 SQTL7 (Andersen S.) KCNJ2, SQTL8 (Timothy S.) CACNA1C, SQTL9 CAV3, SQTL10 SCN4B Jervell–Lange-Nielsen (autosomal recessive) S. JLN I KCNQ1, S. JLN II KCNE1
2	Short QT syndrome	KCNH2 (HERG, SQT1) KCNQ1 (KvLQT1, SQT2), KCNJ2 (Kir2.1, SQT3)
3	Bruguda Syndrome	5CN5A, Ankyrin binding Motif of Nav.1.5, GPD1-L, CACNA1C, CACNB2b
4	Catecholaminergic Polymorphic Ventricular Tachycardia	RyR2, CASQ2

Molecular analysis for two common hereditary thrombophilias, factor V Leiden (FVL) and prothrombin G20210A (PT), can be performed using several standard single nucleotide polymorphism detection methods [1].

Molecular analyses or probes can detect and classify a wide range of infectious agents. This is generally the domain of public health laboratories and clinical pathology, but forensic pathologists must be aware of these techniques and ensure that specimens are collected, stored, and presented properly and promptly. H1N1, Corona Virus, avian influenza, and other viruses are examples.1 Molecular approaches can be used to diagnose extremely rare illnesses such as Leber's optic neuropathy, which can have serious consequences for the next of kin [1].

Pharmacogenetics is the study of genetic differences that lead individuals to respond differently to the same pharmacological dose. Drug concentrations can differ significantly between two people of the same weight, age, and dose. The efficacy or toxicity of a medicine can be affected by genetic differences. A person's reaction to a medicine is a complex attribute regulated by various genes [1].

Individual dose adjustments based on a patient's genotype are aided by genomic polymorphisms of phase I and phase II drug-metabolizing enzymes. Polymorphisms in the cytochrome P4502D6 gene have a significant impact on the metabolism of several medicines, including the analgesics codeine, tramadol, hydrocodone, and oxycodone. Individuals differ in that they can be classified as an extensive metabolizer, a poor metabolizer, an intermediate metabolizer, or an ultra-rapid metabolizer [6].

Molecular pathology approaches can help determine not just the cause of death, but also the manner of death, for example, in the differential diagnosis of accident/suicide or even accident/homicide. This differential diagnosis may also be critical for the regulation of insurance compensations.[6] For instance, a particular dose of a drug detected in an individual's body can be the usual fatal dose which can give the picture of a suicide attempt by that person. However, if we investigate the cases from the pharmacogenomics side, he/she can have an idiosyncrasy in metabolizing that drug which could have led to the accidental accumulation of the drug that can cause death. These situations arise in the case of drugs with low therapeutic index and also drugs of abuse. Similarly, for the sake of understanding, the examination of strangulation-related biomarkers expressed in the lung during postmortem submersion cases can help differentiate between homicide (strangulation) and accident (drowning).

Molecular biology techniques have greatly increased diagnostic sensitivity, accuracy, and validity in forensic medicine, particularly in the field of identification (paternity testing, stain analysis). For more than a decade, these techniques have been used in forensic medicine for a variety of purposes, including determining the cause and manner of death, tissue identification using mRNA and microRNA, examining gene expression levels (survival time, time since death, cause of death), and toxicogenetics [6].

Combining immunohistochemistry with relative mRNA quantification of multiple biomarkers provides valuable insights into the cause of death. In particular, SP-A (Pulmonary surfactant-

associated protein A), MMPs (matrix metalloproteinases), ICAM (intercellular adhesion molecule), CLDN (claudin), and AQP (aquaporin) are important biomarkers identified in the research.

In the investigation of pulmonary alveolar damage using MMPs, ECM, ICAM-1, CLDN, and AQPs, the up-regulation of these markers was observed in cases of sharp instrument injury and hyperthermia. Immunohistochemistry revealed increased levels of MMP-2 and -9. Notably, AQP-5 demonstrated a distinction between strangulation and smothering or choking. Immuno-staining of AQP-5 displayed weakly positive results in a linear pattern in type 1 alveolar epithelial cells during smothering and choking. Conversely, cardiac and brain injury deaths exhibited marked positivity, while most strangulation cases displayed AQP-5-positive granular aggregates and fragments within intra-alveolar spaces. Smothering and choking had lower AQP-5 gene expression compared to other groups.

Regarding cardiac strain, atrial and brain natriuretic peptides (ANP and BNP) increased in pericardial fluid. These peptides showed varied patterns depending on the cause of death. In hypothermia cases, both ANP and BNP levels were high, whereas hyperthermia led to elevated ANP levels, and chronic heart failure resulted in increased BNP levels. However, gene expressions of ANP and BNP were low in hyperthermia, similar to sedative-hypnotic intoxication [7-9].

Human postmortem microbiome research has shown that these communities exist in the host ante mortem or colonize the body after a human or animal surrogate dies. The thanatomicrobiome is the entire assemblage of microorganisms (e.g., bacteria and fungus) discovered in various bodily sites of decomposing corpses [12].

In a study, swabs were taken from the proximal large intestines between 9 to 20 days postmortem. Real-time quantitative PCR (RT-qPCR) was conducted using group-specific primers targeting 16SrRNA genes to detect three common gut bacteria: Bacteroidetes, Lactobacillus, and Bifidobacterium. The results showed that the relative abundance of Bacteroides and Lactobacillus species decreased significantly and exponentially ($p < 0.05$) as the postmortem interval (PMI) increased. These findings suggest that these two bacteria could potentially serve as reliable quantitative indicators for estimating the time since death in medico-legal investigations [10-12].

In a separate study, researchers identified five highly abundant species (Staphylococcus sp., Streptococcus sp., Clostridium sp., Enterococcus sp., and Escherichia sp.) and a total of 21 different bacterial genera as postmortem colonizers. The study highlighted important findings relevant to the field of thanatomicrobiome research. Firstly, it was observed that sampling of cadaver tissue samples should ideally be done within 7 days after death. Secondly, the liver and pericardial fluids were identified as optimal body sites for sampling as they remained relatively free from microbial colonization for up to 5 days postmortem.

In a related thanatomicrobiome investigation, the study examined the relative quantities of commensal gut bacteria that migrated into the liver and ascites of autopsied cirrhotic livers. The results revealed that Enterobacteriaceae were the most commonly translocated bacteria into the affected hepatocyte tissues. These findings shed light on the

dynamics of microbial translocation in diseased liver tissues and its relevance to thanatomicrobiome studies [12,13].

The diversity of bacterial communities in partially skeletonized lower rib bones from 12 corpses was investigated. The study revealed that 99.2% of the sequences belonged to six bacterial phyla: Proteobacteria, Firmicutes, Bacteroidetes, Actinobacteria, Acidobacteria, and Chloroflexi. Interestingly, these communities exhibited similarities to gut-associated bacteria. However, as the bones progressed toward the dry skeletal remains stage, the bacterial communities began to resemble those typically found in soil. Based on these findings, the authors proposed that the nutrient-poor environment of corpse bones, compared to the nutrient-rich nature of soft tissue, along with the preservation of organic nutrients provided by the bones, prevented excessive bacterial growth during the initial years of skeletonization [12,14].

In a study focusing on the bloat stage of decomposition, the sequencing data revealed an increase in Firmicutes (specifically Lactobacillaceae and Bacteroidaceae families) in the abdominal cavity. Proteobacteria was the dominant phylum observed on the skin surfaces of both the head and torso areas throughout the decomposition process. However, once the carcasses ruptured, there was a significant decrease in Firmicutes on the skin. Based on these findings, a "microbial clock" was developed, which accurately estimated the postmortem interval (PMI) within a 3-day range, corroborating the actual time of death. The microbial clock refers to the time-dependent succession of microbial diversity during the decay process, providing valuable insights into the progression of decomposition [12,15].

Few studies were also conducted to assess the time since immersion in an aquatic environment based on microbial colonization. Proteobacteria and Firmicutes were identified as major players. Their colonization and succession were predicted to be useful in real scenarios [12,16,17].

Transcriptome analysis via RNA sequencing was performed on liver tissues from 27 Italian and United States corpses spanning 3.5 hours to 37 days postmortem. Eight liver tissue-specific gene biomarkers (e.g., AMBP and AHSG) were utilized in a highly specific single-blind study, accurately identifying postmortem liver tissues from autopsy-derived organ samples. Mapping results showed that 98-100% of sequencing reads aligned to these liver biomarkers, confirming the potential use of gene expression signatures to validate tissue fragment identities up to 37 days of autolysis [18].

During the autopsy, tissue samples were obtained from the prostates of five cadavers by a medical examiner. Following RNA extraction, cDNA synthesis was performed, and the concentration of cDNA was determined. The cDNA was then subjected to apoptosis-related gene expression profiling using a human PCR Array. The results of the PCR Array demonstrated that, at 38 hours after death, a majority of the genes involved in apoptosis induction and positive regulation (such as caspases) exhibited higher expression levels compared to five days postmortem. The expression of anti-apoptotic genes, including BAG1, BCL2, and the negative regulator of apoptosis XIAP, showed a significant increase in a time-dependent manner. However, the expressions of pro-apoptotic genes such as TP53 and TNFSF10 did not exhibit significant upregulation [19].

A study investigated gene expression shutdown after death by identifying mRNA transcripts that increased in relative abundance postmortem in mice and zebrafish. A time series analysis spanning up to 96 hours postmortem revealed significant increases in the abundance of 1063 genes. The profiles of these transcripts displayed non-random patterns over time. While most transcript levels increased within 0.5 hours postmortem, some exhibited increases at 24- and 48-hour postmortem. Functional analysis of the most abundant transcripts revealed categories such as stress, immunity, inflammation, apoptosis, transport, development, epigenetic regulation, and cancer. These findings suggest a stepwise shutdown of gene expression occurs during organismal death, characterized by the apparent increase of specific transcripts with varying abundance peaks and durations [20].

One could argue that certain pathways may have evolved to promote healing or "resuscitation" after severe injury, which could confer an adaptive advantage. The observed increase in transcripts related to inflammation response, for instance, may suggest that still-functioning cells sense signals of infection or injury following the body's death. Alternatively, these increases could be attributed to the rapid decay of repressors of genes or entire pathways, resulting in gene transcription. A further detailed study is warranted to gain insights into this phenomenon, potentially informing improved preservation methods for organs intended for transplantation [20].

Postmortem transcriptional regulation is a highly complex process involving various cellular components. The degradation rates of mRNA transcripts differ across different types of postmortem tissues and their unique gene expression patterns. Although mRNA molecules can persist for extended periods, they are prone to degradation, with specific genes exhibiting half-lives ranging from minutes to weeks. Postmortem genetic studies have the potential to enhance organ transplantation techniques.

In studies focusing on postmortem gene expression in cardiac tissues, ten reference genes were identified, with cyclophilin A (CYCA) and TATA box-binding protein (TBP) displaying the most stable mRNA. Similarly, in postmortem muscle tissues, succinate dehydrogenase complex subunit A (SDHA) and TBP genes exhibited stable mRNA levels. Moreover, specific mRNA markers associated with forensic body fluid identification, such as PPBP for blood, FDCSP for saliva, MSMB for semen, and MSLN for vaginal secretions, were successfully validated through distinct expression patterns in their respective body fluids.

In a related forensic study, mRNA markers including hemoglobin alpha (HBA), matrix metalloproteinase 7 (MMP7), and matrix metalloproteinase 11 (MMP11) were explored as differentiating markers between menstrual and peripheral blood stains. These findings highlight the potential utility of mRNA markers in forensic investigations [21-24].

Brain RNA degrades linearly after death. 18S rRNA is more stable than Beta-actin mRNA in the postmortem period. Their ratio can be used to predict the Time since death.

Discussion

There are a lot of grey areas in autopsy practice in particular and the field of medicine in general. Molecular medicine

is emerging as a great lens to understand them. The forensic autopsy now truly extends from the scene to the gene. We live in exciting times.[5] It is not uncommon for an autopsy surgeon to encounter cases where there are no Anato-morphological insignia towards the cause of death. The persistent challenge of exact postmortem interval before autopsy lingers on to date. The ultimate goals of medicine are to reduce the disease burden and enhance the longevity of humanity. Replacing morbid organs/tissues with new ones seems to be a logical and practical approach being practiced the world over. With the advent of cost-effective organ transplant technologies, there is a strong need to increase the supply of donor organs to meet the long waiting list of recipients. Molecular transplant medicine is an area of research that's blossoming in biology labs.

It is very much necessary to study the postmortem expression of genes in human tissues to understand the appropriate cellular mechanisms involved in it like apoptosis, stress response, and survival strategies employed by each cell, every organ, and the body as a whole. An insight into these areas may shed new light on the area of cadaver transplant when combined with the emerging technologies in tissue engineering, and regenerative medicine/stem cell medicine for creating bio-engineered organs.

The era of histopathology for confirmation of morbid anatomy/ abnormality is coming to a close and we are inching towards more conclusive evidence in cytogenetics and molecular diagnostics. The day is not so far when we may link a few sets of thanatomarkers/biomarkers for every single mechanism of death.

However, it is always borne in mind that all these techniques will complement and strengthen the traditional autopsy and it's really difficult for any of them to emerge as a substitute for routine autopsies shortly. Human molecular genetics is a very dynamic branch with volumes of literature being cataloged every day. Interpretation of all the findings of the molecular autopsy is fraught with a lot of difficulties like hitherto unreported variants, penetrance patterns, and epigenetic influences to name a few. Hence it is always advisable to seek the opinion of a professional human molecular geneticist as and when required.

Perhaps as of now, there's no single medico-legal center in our country with a dedicated molecular autopsy program. It is advisable to start right now at least in apex centers i.e., at least in one teaching hospital in every state. Molecular techniques in sequencing, gene mining, and diagnostics should be part of the PG curriculum in Forensic Medicine in the future.

The COVID pandemic led to the opening of PCR labs in every nook and corner of the country. Before the COVID-19 era, RT-PCR was a luxury and now it has become a necessity in every teaching hospital. There's a high likelihood that one fine day all our medico-legal centers in India may be upgraded for molecular autopsy work if a situation demands. Apart from all this, the true need for molecular autopsy gets reflected in our day-to-day work if we honestly start admitting our limitations in giving a 'cause of death' to every case based on just gross pathology.

Indications for Molecular Autopsy [5]

- Sudden cardiac death (structural and non-structural heart disease) – genetic panels to assess primary arrhythmia syndromes and/or

cardiomyopathies may be helpful (Comment: if considering an unexplained dilated cardiomyopathy in a person under 30 years, also examine skeletal muscle to assess for a generalized myopathic process)

- Vascular disorders (aortopathy / arteriopathy) – connective tissue disease panels (Marfan Syndrome, Ehlers-Danlos Syndrome, Loeys-Dietz Syndrome, familial thoracic aortic aneurysm, and dissection, syndromic arthropathies) – Sudden deaths in these scenarios.
- Sudden and unexpected death in infants and young children (SIDS / SUDI, SUDC) – a subset of these cases likely involves genetic cardiovascular disease – much still unknown about the pathophysiology of the SUDI cohort.
- Sudden unexpected death in epilepsy (SUDEP) – some preliminary evidence suggests that primary arrhythmia syndromes may present as a seizure disorder. There are also familial forms of true seizure disorders.
- Other complex neurological disorders – based on clinic-pathological phenotype and family history. Some complex congenital disorders – based on clinic-pathological phenotype and family history. Thrombophilias and bleeding disorders – both disorders of platelet function and coagulopathies may have a genetic basis.
- Triad cases in infants – dependent on history, and clinical and pathological findings – may consider bleeding disorders, connective tissue disorders, or metabolic disorders.
- Deaths in the setting of positional restraint, excited delirium, unexplained death in the setting of electronic control device usage – careful consideration of primary arrhythmia syndromes or cardiomyopathies
- Sudden and unexpected death in the setting of a criminal act (i.e., homicide by heart attack) – careful consideration of primary arrhythmia syndromes or cardiomyopathies
- Other uncommon genetic syndromes identified at autopsy that may be incidentally identified at autopsy, such as autosomal dominant polycystic kidney disease, hereditary spherocytosis, connective tissue disorders, genetic cancer syndromes, etc.

Sampling Considerations

10 ml of blood in EDTA and/or 1 Cm^3 fresh Spleen and/or Liver or 2 Cm^3 Muscle or Skin should be preserved for molecular autopsy. Samples are to be transported to the laboratory as early as possible. If there is a delay, samples are to be sent frozen at -80 degrees Celsius. DNA can be directly extracted from the samples for study (Figure 1).

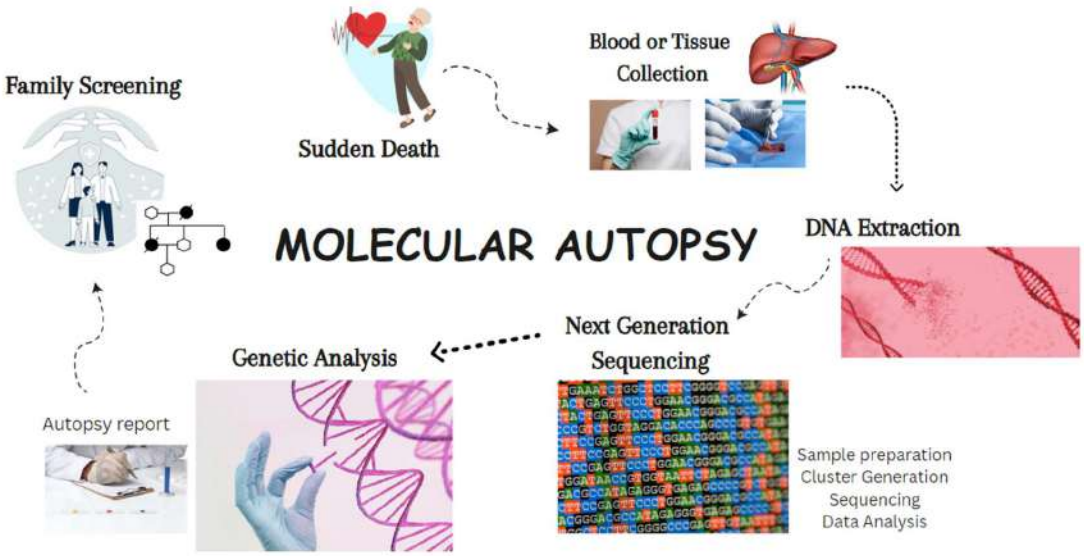


Figure 1. Workflow of Molecular Autopsy.

It is also interesting to note that micro-RNA can be extracted from even Formalin Fixed Paraffin Embedded samples also. Micro RNA is emerging as a very handy tool in forensic settings considering its stability in different settings.

The traditional method to preserve autopsy tissues in formalin for microscopic examination makes the tissues unusable for current PCR and Sanger sequencing-based molecular analysis. Non-formalin-based storage solutions, such as RNA later, should be used. Non-formalin fixatives allow rapid stabilization and protection of the cellular nucleic acids without creating damage (e.g., cross-linking) in the DNA double strands [5].

Indian Scenario

There is no dedicated molecular autopsy program anywhere in India. The problem with the present state of affairs is that few autopsy surgeons try to fit every death into some or the other diagnosis. If negative autopsy rates are reflected in the statistics, it becomes more conducive to establishing the necessity for molecular autopsy programs everywhere. The concept of bringing in the model of differential diagnosis of death during preliminary consideration of the case will solve a lot of unnecessary dogmatic reports in our field.

The niggardly pace of functioning of the criminal justice system leading to undue delay of ancillary investigations reports has created a generation of autopsy surgeons who usurped excess authority in deciding matters related to the cause of death. Moreover, we lack a proper statutory protocol for medico-legal work. Medical and Health being a state subject in our country, there are a lot of administrative impediments to easy reform.

Institutions & Laboratories in India offering Molecular Diagnostic Services

Institutions with DM programs for Medical Genetics have the wherewithal for gene diagnosis. Centre for DNA fingerprinting & Diagnostics and Centre for Cellular & Molecular Biology, Hyderabad offer a range of quality services in the field

of molecular diagnosis. The chain of laboratories of ICMR across the country, if properly equipped, can very easily offer molecular diagnostic services. However, it is always advisable for the autopsy surgeon to discuss the matter well in advance before dispatching the sample to the laboratory to ascertain the feasibility of diagnosis. It's high time we develop cross-institute collaboration channels for the field of Molecular Forensic Medicine to flourish for the benefit of society at large.

Future Directions for Research

In our setup, it is recommended to conduct research to determine the amount of DNA obtained from various tissues at different time intervals after death. This research will help establish a standard protocol for identifying the most suitable sample for DNA extraction. Whenever possible, it is advisable to perform DNA extraction within our institute to overcome the challenges associated with maintaining a cold chain, which can be particularly difficult in our country. Though it would be impractical and foolish on our part to imagine a tremendous change in outcomes of autopsy dilemmas just by introducing a molecular autopsy program, it will certainly usher many new changes in death reporting systems. With high throughput sequencing and next-generation sequencing methods turning cheaper by the day and the cost incurred in molecular diagnosis becoming more economical, we are set to see a large volume of research in the 'thantotranscriptome' genre.

- Postmortem thanatotranscriptome studies may shower a new light on mechanisms of cellular defense that can be exploited for treating diseases. For example, new anti-apoptotic pathways, and anti-stress fighting pathways may be discovered if the high volume thanatotranscriptome is totally sequenced primarily in natural deaths and later in unnatural deaths. A ***Human Thanatotranscriptome Project*** is a need of the hour which will help in archiving the data and may lead to the identification of more causes of death and specific activated genes in specific organs/bodies as a whole. Such an approach will have ramifications for both clinical medicine and forensic medicine. The human thanatotranscriptome may solve some perennial issues plaguing autopsy surgeons like the estimation of the exact time since death.
- Thanatomicrobiome profiling studies may be conducted by selecting different places across the country and in different ecosystems to develop a microbial clock for the proper estimation of time since death. This is something similar to body farms being instituted at a cellular level to study colonization and succession patterns.
- Mining for more Thanatomarkers/ biomarkers of trauma, hypoxia, inflammation, and infection from different tissues. For example, the field of biomarkers of trauma revolutionized greatly in the recent past, markers like S100 calcium-binding protein B, Neuron Specific Enolase, Glial Fibrillary Acidic Protein, Interleukin 6, LDH, Brain-Derived Neurotrophic Factor, Ferritin, Neutrophil gelatinase-associated lipocalin, Microtubule-

associated protein Tau, etc. are under consideration [25].

- Study pharmacogenomic properties of individuals in case of drug abuse-related death to decide the manner as accidental/suicidal. These tests may be carried out as an adjunct to the already existing forensic toxicology services.
- Understanding the epigenetics of postmortem transcription may unravel the role of hitherto unknown areas of the genome described as 'junk'. Activation and silencing of such genes may have some deep secrets for all of us.
- Further research in the realm of thanatoproteomics is also the need of the hour for understanding the proteome-level interactions during survival and death. These studies can have implications for regeneration and transplant medicine.

Conclusion

Molecular Forensic Medicine will add more robustness to medico-legal work and will not only bring out the real cause of death; it will also help diagnosis of genetic diseases in the next of kin of the deceased. The branch will turn out to be a perfect link with clinical branches of medicine. The autopsy surgeon will hold the key responsibility of indicating the genetic nature of findings in the case to the family members and thereby coordinate with geneticists and genetic counselors. In our professional lifetime, we will see the zenith of the rapidly revolutionizing field of Molecular Forensic Medicine. Let us wish India will also be part of this scientific development very soon. The authors also advise the community of forensic pathologists in the country to get benefited from the Department of Health Research (DHR, GoI) sponsored molecular genetics training offered at Indian Council of Medical Research organizations.

Ethics declarations

Funding This study did not receive any funding.

Conflict of interest

The authors declare that they have no competing interests.

Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability

Not applicable.

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CASE REPORT

Safety pins and broken incense sticks inside the urethra of a young male: A case report

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Abstract

The incidence of Lower urinary tract foreign body insertions is low. The motives for such insertion of a variety of objects are difficult to comprehend. We report a case of a 20-year-old male with multiple safety pins and broken incense sticks embedded inside his urethra which were successfully removed cystoscopically.

Keywords: foreign body, urethra, penile

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Introduction

The incidence of Lower urinary tract foreign body insertions is low. The motives for such insertion of a variety of objects are difficult to comprehend. We report a case of a 20-year-old male with multiple safety pins and broken incense sticks embedded inside his urethra.

Case report

A 20-year-old male was referred for recurrent scrotal infections, and obstructive lower urinary tracts symptoms gradually increasing in severity since last 6 months. Patient had undergone incision and drainage twice for scrotal abscess in last 4 months. Patient was obese with BMI of 29.4, normal secondary sexual characteristics with mental retardation. No history was given by the patient or informant of autoerotic or any other inappropriate behavior. Perineal and per rectal examination were normal.

Patient's hemogram was normal, creatinine was 0.7mg%. Urine showed 20-25 pus cells but culture was sterile. Retrograde urethrogram (RGU) was done. Scout film revealed irregular ROS over pubic symphysis (Figure 1).

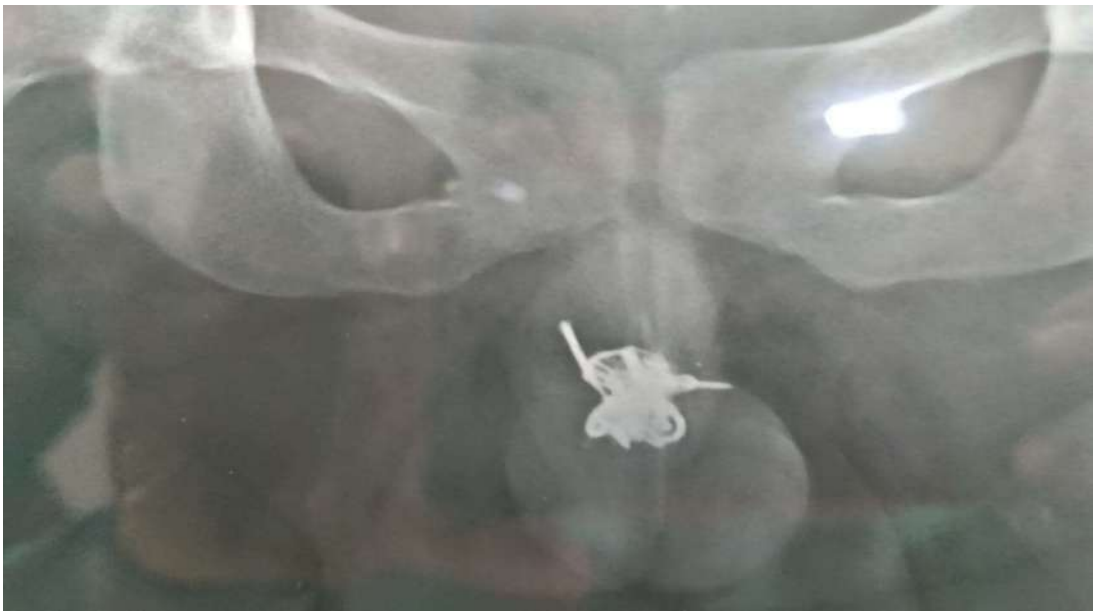

Figure 1. Scout Film Xray showing multiple foreign bodies in the penile urethra.

Retrograde urethrogram revealed irregular filling defect in the penile urethra. Patient underwent Cystourethroscopy which revealed multiple metal-nonmetal foreign bodies (safety pins, hairpins, earbud, plastic stick, incense stick, vegetable twigs) embedded within penile with surrounding mucosal edema. All the foreign bodies, 18 in total were removed cystoscopically using grasper using a 21Fr cystoscopy sheath (Figure 2).

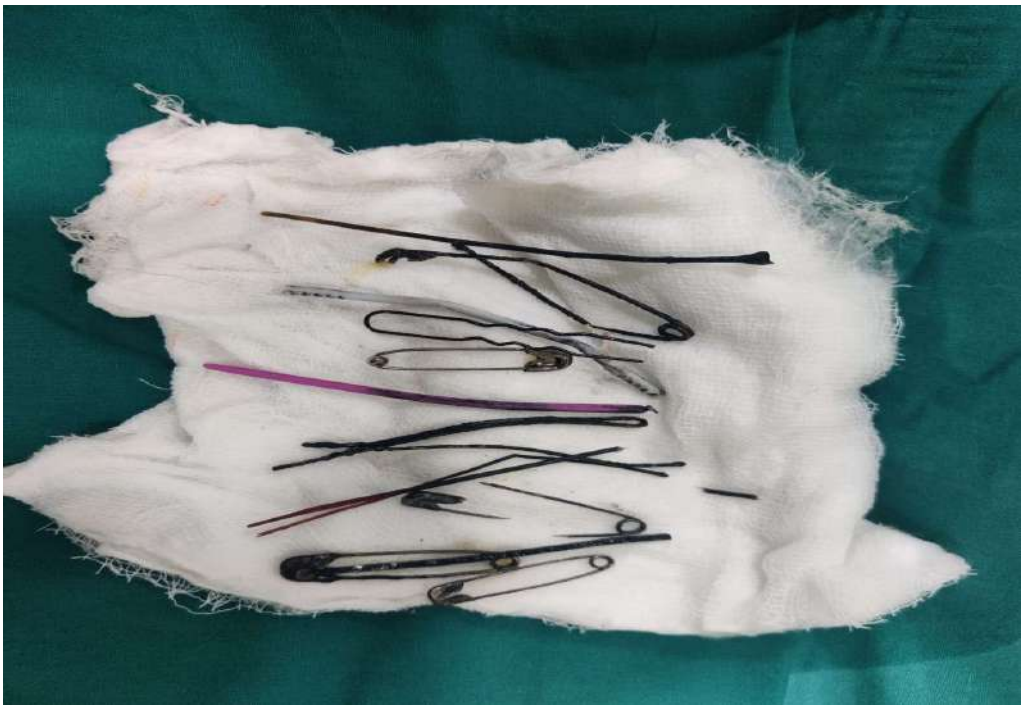

Figure 2. Postoperative image showing all the 18 foreign bodies removed successfully from the patient's penile urethra.

Per urethral Foley catheter was removed after 7 days. Patient voided well after catheter removal. Patient was then referred for psychiatric evaluation and rehabilitation.

Discussion

The wide array of self-inserted foreign bodies include needles, pencils, ball point pens, pen lids, garden wire, copper wire, speaker wire, safety pins, Allen keys, wire-like objects (telephone cables, rubber tubes, feeding tubes, straws, string), toothbrushes, household batteries, light bulbs, marbles, cotton tip swabs, plastic cups, thermometers, plants and vegetables (carrot, cucumber, beans, hay, bamboo sticks, grass leaves), parts of animals (leeches, squirrel tail, snakes, bones), toys, pieces of latex gloves, blue tack, Intrauterine Contraceptive Devices (IUCD), tampons, pessaries, powders (cocaine), fluids (glue, hot wax) [1,2].

The most prevalent motivation of foreign body insertion is autoerotism [2-4]. Some cases are associated with mental and cognitive disorders, factitious disorders, personality disorders, sexual curiosity and practice under the influence of intoxicating substances.[2,4,5] Accidental and iatrogenic foreign bodies occur much more rarely [4,5]. Polyembolokoilamania is a term used for broad group of disorders characterized by self-insertion of objects into body orifices.

Presentation of urethral foreign bodies can range from asymptomatic to dysuria, obstructive lower urinary tract symptoms, haematuria, perineal pain, fever sepsis. Delayed presentation can be due to embarrassment or in mentally disabled patients, like in the case presented. Self-attempts of removal can result in urethral

injuries and strictures. Diagnosis can be with perineal and per rectal examination, x-ray pelvis and cross-sectional imaging. Meatotomy, cystoscopic removal, internal or external urethrotomy, suprapubic cystostomy, and injection of solvents, various such methods have been described. Sometimes a combination of the modalities may be needed. Young Hwii Ko et al. have described removal of foreign bodies in urinary bladder using single laparoscopic port under pneumovesicum [6]. Patients with urethral foreign bodies may need psychiatric evaluation, counselling and rehabilitation to prevent recurrences.

Ethics declarations

Funding This study did not receive any funding.

Conflict of interest

The authors declare that they have no competing interests.

Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability

Not applicable.

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CASE REPORT

Lipiodol Embolism with Pneumonitis and ALI after TACE – A Case Report

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Abstract

Transcatheter arterial chemoembolization (TACE) is a useful palliative therapeutic modality for hepatocellular carcinoma (HCC) and has developed into a successful alternate therapeutic method for people with HCC that is inoperable. TACE is generally secure, however syndrome of acute respiratory distress/Acute Lung Injury with pulmonary lipiodol embolism after TACE was rare and life-threatening, occasionally reported in previous literatures. We report a rare case of lipiodol embolism with pneumonitis/acute lung injury after TACE for HCC.

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Introduction

The most frequent primary liver cancer, hepatocellular carcinoma (HCC), is one of the leading causes of cancer-related death worldwide, and is frequently diagnosed in a more advanced state. Additionally, HCC frequently coexists with cirrhosis and chronic hepatitis, making curative treatment challenging. The palliative treatment for unresectable HCC is Transcatheter artery chemoembolization (TACE) employing a combination of anticancer drugs and lipiodol. Lipiodol, gelatin sponge (gelfoam), and an anticancer agent are injected into the hepatic artery to cause microvascular embolisation and stagnation of the anticancer medicine, which results in the necrosis of cancer cells. Post-TACE hepatic encephalopathy, ischemic cholecystitis, rupture of HCC, hepatic abscess, severe hepatic failure, and possibly pulmonary metastasis with HCC were complications. They also included pulmonary oil embolism, interstitial pneumonitis, chemical pneumonitis, ALI, ARDS, lipoid pneumonia, acute eosinophilic and neutrophilic pneumonia, bilious pleurit [1]. Despite the fact that TACE is generally safe, pulmonary lipiodol embolism is an uncommon and potentially lethal consequence that doctors frequently do not expect [2].

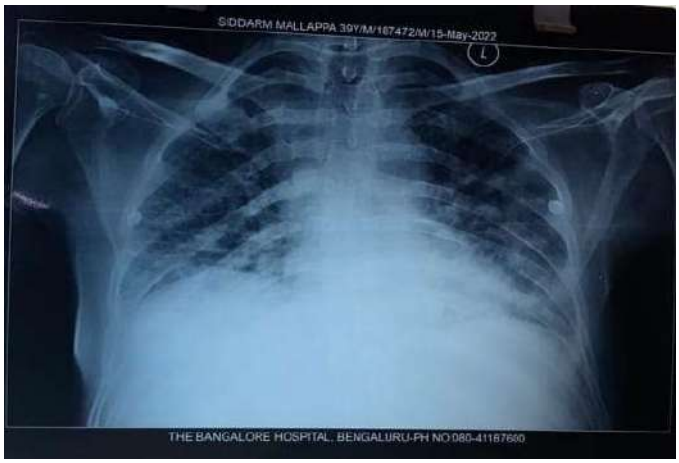
Case Report

A 39 yr old male, Mr.Siddaramu Soddi, resident of Gulbarga, Karnataka state, India, agriculturist by profession was diagnosed to have Hepatocellular Ca in April 2022 and was advised to undergo TACE .

Day 1 - He was admitted to hospital on 13/05/2022 under interventional radiologist for TACE in ward. After basic investigations (which were in normal range except for LFT) and adequate fasting, patient underwent TACE the next day.

He was shifted to ICU post procedure with c/o pain abdomen and at femoral vein access site in an agitated and irritable state. He was hemodynamically stable with BP 130/80 mmhg, HR 103 bpm, RBS 112 mg% and SpO2 of 96-97% at room air. Patient was re-assured. He was given low dose of IV Fentanyl (50 mcg) and IV Hyoscine after which pain subsided and patient was calm in 3-4 hours.

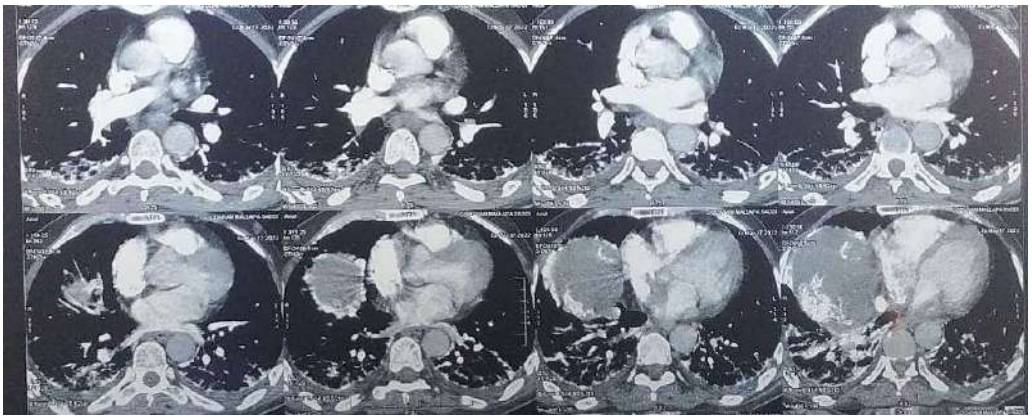
Day 2 – early in the morning spo2 drops to 92% on room air. By afternoon his spo2 further dropped to 88% at room air. His HR increased to 100-110 bpm and BP was stable.2l /min of o2 supplementation was given via nasal canula and spo2 was 94% with oxygen. Clinical examination revealed bronchial breath sounds in bilateral basal lung fields. ABG showed type 1 respiratory failure with Po2 of 60%, cBC showed platelets of 1.17 lacs / cc, LFT was similar to baseline, serum creatinine was normal and procalcitonin was elevated. ECG and 2D ECHO was normal. CXR showed patchy areas of consolidations in bilateral lower lobes with pleural effusion. Pao2: FiO2 ratio being approximately 214.

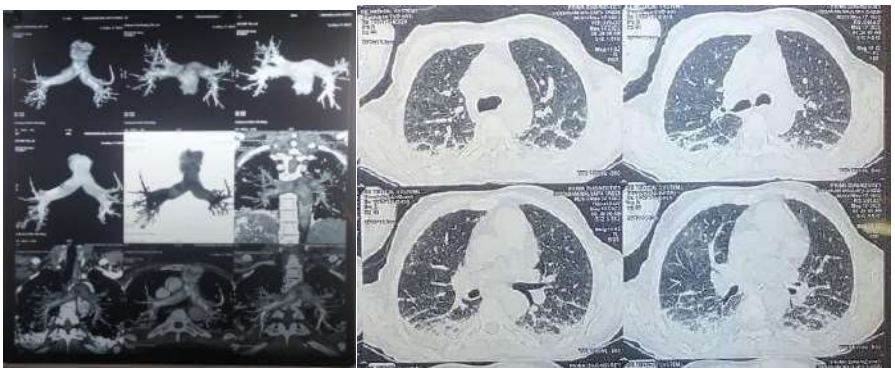


INJ Cefotaxim 1 g iv q12h and Salbutamol with Ipratropium bromide nebulisations every 6th hourly was started.

Day 3 – In view of persistent hypoxia and tachycardia patient underwent CTPA to rule out pulmonary embolism. CTPA showed lipiodal deposition in subsegmental arterial branches of lower lobes and posterior subsegmental branches of upper lobe and confluent parenchymal consolidation with collapse of bilateral lower lobes.

Meanwhile, sputum for AFB was negative and culture had moderate growth of Klebsiella which was sensitive to Meropenem which was started as 1g IV q8h and cefotaxim was stopped.

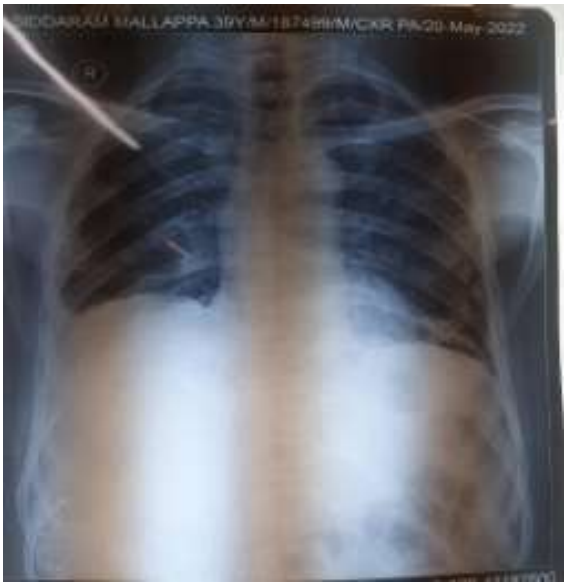




Patient c/o bleeding PR. Repeated CBC showed thrombocytopenia with platelet of 93000/cc. D DIMER was 2350 ng/ml.PT/INR was normal. General surgeon's opinion was taken and managed conservatively.

Inj. Methylprednisolone 40mg IV q6h was started in view of chemical pneumonitis caused by lipiodal deposition. Anti coagulation was not instituted due to thrombocytopenia.Incentive spirometry was started. Awake prone ventilation for 2 hrs, 8hrs apart in a day was started. Oxygen requirements came down to 1l/min with saturations 93-94 %. He was shifted to ward with stable hemodynamics.

Day 4 – Oxygen was stopped. Patient maintained SpO2 94% at room air. Platelets increased to 1.34 lacs/cc, repeat D-Dimer was still elevated 2690ng/ml. CXR repeated showed mild right pleural effusion.



Day 5 – Patient maintained saturation at room air. ABG showed Type 1 respiratory failure with Po2 of 59 mmhg. Antibiotics, steroids, nebulisation along with incentive spirometry, physiotherapy was continued.

Day 6 – patient maintained SpO2 94% at room air. He was subjected for a 6 minutes walk test.He walked > 450 m without any drop in SpO2.

Day 7 – patient was discharged with following treatment and advice.

Tab Predmet 16mg 1-0-1 for 1 day F/B 8mg 1-0-1 for 5 days f/b 8mg 1-0-0 for 5 days.

TabEsmoprazole 20 mg 1-0-0 for 10 days.

Foracort MDI 200mcg 2-0-2 with spacer.

AWAKE PRONING FOR 2 HRS IN A DAY

INCENTIVE SPIROMETRY Q12 H

Follow up visit patient was completely asymptomatic and clinical examination showed no clinical abnormality and adequate functional capacity.

Discussion

In the 1980s, TACE was created using lipiodol and anti-cancer medications using the property of selective accumulation in liver cancer tissue. It works by blocking blood flow, ischemic necrosis of the tumour, maintaining a high concentration of the anti-cancer medication in the tumour for a long time, and suppressing the extracellular efflux of the medication, reducing side effects.

When compared to thrombotic pulmonary embolism, lipiodol pulmonary embolism has a different pathogenesis. The breakdown of oil microemboli is most likely what causes symptomatic pulmonary damage, which may result in pulmonary capillary leakage and non-cardiogenic pulmonary edoema [3,4,5] caused by the harmful unbound free fatty acids that are produced when lipases break down lipiodol enzymatically. respiratory disease risk factors Liver tumours greater than 10 cm are among the lipiodol embolisms, high vascularity of tumour, presence of AV shunting and large Lipiodol volume of more than 20 mL [8]. Lipiodol dosage showed to be the main risk factor for the emergence of pulmonary oil embolism, according to multivariate logistic regression analysis [12]. While the maximum safe dose of Lipiodol was suggested by Chung et al. [6] being between 15 and 20 mL, or roughly 0.25 mL/kg of total body weight, Wu et al. [9] reported that pulmonary oil embolism formation was more likely to occur at dosages above 14.5 mL [10].

Conventional Lipiodol- Based TACE and DEB-TACE both use chemotherapeutic drugs to produce the best therapeutic outcomes in HCC, with doxorubicin being the most often utilised one. Adriamycin along with Lipiodol is also used in many centres.

Doxorubicin is a chemotherapeutic antibiotic anthracycline that blocks DNA topoisomerase II. Systemic doxorubicin seldom has a deleterious effect on the lungs, which is typically associated with cardiotoxicity [12]. Doxorubicin has also been linked to bronchiolitis obliterans organising pneumonia and the capillary leak syndrome in an adult patient [13]. A less harmful version of doxorubicin is pegylated-liposomal doxorubicin (DoxilTM).

Even Doxil^{TM}, though, briefly brought in mild dyspnea. based on data from in vitro, According to Skubitz and Skubitz [14], Doxil^{TM}-induced dyspnea was caused by neutrophils temporarily adhering to the pulmonary circulation and reducing pulmonary compliance. When administered jointly in HCC patients, lipiodol and doxorubicin have the potential to synergistically worsen lung damage than they would either drug alone.

In this instance, a 4F catheter was inserted into the right hepatic artery and a mixture of 15 ml LIPIODOL and 45 ml Doxorubicin was administered into the tumor's feeding channels.

There are numerous things that could be the root of lipiodol pneumonitis. In lymphangiography, lipiodol, an ethyl ester of fatty acids from poppyseed oil, is employed as a contrast agent. An anticancer agent is combined with lipiodol to create an emulsion, which is then injected into an artery to release the anticancer agent over time. Due to the absence of Kupffer cells in tumour tissue, the syphon effect from the tumor's hypervascularity, and the lipiodol's high mucoid characteristics, the lipiodol injection into the hepatic artery selectively distributes in the tumour. It stays in blood

vessels for a long time, anything between a few weeks and a year [10]. These characteristics of lipiodol could have a role in the onset of lipiodol pneumonitis.

There is a report arguing that a bioreaction involving an allergic reaction and radioactively-induced lesions is what causes pneumonitis brought on by lipiodol containing radioactive iodine [11]. The presence of CD 8+ T-cells in BAL fluid, the prevalence of alveolar fibrosis or endothelial damage in interstitial pneumonia, and the clinical and imaging characteristics of radiation pneumonitis all lend credence to this conclusion. However, it has been noted that this method takes several days to weeks to result in pneumonitis, making it appear improbable that this was the patient's actual cause.

All patients received oxygen, anticoagulation, anti-infection, high-dose corticosteroids, and supportive care as part of the treatment and result. In cases of ARDS, assisted mechanical ventilator support therapy was administered [15]. These treatment strategies lacked specificity and lacked distinction from those previously reported [4-7].

In our case we used awake prone ventilation and Incentive Spirometry as one of the strategies which had good effect on ventilation as measured by pulse oximetry and 6 minute walk test along with other treatment mentioned in earlier reports. The anatomical distribution of the pneumonitis on CT which has similarities to early ARDS was the basis of instituting awake proning. Further studies and case reports are needed in utilizing and forming a guideline with regard to utility of awake proning in such cases.

Conclusion

Pulmonary lipiodol embolism and associated pneumonitis is recognized complication of TACE. Respiratory disease risk factors Liver tumours greater than 10 cm are among the lipiodol embolisms, high vascularity of tumour, presence of AV shunting and large Lipiodol volume. Complications can be reduced by limiting the above risk factors. The treatment strategies used in our case can also give an insight into optimal management and assessment of the response to treatment.

Ethics declarations

Funding This study did not receive any funding.

Conflict of interest

The authors declare that they have no competing interests.

Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability

Not applicable.

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CASE REPORT

Atypical presentation of Scalp Actinomycosis as a frontal soft tissue swelling: Case report and review of literature

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Introduction

Actinomycosis of scalp is a uncommon soft tissue infection, rarely affecting the scalp. Only a few cases have been published, with even fewer known to be spontaneous. Actinomyces are anaerobic, filamentous, gram-positive bacteria presenting with subacute or chronic swelling with suppuration, sinuses and/or abscess. Most known forms are cervico-facial, pulmo-thoracic followed by abdomino-pelvic making actinomycosis of scalp a diagnostic dilemma and is confused with carcinoma or tuberculosis. Author reports a rare presentation of scalp swelling associated with ptosis which was mistaken for neoplasm. This case is of significance due to spontaneous non traumatic scalp infection with actinomyces and also highlights the importance of surgical excision and histopathological diagnosis since only handful of spontaneous case present in literature.

Case report

A 52 year old male referred to Neurosurgery Department with history of inability to lift his left eye lid and scalp swelling over the left supra orbital region. There were no features of infection, sinuses or pus discharge and was painless. Significantly there was no preceding trauma or note-worthy past history like diabetes or immunosuppression.

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Examination revealed no compelling neurological deficit. Physical examination disclosed a firm, non-tender,non mobile, non fluctuant, nodular swelling 7cm *7 cm in size in the left supra orbital region associated with ptosis of left eyelid.The swelling was non pulsatile with no evidence of induration or bruit. Routine laboratory tests were within normal limits. CT scan was done which was suggestive of a soft tissue lesion of 6.2 x 1.4 x 4.8 cms in the subcutaneous plane of left frontal and peri-orbital region (Figure 1).

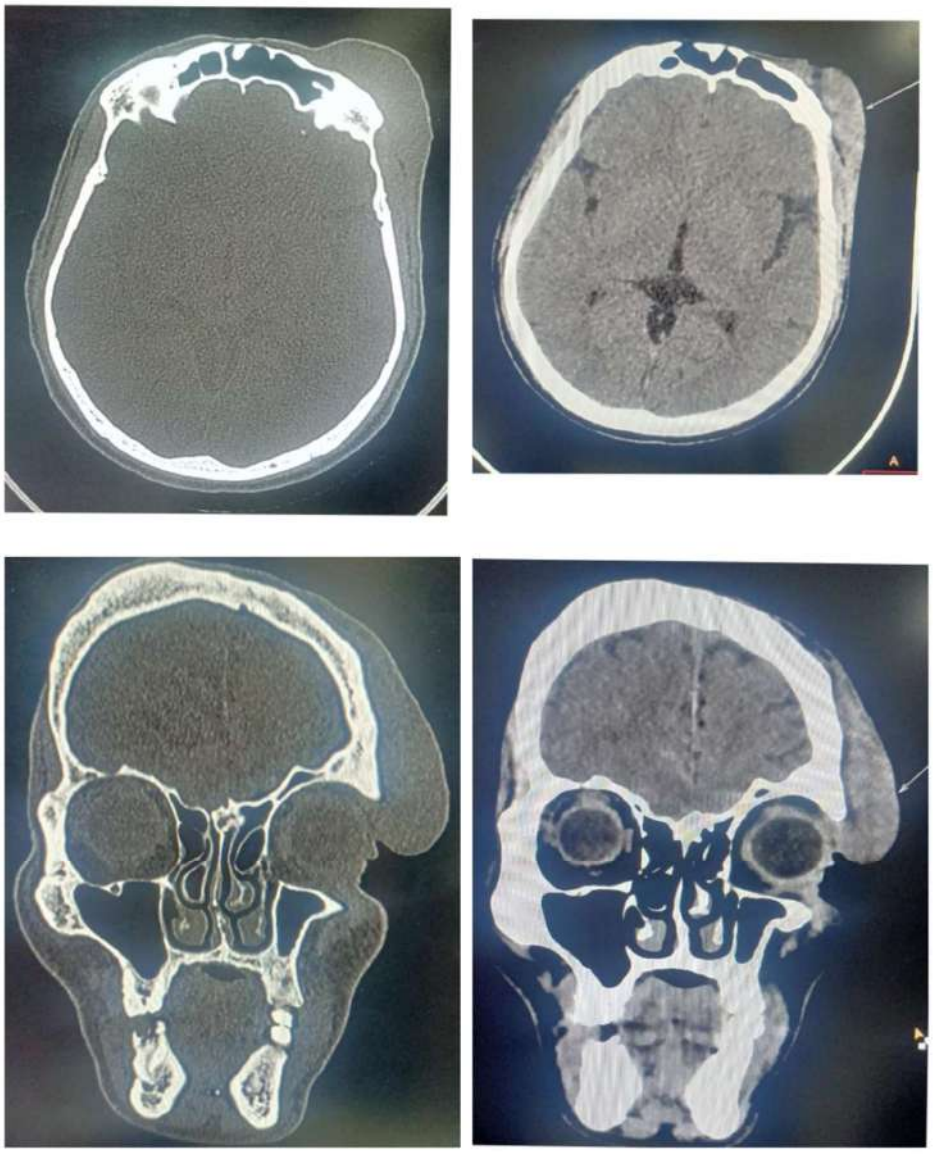

Figure 1: CT scan of brain showing the soft tissue swelling on left frontal and periorbital region.

Surgical excision of the mass was done (Fig 2C) and histopathology revealed a fibromuscular and fibro-collagenous tissue with multiple foci of suppurative abscess like dense inflammation and basophilic variable sized granules of organism with delicate radially arranged branching filaments in the centre of abscess (Fig 2A). The granules show eosinophilic Splendor-Hoeppli reaction surrounding the basophilic radially arranged filaments (Fig 2B). The granules were negative for gram, ZN or PAS staining. Overall features indicates infective pathology with chronic and suppurative inflammatory reaction.

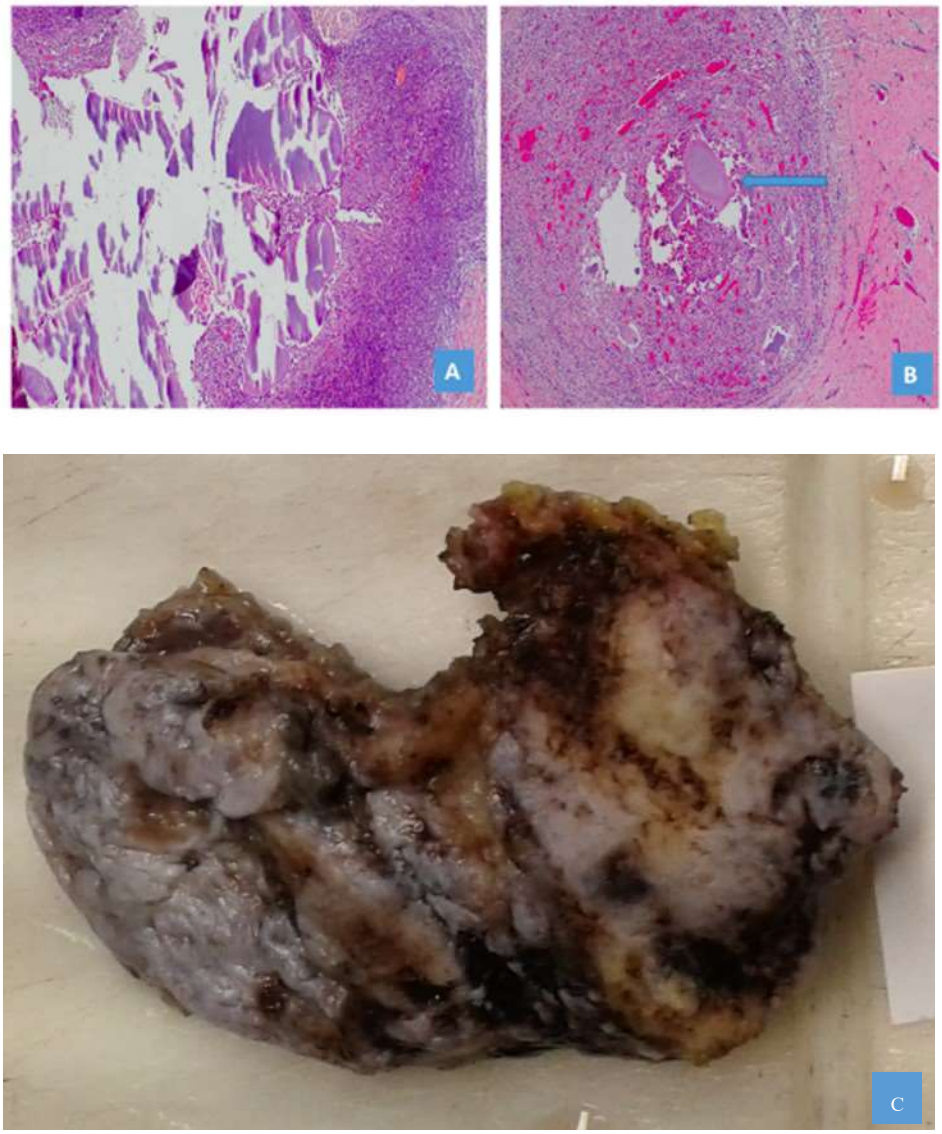

Figure 2. Section showing large granule of actinomyces with radially arranged branching basophilic filaments in the centre of suppurative inflammatory reaction(A,H&E,20X);The central granule with eosinophilic Splendor-Hoeppli reaction(B,H&E,10X);Excised specimen (C)

The morphological differential diagnosis of Actinomycosis or Botryomycosis were considered.It stated an infective pathology with chronic inflammatory reaction with differential diagnosis of Actinomycosis or Botryomycosis. The patient was further treated with regimen of amoxicillin clavulanate 625 mg TDS and doxycycline 100mg BD for 6 months and on routine follow up, there was no evidence of recurrence.

Discussion

In 19th century, the first case of human actinomyces [1] was described and Actinomyces is a gram positive, non-spore forming, pleomorphic, microaerophilic bacilli, earlier misclassified as fungi, habitually found as harmless commensals within the oral and gastrointestinal tract [2,3]. The prevailing species of Actinomyces instigating actinomycosis are Actinomyces israelii, Actinomyces naeslundii, Actinomyces odontolyticus, Actinomyces viscous and Actinomyces meyeri [4].

Actinomycosis is an endogenous disease with no pathogenic species ever isolated from environment and there is also no evidence of human to human transmission [4]. It has association with preceding trauma, tissue ischemia and oral cutaneous contact [5].

Most commonly known forms are cervicofacial 50%, pulmothoracic 30% followed by abdomino pelvic 20% [6]. Less than 4% cranial actinomycosis cases have been reported [7] and almost all of them have been preceded by trauma, making this case fascinating.

Primary cutaneous actinomycosis is an unusual entity owing to low pathogenicity rendering them incapable of penetrating healthy tissue. It is characterized by chronic, slow progressing swelling allied with abscess formation, sinus tracts and tissue fibrosis, mimicking carcinoma or granulomatous disease like tuberculosis [8]. Actinomycosis in the scalp is an significant entity since this lesion over years may involve clavarium [9].

In our case, patient presented with slow growing swelling without any abscess formation or any evidence of sinus tract over the swelling. Histopathology confirmation is mandatory to rule out malignancy or chronic granulomatous disease such as tuberculosis. On HPE,confirmation of sulphur granules lead to diagnosis of actinomycosis. However it is seen only in 25% of cases and can be easily missed in a small biopsy [4].

The treatment of cutaneous actinomycosis involves high dose intravenous antibiotics for 2-6 weeks followed by oral antibiotics for 6-12 months [10].

Surgical resection is required especially in large lesion for better cosmetic outcome and excision biopsy useful in diagnostic dilemma by establishing histopathological confirmation.

In our case, excision provided tissue diagnosis, cosmetically better results and patient was discharged on long term antibiotics.

Conclusion

Scalp Actinomyces is a rare entity which is often misdiagnosed as Neoplasm. Hence it has to be considered in differential diagnosis whenever there is a case of scalp soft tissue lesion and has to be confirmed with histopathological examination and prevent reoccurence by the judicial use of antibiotics.

Ethics declarations

Funding This study did not receive any funding.

Conflict of interest

The authors declare that they have no competing interests.

Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability

Not applicable.

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CASE REPORT

A rare case of Prostatic abscess in an adolescent managed effectively by conservative medical management with antibiotics

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Abstract

Background: Prostatic abscess is uncommon in adults and is infrequently noted in the paediatric population. Surgical drainage with adequate antibiotics is the current recommended management for prostatic abscess larger than 1 cm. However, it is still a topic debate that what should be the appropriate management of a prostatic abscess.

Case presentation: Herein, we present the case of a 16-year-old young adolescent patient with a large prostate abscess without any systemic disease who was successfully managed with antibiotics only and surgical drainage was not required for this patient.

Conclusion: Thus, we conclude that in a young adolescent patient with acute prostatic abscess, medical management with intravenous antibiotics deferring surgical drainage can be used an effective treatment option for management of this condition.

Keywords: prostatic abscess, antibiotics, MRI

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Background

The incidence of prostatic abscess is infrequent in the paediatric population. Surgical drainage with adequate antibiotics is the current recommended guideline for management of prostatic abscess larger than 1 cm [1]. However, it is still a gray area whether that is the only treatment. We present the case of a 16-year-old young adolescent patient with a large prostate abscess without any systemic disease who was successfully managed with antibiotics only and surgical drainage was not required for this patient.

Case presentation

A 16-year-old adolescent boy came with complaints of fever and dysuria and difficulty in passing urine over a period of 5 days to the urology outpatient department. On examination, patient was febrile and was having tachycardia. Past history did not reveal any significant medical illness or past surgery. On Local examination, the penile shaft was normal the preputial skin was retractable. There was evidence of right sided scrotal swelling suggestive of right sided epididymo-orchitis (Figure 1).

Figure 1. Clinical picture of the patient showing swelling over the right side of scrotum suggestive of right sided epididymo-orchitis.

Per rectal examination was painful and revealed boggy tender prostate. Patient was admitted and started on intravenous antibiotics in the form of piperacillin and tazobactam and was catheterised using a 14 F Foley catheter. Laboratory investigations revealed increased leucocyte count of 21000/mm^3 with increased neutrophil count of 91% and a normal serum creatinine. Viral markers of Human Immunodeficiency Virus also came out negative Ultrasound revealed enlarged prostate with size 38 cc with multiple hypoechoic solid cystic areas within the prostate (Figure 2).

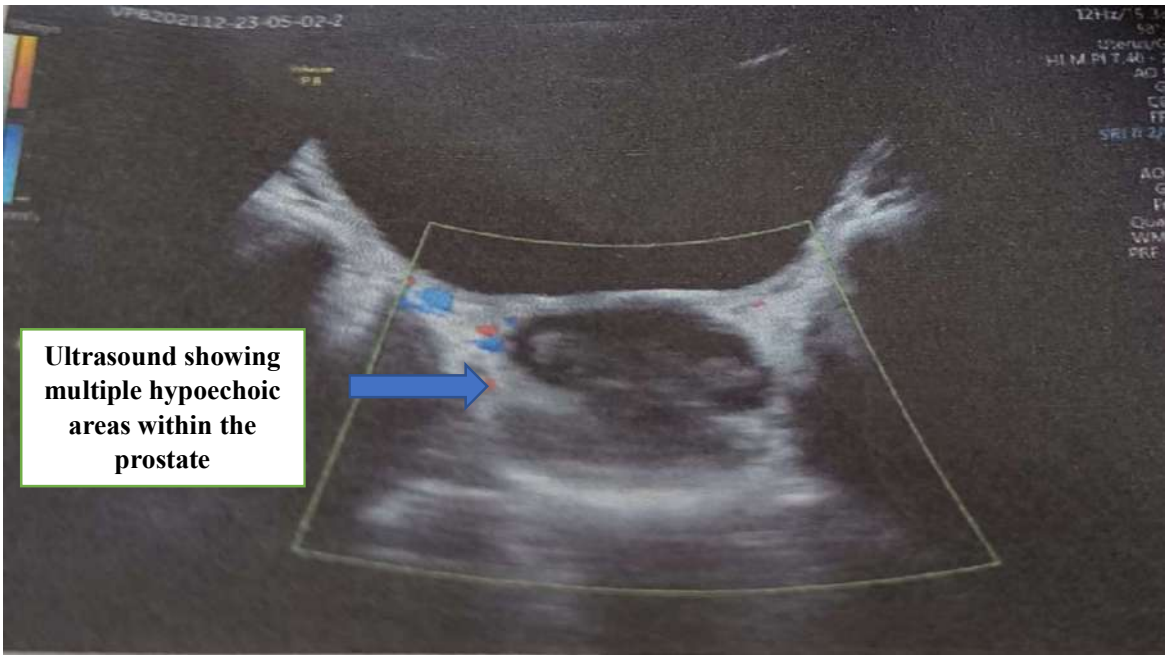

Figure 2. Ultrasound showing enlarged prostate with size of 38 cc with multiple hypoechoic areas within the prostate.

Patient further underwent Magnetic resonance imaging of the pelvis which showed a bulky prostate with a volume of 56 cc with associated significant peri-prostatic fat inflammation. Suggestive of prostatitis. Multiple pockets of collection which appear T1W1 hypointense and T2W1 /STIR hyperintense with postcontrast peripheral enhancement suggestive of prostatic abscess with largest pocket of 21 cc (Figures 3 and 4).

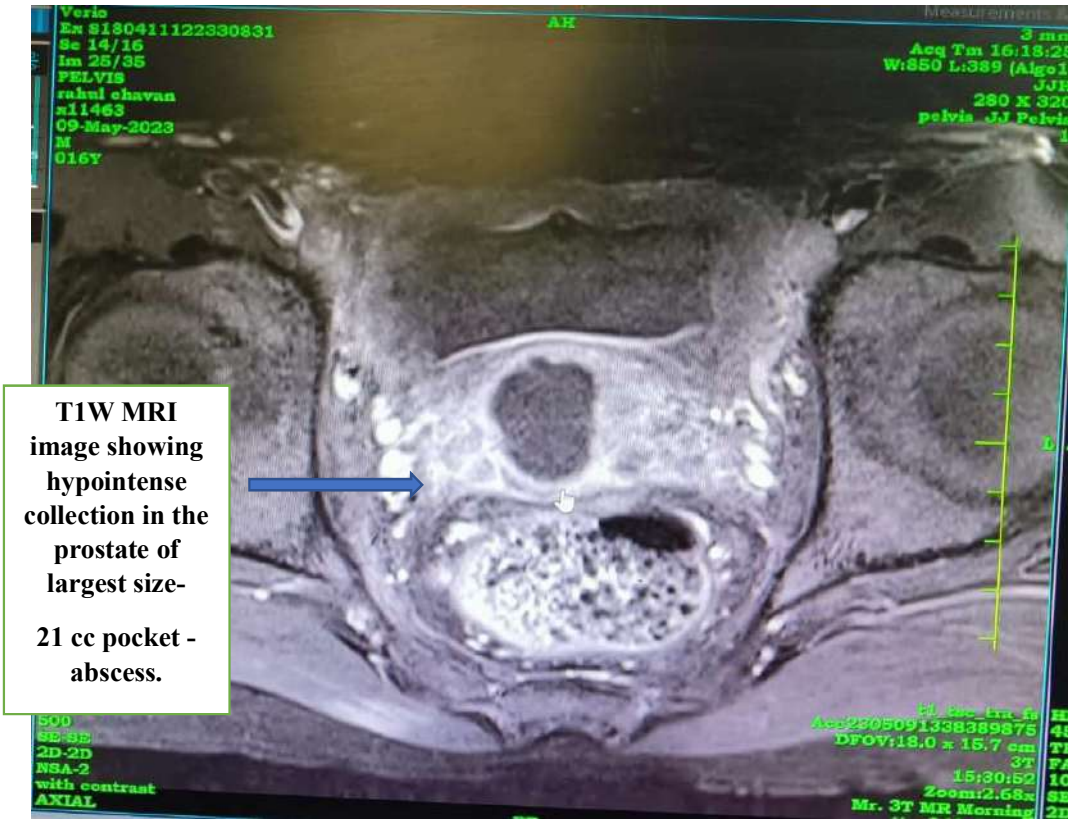

Figure 3. T1W MRI image showing hypointense collection in the prostate with largest pocket size-21 cc prostatic abscess.

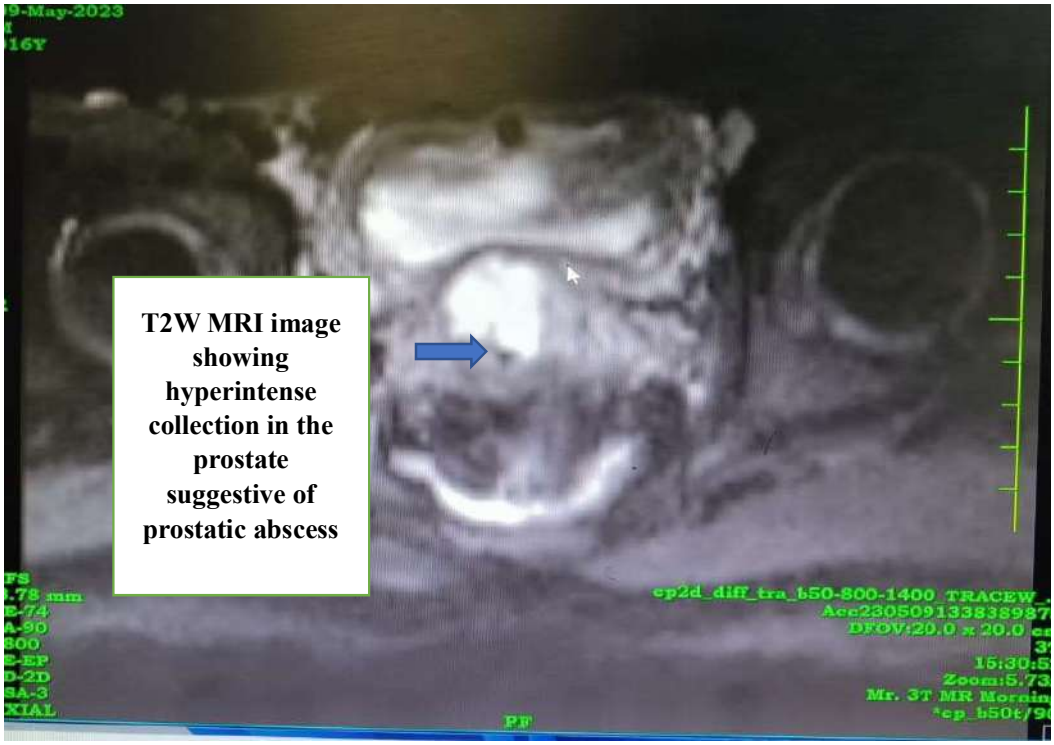

Figure 4. T2W MRI image showing hyperintense collection in the prostate suggestive of prostatic abscess.

Patient gradually improved over a period of 7 days of intravenous antibiotics and did not require surgical intervention. Thus, this case demonstrates successful management of rare prostatic abscess in an adolescent male with intravenous antibiotics without the need of surgical intervention.

Discussion

According to our review of literature, it is very rare for an adolescent to develop prostatic abscess and most of them will end up requiring surgical intervention to treat them. The incidence rate of Prostatic abscess in middle aged men is 0.2–0.5% [2]; however, it can occur at any age [3]. Escherichia coli and Klebsiella pneumoniae are common causative organisms whereas in severely immune compromised patients, we would come across atypical pathogens [3]. The clinical symptoms of prostatic abscess include burning sensation while passing urine, urgency to pass urine, increased frequency of urination, sense of not completely emptying the bladder, and pain in the suprapubic or perineal region.. Some patients only have systemic symptoms, such as fever or malaise [2]. Risk factors of prostatic abscess in adults include diabetes mellitus, chronic kidney disease, liver cirrhosis, liver abscess, human immunodeficiency virus infection, and acquired immune deficiency syndrome. History of previous chemotherapy, previous transplant, or previous urological procedures present with an increased risk of developing prostatic abscess [4]. Very few cases of adolescent patients with prostatic abscess have been reported according to our review of literature. History of previous methicillin-resistant *Staphylococcus aureus* infection and chronic granulomatous disease were presumed to the predisposing factors in these reported patients of prostatic abscess in adolescent patients.[4] However, the most recent case had no identifiable risk factors [5]. The possible risk factors of the currently presented case were because of lack of preputial hygiene and perineal hygiene and a history of recurrent UTIs. There are no standard treatment protocols described for prostatic abscess. Review of literature describes drainage or transurethral deroofing of the abscess in all the previous adolescent patients. In case of slow response to antibiotics, surgical drainage is required as demonstrated by previously reported case reports [6]. Antibiotics alone as a treatment was found to be effective if patient is stable and size of prostatic abscess is less than 1 cm [7]. Oshinomi et al. [8] concluded that in patients with diffuse type prostatic abscess; use antibiotics whereas those with focal or multifocal-type prostatic abscess, consider surgical drainage by transurethral deroofing of the prostatic abscess. However, our case report demonstrated that these patients can be managed by antibiotics alone and they can be curative as well in an adolescent patient with prostatic abscess. In our reported case, antibiotics were effective as he was diagnosed and treated early and he did not have any underlying disease. We believe that treatment with adequate antibiotics for optimally selected adolescent patients with prostatic abscess can be an effective treatment modality.

Conclusion

Thus, we conclude that in a young adolescent patient with acute prostatic abscess, medical management with intravenous antibiotics deferring surgical drainage can be used an effective treatment option for management of this condition.

List of abbreviations:

MRI-magnetic resonance imaging

Conflicts of interest

The authors declares that they do not have conflict of interest.

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