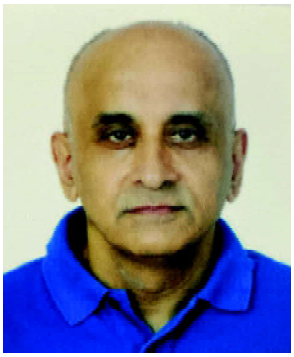
Dr Sumeet Singla



Dr Vipin Mediratta

Dr Amit Aggarwal

Letter to the Editor

Respected Seniors and Dear Readers,

Greetings !

It is an honour and a privilege to serve as the new Editor of the *Journal, Indian Academy of Clinical Medicine*. I owe a huge debt of gratitude to Prof. AK Agarwal, my teacher, mentor, guide and life-coach, under whom I started my journey with *JIACM* doing proof-reading and editing. Subsequently, I served as Secretary, Assistant Editor and Associate Editor under Prof. BB Rewari, Prof. DG Jain and Prof. MPS Chawla, respectively. I had immense learning under each of these doyens of Clinical Medicine and am eager to build upon the foundations established by them.

JIACM has endured and persevered for many decades and held up a shining beacon of light for Clinical Medicine. But, currently we face huge challenges, both logistic and financial. However, the Editorial team at *JIACM* with support of Governing body Members of *Indian Association of Clinical Medicine* shall endeavour to overcome these and maintain (No, improve!) the content, diversity, delivery and visibility of *JIACM*. *We will continue to uphold the highest standards in scientific publishing, encouraging authors to adhere to ethical publishing guidelines*.

I urge our esteemed readers to contribute a wider variety of articles, especially Images, Letters to Editor, Invited Editorials from renowned clinical leaders, Patients' Perspectives, Clinical Methods and even on Ethics and Communication. For the journal to grow and prosper, it should be visible, attractive and accessible to a wider audience. *I request you to inform, invite and involve your students, colleagues and friends from India and abroad to read and contribute to JIACM.*

Our online presence (www.jiacm.in) and archive of past issues, from 2017 onwards, is a free and easily accessible resource for all readers. *We have planned to digitise our older issues, so that the huge repository of knowledge is retained and passed on*.

I would like to thank the Editorial team at *JIACM*, comprising of Dr Vipin Mediratta (Associate Editor) and Dr Amit Aggarwal (Secretary) for their unwavering support. I can assure the readers that we are fully committed towards ensuring an enriched learning experience for you. *We are always available for suggestions (and critiques) for the journal, by phone, email or Whatsapp*.

My gratitude to the Editorial board members and reviewers for giving their time and expertise towards reviewing the manuscripts. You are the heart of the journal. Shri Yashpal Satmukhi is undoubtedly, the backbone and *sutradhaar* of the show. Without him, the journal would not see the light of the day. His deft handling of all aspects of the journal is praiseworthy and gratefully acknowledged.

Friends, a huge responsibility has been entrusted upon me. I seek the blessings of my immediate past Editor, Prof MPS Chawla, for guidance and continued support while helming the journal.

I look forward to continuing the ascent of *JIACM* and supporting the growth and impact of Clinical Medicine.

Warm Regards,

Jai Hind!

Dr Sumeet Singla
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Contains 80 pages from 1 to 80 (inclusive of all advertisements)

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ORIGINAL ARTICLE

JIACM 2024; 25 (1-2): 7-14

A KAP Study of Healthcare Professionals on Antimicrobial Stewardship in a Tertiary Care Hospital

Santosh Kumar Singh, Mangesh Kritya**, Vani Singh********, Ravi Kumar***, Rohit Vashisht****, Seema Patrikar*****, Rahil Arora*****, Abhishek Kumar*******

Abstract

Introduction: *The prevalence of communicable diseases remains a significant burden for developing countries like India, with antimicrobial agents playing a crucial role in treatment. However, irrational and excessive use of these agents has led to a rise in antimicrobial resistance (AMR), prompting the need for effective interventions. The study aimed to assess the Knowledge, Attitudes, and Practices (KAP) of healthcare professionals concerning Antimicrobial Stewardship (AMS) principles and implementation.*

Methods: *A cross-sectional study was conducted over six months in a premier medical college and its affiliated tertiary care hospital in Maharashtra, India. A validated questionnaire was distributed via e-mail and WhatsApp to participants including medical officers, residents, nursing staff, and faculty members. The sample size of 395 was determined based on previous research. Data analysis was performed using SPSS; and the Pearson Chi-square test was employed for categorical data.*

Results: *Study revealed responses from 395 participants across various specialties, with medical officers, residents, nursing staff, and faculty members represented. Only 13% were aware of the WHO's open course on antibiotic stewardship. While a majority understood AMS principles, some knowledge gaps existed, such as the importance of drug administration routes. There was variation in knowledge and attitudes among different groups, with faculty members demonstrating a better understanding of AMS compared to residents. Practice attitudes were assessed regarding prescribing antibiotics for common illnesses like Upper Respiratory Tract Infections (URTI) and acute diarrhoeal illness. While most participants refrained from prescribing antibiotics for these cases, practice attitudes varied. Some respondents were not familiar with terms like pre-authorisation and pre-formulary restriction, indicating a need for increased awareness.*

Conclusion: *The study highlights knowledge-practice gaps among healthcare professionals related to AMS and appropriate antibiotic prescription. The findings emphasize the importance of comprehensive education and training to bridge these gaps and promote responsible antibiotic use. Addressing these issues is essential for combating AMR and improving patient outcomes.*

Keywords: *Antimicrobial stewardship, antimicrobials, antimicrobial resistance, pre-authorisation, pre-formulary restriction.*

Introduction

The prevalence of communicable diseases ranges from 28.05 to 29.57 per 1,000 population, highly burdening for a developing country like India. Antimicrobial agents have a pivotal role, but are being used irrationally and overwhelmingly, causing a rise in resistance. ICMR notified a 66% increase in per capita consumption of antimicrobials in India (2010 as compared to 2000). However, there exist significant knowledge and practice gaps among practicing doctors regarding the principles and implementation of antimicrobial stewardship[1, 2]. Studies have highlighted the irrational use of antimicrobial agents, contributing to the development of resistance[2] and thereby, increasing the cost of treatment. Healthcare professionals can significantly reduce antimicrobial resistance by practicing Antimicrobial Stewardship (AMS). The Antimicrobial Stewardship Programme (ASP) is an efficient and reliable healthcare strategy to encourage suitable use of antimicrobial drugs, through the implementation of evidence-based interventions. It plays a crucial role in combating the rise of antimicrobial resistance and ensuring optimal patient outcomes[3-4].

Furthermore, research indicates a lack of awareness and adherence to guidelines for appropriate antibiotic prescription among healthcare professionals[3-5]. The burden of communicable diseases in developing countries like India further underscores the need to address these gaps[4, 5]. To bridge these knowledge and practice gaps, it is imperative to provide comprehensive education and training on AMS principles and evidence-based interventions[6,7]. By equipping healthcare professionals with the necessary knowledge and tools, we can enhance their understanding and promote

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appropriate use of antimicrobial agents, thereby mitigating the emergence and spread of antimicrobial resistance. AMS is a critical component in the fight against antimicrobial resistance (AMR) and ensuring optimal patient outcomes. Numerous studies have highlighted the knowledge gaps among physicians regarding AMR and appropriate prescribing practices. A study conducted in a tertiary care teaching hospital in Eastern India revealed significant gaps in the knowledge, attitudes, and practices of physicians concerning AMR and prescribing[7,8]. Similarly, a cohort study found that physicians' attitudes and knowledge significantly influenced the quality of antibiotic prescription, emphasizing the need to address these factors to improve prescribing practices[9]. These findings underscore the urgency of enhancing physicians' knowledge and awareness of antimicrobial stewardship to promote AMS use.

A freely available, open WHO online Antimic robial Stewardship programme can be used as a simple and efficient tool to reduce the existing knowledge gap and ensure optimal prescription of antimicrobial agents. The paper on antibiotic stewardship aims to assess the knowledge, attitudes, and practices (KAP) of healthcare professionals regarding antibiotic use and resistance. It investigates their understanding of the importance of responsible antibiotic prescribing and adherence to guidelines, as well as their perception of the impact of antibiotic resistance on patient outcomes and healthcare costs. The study also explores any variations in KAP between different professional levels.

Methodology

This was a hospital-based observational cross-sectional study conducted at a premier medical college in western Maharashtra and its affiliated tertiary care hospital in Pune. The study included faculty, residents from clinical subjects, medical officers, and nursing officers. The study spanned six months, during which a validated questionnaire and consent forms were sent to the participants via e-mail and WhatsApp. Ethical clearance was taken from the institutional ethical committee prior to beginning the study.

The sample size of 395 participants was determined based on the KAP prevalence observed in a previous study by Chatterjee *et al*[2]. All available healthcare workers who prescribed and administered antimicrobials were included in the study. The participant selection was done using a universal sampling method, including all available doctors during the six months. However, doctors from the departments of radiology, anaesthesia, and psychiatry were excluded due to the infrequent use of antimicrobials.

The questionnaire was developed by comparing studies and adapting questions from the freely available online WHO course on Antimicrobial Stewardship: A competency-based approach. The questionnaire consisted of 27 questions with subsections, evaluated on a 5-point Likert scale.

The primary outcome aimed to quantify the existing knowledge gap among different specialty doctors regarding AMS, identify their attitudes, and assess common errors in prescribing antimicrobial agents. The questionnaire incorporated clinical-based scenarios for evaluation.

Data analysis was performed using the Statistical Package for Social Sciences (SPSS® 24.0, USA), and the proportions of each group were defined. The Pearson Chi-square test was used for categorical data, with a significance level set at $p < 0.05$. The findings were reported following the STROBE guidelines.

Results

The questionnaire was shared among healthcare workers at various levels out of which we received responses from 395 participants ranging from various specialties. We received responses from 4 groups, i.e., Medical Officers (51), Residents (196), Nursing staff (114), and faculty (35).

Only 13 % of them had ever visited or participated in the WHO open course on AMS as shown in Fig. 1. Most of the residents and the faculty thought that making a correct diagnosis and using the correct dose are important principles of AMS. This has been depicted in Fig. 2. One Hundred and twenty seven (strongly disagree = 11.39%, disagree = 20.76%) respondents did not consider the route of drug administration as an important factor and 104

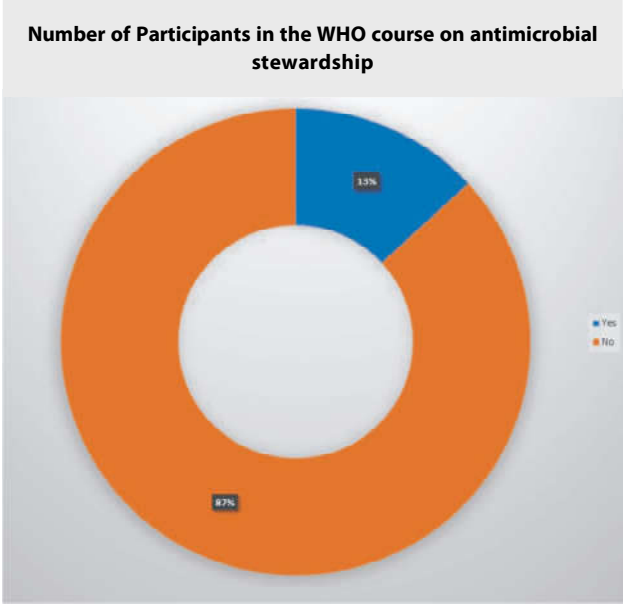

Fig. 1: *51 Respondents who had taken the online WHO course on antimicrobial stewardship.*

(26.33%) of them had no opinion on the statement. One hundred and fifty two (SD = 16.2%, D = 22.29%) did not prefer using antibiotics for a longer duration. Two hundred and forty nine (strongly agree = 28.60%, agree = 34.43%) agreed that microbiology guides the therapy whereas 257 (SA = 34.94%, A = 30.12%) felt that antimicrobial use should be evidence based. Most of the residents and faculty were aware that the likely source, site, likely pathogen, and patient characteristics were important in choosing the correct antibiotic. However, Medical Officers and Nursing Officers considered other factors less important. A large number of participants (53.41%) felt that the emergence of AMR is inevitable.

When asked about the mechanism of AMR, 212 (SA = 25.31%, A = 28.35%) felt that it is caused due to alteration in the target molecule. Only 92 (SA = 8.60%, A = 14.68%) respondents felt that large infrequent dosing is required for concentration-dependent killing whereas 99 (SD = 9.62%, D = 15.44%) felt that optimizing the duration of exposure above MIC would not be useful concentration-dependent killing. On asking about the intervention types of antimicrobial stewardship, 180 (45.56%) were not aware of pre-authorisation and 168 (42.53%) did not know about pre-formulary restriction.

On comparing the knowledge, a significant knowledge gap was observed between the different groups of Medical Officers, Residents, Nursing staff, and Faculty members. Faculty were more rational about AMS knowledge compared to the Residents.

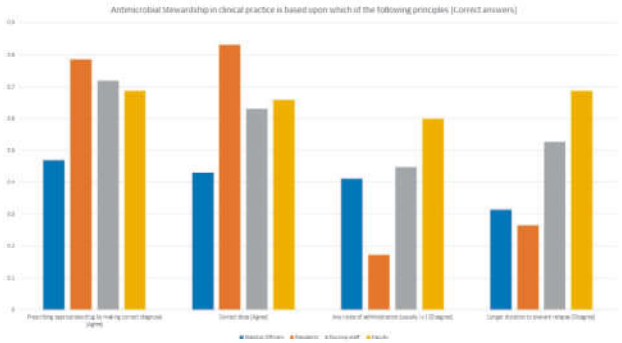

Fig. 2: *Response to the questionnaire on knowledge of respondents.*

A majority 254 (SA = 35%, A = 29%) of respondents believed that ASP is necessary in our hospitals and 245 (SA = 32%, A = 30%) agreed that ASP would reduce the adverse effects of inappropriate antimicrobial prescription. One hundred and twenty one (SD = 14.5%, D = 28.39%) stated that they would not prefer to take their senior's advice and rather take the online WHO competency-based course. All these responses have been summarised in Fig. 3.

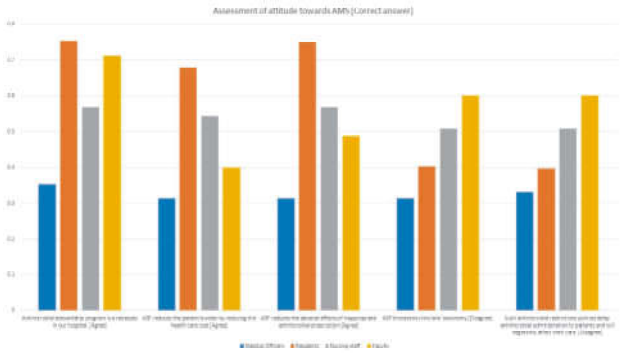

Fig. 3: *Response to the questionnaire on attitude of respondents.*

In the practice part of the questionnaire 194 (SA = 14.18%, A = 34.93%) reported that microbiologists guide the therapy and only 108 (SA = 7.34%, A = 20%) mentioned pharmacologists as the guide for therapy as illustrated by Fig. 4. One hundred and eighteen (SA = 11.14%, A = 18.73%) of the total respondents answered that they would not prescribe antibiotics for Acute bronchitis (URTI) and 134 (SA = 16.45%, A = 17.49%) said they would not give empirical antimicrobials for acute diarrhoeal illness.

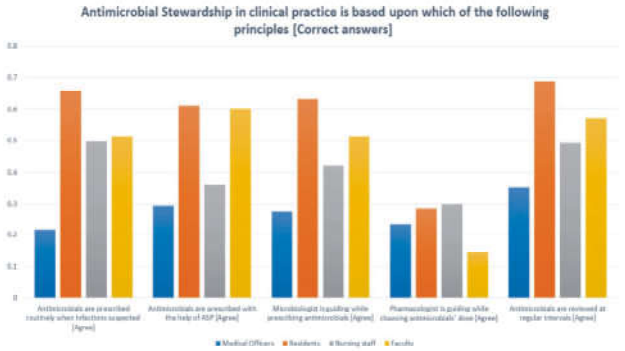

Fig. 4: *Response to the questionnaire on practice of respondents.*

A detailed Table mentioning all the questions and responses has been included in Appendix A.

Discussion

Rampant and irrational use of antibiotics has resulted in the development of AMR. Good knowledge and training of healthcare workers may help in the reduction of AMR[7]. WHO has launched a free online course called "Antimicrobial Stewardship: a competency-based Approach" to further this cause. We, therefore, decided to conduct a study on the KAP of healthcare workers based on this study. It was found that a very limited number of participants (13%) had heard about this course which is quite similar to the findings of Kaur *et al* (11%)[1].

Appendix A:

Knowledge

S.No.	Questions	Correct Answer	Medical Officer (n = 51)	Resident (n = 196)	Nursing Staff (n = 114)	Faculty (n = 35)	p-value
1.	Antimicrobial Stewardship in clinical practice is based upon which of the following principles?						
	Prescribing appropriate drug by making correct diagnosis	Strongly Agree	12 (23.53%)	92 (46.94%)	40 (35.09%)	14 (40.00%)	0.029
	Correct dose	Strongly Agree	12 (23.53%)	84 (42.86%)	38 (33.33%)	12 (34.29%)	0.000
	Any route of Administration (usually i.v.)	Strongly Disagree	7 (13.73%)	13 (6.63%)	17 (14.91%)	8 (22.86%)	0.000
	Longer duration to prevent relapse	Strongly Disagree	7 (13.73%)	25 (12.76%)	18 (15.79%)	14 (40%)	0.000
2.	Which of the following do you think are the important components of antimicrobial stewardship?						
	Microbiology guides the therapy whenever possible	Strongly Agree	6 (11.76%)	64 (32.65%)	31 (27.19%)	13 (37.14%)	0.003
	Indications should be evidence based	Strongly Agree	11 (21.57%)	77 (39.2%)	43 (37.72%)	8 (22.86%)	0.000
	Use broadest spectrum of antimicrobials	Strongly Disagree	6 (11.76%)	18 (9.18%)	21 (18.42%)	10 (28.57%)	0.032
	Appropriate dosage to site and type of infection	Strongly Agree	7 (13.73%)	67 (34.18%)	38 (33.33%)	13 (37.14%)	0.000
	Minimize the duration of therapy	Strongly Agree	3 (5.88%)	36 (18.37%)	28 (24.56%)	8 (22.86%)	0.011
	Give polytherapy in most cases	Strongly Disagree	6 (11.76%)	29 (14.80%)	16 (14.04%)	10 (28.57%)	0.013
3.	To determine the spectrum of antimicrobial therapy, which of the following patient and epidemiological factors you think are important for antimicrobial prescribing practices ?						
	Irrespective of severity of infection, always start treatment with broad spectrum antibiotics	Strongly disagree	10 (19.61%)	37 (18.88%)	35 (30.70%)	12 (34.29%)	0.000
	Likely source of pathogen	Strongly Agree	1 (1.96%)	50 (25.51%)	16 (14.04%)	8 (22.86%)	0.000
	How likely is the infection due to a drug resistant organism?	Strongly Agree	3 (5.88%)	42 (21.43%)	21 (18.42%)	10 (28.57%)	0.000
	Patient characteristics like drug allergies, hepatic and renal function	Strongly Agree	6 (11.76%)	52 (26.5%)	36 (31.5%)	9 (25.71%)	0.000
	Laboratory Reports	Strongly Agree	7 (13.73%)	47 (23.9 %)	39 (34.21%)	8 (22.86%)	0.000
4.	Emergence of antimicrobial resistance is inevitable	Strongly Agree	5 (9.8%)	49 (25%)	12 (10.53%)	6 (17.14%)	0.006
5.	Which of the following are major mechanisms by which microorganisms acquire resistance ?						
	Alteration with antimicrobial target molecule	Strongly Agree	7 (13.73%)	65 (33.16%)	18 (15.79%)	10 (28.57%)	0.000
	Increased import of drug into the bacterial cell or increased influx	Strongly Disagree	10 (19.61%)	16 (8.16%)	16 (14.04%)	10 (28.57%)	0.000
	Inactivation of antimicrobial	Strongly Agree	5 (9.8%)	55 (28.06%)	15 (13.16%)	8 (22.86%)	0.000
6.	For antimicrobial with concentration-dependent killing, the appropriate dosing regimen is						
	Large infrequent dosing	Strongly Agree	0 (0%)	10 (5.10%)	8 (7.02%)	17 (48.57%)	0.000
	Optimizing the duration of exposure with concentration in excess of MIC	Strongly Disagree	7 (13.73%)	11 (5.61%)	13 (11.40%)	7 (20.00%)	0.000
7.	Which of the following factors do you consider while switching from IV to oral regimen ?						
	Your patient is hemodynamically stable	Strongly Agree	1 (1.96%)	54 (27.55%)	29 (25.44%)	10 (48.57%)	0.000
	Irrespective of patient ability to tolerate enteral feeding give i.v. antibiotic till patient is hospitalised	Strongly Disagree	7 (13.73%)	32 (16.33%)	35 (30.70%)	7 (20.00%)	0.000
	Your patient is able to adequately absorb orally administered medications	Strongly Agree	4 (7.84%)	43 (21.94%)	30 (26.32%)	8 (22.86%)	0.000
	There is an orally bioavailable antibiotic to treat your patient's condition	Strongly Agree	1 (1.96%)	39 (19.90%)	32 (28.07%)	5 (14.29%)	0.000
8.	Which of the following steps would you consider for the daily assessment of antimicrobial therapy to ensure continued appropriateness ?						
	Review of microbiologic data is not of much importance	Strongly Disagree	12 (23.53%)	43 (21.94%)	33 (28.95%)	17 (47.57%)	0.000
	Verify the appropriate spectrum of therapy	Strongly Agree	5 (9.80%)	44 (22.45%)	12 (10.53%)	13 (37.14%)	0.000
	Check for adverse effects	Strongly Agree	6 (11.76%)	56 (28.57%)	11 (9.65%)	14 (40%)	0.000
	Evaluate route and duration of therapies	Strongly Agree	9 (17.65%)	51 (26.02%)	33 (28.95%)	9 (25.71%)	0.000
10.	In formulary restriction type of intervention there is restriction of antibiotics by the trained staff before the therapy is initiated.						
		Strongly Agree	3 (5.88%)	26 (13.27%)	13 (11.40%)	5 (14.29%)	0.169

Attitude

S.No.	Questions	Appropriate Attitude	Medical Officer (n = 51)	Resident (n = 196)	Nursing staff (n = 114)	Faculty (n = 35)	p-value
1.	The following set of statements seeks to assess your attitude towards Antimicrobial Stewardship programmes (ASP):						
	Antimicrobial stewardship programme is a necessity in our hospital	Strongly Agree	5 (9.80%)	80 (40.82%)	37 (32.46%)	17 (48.57%)	0.000
	ASP reduces the patient burden by reducing the healthcare cost.	Strongly Agree	6 (11.76%)	66 (33.67%)	9 (7.89%)	4 (11.43%)	0.000
	ASP reduces the adverse effects of inappropriate antimicrobial prescription	Strongly Agree	7 (13.73%)	71 (36.22%)	35 (30.70%)	13 (37.14%)	0.000
	ASP threatens clinicians' autonomy.	Strongly Disagree	4 (7.84%)	33 (16.84%)	26 (22.81%)	9 (25.71%)	0.000
	Such antimicrobial restriction policies delay antimicrobial administration to patients and will negatively affect their care.	Strongly Disagree	6 (11.76%)	32 (16.33%)	24 (21.05%)	7 (25.71%)	0.000
2.	The following set of statements seeks to assess your attitude towards the open online course on Antimicrobial Stewardship: a competency-based approach conducted by WHO. (This question is for those who have participated in this online course.)						
	The course is too lengthy.	Strongly Disagree	10 (21.74%)	14 (12.39%)	13 (14.44%)	13 (38.24%)	0.000
	There is lack of time due to busy hospital schedule.	Strongly Disagree	7 (15.22%)	8 (7.08%)	13 (14.61%)	5 (14.29%)	0.000
	I prefer to follow some other local guidelines.	Strongly Disagree	6 (13.04%)	8 (7.02%)	12 (13.79%)	9 (26.47%)	0.000
	I prefer to take my senior's advice rather than wasting time in such courses.	Strongly Disagree	7 (15.22%)	12 (10.62%)	14 (15.56%)	8 (23.53%)	0.000
	The treatment options discussed by such courses are too ideal to be implemented in daily practice	Strongly Disagree	6 (13.04%)	11 (9.73%)	12 (13.33%)	7 (20.59%)	0.000.
	The course is very helpful and there should be a compulsory participation for all working clinicians.	Strongly Agree	3 (6.52%)	11 (9.82%)	9 (10.23%)	1 (2.94%)	0.000

Practices:

S.No.	Questions	Correct Answer	Medical Officer (n = 51)	Resident (n = 196)	Nursing Staff (n = 114)	Faculty (n = 35)	p-value
1.	In your daily clinical practice of antimicrobial uses, give your opinion to the statements that follow:						
	Antimicrobials are reviewed at regular intervals	Strongly Agree	7 (13.72%)	39 (19.89%)	16 (14.03%)	9 (25.71%)	0.000
	Antimicrobials are prescribed routinely when infections are suspected	Strongly Agree	3 (5.88%)	52 (26.53%)	20 (17.54%)	5 (14.28%)	0.000
	Antimicrobials are prescribed with the help of ASP	Strongly Agree	6 (11.76%)	30 (15.30%)	12 (10.52%)	12 (34.28%)	0.000
	Microbiologist is guiding while prescribing antimicrobials	Strongly Agree	5 (9.80%)	39 (19.89%)	11 (9.64%)	6 (17.14%)	0.004
	Pharmacologist is guiding while choosing antimicrobials' dose	Strongly Agree	3 (5.88%)	15 (7.65%)	9 (7.89%)	1 (2.85%)	0.000
2.	Consider the following case scenario and give your opinion to the statements that follow: A 45-year-old female was consulting you (thinking you an MBBS doctor and a relative) and she was having chronic essential hypertension. She showed you a positive urine culture report done 3 weeks ago, showing the growth of 3 different organisms in large quantities. She told that this culture was done because she had dysuria and urine urgency. She completed several days of antibiotics with the resolution of symptoms. Now she is asymptomatic with a normal physical examination. She has asked you whether there is a need to submit another urine sample for testing ?						
	Urine culture should be collected	Strongly Agree	14 (27.45%)	28 (14.28%)	18 (15.78%)	5 (14.28%)	0.453
	Asymptomatic bacteriuria patients must be given treatment only in pregnancy and invasive urological procedures	Strongly Agree	3 (5.88%)	48 (24.48%)	7 (6.14%)	11 (31.42%)	0.000
	Fluoroquinolones should be used for uncomplicated UTI	Strongly Agree	7 (13.72%)	18 (9.18%)	17 (14.91%)	9 (25.71%)	0.000
	Antibiotics should be advised in the above case because of large growth of organisms	Strongly Agree	3 (5.88%)	29 (14.79%)	8 (7.01%)	12 (34.28%)	0.005
3.	Consider the following case scenario and give your opinion to the statements that follow: An 18-year-old female consults you (thinking you an MBBS doctor and a relative) with fever, abdominal cramping, and diarrhoea for 1 day. She has had 3 bouts of watery, non-bloody diarrhoea. She has just returned from a country with a high prevalence of diarrhoeal illness. She has not taken any recent antibiotics while her physical examination is normal.						
	Patient should be given empiric antimicrobial therapy	Strongly Disagree	12 (23.52%)	27 (13.77%)	17 (14.91%)	9 (25.71%)	0.001
	Stool culture is not required in above case scenario	Strongly Agree	3 (5.88%)	12 (6.12%)	9 (7.89%)	5 (14.28%)	0.000
	Rehydration and watchful waiting without empiric antibiotics is sufficient in most cases of watery diarrhoea	Strongly Agree	4 (7.84%)	46 (23.46%)	17 (14.91%)	14 (40%)	0.000
4.	Consider the following case scenario and give your opinion to the statements that follow: A 25-year-old female consults you (thinking you an MBBS doctor and a relative) with a history of one week of cough and rhinorrhoea but denies fever, chills or night sweats. Her cough is intermittently productive with white sputum. She is not tachycardic or tachypnoeic. On auscultation, bilateral rhonchi and scattered wheeze are heard.						

	The history of productive cough does not differentiate between URTI, acute bronchitis and community acquired pneumonia	Strongly Agree	2 (3.92%)	28 (14.28%)	13 (11.40%)	8 (22.85%)	0.000
	In acute bronchitis, there is no need for a chest X-ray, sputum culture, viral and serological analysis	Strongly Agree	2 (3.92%)	21 (10.71%)	10 (8.77%)	3 (8.57%)	0.000
	Antibiotics can help in early cure of patients with acute bronchitis	Strongly Disagree	7 (13.72%)	19 (9.69%)	10 (8.77%)	8 (22.85%)	0.000
	In patients with acute bronchitis, patient education is the key	Strongly Agree	4 (7.84%)	36 (18.36%)	14 (12.28%)	8 (22.85%)	0.000
5.	Consider the following case scenario and give your opinion to the statements that follow: A 21-year-old male consults you (thinking you an MBBS doctor and a relative) with subcutaneous abscess of 2 cm in diameter on his right leg. He is an athlete at the university and many of his team-mates have similar complaints. He had a similar lesion in the past on his right forearm which drained white pus mixed with blood. He is afebrile and appears non-toxic.						
	Source control is the corner stone in the management of the above case	Strongly Agree	2 (3.92%)	51 (26%)	18 (15.78%)	11 (31.42%)	0.000
	Antimicrobial therapy must be given in this case	Strongly Disagree	3 (5.88%)	11 (5.61%)	14 (12.28%)	5 (14.28%)	0.000
	Thorough cleaning of shared equipment and MRSA decolonisation should be done	Strongly Agree	2 (3.92%)	44 (22.44%)	18 (15.78%)	16 (45.71%)	0.000
	Culture sample should be avoided as contamination may lead to use of overly broad-spectrum antibiotics	Strongly Agree	3 (5.88%)	15 (7.65%)	9 (7.89%)	4 (11.42%)	0.033
6.	To prevent surgical site infections which of the following factors would you consider? [if you are not a surgeon, please ignore this question]						
	Antimicrobial sealants should not be used for surgical sites in preparation for the purpose of reducing SSI	Strongly Agree	1 (1.96%)	25 (12.75%)	11 (9.64%)	2 (5.71%)	0.000
	Perioperative surgical antibiotic prophylaxis should be continued during presence of a wound drain for the purpose of preventing SSI	Strongly Disagree	5 (9.80%)	10 (5.10%)	9 (7.89%)	6 (17.14%)	0.000
	Prolongation of post-operative antimicrobial prophylaxis decreases the risk of SSI	Strongly Disagree	11 (21.56%)	14 (7.14%)	19 (16.66%)	9 (25.71%)	0.000
	Re-dosing of antimicrobials should be considered if blood loss in patient is >1.5 L	Strongly Agree	6 (11.76%)	17 (8.67%)	10 (8.77%)	8 (22.85%)	0.005

Almost all of the participants had good knowledge regarding the principles of AMS except when asked about the route of administration. Only 32.28% of respondents did not feel that it was a principle of AMS which is in line with the results obtained in other studies[1,2,5,8] indicating a high intravenous antimicrobial use in hospitals. Approximately one-fourth of participants gave correct answers regarding the dosing regimen having concentration-dependent killing highlighting a knowledge gap in this topic. The gap found here is higher than that of other KAP studies asking about the same topic[1,9].

This study showed poor practice attitude towards common illnesses such as URTI and diarrhoeal illness as compared to previous similar studies[1,8]. Kaur *et al* found that 71.2% of participants refrained from prescribing antimicrobials for uncomplicated upper respiratory tract infections (URTI), whereas Ghosh *et al* documented 46.87% against 29.87% in our study. Regarding acute diarrhoeal illness, Kaur *et al* reported 56.8% non-prescription, and Ghosh *et al* noted 59.38%, while our study indicated a lower rate of 34% for antimicrobial non-prescription.

When asked about terms such as pre-authorisation and pre-formulary restriction, 54% and 57% had not heard of these terms as compared to 64% and 65%, respectively, reported in a similar study. A difference in guidance of therapy was observed against the previous study. 49% of them said microbiologist and 27% reported pharmacologist-guided therapy versus 16% and 88%, respectively, reported by Kaur *et al*.

There was a significant difference between the answers provided by faculty and residents *versus* the nursing staff and medical officers. This may be because the residents are subjected to better learning opportunities as compared to the other two. But the knowledge and practice gaps extend beyond medical officers to medical students, who play a crucial role as future prescribers in combating antimicrobial resistance. A study conducted among medical students in India revealed significant gaps in their knowledge, attitudes, and practices related to antibiotic resistance[10]. This finding highlights the importance of incorporating comprehensive education and training on antimicrobial stewardship principles, appropriate prescribing practices, and the global burden of antimicrobial resistance into the medical curriculum. By equipping future healthcare professionals with the necessary knowledge and skills, a culture of responsible antimicrobial use can be fostered from the early stages of their careers.

The knowledge-practice gaps observed among healthcare professionals are not limited to specific regions or healthcare settings. A study conducted in a Ghanaian tertiary care hospital demonstrated inadequate knowledge, attitudes, and perceptions concerning antibiotic resistance among physicians, underscoring the need for targeted educational interventions[11]. These gaps have far-reaching implications, as inappropriate prescribing practices

contribute to the development and spread of antimicrobial resistance, leading to increased morbidity, mortality, healthcare costs, and compromised patient safety[12]. Understanding the factors contributing to these gaps is crucial for designing effective interventions and improving the overall quality of antimicrobial use.

The lack of awareness and adherence to guidelines for appropriate antibiotic prescription is a critical issue among healthcare professionals, further contributing to the knowledge-practice gap. Physicians often face challenges in balancing the need to treat patients effectively and the pressure to prescribe antibiotics, even when not clinically warranted[13-16]. Factors such as time constraints, patient demand, diagnostic uncertainty, and limited access to local microbiological data can influence prescribing practices, leading to suboptimal use of antimicrobials. These practices not only contribute to the emergence of antimicrobial resistance but also result in adverse patient outcomes, including increased morbidity, mortality, and healthcare-associated infections[17,18]. Addressing these barriers and promoting adherence to guidelines are essential for improving antimicrobial prescribing practices.

Similar findings have been reported in studies conducted in France, Scotland, and Nepal, where junior doctors demonstrated knowledge gaps and misconceptions related to antibiotic resistance and prescribing practices[20-22]. These studies highlight the global nature of the knowledge-practice gaps and the necessity of implementing multifaceted interventions on a broader scale to address these issues.

The discrepancy between knowledge of faculty and residents in our study may be attributed to the relatively lesser number of faculty respondents.

Developing countries face significant challenges in combating AMR, given the burden of communicable diseases and the emergence of antimicrobial resistance. India, with its large population and high burden of infectious diseases, serves as an example[22-24]. Inadequate prescribing practices and the widespread availability of antibiotics without prescription contribute to the development of antimicrobial resistance[25].

Conclusion

A gap in the knowledge regarding antimicrobial stewardship exists in the HCW population. Antimicrobial stewardship is an important component of the fight against emergence of antimicrobial resistance and it should be implemented and followed with due sincerity. Taking courses such as the free open WHO course on antimicrobial stewardship should be encouraged.

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Outcome Analysis with Directly Acting Antiviral Agents in Chronic Hepatitis C Patients in Relation to Clinical, Laboratory and FibroScan Parameters in a Tertiary Care Centre of North Bengal

Sukomal Jana, Robert Ekka**, Arka Mukhopadhyay***, Debasis Chakrabarti*****

Abstract

***Introduction:** Hepatitis C virus (HCV) infection, one of the most prevalent viral diseases responsible for mortality throughout the world, particularly for its dreaded chronic hepatic complications, is now considered highly amenable to be treated successfully with the very effective antiviral drugs available. Direct-acting antiviral (DAA) agents are receiving discernible attention as a treatment of chronic Hepatitis C because of its improved clinical outcome, sustained virological response (SVR) and reversibility of liver fibrosis.*

***Background and objectives:** There are sparse data regarding rapidity of liver fibrosis regression following HCV eradication. Here we want to establish the reversibility of clinical outcomes, SVR and FibroScan parameters within an established timeframe.*

***Methods:** Total 100 patients with serologically proven HCV infection excluding patients with concomitant Hepatitis B and HIV infection, chronic kidney disease and chronic alcoholics attending North Bengal Medical College and Hospital, both in-patient and out-patient, during a 1.5 years period were enrolled in a prospective, observational, longitudinal study. Post-treatment outcomes with DAA were measured in terms of fibrosis markers (APRI, Median stiffness and METAVIR score by FibroScan), sustained virological response, lab parameters and features of portal hypertension.*

***Results:** Significant clinical improvement was noted both clinically and objectively. Signs of portal hypertension like ascites reduced from 11% to 1%, melena reduced from 16% to 4%, and haematemesis from 6% to 3% after treatment completion. HCV RNA was reduced from baseline mean of 3816581.9 to 9.9 (SD 3.1) which corroborated with the regression of liver fibrosis by reduction of non-invasive parameters like APRI score from baseline mean of 1.3 to 1.0 and median stiffness in FibroScan from mean of 8.76 kPa to 6.70 kPa. Also, there was 64% regression in METAVIR fibrosis stage after completion of DAA.*

***Conclusion:** 12 weeks treatment with DAA led to reduction of features of portal hypertension, and regression of liver fibrosis which was corroborated with achievement of SVR.*

***Key words:** Chronic Hepatitis C, DAA, FibroScan, HCV RNA quantitative assay.*

***Abbreviation:** SOF = Sofosbuvir, DCV = Daclatasvir, VEL = Velpatasvir, DAA = Direct acting antiviral, AST = Aspartate Transaminase, APRI = AST to Platelet Ratio Index.*

Introduction

Hepatitis C virus (HCV) is a leading cause of liver-related morbidity and mortality worldwide. An estimated 71 million people are affected globally by chronic hepatitis C infection[1-3]. HCV accounts for roughly 0.7 million deaths per year across the globe[4]. The estimated prevalence of HCV infection is as high as 5.2% depending on the geographical area[5]. The development of direct-acting antiviral agents (DAA) has been the most significant scientific development for treatment of HCV infection[6]. Prior to the advent of DAAs, because of the progressive and perceived irreversible hepatic fibrosis, HCV infection accounted for more than 70% of chronic liver disease related morbidity and mortality, particularly in nations with a high HCV burden[7]. This perception of irreversibility of hepatic fibrosis has changed as there is evidence of regression in fibrosis stage after successful DAA treatment[8]. The purpose of our study was to investigate post-treatment outcomes with DAA in chronic hepatitis C patients in this part of the country with respect to clinical improvement, sustained virological response, and reversibility of liver fibrosis.

Aims

1. Effectiveness of antiviral regimen for sustained virologic response (SVR).

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2. Improvement of clinical and laboratory parameters after completion of antiviral treatment (DAA).
3. Improvement of FibroScan parameters following treatment.

Material and Methods

This study enrolled chronic HCV patients at North Bengal Medical College and Hospital, Darjeeling between 1st April 2021 and 30th September 2022. It was an observational, prospective, longitudinal study, which enrolled 100 patients of Hepatitis C infection, excluding patients with concomitant Hepatitis B and HIV infection, chronic kidney disease and alcoholic liver disease (patients with liver disease having history of significant amount of alcohol intake, i.e., more than 2 drinks per day for women and more than 3 drinks per day for men for 10 years or more [1 drink equals ~14 g of ethanol, which is 1 beer, 4 oz of wine, or 1 oz of 80% spirits]) and other causes (e.g., Wilson's disease, etc.). HCV infection was confirmed by HCV-RNA quantification assay in all patients. Cirrhosis was diagnosed by experienced radiologists in the Radiology Department, based on the results of imaging modalities such as ultrasonography (USG) and FibroScan (LOGIQ P9 GE MAKE shear wave transient Elastography). Seven patients with massive ascites in whom FibroScan was difficult to perform, were excluded. Clinical outcomes and other laboratory parameters (i.e., complete blood count, liver function tests, etc.,) were evaluated in all patients. AST to platelet ratio index (APRI) score, a useful non-invasive method of assessing liver fibrosis, was also evaluated.

APRI score calculation

APRI score = (AST/ULN) x 100)/platelet count (10^9/L)

For APRI, ULN signifies the upper limit of normal for AST which was taken as 40 U/L in our study.

APRI score greater than 0.7 and greater than 1.0 was used for predicting significant hepatic fibrosis and cirrhosis respectively[9].

Table I: Liver FibroScan.

Liver Fibrosis staging	METAVIR score	Median stiffness (kPa)
Normal-Mild	F1	6.48 - 6.60
Mild-Moderate	F2	6.60 - 8.07
Moderate-Severe	F3	8.07 - 9.31
Cirrhosis	F4	>9.31

Table I shows Optimal LOGIQ S8 shear wave elastography cut-off values in terms of shear wave speed (m/s) and Young's Modulus (kPa) for classifying fibrosis stage in the patient population under evaluation. Data was acquired using R3.1.9 equivalent software and the C1-6-D probe.

Treatment with DAAs

Standard treatment protocol was followed as per the National Viral Hepatitis Control Programme guidelines[10]:

- Non cirrhotic: Sofosbuvir + Daclatasvir (400/60 mg) for 12 weeks.
- Cirrhosis without decompensation: Sofosbuvir + Velpatasvir (400/100 mg) for 12 weeks.
- Cirrhosis with decompensation: Sofosbuvir + Velpatasvir (400/100 mg) for 24 weeks.

Patients were evaluated 12 weeks post-treatment (i.e., at 24th week and 36th week in non-cirrhotic, compensated cirrhosis and decompensated cirrhosis, respectively) compared to baseline data.

Statistical analyses

Variables were reported as mean ± SD. Categorical variables were compared by Chi-squared test. Continuous variables were compared by Student's t-test. Statistical analyses were performed using IBM SPSS software, version 21 with p value < 0.05 considered statistically significant.

Results

Characteristics of patients

A total of 100 patients, ranging from 19 to 70 years of age, 60 (60%) patients were in the age bracket of 35 to 54 years and the mean age at diagnosis was found to be 41.9 (± 11.2) years. Majority of the infected people were male (78%) *versus* female (22%). 15% of patients had a definite history of IV drug abuse. 13% patients had pedal oedema, 11% patients had icterus, and only 2% patients had fever.

Among 100 patients, 57 were non-cirrhotic, whereas 43 were cirrhotic (20 were compensated and 23 were decompensated).

As a complication of portal hypertension in decompensated cirrhosis, melena (16%) was more common at presentation compared to haematemesis (6%). During baseline clinical evaluation, splenomegaly was more prevalent compared to hepatomegaly (27% vs 7%), and 11% patients had clinical ascites.

Baseline biochemical parameters were recorded as mean ALP 103.3 IU/L, mean SGPT 77.3 IU/L, mean SGOT 79.5 IU/L. Pre-treatment mean platelet count was 1.70,000/mm^3.

Mean HCV RNA was 3816581.9 copies/ml. 12 weeks post-treatment, overall mean HCV RNA was reduced to 9.9

copies/mL.

The number of patients with melena was reduced from 16 to 4 patients, haematemesis was reduced from 6 to 3 patients, and ascites was reduced from 11 to 1 patient as compared to baseline *versus* post-treatment.

APRI score

For Daclatasvir receiving patients (n = 57) mean APRI of 0.71 was reduced to 0.66 (Fig. 1). Before treatment, there were 10 patients with APRI score >1 which was reduced to 6 patients. Similarly, patients with APRI score ≤0.7 rose from 32 to 37 following Daclatasvir treatment.

For Velpatasvir receiving patients (n = 43), pre-treatment APRI score of 2.15 was reduced to 1.49 post-treatment (Fig. 2). Patients with APRI score >1 were 30, which was reduced to 23, and patients with APRI score ≤0.7 rose from 4 to 11 after Velpatasvir treatment. Overall, the pre-treatment mean APRI score of 1.33 was reduced to 1.01 post-treatment.

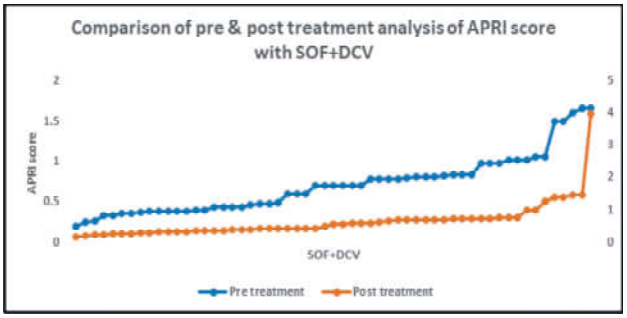

Fig. 1: *Comparison of APRI score in patients treated with Sofosbuvir (SOF) and Daclatasvir (DCV).*

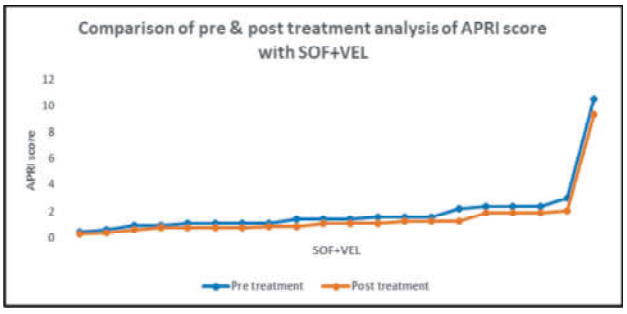

Fig. 2: *Comparison of APRI score in patients treated with Sofosbuvir (SOF) and Velpatasvir (VEL)*

FibroScan

Among Daclatasvir treated patients, pre-treatment liver stiffness of 6.88 kPa was reduced by 10.47% to 6.16 kPa (Fig. 3); for Velpatasvir, it was reduced by 34.13%, from 11.25 kPa to 7.41 kPa (Fig. 4). Overall baseline median stiffness of 8.76 kPa was reduced to 6.70 kPa (-23.52%) after treatment.

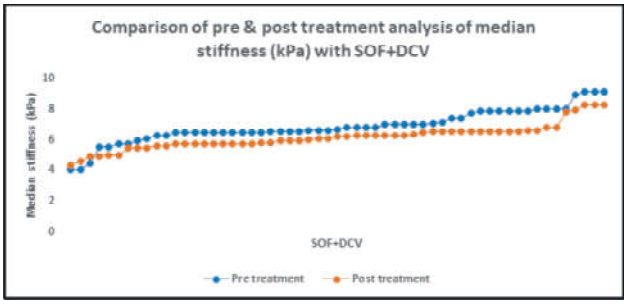

Fig. 3: *Comparison of median stiffness in patients treated with Sofosbuvir (SOF) and Daclatasvir (DCV).*

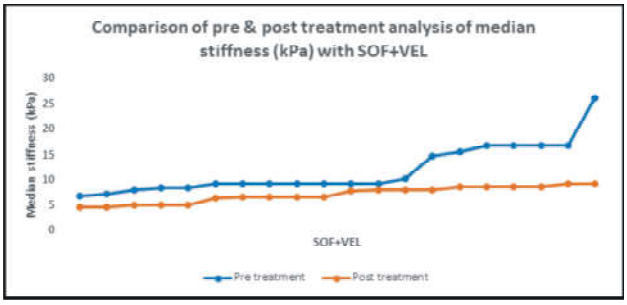

Fig. 4: *Comparison of median stiffness in patients treated with Sofosbuvir (SOF) and Velpatasvir (VEL).*

Discussion

Donahue *et al* reported that the HCV prevalence in Baltimore, Maryland, was 85% for IDUs (Injection drug users)[10]. Quite interestingly, only 15% of patients had a definite history of IV drug abuse in our study. This points to the fact that other modes of viral transfer in adults like unsafe medical practices (of repeated syringe use), occupational exposure, sexual exposure, using same razor for multiple people in saloons and many others are yet to be thoroughly explored at the community level. This study found that history of melena was more common at presentation compared to haematemesis (16% vs 6%), only 2% patients had fever, 11% patients had icterus and 13% patients had pedal oedema. During baseline clinical evaluation, splenomegaly was more prevalent compared to hepatomegaly (27% vs 7%), and 11% patients had clinical ascites. All this baseline clinical evaluation depicted the fact that signs and symptoms of portal hypertension contributed to the most significant presenting complications of HCV infection where splenomegaly was the most consistent sign followed by a history of melena and ascites.

Ascites was reduced to 1% (down from 11% at baseline,

Chi square 8.173, p value 0.002). Only 4% patients reported melena (compared to 16% at baseline, Chi square 21.875, p value <0.001) and 3% reported haematemesis (compared to 6% at baseline, Chi square 48.454, p value <0.001) after 36 weeks of starting DAA. Similar improvement was noticed in platelet count as well, with a baseline mean of 1.70,000/mm^3 (SD 0.6) to 12 weeks post-treatment mean value of 1.90,000/mm^3 (SD 0.6) (p value <0.001).

In our study, the most dramatic change was noticed in HCV RNA status where a baseline mean of 3816581.9 (SD 775582.8) was reduced to a mean of 9.9 (SD 3.1) with a t value of 4.921 and a p value of <0.001 after 12 weeks of treatment completion. This data re-establishes the excellent sustained virologic response (SVR) after giving DAAs for treating HCV infection.

APRI score was improved following treatment, which was statistically significant (from a baseline mean of 1.3, (SD 1.6) to post-treatment mean of 1.0, (SD 1.3), t value 3.933, p value <0.001). But one patient had a deterioration of APRI score from 0.26 to 4 which also corresponded to the deterioration of median stiffness value from 6.49 to 7.82.

FibroScan revealed that the mean baseline median stiffness improved from 8.76 (SD 3.9) to 12-week post-treatment median stiffness of 6.70 (SD 1.2) with a p value of <0.001. In a previous study, it was found that 61.9% patients had regression in METAVIR fibrosis stage after successful DAA treatment[8]. However, in our study we found 64% regression in METAVIR fibrosis stage, while a deterioration of 6% in METAVIR fibrosis stage.

Ascites, being a hindering factor while performing transient elastography, posed a challenge while performing liver stiffness. As a result, data from the excluded patients with ascites could not be assessed. Real time elastography could yield better results in such cases and leaves a path for further studies[11].

Genotype evaluation was not done in this study as pan genotypic regimen was used in our patients. There is very limited data available globally showing variability in the effect of existing treatment upon different genotypes[12,-14].

However, the data in this study further strengthens the impact of DAAs in HCV infection while preventing hepatic complications which is probably explained by regression of fibrosis, intra-hepatic blood flow and the function of hepatocytes perhaps improves and leads to improvement in hepatic outcomes.

Conclusion

We conclude that those who were infected with hepatitis C mostly presented in the 4th to 5th decade and were diagnosed either incidentally or after a complication, mainly in the form of signs and symptoms suggesting portal hypertension. So, it is a mandatary to perform hepatitis C serology along with HCV RNA quantitative assay in all such patients. Patients who had SVR (sustained virological response) after receiving DAAs therapy displayed a substantial Fibro Scan value decline, which correlated with the regression of the validated fibrosis score APRI except one patient whose APRI score and fibrosis measurement value deteriorated; though we did not really know the exact reason in this patient; there was a possbility of effect of confounding factors (co-morbidities). Whether the improvement of these non-invasive parameters in the form of APRI score and METAVIR score represent a real fibrosis regression or merely a resolution of chronic liver inflammation with subsequent improvements in FibroScan value and laboratory parameters have to be investigated by histopathological sampling or better correlation between non-invasive and invasive methods. Again, a longer follow-up is needed to monitor long-term effect of DAAs while curing an HCV infection and its chronic complications. Moreover, the present study was a single centre study and the sample size was too small to extrapolate the conclusions to the entire population.

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ORIGINAL ARTICLE

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Coronary Artery Calcium Score (CACS) – A Comparative Study in Diabetic and Non-Diabetic Patients

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Abstract

Introduction: Diabetes mellitus is a common metabolic disorder that shares the phenotype of hyperglycaemia[1]. Recently, diabetes has emerged as a leading cause of coronary heart disease[2]. Although, a variety of methods are available to assess CAD risk in diabetic patients, coronary artery calcium score(CACS) is most sensitive among all these methods. The CAC score is an independent predictor of the risk of major cardiovascular events. It has demonstrated superiority over the Framingham risk score, CRP level and carotid intima-media thickness[3].

Aims and objectives: To compare coronary artery calcium score among diabetics and non-diabetics and to observe the association of ECG changes and CACS score.

Methodology: All patients were assessed by clinical evaluation and investigations. CACS was calculated by using 128 slice single source CT-scan machine by the Agatston method.

Results: In the present study, 80 patients were taken, of which 40 were diabetic and 40 were non-diabetic. Majority of patients in the diabetic group 21 (52.5%) were in the age group of 51 - 60 years whereas in the non-diabetic group, age groups of 51 - 60 and 41 - 50 years were equal 17 (42.5%) in number. Among diabetics, 7 (17.5%) patients had CACS in mild category and 33 (82.5%) patients were in moderate-to-severe category. In non-diabetics, patients with CACS in mild category were 21 (52.5%) and in the moderate-to-severe category were 19 (47.5%). Among various age groups, the severity of CACS increased with increasing age. Proportion of patients having moderate-to-severe CACS score increased with increasing value of HbA1C (83.3% in 9 - 11% HbA1C category and 94.7% in >11% HbA1C category).

Conclusion: CACS is higher in diabetics than in non-diabetics and is usually associated with increased risk of CAD. CACS can be an important non-invasive investigation for early detection of CAD.

Key words: CAD, T2DM, CACS, CHD, DM.

Introduction

Diabetes is a chronic disease, caused due to insufficient production of insulin by the pancreas or when it cannot be utilised effectively at the cellular level. The prevalence of diabetes in the age groups between 20 to 70 years worldwide was estimated to be 8.9% in 2021 according to the International Diabetic Federation. The prevalence of diabetes is on an increasing trend as the number of adult diabetics is projected to rise from 382 million to 592 million as compare from 2013 to 2035. In 2013, 5.1 million people died because of complications of hyperglycaemia. Prevalence of CAD in diabetic patients is 21.4% (known diabetics 25.3% and newly diagnosed diabetics 13.1%). With an increasing incidence worldwide, DM and CAD are likely to be a leading cause of morbidity and mortality in the future[1].

Diabetes-related complications affect many organ systems which are responsible for most of the morbidity and mortality associated with the disease. More recently, diabetes has also been an important factor in the development of coronary heart disease (CHD). Diabetes associated complications usually do not appear until the second decade of hyperglycaemia. In contrast, diabetes-associated CHD risk, related in part to insulin resistance, may develop before hyperglycaemia is established[2]. Atherosclerosis is the major threat to macro-vascular complications in diabetics. Dyslipidaemia is highly corelated with atherosclerosis and up to 97% of diabetic patients are dyslipidaemic[4]. The coronary artery calcium score is a measurement of the amount of calcium in the walls of arteries that supply heart muscles. It is measured by taking a special CT scan of the heart. The scan shows the amount of hardening of arterial wall (caused by atherosclerosis). The results of the scan makes it possible to estimate the risk of a heart attack or stroke in the next 5 - 10 years.

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The main methods for the quantification of CAC score are, determination of the volume of calcium, and determination of the calcium mass score. These are the most widely used parameters, especially by the Agatston method, which is used for most of the studies and publications, involving risk stratification and is also the method mostly used in clinical practice. The calcium volume score and calcium mass score have shown better reproducibility[5]. In this study we compare CACS to assess CAD risk in diabetics.

Aims and objectives

- To compare coronary artery calcium score in diabetics and non-diabetics.
- To obsereve association of ECG changes with CACS score among diabetics and non-diabetics.

Methodology

This cross-sectional observational study was carried-out at the Departments of Medicine and Radiology, LLRM Medical College and SVBP Hospital, Meerut, Uttar Pradesh from October to December-2021. All diabetic patients with age 30 - 60 years with no symptoms of CAD admitted during the study duration and willing to take part in the study were included. Equal number of non-diabetic patients who were fulfilling the inclusion and exclusion criteria were included in the study. Informed consent was taken from all patients. The clearance was taken from Institutional Ethics Committee, LLRM Medical College (approval – SC-1/2021/A246, dated 27/12/2021). All procedures followed guidelines laid down by the Declaration of Helsinki (2013). All selected patients were interviewed and relevant investigations including ECG and CT scan were done. CACS was calculated for both diabetic and non-diabetic patients and ECG was used to assess CHD risk.

The method used for quantification of CAC score was the Agatston method[5].

Agatston method: The Agatston method is the most widely used method used for calculating coronary artery calcium score. It uses those lesions which have a density above 130 HU. Weighted sum of all the lesions is taken and the area of calcification is multiplied by a factor related to maximum plaque attenuation. Multiplication factors used were 130 - 199 HU, factor 1; 200 - 299 HU, factor 2; 300 - 399 HU, factor 3; and ≥400 HU, factor 4. The CAC score was done by CT, based on axial slices, using slice thickness of 3 mm, without any overlapping or gaps, limited to cardiac region, acquired in synchrony with the electrocardiogram prospectively, at a predetermined moment in the R-R interval, usually in the mid/late diastole, without the use of intravenous contrast medium[5].

The effective dose of radiation is usually low, typically less than 1.5 mSv, which is the recommended dose for use in image acquisition, according to the Society of Cardiovascular Computed Tomography. Calcification was identified as areas of hyper attenuation of at least 1 - 2 mm with >130 Hounsfield units (HU) or ≥3 adjacent pixels[5].

Inclusion criteria

- Covid-negative patient with type 2 Diabetes Mellitus for diabetic group and age, sex-matched non-diabetic patients for non-diabetic group.
- >18 years.
- Patients consenting to take part in the study.
- Asymptomatic for coronary artery disease at the time of presentation.

Exclusion criteria

Patients having CAD and hypertension, smokers, alcoholic, malignancy – multiple myeloma, lymphoma, malignancy of lung, breast, patients on thiazide diuretics, there with chronic renal failure, thyroid disease – hypothyroidism, hyperthyroidism, primary hyperparathyroidism, hypervitaminosis-D, critically ill patients, morbidly obese patients, and pregnant patients were excluded from study.

All data was compiled and analysed at the end of the study by applying appropriate statistical tests, using EPI info Software. Unpaired student T-test was applied.

Observation and results

Table I shows the demographic profile of patients of both diabetic and non-diabetic groups. Out of 40 diabetic patients, majority of 21 (52.5%) were in the age group of 51 - 60 years followed by 12 (30%) in 41 - 50 years and 7 (17.5%) in 31 - 40 years age group. Among non-diabetic patients, 17 (42.5%) were in 51 - 60 age group, 17 (42.5%) patients in 41 - 50 age group and 6 (15%) patients in 31 - 40 age group. In diabetic patients, 13 (32.5%) were males and 27 (67.5%) were females. Among 40 non-diabetic patients, 23 (57.5%) were males and 17 (42.5%) were females. There was no significant age and gender variation between both groups.

Fig. 1 is a bar graph showing distribution of CACS in diabetic and non-diabetic patients. Out of 40 diabetic patients, 7 (17.5%) had mild CACS and 33 (82.5%) had moderate-to-severe CACS. Out of 40 non-diabetic patients, 21 (52.5%) had mild score and 19 (47.5%) had moderate-to-severe score. We can see that diabetic patients had more severe CACS than the non-diabetic group. On statistical analysis, this difference of CACS score between diabetic and non

diabetic patients was found to be highly significant.

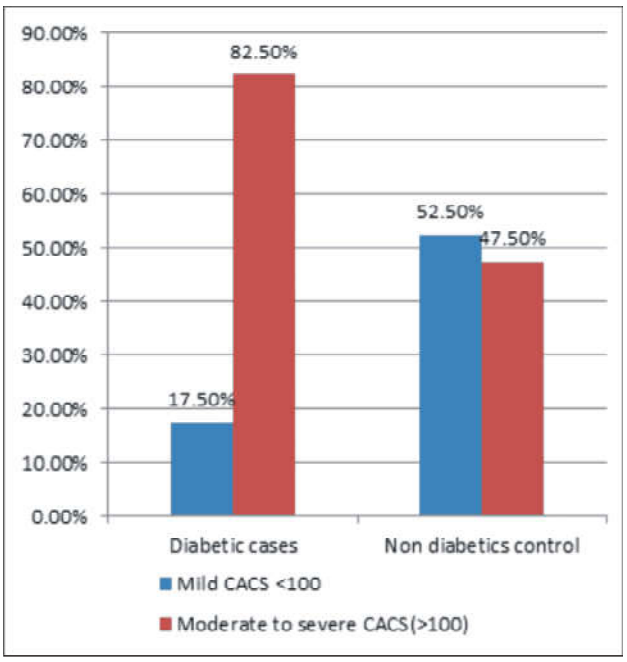

Fig. 1: *Distribution of CACS in diabetics and non-diabetics.*

Table I: Distribution of age and gender in diabetic and non-diabetic groups.

	Diabetic cases		Non-diabetic controls	
Age groups (years)				
18 - 40	7	17.5%	6	15%
41 - 50	12	30%	17	42.5%
51 - 60	21	52.5%	17	42.5%
Total	40	100%	40	100%
Gender				
Male	13	32.5%	23	57.5%
Female	27	67.5%	17	42.5%
Total	40	100%	40	100%

In Table II, CACS is shown in various age groups among diabetics and non-diabetics. In 18 - 40 years age group among diabetics, 57.1% of patients had moderate-to-severe CACS while among non-diabetics 33.3% were in moderate-to-severe category. On statistical analysis this difference was found to be insignificant. In 41 - 50 years age group, moderate-to-severe CACS was found in 83.3% and 64.7% among diabetics and non-diabetics respectively, but this difference was also insignificant. In older age group (51 - 60 years) most of the diabetic patients (90.5%) had moderate-to-severe CACS, whereas only 35.3% of non-diabetics had CACS >100. This difference in CACS among diabetics and non-diabetics was statistically highly significant (p = .001).

Table II: Mean level of CACS in different age groups among diabetic cases and non-diabetic controls.

	Diabetic			Non-Diabetic			Statistical analysis
Age Group	Mild (<100) No (%)	Modrate -to- severe (>100) No (%)	Total No	Mild (<100) No (%)	Modrate -to- severe (>100) No (%)	Total No	
18 - 40	3 (42.9)	4 (57.1)	7	4 (66.7)	2 (33.3)	6	$X^2 = 0.737$, P value = 0.39
41 - 50	2 (16.7)	10 (83.3)	12	6 (35.5)	11 (64.7)	17	$X^2 = 1.2219$, P value = 0.26
51 - 60	2 (9.5)	19 (90.5)	21	11 (64.7)	6 (35.3)	17	$X^2 = 12.710$, P value = **0.0003**
Total	7 (17.5)	33 (82.5)	40 (100%)	21 (52.5)	19 (47.5)	40 (100%)	$X^2 = 10.7692$, P value = **0.001**

In Table III, association of HbA1C and CACS was observed among diabetic patients. It was observed that in patients with HbA1C in the range of 7 - 9%, 66.7% of patients were having moderate-to-severe CACS. Proportion of patients having moderate-to-severe CACS increased with increasing value of HbA1C (83.3% in 9 - 11% HbA1C category and 94.7% in >11% HbA1C category). On statistical analysis this difference was not found to be significant.

Table III: Association of HbA1C with CACS among diabetic patients.

HbA1C	CACS		Total
	Mild	Modrate-to-Severe	
7 - 9	5 (33.3%)	10 (66.7%)	15
9 - 11	1 (16.7%)	5 (83.3%)	6
>11	1 (5.3%)	18 (94.7%)	19
Total	7 (17.5%)	33 (82.5%)	40

$X^2 = 4.578$, *P value = 0.101.*

Table IV: Association of ECG changes with CAC score in diabetics and non-diabetics.

Group	Diabetic group (n = 40)	Non-diabetic group (n = 40)	T-test (p value)
ECG changes No.(%)	14 (35%)	1 (2.5%)	$X^2 = 13.866$,
CACS (mean ± SD)	413 ± 79.1	136 ± 128.8	***P value <0.05***

Table IV shows the ECG changes found in both diabetic and non-diabetic group. Out of 40 diabetic patients, 14 patients had ECG changes, in these 14 patients mean CACS was 413 ± 79.1 and in non-diabetics only one patient was found to have ECG changes with a CACS of 136 ± 128.8, and the association between ECG changes in the two groups was statistically significant (p value < 0.05). It shows that ECG

changes were more in diabetic patients who had a high CACS (>200), as compared to non-diabetics – with only one patient having ECG changes.

Discussion

According to the Framingham study, risk of cardiovascular mortality in men with diabetes is twice, and four times in women with diabetes when compared to non-diabetic population. Risk of developing acute myocardial infarction is fifty per cent higher in diabetic men whereas risk is 50% in women living with diabetes[5]. In diabetics, along with the characteristic pattern of increased triglyceride and decreased HDL cholesterol, abnormalities are seen in the structure of lipoprotein particles. Predominately small and dense form of LDL is found in diabetic patients. These small LDL particles are more atherogenic than large LDL particles. Both insulin deficiency and insulin resistance promote dyslipidaemia by increasing oxidation, glycosylation and by triglyceride enrichment of lipoprotein. All these factors contribute to increased atherogenicity in a diabetic patient[6]. Therefore, measurement of CACS by electron beam tomography has been shown to be a powerful predictor of coronary heart disease in asymptomatic diabetic patients, which can enhance prediction of adverse cardiovascular events early.

In the present study, we enrolled 80 patients, out of which 40 patients were diabetic and 40 non-diabetic. Maximum number of patients in both groups were between the age group of 50 to 60 years. A similar finding was seen in a study by Subhashish Agarwal *et al*[7], in whose study maximum patients were also in the age group of 61.4 years with a mean SD of 9.1. In the present study, in the diabetic group, 13 were male (32.5%) and 27 were female (67.5%); and in the non-diabetic group, 23 males (57.5%) and 17 females (42.5%). Similar findings were also seen by Agarwal *et al*[7]. It was observed in the present study that diabetic patients had higher CAC score as compare to non-diabetics. A similar study was also conducted by Elkeles *et al* which included measurement of CACS by electron beam tomography. They observed that only 23% patients among type 2 diabetics had low CACS[8].

In the present study it was observed that in older age group (51 - 60 years) most of the diabetic patients (90.5%) had moderate-to-severe CACS, whereas only 35.3% of non-diabetics had CACS >100. This difference in CACS among diabetic and non-diabetic patients was statistically highly significant (p = .001). Yuichiru Yano *et al* also found higher risk of coronary heart disease with increased CACS with increasing age[9].

Proportion of patients having moderate-to-severe CACS increased with increasing value of HbA1C (83.3% in 9 - 11% HbA1C category and 94.7% in >11% HbA1C category). Jing Yu *et al* observed that an increase in 1% of HbA1C was related to a 24% increase of CACS progression risk (HR = 1.24, 95% CI: 1.21 to 1.28) leading to statistically significant result[10].

In our study 14 patients in the diabetic group had ECG changes in which CAC score in comparison to the non-diabetic group was significantly high ($p < 0.05$). Similar study was done by Zhu *et al* which included five hundred eighty-eight outpatients with suspected CAD comprising 208 diabetic and 380 non-diabetic patients. Coronary artery plaque and CAC scores were measured; it showed that the diabetic group had significantly higher CAC scores in LAD than that in the non-diabetic group[11]. Elkeles *et al* observed that type 2 diabetic and non-diabetic subjects who had undetectable coronary artery calcification were observed to have similar mortality. On the contrary those subjects who have high CACS were found to have high cardiovascular risk. Thus not all those with type 2 diabetes are at similar cardiovascular risk[8].

Conclusion

Diabetes is characterised by high cardiovascular mortality. In diabetes, multi-vessel coronary atherosclerosis is often present before ischaemic symptoms occur and before treatment is instituted. A delayed recognition of various forms of cardiovascular diseases worsens the prognosis and survival in diabetics. Thus measurement of coronary artery calcium score (CACS) has been shown to be a powerful predictor of coronary heart disease events in asymptomatic diabetic subjects, especially among older age groups and patients with higher value of HbA1C. Hence, CACS can be used as a non-invasive test for early detection of the risk of CAD in diabetics.

Recommendation

- Since CACS of diabetics was significantly higher, it is recommended that CACS should be used for assessing the risk of occurrence of CAD among diabetics, so that sudden cardiac death can be avoided. CACS being a non-invasive procedure, can be used as a screening procedure for high-risk patients to predict coronary heart disease.
- A large study of multicentric origin is needed in order to get stabilised and quantified exact co-relation. This study is a modest attempt to assess CACS as a risk of CAD in diabetics.

Limitation

The limitation in this study is that it was a cross-sectional

study, so follow-up of patients could not be done and the sample size was small (80) because study was done during COVID era.

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ORIGINAL ARTICLE

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Treatment Adherence in Relation to Emotion Regulation among Patients of CKD with and without Haemodialysis

Amra Ahsan, Shaurya Kaul*, Narinder Pal Singh**, Anish Kumar Gupta***

Abstract

***Background:** This cross-sectional study investigates medication non-adherence in Chronic Kidney Disease (CKD) patients, emphasizing the impact of emotion regulation. The research explores the extent of non-adherence and its association with factors such as patient demographics, focusing on CKD patients with and without haemodialysis. Addressing the deficiency in high-quality research, the study aims to provide insights for healthcare practitioners to implement effective adherence interventions in this population.*

***Methods:** This cross-sectional study on CKD included 160 participants, equally distributed between those undergoing haemodialysis and those not. Sample size was determined using Green's table. Participants met specific inclusion criteria and were assessed using the Emotional Regulation Questionnaire and Morisky Medication Adherence Scale (MMAS). Data analysis involved SPSS 25.0, employing statistical tests for associations.*

***Results:** In this study of 160 CKD patients, those undergoing dialysis (n = 80) faced higher medication non-adherence, with 57.5% reporting low adherence compared to 28.7% in the non-dialysis group (n = 80). Non-adherence reasons included forgetfulness and travel-related challenges. Emotion regulation analysis revealed significantly lower cognitive reappraisal (p = 0.0087*) and expressive suppression (p = 0.0001*) scores in dialysis patients. Demographic factors and pill burden did not impact adherence, but having multiple co-morbidities significantly correlated with non-adherence in dialysis patients (p = 0.0076*). Emotion regulation strategies did not significantly influence adherence in either patient group.*

***Conclusion:** Findings indicated prevalent non-adherence, with 57.5% of dialysis patients exhibiting low adherence. Emotion regulation was lower in dialysis patients. Forgetfulness was a primary non-adherence reason. Demographic factors minimally impacted adherence, but multiple co-morbidities affected dialysis patients. The study emphasizes the need for targeted interventions to enhance medication adherence in CKD.*

***Key words:** Medication adherence, dialysis, Chronic kidney disease, emotion regulation.*

Introduction

Adherence to treatment involves a collaborative agreement between patients and healthcare providers, measured by how closely individual behavior aligns with jointly established health recommendations[1]. This behaviour is intricate, dynamic, and varies among individuals, featuring unique and evolving reasons for non-adherence. The management of chronic conditions, such as Chronic Kidney Disease (CKD) with multiple medications, poses adherence challenges[2]. Globally, CKD is a significant public health concern, and non-adherence heightens health risks and healthcare costs[3,4]. Current literature suggests that non-adherence to medication regimens may signal cognitive decline and emotional or psychological issues, including depression[5-10]. Consequently, researchers are increasingly exploring emotion regulation and psychological flexibility in chronic diseases, acknowledging their potential impact on treatment non-adherence. It is imperative to address these factors in adherence interventions. Despite the importance of medication adherence in CKD patients, there is a deficiency in high-quality research on this topic, posing challenges for healthcare practitioners in implementing effective non-adherence measures. This cross-sectional study aimed to shed light on the extent of non-adherence and its association with various factors, including patient demographics, emotion regulation in CKD patients with and without haemodialysis.

Methods

Sample

This research focused on individuals who had CKD, encompassing those undergoing haemodialysis. The study involved participants from the outpatient department and

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dialysis unit at SGT University and hospitals in the NCR-Delhi, with selection based on specific inclusion and exclusion criteria. Initially, 185 individuals were invited, but 22 declined participation. Thus, 163 participants were initially enrolled, with three later excluded, leaving a final analysis of 160 participants, evenly distributed between those on dialysis and those not.

Sample size analysis

The sample size was determined using Green's computed table, considering multiple correlation co-efficients for MMAS-8, and ERQ questionnaires, each with 8, and 10 predictors, respectively. Power analysis, factoring in alpha, power, and effect size, indicated a need for 117 participants to achieve 0.8 power at alpha = 0.05. To facilitate calculation, the study included a total of 160 participants.

Inclusion criteria

- Adults (18 years or older) of any gender.
- Clinically stable CKD patients (stage 3 onwards) with or without haemodialysis for at least 3 months.

Exclusion criteria

- No current hospitalisation or history of hospitalisation in the previous month.
- No history of substance abuse, psychiatric illness, cognitive impairment, or conditions hindering participation.
- No concurrent psychological treatment at the time of recruitment or within the previous three months.

Study design

The study adopted a cross-sectional design, examining emotion regulation and treatment adherence among CKD patients with or without haemodialysis. Data collection occurred at a single point in time.

Measures

Emotional Regulation Questionnaire (ERQ) (Gross and John, 2003)[11]: The Emotion Regulation Questionnaire (ERQ) is a 10-item scale measuring individuals' emotional regulation tendencies through Cognitive Reappraisal and Expressive Suppression. The cognitive reappraisal section of the ERQ encompasses a scale of 6 to 42, while the expressive suppression section ranges from 4 to 28. Higher scores on either subscale indicate a higher degree of employing the respective strategy. Participants rate each item on a Likert scale from 1 to 7. Established by Gross and John, the ERQ demonstrates good reliability (Cronbach's alpha of .79 for reappraisal and .73 for suppression) and test-retest reliability of .69 over three months. Convergent and discriminant validity analyses indicate correlations of reappraisal with reinterpretation ($\alpha = 0.43$; $p < 0.05$) and emotional state management ($\alpha = 0.20$; $p < 0.05$), and suppression with a sense of inauthenticity ($\alpha = 0.47$; $p < 0.05$). In the present study, Cronbach's alpha was .717, affirming high internal consistency.

Morisky Medication Adherence Scale (MMAS-8) questionnaire (Morisky *et al*)[12]: MMAS-8, a diagnostic tool for non-adherence, comprised 8 questions. Treatment adherence was categorised as low, moderate, or good. The MMAS-8 exhibited a reliability of .539 in this study.

Procedure

The cross-sectional study enrolled 160 subjects through a convenient sampling technique. Informed written consent was obtained, and participants were briefed about the research and ethical considerations. Socio-demographic and clinical characteristics were collected, and participants underwent interviews and completed questionnaires assessing emotion regulation and medication adherence. A pilot study with 30 - 40 participants informed protocol modifications.

Statistical analysis

Data analysis involved SPSS version 25.0. Categorical variables were presented using frequencies and percentages, while numerical variables were expressed through means and standard deviations. Scale scores were graphically represented. The association between treatment adherence and independent variables was assessed using statistical tests such as the Chi-square test for categorical variables and independent paired t-test for continuous variables. A significance level of $p < 0.05$ was considered statistically significant.

Results

Among 160 individuals, the dialysis group (n = 80) exhibited a mean age of 51.85 ± 13.96 years, ranging from 20 to 75 years, while the non-dialysis group (n = 80) had a mean age of 55.37 ± 14.40 years, ranging from 19 to 88 years. In the non-dialysis cohort, a significant majority were married (91.2%), unemployed (75%), and literate (87.5%). Among those undergoing dialysis, the majority were men (63.7%), married (85%), unemployed (81.2%), and literate (75%). Stage 3 and stage 4 CKD collectively constituted more than 98% of patients not receiving dialysis. The demographic and clinical characteristics of participants are summarised in Table I. The prevalent comorbidity was hypertension,

followed by diabetes with hypertension and cardiovascular disease.

For CKD patients with and without dialysis, the average number of prescribed medicines per prescription was 6.38 ± 2.81 and 5.07 ± 1.92, respectively. Patients undergoing dialysis experienced a higher pill burden, with over three-fourths of them taking more than five medications per prescription.

Table I: Demographic and clinical characteristic of the study participants.

S.N.	Variables	Dialysis group	Non-dialysis group
1.	Gender		
	Male	51 (63.7)	43 (53.7)
	Female	29 (36.3)	37 (46.3)
2.	Age mean ± SD (years)	51.85 ± 13.96	55.37 ± 14.40
	18 - 40 years	21 (26.3)	13 (16.3)
	41 - 60 years	32 (40)	38 (47.5)
	61 - 80 years	27 (33.7)	25 (31.2)
	>80 years	0	4 (5)
3.	Stages of CKD		
	Stage 5 (eGFR<15 ml/min)	80 (100)	1 (1.25)
	Stage 4 (eGFR 15-29 ml/min)	-	39 (48.75)
	Stage 3 (eGFR 30-59 ml/min)	-	40 (50)
4.	Co-morbidities along with CKD		
	Hypertension	43 (53.6)	54 (67.5)
	Diabetes	5 (6.3)	0
	Diabetes and hypertension	22 (27.5)	19 (23.7)
	Cardiovascular disease along with hypertension	5 (6.3)	2 (2.5)
	Cardiovascular disease along with diabetes and hypertension	5 (6.3)	5 (6.3)
5.	Duration of dialysis (Months)	29.52 ± 24.58	-
	• <6	4 (6.7)	-
	• 6 - 12	25 (31.7)	-
	• >12	51 (61.6)	-
6.	Frequency of Dialysis		
	• Two times/week	37 (46.2)	-
	• Three times/week	43 (53.8)	-
7.	Medications		
	Average medication prescribed	6.38 ± 2.81	5.07 ± 1.92
	• <5	14 (17.5)	39 (48.75)
	• ≥5	66 (82.5)	41 (51.25)

Figures in parentheses represent the percentage of patients who answered the respective question.

Table II: Participants response about medicines.

S. No.	Problem statement associated with the respondents (The 8-item Morisky Adherence Questions)	Dialysis group	Non-dialysis group
1.	Forget to take medications	35 (43.7)	52 (65)
2.	Miss to take medications for reasons other than forgetting.	19 (23.7)	27 (33.8)
3.	Discontinued taking medications without notifying doctors since the patient felt worse when he or she took them.	17 (21.3)	26 (32.5)
4.	During travel or leave home, sometimes forget to bring medications.	29 (36.3)	24 (30)
5.	Did you take your medications yesterday?	61 (76.3)	58 (72.5)
6.	When responders believe their health is under control, they stop taking medications.	28 (35)	24 (30)
7.	Feel hassled about sticking to treatment plan	29 (36.3)	36 (45)
8.	Difficulty remembering to take all the medications		
	• Never/rarely	26 (32.5)	37 (46.3)
	• Once in a while	10 (12.5)	15 (18.7)
	• Sometimes	13 (16.3)	24 (30)
	• Usually	14 (17.5)	3 (3.8)
	• All the time	17 (21.2)	1 (1.2)

Figures in parentheses represent the percentage of patients who answered the respective question. N = 80 in each group.

In the study, it was found that 21.2% of individuals undergoing dialysis faced challenges in remembering to take medications at all the time, whereas only 1.2% of those not undergoing dialysis encountered similar difficulties. The most commonly cited reasons for non-adherence included forgetting to take medications, feeling compelled to adhere to a treatment plan, and neglecting to pack medications when traveling (refer to Table II).

The survey revealed that a substantial majority of participants, exceeding 90%, indicated low to moderate adherence levels in both dialysis and non-dialysis groups. Specifically, in the MMAS-8 assessment, 57.5% of individuals undergoing dialysis reported low adherence, compared to 28.7% in the non-dialysis group. Moderate adherence was reported by 38.7% of dialysis patients versus 70% of non-dialysis patients, while good adherence was reported by 3.8% of dialysis patients and 1.2% of non-dialysis patients. Fig. 1 illustrates a comparative analysis of medication non-adherence on the MMAS-8 scale between dialysis and non-dialysis group.

Emotion regulation

Cognitive reappraisal scores were 22.32 ± 8.40 for dialysis patients and 25.48 ± 6.53 for non-dialysis patients,

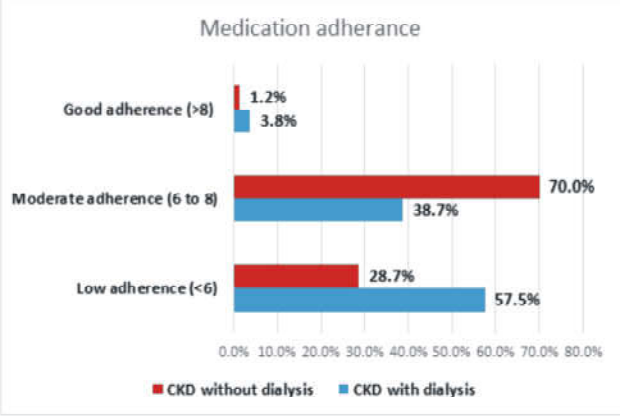

Fig. 1: *Morisky Medication Adherence Scale score in dialysis and non-dialysis group.*

signifying a statistically significant difference (p = 0.0087*). Expressive suppression scores were 14.11 ± 5.80 for dialysis patients and 17.33 ± 4.86 for non-dialysis patients, showing a highly significant distinction (p = 0.0001*). Notably, nearly half of CKD patients displayed low emotion regulation. Importantly, non-dialysis patients exhibited higher cognitive reappraisal and expressive suppression scores, suggesting more frequent and effective utilisation of these strategies than their dialysis counterparts.

Table III: Emotion regulation in patients with and without dialysis on emotion regulation questionnaire scale.

Emotion regulation strategy	Likert scale score	Dialysis group		Non-dialysis group		p value
		N (%)	Mean ± SD	N (%)	Mean ± SD	
Cognitive reappraisal	Agree (score 25 to 42)	30 (37.6)	30.66 ± 5.23	46 (57.5)	29.74 ± 3.84	
	Disagree to neutral responses (score 19 to 24)	25 (31.2)	21.76 ± 1.53	26 (32.5)	21.88 ± 1.70	
	Disagree (score 06 to 18)	25 (31.2)	12.88 ± 4.28	08 (10)	12.5 ± 3.85	
	Total	80	22.32 ± 8.40	80	25.48 ± 6.53	0.0087*
Expressive suppression	Agree (score 17 to 28)	25 (31.2)	20.96 ± 3.42	44 (55)	20.97 ± 2.92	
	Disagree to neutral responses (Score 13 to 16)	24 (30)	14.20 ± 1.17	26 (32.5)	14.11 ± 1.14	
	Disagree (score 4 to 12)	31(38.8)	8.51 ± 2.61	10 (12.5)	9.7 ± 1.88	
	Total	80	14.11 ± 5.80	80	17.33 ± 4.86	0.0001*

**Independent t-test statistics, p <0.05 significant at 95% CI. N = 80 in each group.*

Factors affecting medication adherence

Tables IV and V compare adherence factors among dialysis and non-dialysis patients. Gender, age, education, and employment status showed no significant impact on adherence in both groups (p >0.05). Regardless of gender, age categories (18 - 40, 41 - 60, >60 years), literacy, or employment, adherence remained consistent. Pill burden also did not significantly affect adherence (p >0.05). However, having multiple co-morbidities was significantly linked to non-adherence in dialysis patients (p = 0.0076*), suggesting a potential barrier. Emotion regulation strategies, cognitive reappraisal, and expressive suppression did not significantly influence adherence in either patient group (p >0.05).

Table IV: Factors affecting medication adherence in dialysis group.

S. No.	Variables	Non-adherence#	Adherence^	p value
1.	Gender			
	Male	26	25	0.3028
	Female	20	9	
2.	Age			
	18 - 40 years	9	12	0.408
	41 - 60 years	20	12	
	>60 years	17	10	
3.	Education			
	Illiterate	10	11	0.3565
	Literate	36	23	
4.	Employment status			
	Employed	7	8	0.5109
	Unemployed	39	26	
5.	Pill burden			
	<5 Medication/prescription	8	6	0.8709
	≥5 medication/prescription	38	28	
6.	Co-morbidities			
	Single	23	24	0.0076*
	Multiple	23	10	
7.	Emotion regulation			
	a) Cognitive reappraisal			
	Score >25	20	10	0.3038
	Score <25	26	24	
	b) Expressive Suppression			
	Score >17	13	12	0.4773
	Score <17	33	22	

**chi square statistics, p value <0.05 considered significant at 95% CI #N = 46 ^N = 34.*

Table V: Factors affecting medication adherence in non-dialysis group.

S. No.	Factors	Non-adherence#	Adherence^	p value
1.	Gender			
	Male	12	31	0.741
	Female	11	26	
2.	Age			
	18 - 40 years	4	9	0.9776
	41 - 60 years	11	27	
	>60 years	8	21	
3.	Education			
	Illiterate	2	8	0.884
	Literate	21	49	
4.	Employment status			
	Employed	8	12	0.5188
	Unemployed	15	45	
5.	Pill burden			
	<5 medication/prescription	13	28	0.7051
	≥5 medication/prescription	10	29	
6.	Co-morbidities			
	Single	14	28	0.4014
	Multiple	9	29	
7.	**Emotion regulation**			
	a) **Cognitive reappraisal**			
	Score >25	13	33	0.860
	Score <25	10	24	
	b) **Expressive Suppression**			
	Score >17	12	32	0.7006
	Score <17	11	25	

**chi square statistics, p value <0.05 considered significant at 95%, CI #N = 23, ^N = 57.*

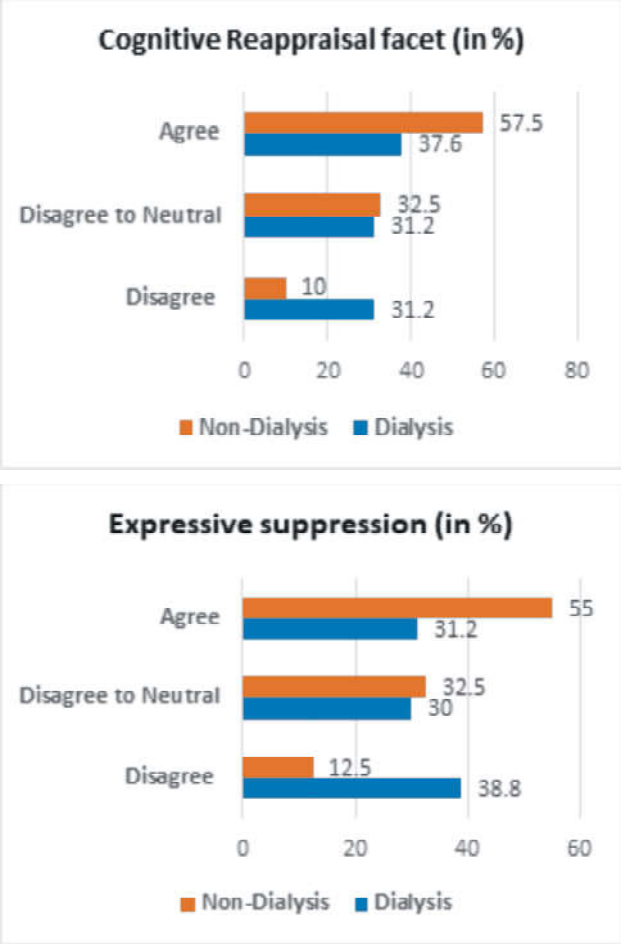

***Fig. 2:** Emotion regulation on emotion regulation questionnaire scale in dialysis and non-dialysis group.*

Discussion

The increase in life expectancy and aging populations have influenced the use of lifelong medications for chronic diseases. Unfortunately, almost half of the patients do not follow their prescribed drug regimens, leading to the frequent underestimation of the full benefits of these treatments. Clinical studies have revealed that people with acute illnesses are more likely to adhere to their medications compared to those with chronic conditions[13,14]. Effectively managing chronic illnesses such as CKD is crucial to minimise their impact, improve health outcomes, prevent further progression, and reduce healthcare costs[15,16]. Given the complexity of medication schedules and the varied behaviours related to treatment adherence, it is reasonable to expect a significant amount of non-adherence in CKD patients.

Non-adherence to treatment can stem from individual and evolving reasons, and attitudes towards following treatment plans may vary for different medications. CKD patients, whether on dialysis or not, often go through emotional disturbances that significantly impact their overall quality of life. These disturbances encompass various aspects such as mental, emotional, spiritual, social, physical, and financial concerns[18,17]. Existing literature has highlighted that non-adherence to medication regimens could be indicative of cognitive decline and emotional or psychological issues[5-10]. As a result, researchers have been increasingly focusing on studying emotion regulation in chronic diseases, recognising their potential impact on treatment non-adherence. It is crucial to address these factors in adherence interventions. There is a lack of high-quality research on this subject, which can present challenges for healthcare practitioners in implementing

effective non-adherence measures for their patients. This cross-sectional study aimed to provide insights into the extent of non-adherence and its correlation with various factors, including patient demographics, emotion regulation, in patients with and without haemodialysis.

Numerous studies have investigated the adherence to pharmacological treatments among individuals with or without maintenance haemodialysis[18-21]. These studies report a wide range of statistics depending on the specific aspect of drug therapy being addressed, but overall, they consistently reveal that poor drug adherence is prevalent among CKD patients. The significant disparities in low adherence rates can be attributed to several factors. Firstly, there is no consensus on the ideal percentage of non-adherence, as the definition of drug adherence often lacks clarity. Secondly, the methods used to measure drug adherence are not highly reliable and tend to overestimate adherence levels. The lack of user-friendly and accurate tools for monitoring drug adherence remains a major obstacle to making significant progress in addressing medication adherence challenges, and it also contributes to the clinical practice's insufficient attention to drug adherence. In this study, we selected the Morisky questionnaire because it is a reliable and widely used tool in numerous other research studies.

In the present study, results revealed that among patients undergoing dialysis, a majority of respondents (57.5%) displayed low adherence to medication regimens, while only a small percentage (3.8%) demonstrated good adherence based on the MMAS-8 scale. Among patients not receiving dialysis, more than one fourth (28.7%) showed low adherence, and only a minimal percentage (1.2%) exhibited good adherence using the same scale. Moreover, patients on dialysis tended to have a slightly higher average number of prescribed medications compared to those not on dialysis. The existing literature has demonstrated that estimates of medication non-adherence vary depending on the assessment method used. For CKD patients, non-adherence estimates ranged from 17% to 74%, while for hemodialysis patients, the range was from 3% to 80% in different studies [18,22,23]. This variability can be attributed to differences in how non-adherence is defined and measured across these studies.

Emotion regulation is a complex psychological process involving various strategies that individuals use to influence the emotions they experience, when they experience them, and how they express these emotions[24]. This process has implications for a wide range of psychological and physical outcomes related to disease management and treatment. Gross and John suggest two main strategies for down-regulating emotions: Cognitive reappraisal was described as the process of reinterpreting and reevaluating emotional responses to specific situations, which helps individuals effectively manage and cope with their emotions; and expressive suppression, on the other hand, involves controlling or concealing emotions by inhibiting emotional displays[11]. The study's findings indicated that patients not receiving dialysis demonstrated higher levels of emotion regulation and tended to employ cognitive reappraisal and expressive suppression more frequently or effectively compared to patients on dialysis. These results suggest that patients not undergoing dialysis may possess more effective emotion regulation strategies, as they appeared to be more adept at reevaluating their emotional responses and controlling their outward emotional expressions. Conversely, patients on dialysis may have encountered more challenges in managing their emotions, leading to lower scores in both cognitive reappraisal and expressive suppression.

The study revealed a high prevalence of medication-related problems, such as forgetting to take medications, discontinuing medications without informing doctors, and facing difficulties in adhering to medication regimens during travel or when feeling well. Similar findings have been consistently observed in other studies, highlighting that forgetfulness is a primary reason for non-adherence in patients with chronic diseases[25]. These responses highlight specific areas where targeted interventions and support can be employed to improve medication adherence in both patient groups.

Medication adherence is a complex issue influenced by various factors, including age, gender, education, employment status, pill burden (polypharmacy), and comorbidities[18]. These characteristics can vary significantly among individuals and may change over time, making it challenging to address non-adherence using a one-size-fits-all approach. The study findings suggested that certain factors, such as the presence of multiple co-morbidities might have some influence on treatment adherence among patients on dialysis. However, overall, the study revealed that adherence behavior was not significantly affected by factors like gender, age, education, employment status, pill burden, or emotion regulation strategies for both patient groups. These findings were consistent with another study conducted by[26]. These insights are valuable for healthcare professionals as they shed light on factors that may impact patient adherence and can help in designing targeted interventions to improve treatment compliance, particularly in the context of patients undergoing dialysis.

When interpreting the findings of this study, it is important to consider certain limitations. Firstly, the study did not identify specific drug classes or subclasses that may be associated with non-adherence to prescribed medications.

Secondly, the research was unable to analyse chemical indicators of non-adherence. Further investigations are needed to gain a comprehensive understanding of the factors and mechanisms influencing emotion regulation and psychological flexibility in individuals with CKD.

Despite these limitations, the current study conducted in patients undergoing maintenance haemodialysis in India contributes to advancing our understanding of this topic. There is a scarcity of studies that specifically address medication non-adherence among CKD patients, whether they are receiving dialysis or not. Therefore, these results provide valuable insights into the differences in emotion regulation strategies between patients on dialysis and those who are not. While more research is required to fill the gaps in knowledge, this study serves as an important step in examining the factors that may impact medication adherence in CKD patients undergoing dialysis.

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ORIGINAL ARTICLE

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Sepsis Outcome in Patients with Metabolic Syndrome and its Correlation to Procalcitonin and C-Reactive Protein

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Abstract

Background: Metabolic syndrome (MetS) is the emerging subject where people are more prone to illness due to varied causes. Sepsis is the most common cause of death in a hospitalised individual – more than myocardial infarction. In this study we will elicit the correlation of metabolic syndrome and its outcome in sepsis patients with reference to markers like C-Reactive Protein (CRP) and Procalcitonin (PCT). We aimed to assess outcome of patients in accordance with severity of sepsis in MetS and study its relationship with serum PCT and CRP levels.

Methods: This was a comparative, case-control study carried out between November 2014 and 2016. 140 subjects with definable sepsis were studied; 70 each with or without MetS. All of them were worked-up for MetS and also for sepsis markers like PCT and CRP.

Results: 50.7% patients belonged to the age group 51 - 70 years with male preponderance in the case group. 84.5% patients who had sepsis and MetS succumbed to their illness compared to the control group (15.9%). Higher the value of PCT in cases, higher was the mortality (88.2% vs 19.6%). The rate of organ dysfunction and SOFA scores was also higher (97.2%, 90.1% vs 52.2%, 46.4%) and (15.1 vs 10.3) respectively among the cases when compared to that of control group.

Conclusion: Patients with sepsis and MetS had higher mortality rates than individuals without MetS. Also the SOFA score among the cases was higher with increased PCT values and decreased duration of stay in hospital due to mortality.

Key words: Metabolic syndrome, Sepsis, Procalcitonin, CRP.

Introduction

Metabolic Syndrome (MetS) is emerging as a global epidemic; more than one quarter of the world's adult population is affected by it and with a steadily increasing presence in many countries. MetS is an inflammatory entity which combines obesity, dyslipidaemia, insulin resistance, and hypertension, albeit with incompletely understood mechanisms. Worldwide prevalence of MetS ranges from <10% to as much as 84%[1,2]. MetS is a state of chronic low grade inflammation as a consequence of complex interplay between genetic and environmental factors[3,4]. Sepsis is the most common cause of death in a hospitalised individual than myocardial infarction. It is defined and diagnosed by nonspecific alterations in physiology that would be amenable to specific interventions. The morbidity and mortality of patients in sepsis with MetS is higher. Sepsis and MetS are inter-related and are inflammation-related diseases where MetS can increase the risk of complications in sepsis[5]. CRP and PCT are a few of the many markers used in the diagnosis of sepsis and its severity.

CRP is designated as an acute phase reactant which is released in inflammatory states like rheumatoid arthritis and infection[6]. The CRP response is very non-specific and can never be used as a single diagnostic tool; however, it is very helpful in several disease states. Besides its use in the diagnosis and severity of sepsis, CRP has also been evaluated as a prognostic marker.

PCT is produced in response to pro-inflammatory stimuli, in particular by bacterial products[7], hence it is a perfect tool to differentiate between viral and bacterial infections, (e.g., Gendrel *et al* 1999)[8]. Patients with bacteraemia usually have significantly high PCT levels[9] and persistent increase or failure to decline in the PCT levels has been related to higher mortality rates in various studies[10].

In this study, we studied the correlation of MetS and its outcome in patients of sepsis with reference to the above mentioned markers. There have been some studies on MetS and its correlation to diabetes, hypertension, and other non-infectious diseases like COPD. However, there are not many studies that have looked at the intraction of infection and MetS. In this study we tried to assess the outcome of patients in accordance with severity of sepsis in MetS and to find its relationship with serum PCT and CRP levels.

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Material and Methods

This was a comparative, case-control study carried out over a period of two years between November 2014 and August 2016. Subjects with sepsis with MetS who were diagnosed as per the WHO criteria and were being treated for the same were enrolled. Controls included patients with sepsis without MetS. The proposed study sample size was 70 subjects and 70 controls. The sampling was done by simple random method. The detailed patient data was obtained and documented in a proforma which included detailed history, clinical examination. All individuals underwent biochemical tests like fasting venous blood sugar, fasting lipid profile, total leukocyte count, renal function and liver function tests, serum CRP, and serum PCT. Patients were included in the study if they gave informed consent, were greater than 18 years and met the criteria of sepsis and were included in the cases group of the study it they met criteria for MetS. Pregnant women, trauma cases, surgical cases, patients with cardiac shock and those who refused to give an informed consent were excluded from the study.

Statistical methods used in the study were chi square test. Mann-Whitney test was used as an alternative test to the independent sample t-test. Independent-samples T-test was used compare to means for two groups of cases. Kruskal-Wallis test was used. All the statistical calculations were done using SPSS for windows (Version 16.0).

Methods of collection of data: Individuals admitted to JSS Hospital's intensive care unit with sepsis with/without MetS were screened as per inclusion and exclusion criteria after obtaining their consent. All study subjects were subjected to a detailed clinical examination to see whether the individuals met the criteria of sepsis and assessed for vital parameters and SOFA score (Appendix 1). Examination for metabolic syndrome: Central obesity: waist girth ≥90 cm, dyslipidaemia: TG ≥1.7 mmol/L (150 mg/dL), HDL-C <40 mg/dL (male), <50 mg/dL (female), Blood pressure ≥140/90 mmHg (or treated for hypertension), fasting plasma glucose ≥6.1 mmol/L (110 mg/dL) was also done.

PCT was measured in Roche e411 Electrochemiluminescence (ECLIA) automated analyser using PCT kit from BRAHMS Diagnostica, Berlin, Germany. A value of PCT >0.5 ng/mL was taken as pathological, 0.5 to 2 ng/mL indicated that systemic infection could not be ruled-out, 2 to 10 ng/mL indicated greater chances of sepsis, and a value of PCT above 10 ng/mL indicated severe bacterial sepsis.

CRP was performed using immunoturbidimetric (Tina-quant CRP detection method; Roche Diagnostics Indianapolis) performed on a Hitachi 717 automated analyser.

Appendix 1

Sepsis criteria:

1. Fever (oral temperature >38° C [>100.4° F]) or hypotharmia (<36° C [<96.8° F]).
2. Tachypnoea (>24 breaths/min).
3. Tachycardia (heart rate >90 beats/min).
4. Leukocytosis (>12,000/μL), leukopenia (<4,000/μL), or >10% bands.
5. Cardiovascular: Arterial systolic blood pressure ≥90 mmHg or mean arterial pressure ≥70 mmHg that responds to administration of IV fluids.
6. Renal: Urine output <0.5 mL/kg per hour for 1 h despite adequate fluid resuscitation.
7. Respiratory: PaO_2/FIO_2 ≥250 or, if the lung is the only dysfunctional organ, ≥200.
8. Haematologic: Platelet count <80,000/μL or 50% decrease in platelet count from highest value recorded over previous 3 days.

Results

140 patients who participated in this study were between the age group 30 to 80 years with highest percentage of individuals of MetS being in the age group of 51 - 70 years (50.7%). Among 140 patients, 61 were females and 79 were males. When correlated to MetS, there was male preponderance (54.9% vs 45.1%).

Of total 140 cases, most patients were diagnosed to have bronchopneumonia with sepsis, followed by urinary tract infection and acute febrile illnesses (22.8%,22.1% and 20% respectively). The mean leukocyte count among individuals with MetS was 17,446 cells/cumm with a standard deviation of 8,182 which was higher when compared to the mean of individuals without MetS ($p < 0.001$). The mean SOFA Score among individuals with MetS was higher when compared to individuals without MetS (15.1 vs 10.3, $p < 0.001$) Table I. We noted that patients with MetS had a higher percentage of renal and hepatic derangement (97.2%,90.1% vs 52.2%, 46.4%), which was statistically significant.

In the present study, the mean and median PCT among individuals with MetS was much higher than individuals without MetS (68.13 ng/mL and 72.00 ng/mL, *versus* 24.11 and 20.00 respectively). When C-reactive protein was compared in individuals between the two groups, the mean values were found to be 79.99 mg/L and 80.24 mg/L respectively which was statistically significant ($p = 0.015$).

When duration of hospital stay was taken into consideration, the mean value of individuals without MetS was 9.51 days with a standard deviation of 4.66 days, and was higher than in the patients with MetS (4.55 days, SD 4.00 days, p <0.001) as there were more deaths among this group (Table II).

With respect to outcome, the percentage of patients without MetS who improved was higher (84.1% vs 11.3%) and mortality was higher (84.5 vs 15.9% p <0.0001) in the MetS group (Table III).

Table I: Total leukocyte count and SOFA score in correlation to metabolic syndrome.

	Without Metabolic Syndrome	With Metabolic Syndrome
Mean	**Mean (SD)**	**Mean (SD)**
Total Leukocyte Count/mm^3	12652 (5847)	17446 (8182)
SOFA Score	10.3 (2.5)	15.1 (3.6)

Table II: Correlation of procalcitonin, C-reactive protein, duration of hospital stay.

	Without Metabolic Syndrome			With Metabolic Syndrome			P value
	Mean	**SD**	**Median**	**Mean**	**SD**	**Median**	
PCT (ng/mL)	24.11	18.67	20.00	68.13	36.92	72.00	**<0.001**
CRP (mg/L)	79.99	38.37	75.00	80.24	61.43	54.00	**0.015**
Duration of stay in hospital (days)	9.51	4.66	10.00	4.78	4.55	4.00	**<0.001**

Table III: Correlation of outcome in the study.

		Without Metabolic Syndrome		With Metabolic Syndrome	
		Number of patients	**Percentage of patients**	**Number of patients**	**Percentage of patients**
Outcome	Improved	58	84.1%	8	11.3%
	DAMA*	0	.0%	3	4.2%
	Death	12	15.9%	59	84.5%

*P <0.0001, *Discharge Against Medical Advice.*

High CRP values, among people who died, were observed in 49 individuals with MetS (84.5%) and 53 patients with high CRP values (84.1%) improved (non-significant p value). But PCT values in individuals with MetS who succumbed were higher compared to those who improved with high PCT levels in the control group with percentage of 88.2% and 80.4% respectively (p <0.0001) (Table IV). The median SOFA score among individuals with MetS was higher (16) compared to those individuals without MetS (12.0) Table V.

Table IV: Correlation of outcome in CRP and PCT with metabolic syndrome.

			Without Metabolic Syndrome			With Metabolic Syndrome		
			Improved	**DAMA**	**Death**	**Improved**	**DAMA**	**Death**
CRP	Normal	No. of patients	5	0	1	1	1	11
		%	83.3	0	16.7	7.7	7.7	84.6
	High	No. of patients	53	0	10	7	2	49
		%	84.1	0	15.9	12.1	3.4	84.5
	p value			0.9			0.7	
PCT	Normal	No. of patients	17	0	1	3	0	0
		%	94.4	0	5.6	100	0	0
	High	No. of patients	41	0	10	5	3	60
		%	80.4	0	19.6	7.4	4.4	88.2
	p value			0.2			**<0.0001**	

Table V: Correlation of SOFA score with metabolic syndrome in relation to outcome.

		SOFA Score	
			Median
Without Metabolic Syndrome	Outcome	Improved	10.0
		DAMA	.
		Death	12.0
With Metabolic Syndrome	Outcome	Improved	11.5
		DAMA	16.0
		Death	16.0

When the diagnosis of sepsis and outcome of the patients were correlated with MetS, we found that mortality was significantly elevated in patients with MetS and the number of patients improved was higher in the control group.

Discussion

MetS and Sepsis represent an inter-related escalating disease burden for modern healthcare systems. The

association between them is related to their inflammatory link. Sepsis is an acute inflammatory reaction which recruits several systems, whereas in MetS, inflammation is chronic and subclinical, without the classic clinical inflammatory manifestation. There are no studies correlating sepsis in MetS; most of the studies are done on outcome of patients with obesity in critical illness.

This study attempts to relate the severity of sepsis to increased morbidity and mortality in patients with MetS, apart from other known risk factors. The subjects in the study with sepsis and MetS were comparatively older than those in the control group (sepsis without MetS).

Similar to our study, Shastri *et al*[11], showed that TLC was higher in patients with MetS with statistically significant difference ($p < 0.0001$). Thus, TLC in obese patients of MetS can be used as a predictor for future complications.

Procalcitonin (PCT) has the highest diagnostic accuracy. It is also useful for monitoring the course and severity of the systemic inflammation. Meisner *et al*[12] found that higher SOFA score levels were associated with significantly higher PCT plasma concentrations whereas CRP was elevated irrespective of the scores observed which was in contrary to the present study. In a study by Castelli[13], PCT and CRP concentrations were higher in patients in whom infection was diagnosed at comparable levels of organ dysfunction although correlation with the SOFA score was weak.

The PCT was elevated in about 119 individuals with a maximum percentage of individuals among cases, of sepsis with MetS resulting to 88.2% among individuals who died and this was backed by a study done by Balci *et al*[14].

In this study we found that patients with MetS admitted with sepsis had higher mortality (84.5%) compared to those without MetS ($p < 0.0001$). A study done by Olivgeris *et al*[15] also showed increased mortality among obese ICU patients (76.3% versus 43.7%; $P = 0.001$).

Sepsis is the leading cause of death in hospitals despite the structured approaches. Additionally, MetS increases the risk for complications of sepsis, likely relating in part to the maladaptive cardiometabolic alterations. Of a total of 140 cases, most of the patients were diagnosed to have bronchopneumonia with sepsis, followed by urinary tract infection and acute febrile illnesses, occupying a percentage of 22.8%, 22.1% and 20% respectively. Among them, patients with urinary tract infection and bronchopneumonia with MetS had higher mortality compared to the control group, reason for which is beyond the scope of this article.

Our results indicate that PCT concentrations are associated with the severity of MODS as assessed by the SOFA score. These results are in general agreement with studies in which PCT levels were compared with the severity of sepsis by sepsis-related score systems. PCT has several advantages in severely ill patients compared with CRP. The most striking one demonstrated in this study, is the enormous range of PCT reactivity resulting in a marked increase in PCT plasma levels, especially during severe stages of sepsis and systemic inflammation. In contrast, CRP levels are often found to be already increased to maximal concentrations in patients with low SOFA scores. Thus, CRP cannot provide information as to further increases in organ dysfunction and the inflammatory progress respectively. Further advantages of PCT are its more rapid kinetics; PCT reacts faster than CRP both during an increase or decrease of inflammation. Novel scientific tools are being sought for insights into underlying biological mechanisms, with impressive attempts at new therapies. Increasing understanding of the inflammatory cascade has given new insights and provided several markers that, in conjunction with other manifestations of sepsis, can be useful indicators of infection.

To conclude, the mortality and morbidity along with multiorgan dysfunction is higher among individuals with sepsis and MetS than in individuals without MetS. PCT is a better marker of sepsis than CRP in predicting outcome of sepsis.

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MEDICAL COUNCIL OF INDIA (MCI) GUIDELINES FOR AUTHORS

As per MCI guidelines updated on 12th February 2020, credit for publication(s) is given to the first three authors or the corresponding author. Henceforth, it will now be mandatory to indicate the name of the correspoding author in every submission to the JIACM.

The name of the corresponding author with his/her affiliation, address, telephone number, and E-mail ID must be indicated separately in the title page of the submitted manuscript.

ORIGINAL ARTICLE

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Efficacy of a Cardiac Rehabilitation Initiative Guided by Nursing Professionals on the Quality of Life among CABG Patients at Tertiary Care Hospitals in Delhi

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Abstract

Introduction: Cardiovascular diseases are a global health concern, with CABG as a crucial intervention. This article explores the often-overlooked role of nursing professionals in cardiac rehabilitation conducted in Delhi, India.

Methodology: In our study, we employed a one-group pre-test, post-test design to assess the impact of nursing-led cardiac rehabilitation on the quality of life (QoL) of CABG at a tertiary care hospital in Delhi. Purposive sampling technique was used. Data collection involved pre- and post-operative QoL assessments using the WHO BREF tool, along with demographic, lifestyle, and physiological data. The rehabilitation programme, spanning three months and guided by experienced nursing professionals, included patient education and telephonic support. Data analysis, adhering to ethical standards, showed significant QoL changes ($p < 0.05$).

Results: In our study involving 66 patients, a significant enhancement in quality of life (QoL) scores was observed after a 3-month cardiac rehabilitation programme ($p < 0.001$), spanning physical, psychological, social, and environmental domains ($p < 0.001$). Notably, QoL scores were positively associated with patients' education levels ($p < 0.013$) and the type of treatment received, favouring medication ($p < 0.045$). Physiological parameters exhibited significant improvements including weight loss, reduced BMI, enhanced ejection fraction percentage, lowered systolic blood pressure, and favourable changes in lipid profiles and fasting blood sugar levels (all p-values < 0.001).

Conclusion: Our study demonstrates the substantial positive impact of nursing-led cardiac rehabilitation initiative on the quality of life and health outcomes of elective CABG patients.

Key words: Cardiac rehabilitation programme, cardiac rehabilitation initiative, CAD, quality of life, CABG.

Introduction

Cardiovascular diseases (CVDs) continue to be a global health challenge, contributing significantly to morbidity and mortality rates worldwide. Projections indicate that by the year 2020, cardiovascular diseases are expected to emerge as the predominant contributor to global disability. These conditions are responsible for a significant proportion of mortality, accounting for approximately 10% of deaths among individuals under the age of 35, about one-third of fatalities in the age group of 35 to 45 years, and a substantial three-quarters of deaths among those aged 45 and older[1,2]. Among the various interventions employed for the management of CVDs, Coronary Artery Bypass Grafting (CABG) stands as a critical surgical procedure, often recommended for individuals with complex coronary artery disease[3,4]. While CABG offers a lifeline to patients by restoring blood flow to the heart muscle, post-operative rehabilitation and the improvement of patients' quality of life (QoL) remain paramount considerations in their overall journey towards recovery.

Background

The significance of enhancing the QoL in post-CABG patients cannot be overstated. Impaired QoL can lead to diminished physical and psychological well-being, affecting not only the patients themselves but also their families and society at large. In response to this critical concern, numerous cardiac rehabilitation programmes have been developed worldwide, aiming to optimise patients' recovery following CABG. These programmes typically involve a multidisciplinary approach, with healthcare professionals playing pivotal roles in providing comprehensive care and support[5-7].

In the dynamic healthcare landscape of India, particularly in the bustling metropolis of Delhi, where the prevalence of CVDs is notably high, the role of nursing professionals in cardiac rehabilitation has been gaining prominence. Nursing

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professionals, with their expertise in patient care and close involvement in the recovery process, have the potential to influence the outcomes and QoL of CABG patients significantly[8-10]. However, there exists a notable gap in research assessing the specific impact of cardiac rehabilitation programmes guided by nursing professionals on the QoL of CABG patients within the Indian context.

While research on cardiac rehabilitation post-CABG is extensive, studies conducted within the Indian context, and particularly in tertiary care hospitals in Delhi, have been relatively limited, with most focusing on the roles of physicians and physiotherapists. The specific contributions of nursing professionals, who are often at the forefront of patient care, remain underexplored in this context. This research gap is particularly relevant as nursing professionals can play a pivotal role in addressing the unique socio-cultural factors, patient preferences, and healthcare challenges prevalent in Delhi's healthcare system.

Furthermore, existing research on the efficacy of cardiac rehabilitation programmes often lacks comprehensive evaluation of patient-reported outcomes, especially QoL measures. As QoL is an essential determinant of overall recovery and well-being, understanding how nursing-guided cardiac rehabilitation influences these outcomes becomes imperative.

This research endeavours to bridge this gap by investigating the efficacy of a cardiac rehabilitation initiative led by nursing professionals on the QoL among CABG patients in tertiary care hospitals in Delhi. By shedding light on the contributions of nursing professionals in cardiac rehabilitation, this study aims to inform healthcare practices and policies, potentially leading to improved patient outcomes and better QoL in this vulnerable patient population.

Methodology

A one-group pre-test, post-test research design was employed to measure the outcome variable (quality of life) both before and after the intervention to assess any changes at 3-months intervals for patients who were planned for elective CABG. It was conducted at Dr. Ram Manohar Lohia Hospital, a prominent tertiary care hospital in Delhi known for its cardiac care services. The hospital provided a suitable environment for conducting this research due to its diverse patient population and established cardiac care facilities.

Ethical approval was obtained from the institutional ethics committee. Informed consent was obtained from all participants, ensuring their voluntary participation and confidentiality of their data. Participants were informed about their right to withdraw from the study at any time without consequences.

This study targeted a sample size of 66 patients who were planned for elective CABG admitted to Dr RML Hospital. Participants were selected using purposive sampling, ensuring they met the inclusion criteria which included adults aged 18 years or above, able to communicate in Hindi or English, willing to participate in the cardiac rehabilitation initiative and planned for elective CABG. All those who had left ventricular ejection fraction less than 30%, were on ventricular assistive devices and uncontrolled diabetes mellitus, preoperative intensive stay and post procedure who developed hypotension/hypoperfusion, ventilator support (>72 hours), post operative CPR, reopening of chest, any physical disability leading to inability to perform physical activity, severe cognitive impairment, and those who had attended any kind of cardiac rehabilitation programme in the past were excluded from the study.

Pre-test assessment was done before the cardiac rehabilitation initiative began; demographic data, baseline data on lifestyle, dietary, physiological and biochemical parameters and quality of life were collected using standardised WHO BREF assessment tool on the day of hospitalisation before the CABG procedure. This was followed by patient education about cardiovascular diseases, CAD, function of heart, CABG surgery, importance of self care, instruction to be followed after discharge from hospital, lifestyle modification, dietary advices, exercises backed by voice over video and importance of cardiac rehabilitation. Thereafter, return demonstration and handholding till desired proficiency was achieved. On 3rd day post-procedure, patients were encouraged to do breathing exercises followed by the care of incision site, and signs of wound infection were taught and counselling about lifestyle modification which included dietary, lipid, weight, and risk factor management, follow-up, medication adherence and reinforcement of exercise programme was done on a one-to-one basis. Individualised discharge counselling, clarification of doubts and reinforcement in order to ensure regular implementation of the cardiac rehabilitation initiative, and a booklet along with activity log sheet was given to patients for easy reference and to maintain the record of the exercise done every day.

After hospital discharge, telephonic support was provided on a weekly basis to reinforce various aspects of health management, including dietary control, lipid management, alcohol and smoking cessation, stress reduction, blood pressure regulation, regular physical activity, and medication adherence. 3 months after CABG, physiological and biochemical parameters were measured again and the same quality-of-life assessment tools used in the pre-test were

administered to the participants to measure changes in their quality of life. Nursing professionals with expertise in cardiac care guided and supervised the rehabilitation initiative. The programme spanned over a period of 3 months.

The WHOQOL BREF tool was employed to evaluate the quality of life in patients both before the procedure and three months after the procedure. This assessment encompassed four key domains: physical health, psychological well-being, social relationships, and environmental factors. These domains included a total of 24 facets related to the quality of life. The scoring system ranged from 1 to 5, with a reverse scale (5 to 1) for negatively phrased items. To standardise the scores and make them comparable with the WHOQOL-100, a preliminary transformation was applied to the raw scores. This transformation method converted the scores to a range between 4 - 20. In this range, a higher score indicated a higher quality-of-life. Each domain had a maximum score of 20, and the mean score of items within each domain was used to calculate the domain score. These domain scores were scaled positively, where a higher score denoted a higher quality of life.

Data collection commenced from May 2022 and continued until the completion of the 3-month cardiac rehabilitation initiative. In the present study, past smoking, tobacco use, and alcohol intake was defined if the patient had ceased taking them for the past six months. The data were checked, coded, and entered into Microsoft excel sheet and exported to SPSS Version 26 for analysis, cleaned and checked for outliers and completeness. Descriptive statistics were used to summarise the demographic characteristics of participants. Frequencies, and percentages, were computed. Paired-sample t-tests and ANOVA tests were employed to compare pre-test and post-test scores on quality-of-life measures. Statistical significance was set at $p < 0.05$.

Result

The study involved a total of 66 patients, with 6 patients having been lost to follow-up during the course of the study. The mean age of study participants was 51 to 60 years with male predominance. The majority of patients were Hindu, married, stayed in nuclear families, had education up to the primary school level, were skilled workers, and belonged to the upper lower class. The majority of them had been past smokers, and 25% of participants had a family history of CAD (Table I).

There was a significant improvement in the quality-of-life score after administration of the cardiac rehabilitation initiative at 3-month intervals, with a change in mean score from 40.63 ± 7.13 to 84.13 ± 5.66 ($p < 0.001$) (Table II). Quality-of-life domain-wise analysis revealed significant improvement in the post-test physical, psychological, social, and environmental domains of quality-of-life, with scores of 15.48 ± 0.93, 14.97 ± 1.34, 9.40 ± 1.90, and 10.12 ± 1.68, respectively, ($p < 0.001$) (Table III).

Table I: Frequency and percentage distribution of socio-demographic characteristics of CABG patients N = 60.

S. No.	Variables	Frequency	Percentage (%)
1.	Age in Years		
	Below 40	3	(5%)
	41 - 50	8	(13.3%)
	51 - 60	23	(38.3%)
	Above 60	26	(43.3%)
2.	Gender		
	Male	53	(88.3%)
	Female	7	(11.7%)
3.	Religion		
	Hindu	50	(83.3%)
	Muslim	5	(8.3%)
	Christian	0	(0%)
	Sikh	5	(8.3%)
4.	Marital Status		
	Single	1	(1.7%)
	Married	59	(98.3%)
5.	Type of Family		
	Joint family	27	(45%)
	Nuclear family	33	(55%)
6.	Education of the patient		
	Profession	5	(8.3%)
	Honours Graduate	7	(11.7%)
	Intermediate or Diploma	3	(5.0%)
	High school certificate	17	(28.3%)
	Middle school certificate	14	(23.3%)
	Primary school certificate	11	(18.3%)
	Illiterate	3	(5.0%)
7.	Occupation of the patient		
	Unemployed Legislators, Senior Officials and Managers	0	(0%)
	Professionals	3	(5.0%)
	Technicians and Associate Professionals	1	(1.7%)
	Clerks	0	(0%)

	Skilled Workers and Shop and Market Sales Workers	18	(30.0%)
	Skilled Agricultural and Fishery Workers	15	(25.0%)
	Craft and Related Trade Workers	1	(1.7%)
	Plant and Machine Operators and Assemblers	1	(1.7%)
	Elementary Occupation	5	(8.3%)
	Unemployed	16	(26.7%)
8.	Total monthly income		
	≥123,322	0	(0.0%)
	61,663-123,321	1	(1.7%)
	46,129-61,662	0	(0%)
	30,831-46,128	4	(6.7%)
	18,497-30,830	16	(26.7%)
	6,175-18,496	20	(33.3%)
	≤6,174	19	(31.7%)
9	Residence		
	Urban	35	(58.3%)
	Rural	25	(41.7%)
10	Smoking		
	Past	29	(48.3%)
	Current	2	(3.3%)
	Never	29	(48.3%)
11	Alcohol Intake		
	Past	28	(46.7%)
	Current	0	(0%)
	Never	32	(53.3%)
12	Tobacco use		
	Past	20	(33.3%)
	Current	2	(3.3%)
	Never	38	(63.3%)
13	Family history of CAD		
	Yes	18	(30.0%)
	No	42	(70.0%)
14	Type of investigation undergone		
	Angiography	0	(0%)
	Echocardiography	0	(0.0%)
	TMT	0	(0.0%)
	ECG	0	(0%)
	Echocardiography, ECG & Angiography	60	(100%)
15	Type of treatment undergone		
	Medication	57	(95.0%)
	Thrombolytic therapy	0	(0%)
	Coronary Angioplasty	2	(3.3%)
	Intra-coronary stent	1	(1.7%)
	Any other, specify	0	(0%)
16	Co-morbidity history		
	Diabetes mellitus	12	(20%)
	Hypertension	10	(16.7%)
	Diabetes mellitus and Hypertension	15	(25%)
	Bronchial asthma	0	(0%)
	Any other chronic illness	1	(1.7%)
	No co-morbidity history	22	(36.7%)
17	Dietary habits		
	Non-Vegetarian	35	(58.3%)
	Vegetarian	25	(41.7%)

Table II: Mixed method ANOVA to compare pre-test and post-test quality-of-life scores of CABG patients. (N = 60).

Time points #	Mean ± SD	Within Group Comparison 'F' value (p value)	Within subject 'F' value (p value)	Between subject 'F' value (p value)	Interaction Group*time 'F' value (p value)
1.	40.63 ± 7.13	F = 1730.847	F = 481.251	F = 140.722	F = 145.819
2.	84.13 ± 5.66	**p <0.001***	**p <0.001***	**p <0.001***	**p <0.001***

#Time points *1= Pre-test, 2 = Post-test (3 months), *Level of significance p <0.05*

Table III: Comparison of pre-test and post-test (3 months) quality-of-life domains of CABG patients. (N = 60).

QOL domains	Pre-test Mean ± SD	Post-test Mean ± SD	Test value	P value
Physical	4.75 ± 0.95	15.48 ± 0.93	2258.545	**<0.001***
Psychological	5.05 ± 1.80	14.97 ± 1.34	852.104	**<0.001***
Social	8.87 ± 2.49	9.40 ± 1.90	16.723	**<0.001***
Environmental	8.23 ± 2.00	10.12 ± 1.68	150.922	**<0.001***

*Repeated measures ANOVA test; *Level of significance P <0.05.*

A significant association was observed between the post-test quality-of-life score and the education level of patients (p <0.013). Furthermore, the analysis also unveiled that quality of life scores among CABG patients had a notable connection with the "Type of Treatment Undergone" (p <0.045). Specifically, patients who underwent "Medication" as a treatment option displayed higher quality of life scores in comparison to those who underwent other types of treatment. These findings imply that the choice of treatment, particularly medication, may have had a positive

impact on the quality-of-life of CABG patients in this study (Table IV). It is crucial to emphasize that all other variables and categories in Table IV, including age, gender, religion, marital status, and various lifestyle factors, did not exhibit a statistically significant association with the quality of life scores.

Table IV: Association of pre-test, post-test quality-of-life scores of CABG patients with selected variables N = 60.

Variable	Categories	Pre-test		Post-test	
		Test value	p-value	Test value	p-value
Age		0.020	0.830	0.077	0.402
Gender	Male	-0.173	0.059	-0.086	0.348
	Female				
Religion	Hindu	-0.124	0.179	-0.037	0.692
	Muslim				
	Christian				
	Sikh				
Marital status	Single	-0.090	0.328	-0.099	0.284
	Married				
Type of family	Joint family	-0.254	**0.005***	-0.047	0.613
	Nuclear family				
Education of the patient	Profession	-0.264	**0.004***	-0.226	**0.013***
	Honours Graduate				
	Intermediate or Diploma High school certificate				
	Middle school certificate				
	Primary school certificate Illiterate				
Occupation of the patient	Legislators, Senior	-0.135	0.143	-0.081	0.381
	Officials and Managers				
	Professional				
	Technicians and Associate Professionals				
	Clerks				
	Skilled Workers and Shop and Market Sales Workers				
	Skilled Agricultural and Fishery Workers				
	Craft and Related Trade Workers				
	Plant and Machine Operators and Assemblers				
	Elementary Occupation				
	Unemployed				
Total monthly income	≥123,322	-0.400	**<0.001***	-0.146	0.113
	61,663 - 123,321				
	46,129 - 61,662				
	30,831 - 46,128				
	18,497 - 30,830				
	6,175 - 18,496				
	≤6174				
Residence	Urban	0.050	0.589	-0.024	0.798
	Rural				
Smoking	Past	0.021	0.820	0.079	0.389
	Current				
	Never				
Alcohol Intake	Past	-0.062	0.502	-0.064	0.490
	Current				
	Never				
Tobacco use	Past	-0.111	0.227	0.011	0.907
	Current				
	Never				
Family history of CAD	Yes	-0.143	0.120	0.128	0.164
	No				
Type of investigation undergone	Angiography	-0.010	0.911	-0.139	0.131
	Echocardiography				
	TMT				
	ECG				
	Echocardiography, ECG and Angiography				
Type of treatment undergone	Medication	0.052	0.573	0.183	**0.045***
	Thrombolytic therapy				
	Coronary Angioplasty				
	Intra coronary stent				
	Any other, specify				
Co-morbidity history	Diabetes mellitus	-0.002	0.981	-0.092	0.320
	Hypertension				
	Diabetes mellitus and Hypertension				
	Bronchial asthma				
	Any other chronic illness				
	No comorbidity history				
Dietary habits	Non-Vegetarian	-0.038	0.677	0.077	0.404
	Vegetarian				

Paired t-test

Significant changes were observed in various physiological parameters following a 3-month intervention period. A highly significant decrease in weight (p - value <0.001) occurred, with values shifting from 64.61 ± 10.66 on day-1

to 59.11 ± 10.46 at the end of the 3-month period. Similarly, BMI exhibited a highly significant decrease (p - value <0.001), transitioning from 24.66 ± 5.11 Kg/m^2 on day-1 to 22.56 ± 4.95 Kg/m^2 after 3 months. Notably, ejection fraction percentage demonstrated a highly significant increase (p - value <0.001), rising from 43.10 ± 6.76% on day-1 to 59.13 ± 2.51% over the 3-month period. Systolic blood pressure also exhibited a highly significant decrease (p - value <0.001), declining from 127.32 ± 18.56 mmHg on day-1 to 116.92 ± 5.39 mmHg after 3 months (Table V).

Table V: Comparison of physiological parameters before and after the intervention N = 60.

Physiological	Mean ± SD					
parameters	**Day-1**	**Day-75**	**MD**	**SE_{MD}**	**'t' value**	**p- value**
Weight (Kgs)	64.61 ± 10.66	59.11 ± 10.46	5.49	0.12	47.01	**<0.001***
Height (cms)	162.54 ± 10.11	162.54 ± 10.11	0.00	–	–	–
BMI (Kg/m^2)	24.66 ± 5.11	22.56 ± 4.95	2.10	0.05	40.59	**<0.001***
Ejection Fraction (%)	43.10 ± 6.76	59.13 ± 2.51	-16.03	0.88	18.23	**<0.001***
Heart Rate (per minute)	76.28 ± 10.50	77.35 ± 5.18	-1.07	0.90	-1.18	0.241
Systolic BP (mmHg)	127.32 ± 18.56	116.92 ± 5.39	10.41	2.14	4.86	**<0.001***
Diastolic BP (mmHg)	76.81 ± 11.03	77.97 ± 13.10	-1.15	2.28	-0.51	0.615

A highly significant decrease in total cholesterol levels (p - value <0.001) was observed, with levels decreasing from 196.10 ± 20.56 mg/dL on day-1 to 149.13 ± 22.87 mg/dL after 3 months. Similarly, a highly significant decrease in LDL cholesterol levels (p - value <0.001) occurred, with levels going from 120.82 ± 14.05 mg/dL on day-1 to 92.97 ± 9.05 mg/dL after 3 months. Conversely, there was a highly significant increase in HDL cholesterol levels (p - value <0.001) from 34.47 ± 2.68 mg/dL on day-1 to 54.40 ± 3.52 mg/dL after 3 months. Additionally, there was a highly significant decrease in triglyceride levels (p - value <0.001) from 180.52 ± 28.62 mg/dL on day-1 to 144.02 ± 25.95 mg/dL after 3 months, and a significant decrease in fasting blood sugar levels (p - value <0.001) from 118.63 ± 36.40 mg/dL on day-1 to 100.98 ± 9.75 mg/dL after 3 months. (Table VI).These findings collectively indicate that the intervention had a significant and positive impact on these physiological and biochemical parameters during the study period as demonstrated by the statistically significant changes observed in the post-test following the 3-month intervention.

Table VI: Comparison of biochemical parameters before and after the intervention among CABG patients. (N = 60).

Biochemical	Mean ± SD					
parameters	**Day-1**	**Day-75**	**MD**	**SE_{MD}**	**'t' Value**	**p-value**
T Cholesterol (mg/dL)	196.10 ± 20.56	149.13 ± 22.87	46.97	2.96	15.87	**<0.001***
LDL Cholesterol (mg/dL)	120.82 ± 14.05	92.97 ± 9.05	27.85	1.72	16.18	**<0.001***
HDL Cholesterol (mg/dL)	34.47 ± 2.68	54.40 ± 3.52	-19.93	0.58	-34.62	**<0.001***
TRI (mg/dL)	180.52 ± 28.62	144.02 ± 25.95	36.50	3.02	12.07	**<0.001***
Fasting blood sugar (mg/dL)	118.63 ± 36.40	100.98 ± 9.75	17.65	4.01	4.40	**<0.001***

Discussion

The findings of this study present several significant insights into the management of coronary artery disease (CAD) and the impact of cardiac rehabilitation initiatives on CABG patients. We will delve into key aspects of the results, considering their clinical relevance, implications, and avenues for future research. Emerging economies, such as India, and middle-income countries in South East Asia, are grappling with a significant coronary artery disease (CAD) epidemic[11,12].

In our study, first and foremost, the substantial improvement in quality-of-life scores following the cardiac rehabilitation initiative is a noteworthy observation. The mean quality-of-life score increased significantly from baseline, emphasizing the effectiveness of such programmes in enhancing the overall well-being of CABG patients. This result aligns with previous research indicating that comprehensive rehabilitation, encompassing physical, psychological, social, and environmental dimensions is crucial for CAD patients' recovery and overall quality-of-life[13,14,15]. Moreira *et al* showed improvement in the physical domain only[16]. In another study that implemented a cardiac rehabilitation programme with an emphasis on psychological aspects and the quality-of-life of patients with coronary artery disease, there was an observed enhancement in their self-efficacy, self-regulation, and self-care abilities[5]. Our findings reinforce the importance of cardiac rehabilitation as an integral component of CAD management, echoing the recommendations of professional organisations and guidelines. A similar study conducted in Karachi found significant improvement in the physical and psychological domain but not in the social domain among younger

patients, and also shows a lower psychological score among female patients[17,18].

Of particular interest is the association between education level and quality-of-life scores. Our study-revealed that patients with lower education levels exhibited comparatively lower post-test quality-of-life scores. This observation highlights the need for tailored interventions to address the diverse educational backgrounds of CAD patients. Healthcare providers should consider educational disparities in designing and implementing rehabilitation programmes to ensure equitable access and outcomes. Future research in this area could further elucidate the specific needs of patients with varying educational backgrounds and guide the development of targeted interventions.

Furthermore, the connection between the type of treatment undergone and quality-of-life scores is intriguing. Patients who underwent medication-based treatment demonstrated higher quality-of-life scores compared to those who underwent other forms of treatment. While this finding suggests the potential benefits of medication-based approaches, it also raises questions about the interplay between treatment modalities and their impact on patients' well-being. Further investigations are warranted to explore the mechanisms underlying this association and to identify the optimal treatment strategies for different subsets of CAD patients.

Our study also revealed significant changes in various physiological parameters following a 3-month intervention period, reflecting substantial improvements in participants' health. Participants experienced a noticeable reduction in weight and BMI, suggesting successful weight management and a shift towards a healthier body composition. Ejection fraction percentage increased significantly, indicating improved heart function and cardiac output, potentially reducing the risk of cardiovascular diseases. The significant decrease in systolic blood pressure suggests improved regulation and the potential for a reduction in health issues related to hypertension. This finding aligns with results from other studies as well[6,19]. Another study revealed that engaging in physical activity represents a potent factor in enhancing both physical and psychosocial well-being, functional abilities, and overall health. These factors serve as robust markers of an individual's quality-of-life[7].

Total cholesterol and LDL cholesterol levels decreased significantly, while HDL cholesterol levels increased significantly. These changes in cholesterol profiles indicate a positive impact on lipid metabolism and heart health. Triglyceride levels and fasting blood sugar levels decreased significantly, suggesting potential benefits for metabolic health and a reduced risk of metabolic disorders. Similar findings from another study also revealed significant improvement in triglyceride levels compared to the control group[6].

In summary, our 3-month intervention demonstrated substantial improvements in various physiological parameters, pointing to enhanced overall health and potential implications for the prevention and management of chronic diseases. Further research is needed to delve into the mechanisms behind these improvements and to assess their long-term sustainability.

Implications: The implications of this study are multifaceted. Firstly, it underscores the pivotal role of cardiac rehabilitation programmes in enhancing the quality-of-life for individuals with coronary artery disease, emphasizing the importance of their integration into clinical practice and healthcare policy. The comprehensive nature of quality-of-life improvements, encompassing physical, psychological, social, and environmental domains, highlights the holistic impact of such initiatives. Secondly, the findings underscore the significance of tailored interventions, considering patients' education levels and treatment choices, as this customisation could yield more favourable outcomes. Beyond clinical practice, these results call for further research efforts, particularly studies with control groups, diverse populations, and objective measures, to strengthen the evidence base and refine the strategies for managing coronary artery disease. Overall, this study contributes to the broader understanding of cardiac rehabilitation and its potential to improve the well-being of CAD patients, both clinically and beyond.

Limitations: This study acknowledges several limitations. First, the absence of a control group restricts our ability to establish causal relationships between the cardiac rehabilitation initiative and the observed improvements. Additionally, the predominantly male and age-restricted sample may limit the generalisability of the findings to broader CAD patient populations. Moreover, reliance on self-reported data introduces potential biases, such as response bias. These limitations emphasize the need for caution in interpreting the results and call for further research with more diverse samples, objective measures, and controlled study designs to strengthen the evidence base for cardiac rehabilitation interventions.

Conclusion

This study demonstrates the profound positive effects of a cardiac rehabilitation initiative on the quality-of-life and various physiological and biochemical parameters in patients with coronary artery disease. The comprehensive enhancements in quality-of-life, encompassing physical,

psychological, social, and environmental domains, underscore the holistic benefits of cardiac rehabilitation. Furthermore, the findings emphasize the importance of individualised treatment plans, considering patients' education levels and treatment choices, in optimizing outcomes. While this research provides valuable insights, the absence of a control group and the specific demographic characteristics of the sample warrant further investigation. Nonetheless, the results underscore the pivotal role of cardiac rehabilitation in improving the well-being of CAD patients and highlight the necessity of broader integration of such programmes into clinical practice and healthcare policy.

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ORIGINAL ARTICLE

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Assessment of Determinants Affecting Treatment Outcomes in Rifampicin Sensitive Pulmonary Tuberculosis-HIV Co-infected Patients

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Introduction

Although there have been rapid advances in medical science and technology, Tuberculosis (TB) continues to remain an important public health problem with crippling and alarming figures for morbidity and mortality worldwide, but more in the developing and underdeveloped countries[1].

Human immunodeficiency virus (HIV) leads to immunosuppression, pre-disposing patients to other infections, which ultimately prove to be fatal. One of the life-threatening infections in HIV/AIDS patients is Tuberculosis which is more common, more virulent and more deadly in HIV patients, compared to an immune-competent individual[2].

There are still a large number of people living with HIV (PLHIV) who have tuberculosis but are undiagnosed due to atypical symptoms and signs and low bacillary load. It is critical to bridge this gap. Since TB variably affects PLHIV, it is crucial to have an appropriate prevention programme, earlier diagnosis and adequate treatment[2].

As per the latest India TB report, globally the incidence of HIV positive TB cases was approximately 7,03,000 (6,33,000 - 7,76,000), mortality was 1,87,000 (1,58,000 - 2,18,000). In India, the incidence was 54,000 (46,000 - 63,000), and mortality was 11,000 (9,900 - 13,000)[3].

Even though HIV prevalence among incident cases of TB is low in India when compared to the global prevalence of 12.6%, TB-HIV co-infected patients in absolute numbers are vast. Such numbers give rise to a large number of deaths, and transmissible cases, and a considerable burden on the existing healthcare system[4].

HIV-TB co-infection does not have a good prognosis. HIV itself poses a serious threat for developing drug-resistant TB, which has a poor outcome and HIV infection debilitates the patient further, reducing compliance to antitubercular treatment (ATT).

This study was designed to assess the treatment outcomes in HIV-TB patients who are not drug resistant and to evaluate any possible factors that may be significantly associated with these treatment outcomes.

Material and Methods

Study design

An observational, prospective study was conducted among rifampicin sensitive pulmonary tuberculosis-HIV co-infected OPD and indoor patients who met the inclusion and exclusion criteria at Rajan Babu Institute for Pulmonary Medicine and Tuberculosis (RBIPMT), GTB Nagar, Delhi and attached Integrated Counselling and testing centre (ICTC) from 1st September 2017 to 30 September 2018, and followed-up till completion of the treatment.

Sample size

The average number of HIV-TB patients who were started on ATT at RBIPMT OPD and attached ICTC over the last year was 22, with a prevalence of 2%[5].

Sample size was calculated by the formula-

$N = 4pq/d^2$

p = prevalence from previous studies or expected prevalence.

q = 1-p

d = allowable error (5 - 20% of p) (0.5).

For this study, p = 0.02, thus q = 1-0.02 = 0.98

Allowable error d was taken as 8% of 0.5

Thus, sample size was 49.

Considering, the prevalence of extra-pulmonary TB cases, multidrug resistant tuberculosis cases and lost to follow-up cases, the sample size was taken as 30.

Inclusion criteria

1. All HIV positive – rifampicin sensitive TB co-infected

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patients.

2. All patients who gave written consent and were willing to follow-up up till completion of TB treatment.

Exclusion criteria

1. Any drug resistance.
2. Extra-pulmonary TB.
3. Age less than 14 years.
4. Diabetes mellitus.
5. Pregnancy.

Consent and Ethical consideration

The study was conducted with approval from the Institutional Human Ethics Committee. Every consecutive patient was included in the study after obtaining an informed, written consent.

Material and Methods

Demographic history and symptoms of the patients were noted, along with their weight at baseline. Patients were followed-up till the end of intensive phase (IP), 2 months into continuation phase (CP), and at end of treatment for:

1. Improvement or same/worsening of symptoms.
2. Change in weight.
3. Sputum smear status.

At the end of the study, patients were divided into various groups based on possible treatment outcomes[2] and compared for possible significant factors.

Statistical Analysis

SPSS version 18.0 software was used to analyse descriptive studies. If data was skewed, continuous variables were presented as mean (SD) or median. Chi-squared test was used to compare nominal categorical data between the groups. P value < 0.05 was considered as a statistical significant difference.

Results

A total of 54 patients included in the study, were divided into two groups; group A who had successful outcomes included 35 patients and group B comprised of 19 patients who had unsuccessful outcomes (lost to follow-up, treatment failure and death).

Most patients 24 (44.4%) were in the age group of 30 - 40 years. 44 (81.5%) were male and 10 (18.5%) were female.

Out of total 54 patients who were enrolled at the beginning of study, 4 patients were lost to follow-up. So, further analysis was done on 50 patients. Out of 50, six patients died before the first follow-up at end of IP. Out of the 44 remaining three patients died before the second follow-up at mid CP. Out of 41 patients remaining, 1 patient died before the final follow-up at end of CP.

As shown in Table I, weight was increased in 59.1%, 61%, and 62.5% patients at end IP, mid CP, at end of CP respectively. There was a significant association of increase in weight with successful outcomes at end IP.

Table I: Comparison of weight (kg) between the groups at each follow-up compared to baseline.

Weight (kg) at each follow-up	No. of patients N = 54	Group A	Group B	p-value
	No. (%)	No. (%)	No. (%)	
At the end of IP	N = 44	35	9	
Reduced or same	18 (40.9%)	10 (55.6%)	8 (44.4%)	**0.001**
Increased	26 (59.1%)	25 (96.2%)	1 (3.8%)	
At mid CP	N = 41	35	6	
Reduced or same	16 (39%)	10 (62.5%)	6 (37.5%)	Not applicable
Increased	25 (61%)	25 (100%)	0	
At the end of treatment	N = 40	35	5	
Reduced or same	15 (37.5%)	10 (66.7%)	5 (33.3%)	Not applicable

As shown in Table II there was significant association of improvement of symptoms at end IP and mid CP with successful outcomes.

Table II: Comparison of symptoms between the groups at each follow-up compared to baseline.

Symptoms at each follow-up	No. of patients N = 54	Group A	Group B	p value
	No. (%)	No. (%)	No. (%)	
At the end of IP	N = 44	35	9	
Improved	22 (50%)	21 (95.5%)	1 (4.5%)	**0.008**
Same or worsen	22 (50%)	14 (63.6%)	8 (36.4%)	
At mid CP	N = 41	35	6	
Improved	33 (80.5%)	32 (97%)	1 (3%)	**0.00002**
Same or worsen	8 (19.5%)	3 (37.5%)	5 (62.5%)	
At the end of treatment	N = 40	35	5	
Improved	35 (87.5%)	35 (100%)	0	Not applicable
Same or worsen	5 (12.5%)	0	5 (100%)	
Increased	25 (62.5%)	25 (100%)	0	

There was a significant association of (reduced/same)

weight and sputum smear positive status at end of IP with unsuccessful outcomes (Table III).

Table III: Comparison of (reduced/same) weight and sputum smear positive status between the groups at each follow-up.

(Reduced/same) Weight (kg) and sputum smear positive status at each follow-up	No. of patients N = 54	Group A	Group B	p value
	No. (%)	No. (%)	No. (%)	
At the end of IP	N = 44	35	9	
Present	11 (25%)	3 (27.3%)	8 (72.7%)	**0.000001**
Absent	33 (75%)	32 (97%)	1 (3.0%)	
At mid CP	N = 41	35	6	
Present	4 (9.8%)	0	4 (100%)	Not applicable
Absent	37 (90.2%)	35 (94.6%)	2 (5.4%)	
At the end of treatment	N = 40	35	5	
Present	5 (12.5%)	0	5 (100%)	Not applicable
Absent	35 (87.5%)	35 (100%)	0	

In this study, there was a significant association of (reduced/same) weight and symptoms of patients (worsened/same) at the end of IP and mid CP with unsuccessful outcomes (Table IV).

Table IV: Comparison of reduced/same weight and worsened/same symptoms of patients between the groups at each follow-up.

(Reduced/ same) Weight(kg) and symptoms of patients (worsened/ same) at each follow-up	No. of patients N = 54	Group A	Group B	p value
	No. (%)	No. (%)	No. (%)	
At the end of IP	N = 44	35	9	
Present	14	6	8	**0.00003**
Absent	30	29	1	
At mid CP	N = 41	35	6	
Present	6	1	5	**0.0001**
Absent	35	34	1	
At the end of treatment	N = 40	35	5	
Present	5	0	5	Not applicable
Absent	35	35	0	

There was a significant association of sputum positive status and symptoms of patients (worsened/same) at end of IP (first follow-up) with unsuccessful outcomes (Table V).

Table V: Comparison of sputum positive status and worsened/same symptoms of patients between the groups at each follow-up.

Sputum positive status and symptoms of patients (worsened/same) at each follow-up	No. of patients N = 54	Group A	Group B	p value
At the end of IP	N = 44	35	9	
Present	15	7	8	**0.00010**
Absent	29	28	1	
At mid CP	N = 41	35	6	
Present	4	0	4	Not applicable
Absent	37	35	2	
At the end of treatment	N = 40	35	5	
Present	5	0	5	Not applicable
Absent	35	35	0	

Discussion

Current trends indicate an increased mortality for HIV positive patients developing multi drug resistant-TB. But there remains an unanswered question regarding the outcome of HIV positive patients with drug sensitive TB taking proper ATT.

It is seen that HIV-TB co-infection is an important public health problem, with poor prognosis; also, HIV is an independent risk factor for drug resistant- TB, which has a uniformly poor prognosis; and HIV is a risk factor for default to treatment[6].

This study was conducted to evaluate the effects of factors at the end of intensive phase, 2 months into continuation phase and end of continuation phase on treatment outcomes of rifampicin sensitive pulmonary TB-HIV co-infected patients under RNTCP.

In this study successful outcomes were seen in 64.8% of patients and unsuccessful outcomes in 35.2% patients. 75.9% patients were less than 40 years of age. 44 patients were male and 10 patients were female. In the study done by Kamath *et al*, HIV-TB co-infection was present in 61.3% patients in age group 31 - 45 years, and 75.3% among males, similar to our study[7].

Follow-up: Out of total 54 patients who were enrolled, 4 patients were lost to follow-up. 6 patients died before the first follow-up at end IP and 3 patients died before the second follow-up at mid CP and 1 patient expired before the final follow-up at end CP.

Comparison of different parameters at all the follow-up: On comparison of weight between the groups across the time period of follow-up, weight was increased in

59.1%, 61%, and 62.5% patients at end IP, mid CP and at the end of treatment, respectively. There was a significant association (p value = 0.001) of increase in weight at end IP with successful outcomes. Montalvo *et al* stated in their study that TB-HIV co-infected patients who died during TB treatment lost weight ($p < 0.001$) while who survived, gained weight ($p < 0.001$)[8].

Wasting occurs frequently during HIV infection and increases with disease progression. As malnutrition is common among HIV-infected individuals, especially where there is co-infection with TB, bioimpedance analysis might be a good approach to prevent deaths among patients with the TB-HIV co-infection[8].

According to our study, there was a significant association of improvement in symptoms at end IP (p value = 0.008) and mid CP (p value = 0.00002) with successful outcomes.

In our study, sputum smear was negative in majority of patients at all the follow-ups. There was a significant (p = 0.00009) association of negative sputum smear at mid CP with successful outcomes.

In a study by Tweya *et al*, there was poorer TB treatment outcome in fifty six per cent patients who had sputum smear positive PTB-HIV co-infection adjusting for gender, age and year of TB registration[9]. This may be due to better treatment compliance and health status which subsequently aid in improvement of symptoms and radiological involvement due to reduced bacillary load.

In our study, there was a significant association (p value = 0.000001) of (reduced/same) weight and sputum smear positive status at end of IP with unsuccessful outcomes. In a study by Krapp *et al* unsuccessful outcome was independently associated with an initial smear 2+ (odds ratio [OR] 2.46, 95% CI 1.14 - 5.31), a positive smear at month 2 (OR 4.0, 95% CI 1.30 - 12.31) and body weight gain) 5% at end of treatment (OR 2.35, 95% CI 1.17 - 4.72)[10].

There was a significant association of (reduced/same) weight and symptoms of patients (worsened/same) at end of IP (p value = 0.00003) and mid CP (p value = 0.0001) with unsuccessful outcomes in our study.

Also, there was a significant association (p value = 0.00010) of sputum positive status and symptoms of patients (worsened/same) at end of IP (first follow-up).

During follow-up, most of these patients had improvement in symptoms, increase in weight and sputum smear status was negative were associated with successful outcomes.

Majority of patients who had unsuccessful outcomes during follow-up, had worsening in symptoms, decrease in weight and sputum smear status remained positive.

Conclusion

Tuberculosis and HIV co-infection impacts patient health adversely and simultaneous treatment of both diseases poses a serious challenge to the healthcare system and patients' wellbeing. Detection of worsening of symptoms, smear status and intervening at the earliest with proper counselling for an adequate nutritional diet at each follow-up can help in improving outcomes in such patients.

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ORIGINAL ARTICLE

JIACM 2024; 25 (1-2): 49-53

Evaluation of Platelet Indices in Patients with Uncomplicated Essential Hypertension

Aanchal Mangal, Yad Ram Yadav**, Pawan Kumar**, Sanjiv Maheshwari****

Abstract

***Introduction:** Hypertension is a prothrombotic or hypercoagulable state resulting in platelet dysfunction. Assessments of platelet indices and their bioactivity may be of vital importance for predicting the occurrence and monitoring the progression of hypertension.*

***Material and Methods:** This case control study was conducted on 250 patients with essential hypertension (cases), along with age and sex matched normotensive individuals (controls, n = 100), attending medical OPD of the Department of Medicine, JLN Medical College, Ajmer, over a period of two years. Estimation of blood pressure and platelet indices was done.*

***Result and Observations:** In our study, mean platelet volume (MPV) was 9.26 ± 0.44 fL, mean platelet distribution width (PDW) was 13.62 ± 1.30 fL, mean platelet count was 291.02 ± 60.40 * 10^3/mL and mean plateletcrit (PCT) was 0.27 ± 0.05% in cases group. MPV was 8.11 ± 0.16 fL, mean PDW was 9.94 ± 0.73 fL, mean PLT was 285.88 ± 60.55 *10^3/mL and mean PCT was 0.23 ± 0.04% in control group. The difference in MPV, PDW and PCT in both groups was found statistically significant. MPV value also increased with increase in grading of hypertension. The association between grading of hypertension and MPV was found statistically significant (p - value <0.01).*

***Conclusion:** MPV, PDW and PCT values are higher in hypertensive patients as compared to controls. MPV has linear correlation with grading of hypertension.*

***Key words:** Blood pressure, mean platelet volume, platelet distribution width, plateletcrit, platelet count,*

Introduction

Hypertension is a leading modifiable risk factor for premature death and cardiovascular disease, and a major public health challenge as per World Health Organisation[1].

Hypertension causes target organ damage by direct physical effect of increased blood pressure (BP) as well as the active promotion of atherosclerosis and thrombogenesis[2,3]. Evidence for a prothrombotic or hypercoagulable state in hypertension has been shown[4]. This may be due, at least in part, to the prothrombotic state associated with inappropriate platelet activation (such as increased aggregation *ex-vivo* and release of soluble P-selectin [sP-selectin])[5,6]. It has been widely acknowledged that if diagnosis is made at an early stage of hypertension, it can prevent cardiovascular disease and reduce the burden of morbidity and mortality[7].

Platelet indices comprise platelet distribution width (PDW), mean platelet volume (MPV), plateletcrit (PCT), and blood platelet count (PLT). MPV and PDW are the simple platelet indices, which increase during platelet activation[8]. Mean platelet volume (MPV) is a marker of average platelet size and activation, and its increased level reflects active large platelets. Some clinical studies have shown that active large platelets contain denser granules, which are metabolically and enzymatically more active than small ones and have a higher thrombotic potential[9]. Increased MPV has been found to be related with mortality after following acute myocardial infarction and re-stenosis[10], and this finding has been reported with hypertension in the background[11]. There is evidence from both retrospective and prospective studies supporting the validity of MPV as a marker of vascular risk and predictor of thrombotic complications in hypertensive patients[12,13].

Likewise, PDW is a simple, practical and specific marker of activation of coagulation, which is used to decide the heterogeneity of platelet size. Several studies have reported that platelet activation has a relationship with cardiovascular morbidity and mortality[14,15,16].

Increased platelet activation and aggregation are involved in the pathogenesis of elevated blood pressure. Many researchers have illustrated that the platelet occupies an important position in mediating immune response and maintaining vascular homoeostasis, atherosclerosis, and

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inflammation. Moreover, the use of antiplatelet therapies in hypertension supports the hypothesis that platelets play a pivotal role in the pathogenesis. Thus, assessment of platelet indices and their bioactivity may be of vital importance for predicting the occurrence and monitoring the progression of hypertension. Aim of our study was to find the correlation, if any, between various platelet indices with presence of hypertension and with grading of essential hypertension.

Material and Methods

This case-control study was conducted on 250 hypertensive patients and 100 age- and sex-matched normotensive healthy individuals (controls), having age >18 years, attending the Medicine OPD at JLN Medical College Hospital, Ajmer, over a period of two years (January 2020 to January 2022).

Individuals with essential hypertension, both newly diagnosed and established cases, not on treatment or if on treatment, only on Angiotensin-Converting Enzyme inhibitors (ACEI), were included in the study.

Individuals with secondary hypertension, cardiovascular disease, diabetes mellitus, peripheral vascular disease, cerebral infarction, thromboembolic events or on drugs affecting platelet functions or those who have undergone coronary artery bypass surgery, coronary stenting, were excluded.

Information was collected in a pre-designed format from each patient. Consenting patients underwent detailed history, thorough clinical examination and relevant laboratory tests including a Complete Blood Count. Platelet indices were estimated using 3 mL of aseptically collected venous blood in an EDTA coated vial, after an overnight fasting and taken to the central laboratory. The blood sample was aspirated (minimum of 70 microlitre) and diluted to specified ratio and stained. The sample was then fed into flow cells by sheath flow mechanism. PLT, PDW, MPV and PCT were measured by an autoanalyzer (Sysmex XN-1000 made in Japan) via the flow cytometry principle.

In each subject, BP was measured using standard digital sphygmomanometer on two separate occasions at 5 minutes interval, after at least 15-minute restand was then averaged. During this 30-minute proceedings, the participants were required to refrain from smoking or consuming caffeine.

Observations and results

Distribution of subjects has been depicted in Fig. 1. Most of the subjects belonged to 46 - 60 years age group, followed by 61 - 75 years age group.

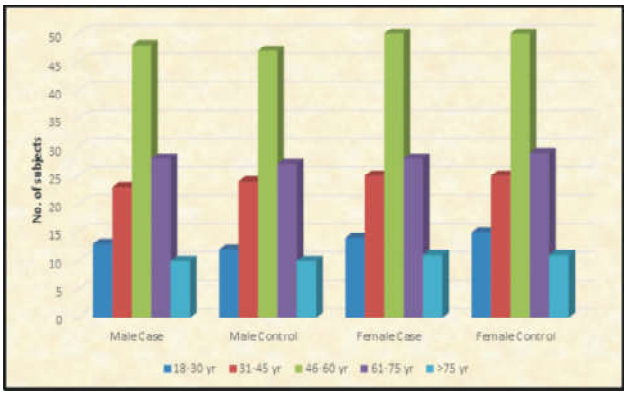

Fig. 1: *Showing distribution of cases and controls as per age-groups and gender.*

In our study, 51.20% patients were female and 48.80% patients were male.

The mean systolic blood pressure was 170.40 ± 16.99 mm of Hg and mean diastolic blood pressure was 101.08 ± 12.85 mm of Hg among cases. Mean systolic blood pressure was 101.08 ± 12.85 mm of Hg and mean diastolic blood pressure was 69.07 ± 5.78 mm of Hg among controls. Out of the total, 37.20% patients belonged to grade 2 hypertension, 33.60% patients belonged to grade 1 hypertension and 29.20% patients belonged to grade 3 hypertension.

Table I: Showing various platelet indices in cases and controls.

Platelet indices	Cases		Controls		p value
	Mean	SD	Mean	SD	
MPV(fL)	9.26	0.44	8.11	0.16	**0.001**
PDW(fL)	13.62	1.30	9.94	0.73	**0.001**
PLT(10^3/ml)	291.02	60.40	285.88	60.55	0.343
PCT(%)	0.27	0.05	0.23	0.04	**0.001**

Analysis of various platelet indices showed (Table I) higher value of MPV in patients with essential hypertension (9.26 ± 0.44 fL) when compared with normotensive controls (8.11 ± 0.16 fL) (p <0.001, significant). The mean platelet distribution width was higher in patients with essential hypertension (13.62 ± 1.30 fL) as compared to normotensive controls (9.94 ± 0.73 fL) (p <0.001, significant). The mean platelet count in patients with essential hypertension was 291.02 ± 60.40 per 10^3/mL and in normotensive controls was 285.88 ± 60.55 per 10^3/mL (p 0.343, insignificant). Similarly, the mean plateletcrit was also higher in patients with essential hypertension (0.27 ± 0.05%) when compared with normotensive controls (0.23 ± 0.04%) (p <0.001, significant).

Table II: Showing association of mean platelet volume and grade of hypertension.

Grade of hypertension	MPV(fL)		p-value
	Mean	SD	
1	8.72	0.10	**0.001**
2	9.38	0.10	**0.001**
3	9.73	0.22	**0.001**

MPV value increased with increase in grade of hypertension. The association between grade of hypertension and MPV was found statistically significant (p = <0.001).

Table III: Showing association of platelet distribution width and grade of hypertension

Grade of hypertension	PDW(fL)		p-value
	Mean	SD	
1	13.67	1.25	0.601
2	13.50	1.25	0.601
3	13.68	1.41	0.601

The association between grade of hypertension and PDW was found statistically insignificant (p = >0.05).

Table IV: Showing association of platelet count and grade of hypertension.

Grade of hypertension	PLT(10^3/mL)		p-value
	Mean	SD	
1	295.79	54.54	0.404
2	292.09	64.03	0.404
3	284.15	62.24	0.404

The association between grade of hypertension and PLT was found statistically insignificant (p = >0.05).

Table V: Showing association of plateletcrit and grade of hypertension.

Grade of hypertension	PCT(%)		p-value
	Mean	SD	
1	0.26	0.04	0.07
2	0.27	0.06	0.07
3	0.28	0.07	0.07

The association between grade of hypertension and PCT was found statistically insignificant (p = >0.05).

Discussion

Concern about the increased prevalence of hypertension has heightened interest to explore an association between some convenient, and rapidly obtained indices with blood pressure among healthy populations; and we found PDW, MPV and PCT are such indices that correlate with elevated blood pressure levels.

Pathophysiology of elevated blood pressure is multifaceted including vasoconstriction, vascular wall remodelling, and *in situ* thrombosis. Activated platelets may possibly secrete several growth factors and cytokines that influence remodelling of the vessel. Shear forces, the renin-angiotensin system, endothelial dysfunction, elevated catecholamine levels, and the presence of co-morbid conditions promotes the increased activation of platelets in hypertensive patients.

Hypertensive patients exhibit impairment of the autonomic system that includes abnormal parasympathetic and increased sympathetic nervous system activity. The effects of an over-activated sympathetic nervous system on the haemostatic system occur in two ways.

First, platelet activation via alpha2-adrenoreceptor stimulation, which causes shape change and thereby increases MPV.

Second, larger, activated platelets which are sequestered in the spleen can be released into the circulatory system following the elevated levels of adrenaline that contribute to increased MPV levels and heterogenicity (PDW).

In our study, platelet indices, namely mean platelet volume (MPV), platelet distribution width (PDW), platelet count (PLT) and plateletcrit (PCT) were compared between patients with hypertension and persons without hypertension.

Mean platelet volume

MPV is a marker of platelet function and activation. It has been shown that platelet size, measured as MPV, correlates with their reactivity. Larger and hyper-reactive platelets accelerate intracoronary thrombus formation, which leads to a cascade of clinical events, culminating in an acute coronary syndrome.

According to Zheng *et al*[17], larger platelets are more active compared to smaller ones, both metabolically and enzymatically, and are more likely to have a thrombotic potential.

In our study, MPV was higher in patients with essential hypertension (9.26 ± 0.44 fL) when compared with normotensive controls (8.11 ± 0.16 fL) and there was a statistically significant difference between the two groups (p = <0.001). Also, mean platelet volume increased with increase in grading of hypertension. The association between grading of hypertension and MPV was found

statistically significant (p = <0.001).

Some studies have reported a relationship between MPV and hypertension in different patient groups. Surgit *et al*[18] studied that the MPV levels were significantly higher in resistant hypertension group than in the controlled hypertension and normotensive group (p = <0.001).

Guven *et al*[19], found that MPV was significantly higher in masked hypertensive (8.8 ± 1.6 fL) and essential hypertensive patients (9.1 ± 1.7 fL) than those of normotensive control individuals (7.8 ± 0.8 fL) (p = 0.01 and p = 0.003, respectively), whereas there was no significant difference between the masked hypertensive and essential hypertensive individuals (p >0.05).

Platelet Distribution Width

PDW reflects heterogenicity of platelet volume distribution and is also a marker of platelet activation. Earlier findings have established that raised PDW and MPV levels are an independent risk factor for myocardial infarction including coronary heart diseases[20,21]. In our study, mean PDW was higher in patients with essential hypertension(13.62 ± 1.30 fL) when compared with normotensive controls (9.94 ± 0.73 fL) and there was a statistically significant difference between the two groups (p = <0.001). Ya-GuoZheng *et al*[22], found that MPV and PDW were significantly higher in patients with idiopathic pulmonary hypertension than in age and sex-matched control subjects (11.4 ± 0.9 fL v/s 10.3 ± 0.9 fL and 14.3 ± 2.9% v/s 11.9 ± 1.9%, respectively; p = 0.000).

Platelet Count

In our study, the mean platelet count in patients with essential hypertension was 291.02 ± 60.40 per 10^3/mL and in normotensive controls was 285.88 ± 60.55 per 10^3/mL which was statistically not significant (p = 0.343).

Plateletcrit

In our study, mean plateletcrit was higher in patients with essential hypertension (0.27 ± 0.05%) when compared with normotensive controls (0.23 ± 0.04%) and there was a statistically significant difference between the two groups (p = <0.001).

Conclusion

We conclude that mean platelet volume, platelet distribution width and plateletcrit are increased in hypertensive patients.

Also, mean platelet volume has linear correlation with grades of hypertension and it can be a predictor of the grade of hypertension. Hence, assessment of platelet indices may be of vital importance for predicting the occurrence and monitoring the progression of hypertension and its complications; however, long-term, large size, prospective studies are needed to substantiate this conclusion.

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REVIEW ARTICLE

JIACM 2024; 25 (1-2): 54-60

Hydroxychloroquine in Obstetrics: Newer Perspectives

Nazia Parveen, Sandhya Jain***

Abstract

Hydroxychloroquine (HCQ) was developed during World War II to treat malaria. It has been extensively used to treat a diverse range of autoimmune diseases including systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) during pregnancy for many decades. Additionally, HCQ was also used in cases with refractory antiphospholipid syndrome. The drug's exact mechanism of action in individual diseases is not clear and multiple possible explanations have been proposed for its immunomodulatory and anti-inflammatory actions. The safety of HCQ during pregnancy and lactation is well established by evidence of no major congenital malformation. There is no increased risk of adverse perinatal outcomes at a daily dose of 400 mg or less. It is also safe to use while breastfeeding. In recent years, HCQ has received significant attention because of its possible role in treatment for the highly infectious respiratory disease, COVID-19. Its role was also studied in preeclampsia, chronic placental inflammation, and repeated implantation failure during In Vitro Fertilisation (IVF). The most common adverse effects after long-term exposure include retinopathy and cardiotoxicity. HCQ is not indicated for patients having pre-existing retinopathy or other retinal diseases; conduction block or other arrhythmias; and/or severe liver or kidney disease. The recent updates for HCQ use in various conditions in obstetrics have been highlighted.

Key words: Pregnancy; hydroxychloroquine; preeclampsia; antiphospholipid syndrome.

Introduction

Hydroxychloroquine sulfate (HCQ) and Chloroquine phosphate (CQ) are derived from quinacrine. HCQ is an antimalarial medication, first approved by the FDA in 1955. HCQ has been used in the treatment of SLE in pregnancy since the early 1990s. Owing to its multiple immune modulatory and anti-inflammatory effects, HCQ has become an established therapeutic agent for pregnant patients at a dose of 200 - 400 mg/day for the treatment of autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), and undifferentiated connective tissue disease (UCTD). It also has a role in the regulation of glucose and lipid metabolism[1]. HCQ has been shown to have antiviral effects against several viruses.

Pharmacokinetics in pregnancy

The pharmacokinetics of HCQ are complex and not completely understood. This is because of its large volume of distribution, significant tissue binding, and long elimination half-life. Historically, terminal elimination half-life of HCQ was considered very long, (40 - 50 days), but more recent studies suggest a shorter half-life of about 5 days[2]. It has a high volume of distribution of 44,000 L and extensive tissue uptake[3]. HCQ can be detected in plasma for more than 42 days and takes around 6 - 8 weeks for complete elimination from the body. The drug takes at least 6 months of therapy, to reach a steady-state concentration of 95%, hence a shorter duration of therapy may not provide the full therapeutic results. The efficacy is further affected by variable pharmacokinetics among individuals[4]. Dose adjustments are not needed during pregnancy[5]. HCQ is available as 200 mg HCQ sulfate tablets, which contain 155 mg HCQ base. The daily dosage of HCQ may vary according to indication; however, the American Academy of Ophthalmology (2016-AAO) recommends no more than 5 mg/kg/day of real body weight in SLE to decrease retinopathy occurrence[6]. The complete remission of disease is related to higher blood concentrations, while lower blood levels may result in treatment failure. It is metabolised by cytochrome P450 enzyme in the liver, is predominantly excreted by the kidneys, and a small fraction is excreted in faeces, skin, and breast milk.

Mechanism of action

HCQ ($C_{18}H_{26}ClN_3O$) is a derivative of chloroquine. Though the exact mechanism of action is not fully understood, it has well-known anti-inflammatory and immunomodulatory effects as shown in Fig. 1.

Inhibition of TLR-7 and TLR-9: HCQ causes suppression of endosomal Toll Like Receptors (TLR) activation by direct binding to nucleic acids rather than inhibition of endosomal

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acidification. This results in inhibition of Interferon (IFN)-I production by plasmacytoid dendritic cells[7]. Inhibition of IFN-I production is also caused by inhibition of cyclic GMP-AMP synthase (cGAS) activity and STING (stimulator of interferon genes) pathway[8].

Inhibition of autophagy: Lysosomes have a main role in generating immune responses by regulating antigen processing. HCQ preferentially accumulates in lysosomes and raises their pH (Fig. 1), which inhibits antigen processing, prevents the alpha and beta chains of the major histocompatibility complex (MHC) class II from dimerizing, inhibits antigen presentation of the cell, and reduces the inflammatory response. By inhibiting lysosomal functions, it leads to inhibition of major histocompatibility complex (MHC) class II-mediated autoantigen presentation by antigen presenting cells to CD4+ T cells[9].

Inhibition of inflammatory cytokine production and angiogenesis: HCQ decreases mRNA expression of various Interleukins, e.g., IL-1α, IL-6, and Tumour Necrosis Factor (TNF-α) in cutaneous lupus erythematosus skin lesions. It also decreases vascular endothelial growth factor (VEGF) expression and results in inhibition of angiogenesis. It reduces local inflammation by decreasing mononuclear cellular infiltrate in the skin[10].

Antithrombotic effects: HCQ reduces blood cells aggregation and blood viscosity, lowers platelet aggregation by inhibition of phospholipase A2 *in vitro*. It decreases antiphospholipid antibodies (aPL) binding to phospholipid bilayers in trophoblast. It has shown a reduction in thromboembolic risk in SLE. The HCQ exposed SLE patients showed an 83% reduction in VTE risk in a case control study of 272 patients with SLE[11].

Effects on endothelial dysfunction: HCQ activates Extracellular signal regulated kinase 5 (ERK5) protein kinase and inhibits Vascular cell adhesion molecule 1 (VCAM-1) expression. ERK5 is a mitogen-activated protein kinase that

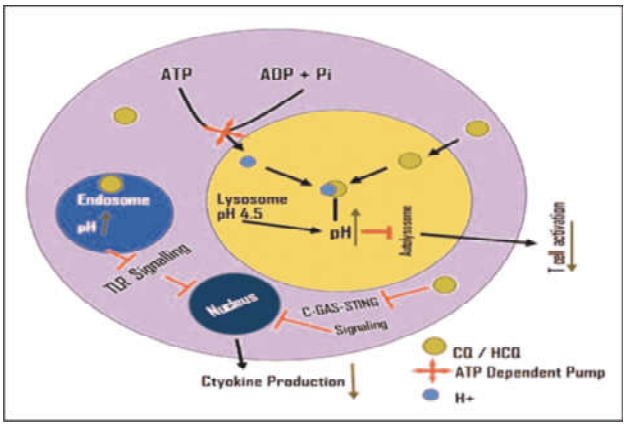

Fig. 1: *Mechanism of action of HCQ in the intracellular space.*

inhibits endothelial inflammation and dysfunction. This mechanism is responsible for anti-diabetic actions, lipid lowering effects and antioxidant actions[12-14] (Fig. 1). It causes reduced phosphorylation of protein kinase C, thus regulating nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase activation on the plasma membrane[15].

Metabolic effects: It has been shown in *in vitro* studies that HCQ improves insulin secretion and peripheral insulin sensitivity. HCQ also lowers glycated haemoglobin levels in patients with type 2 diabetes and rarely can cause hypoglycaemia. The prevalence of diabetes in patients with RA is similar to that of other patients; however, RA patients have sedentary lifestyles and often treated with corticosteroids that induce weight gain. Most of the anti-diabetic and lipid lowering effects of HCQ have been observed in RA patients. In a prospective observational cohort of 4,905 RA patients, 77% of patients had a reduction in relative risk of diabetes[13-14].

Antiviral effects: HCQ decreases the endosomal pH and prevents pH dependent virus-cell interaction. It also interferes with glycosylation of the angiotensin-converting enzyme 2 (ACE2) receptor, resulting in inhibition of SARS-CoV-2 S protein – ACE2 interaction[16].

Safety of HCQ in pregnancy and lactation

HCQ is a pregnancy category C drug and its use during pregnancy and breastfeeding is considered safe[17]. HCQ crosses the placental barrier and has foetal serum concentrations equal to those measured in maternal blood. HCQ is also excreted in breast milk, in a very small fraction of around 2% of maternal dose, which is considered safe[18]. The safety of HCQ in pregnancy has been established by various studies as shown in Table I. No adverse perinatal outcomes were reported with daily maternal doses of HCQ ≤400 mg. There was no increased risk of pre-term labour as shown by Bérard *et al* in a large cohort study involving 2,33,748 pregnant women exposed to HCQ[19]. There has been an increased use of HCQ use during pregnancy in the past 13 years (from 6.3% in 2005 to 60.9% in 2017), based on the reported safety profile of HCQ in pregnancy[20].

Role of HCQ in Obstetrics

Role of HCQ in SLE

SLE is a chronic autoimmune inflammatory disease that can virtually affect any organ or system. It has been seen that nearly 90% of SLE cases develop in women, more common in African-American women. Because of the fear of poor pregnancy outcomes [miscarriage, stillbirth, preterm labour, intrauterine growth restriction (IUGR), and pre-

eclampsia], these women were not advised to conceive in older times. The favourable pregnancy outcomes are seen for most women with quiescent lupus activity for at least 6 months before conception; absent lupus nephritis; neither antiphospholipid syndrome nor lupus anticoagulant are detected; and no superimposed preeclampsia. Pregnant women with SLE are also screened for anti-SS-A (antiRo) and anti-SS-B (anti-La) antibodies in addition to serum complement levels (C3 and C4), dsDNA titres, and antiphospholipid antibodies at the beginning of pregnancy because of associated foetal complications of congenital heart block in foetus.

Table I: Various studies regarding the safety of HCQ in pregnancy

Studies	Number of the study population	Results
Huybrechts *et al* (2020)[21]	HCQ exposed-1867 pregnancies HCQ unexposed-19,080 pregnancies	No substantial rise in significant congenital malformations in newborns exposed to HCQ during the first trimester of pregnancy
Mother To Baby/ Organisation of Teratology Information Specialists Autoimmune Diseases in Pregnancy Cohort study[22]	HCQ exposed-279 HCQ unexposed-279	No increased risk of structural congenital anomalies
Andersson *et al*, in 2021[23]	HCQ/CQ exposed-12,40,875 pregnancies	No increased risk of major birth defects, small for gestational age, preterm birth
PATCH study 2020[24] (Preventive Approach To Congenital Heart Block with HCQ)	54 women with SLE (who have previously had a pregnancy complicated by third degree heart block) HCQ started before the end of the 10th week of pregnancy and was maintained throughout delivery.	reduces the recurrence of CHB in anti-SSA/Ro-exposed pregnancies by more than 50%

Treatment modalities for SLE

There is no cure for SLE at present and complete remission of the disease is rare to achieve. HCQ should be continued during pregnancy because therapy interruption can precipitate a flare. For women not previously using HCQ, it should be initiated in the first trimester because its use is associated with an 85% reduction in the risk of having a small-for-gestational-age neonate, in addition to the reduced risk of foetal congenital heart block by 50% in women with anti-SSA antibodies. Further, the beneficial role of HCQ in SLE in terms of decreased incidence of pre-eclampsia is observed in a recent meta-analysis[25]. The ACOG recommends to start low-dose aspirin in SLE before 16 weeks as a preventive measure of pre-eclampsia. Multiple national and international rheumatology guideline groups recommend use of HCQ to manage SLE during pregnancy for all women with lupus as the standard of care[26-29].

Neonatal Lupus Syndrome

Neonatal lupus is characterised by lupus dermatitis, various haematological manifestations and occasionally congenital heart block. Maternal treatment with HCQ is the only modality which lowers the risk of neonatal lupus. Cutaneous manifestations appear at 4 to 6 weeks of age, present in 30 to 40 per cent of infants. These are usually seen in women with anti-SS-A and SS-B antibodies and nearly 50% of women have these antibodies. The incidence of foetal myocarditis is only 2 to 3 per cent in foetuses of mothers with these antibodies[30,31]. The risk of congenital heart block rises to 20 per cent with a prior affected child. The cardiac lesion is permanent, and a pacemaker is generally necessary. The long-term prognosis is poor[24,32].

Role of HCQ in pre-eclampsia

Pre-eclampsia has a complex pathogenesis, especially the early onset pre-eclpmsia. This syndrome is characterised by inflammation and oxidative stress resulting in cellular dysfunction, apoptosis, and hypoxia. The activation of NADPH oxidase leads to the formation of reactive oxygen species, which leads to activation of the Nuclear factor kappa-light-chain-enhancer of activated B cells (NEκB) controlled pathways, resulting in cell death by apoptosis[33-35]. The combination of ischaemia, NFκB activation and apoptosis is a trigger for the expression of TLR 7and 9, which further causes release of interferon α (IFNα) and the production of pro-inflammatory cytokines, such as interleukin 6 (IL6) and tumour necrosis factor α (TNFα). The sFlt-1 levels start rising with high TNFα and IL6 levels.

Since HCQ has anti-inflammatory, anti-oxidant and anti-thrombotic effects, it acts by inhibiting the production and release of specific cytokines and prostaglandins and decreasing NADPH oxidase activity and TLR activation; it may also reduce the production of reactive oxygen species. Moreover, HCQ safety in pregnancy is well established; hence many authors have proposed HCQ as a promising adjuvant treatment for preeclampsia.

Rahman *et al* reported that HCQ could reduce the oxidative stress-induced placental and endothelial dysfunction based on its antioxidant and anti-inflammatory action along with a positive effect on angiogenesis[33]. HCQ along with low-dose aspirin may be beneficial in the treatment of women with SLE along with Antiphospholipid syndrome (APS), by reducing the risk of thrombosis. The results showed increased rate of live births and a reduction of placenta-mediated complications (pre-eclampsia, IUGR and placental abruption)[36]. Mekinian *et al* studied the role of HCQ in patients with APS or asymptomatic carriers of antiphospholipid antibodies. The addition of HCQ to conventional treatment (aspirin and heparin) resulted in a

decreased rate of pre-eclampsia and/or HELLP (haemolysis, elevated liver enzymes, and low platelets) syndrome and fall in pregnancy losses from 81 to 19% in the group receiving HCQ[37].

Based on these promising results, HCQ may be a new preventive and therapeutic modality for patients with definite risk factors for pre-eclampsia and prior to the onset of severe complications. However, further research is still needed to prove the efficacy of HCQ in prevention and treatment of pre-eclampsia, and more results in this aspect are expected in future.

Role of HCQ in Antiphospholipid Syndrome (APS)

Antiphospholipid syndrome (APS) is a condition of autoantibody-mediated acquired thrombophilia that predisposes to recurrent thrombosis or pregnancy morbidity. This is characterised by persistently positive serum tests for antiphospholipid antibodies (aPLs) plus arterial and/or venous thromboses or pregnancy morbidity. Lupus anticoagulant is the only APA that has been consistently associated with adverse pregnancy outcomes. Around 30% of patients with SLE have aPLs. APS can have three different types of presentations: Thrombotic APS, Obstetric APS and Asymptomatic aPL Carriers.

HCQ in thrombotic APS: HCQ was used as an orphan medicinal product, licensed by European Medicines Agency for the treatment of cases with recurrent and refractory APS, despite adequate anticoagulation. The beneficial role of HCQ is mediated via anti-thrombotic, antiplatelet, and immunomodulatory properties[38,39]. Studies have also suggested that HCQ reduces endothelial dysfunction, improves vascular elasticity and improves blood flow[40]. Moreover, the risk of bleeding associated with HCQ is extremely low.

HCQ in Obstetric APS: The underlying pathology of obstetric APS involves placental thrombosis, inflammation, and complement activation. The use of low dose aspirin (LDA) and heparin is the current standard treatment in obstetric APS with an overall successful pregnancy outcome rate of 70%. However, the remaining 20 - 30% of women with obstetric APS do not respond to heparin and LDA. Better outcomes have been seen in retrospective studies of HCQ as an adjunctive therapy in patients with obstetric APS in addition to the standard treatment[38]. Sciascia *et al* reported higher rate of live births (67% vs 57%; $p = 0.05$) and a lower prevalence of pregnancy morbidity (47% vs 63%; $p = 0.004$)[36]. Gerde *et al* reported better pregnancy outcomes (97.1% (67/69) vs 62.5% (20/32); $p < 0.001$) and lower pregnancy complications in 87 women with refractory primary obstetric APS treated with HCQ compared to standard treatment alone (8.7% (6/69) vs 37.5% (12/32); $p < 0.001$)[41].

HCQ for Asymptomatic aPL Carriers

These individuals have no history of thrombosis (aPL carriers) with aPL, but are also at increased risk of developing thrombosis. In this sub-group, primary prophylaxis with aspirin should be used for prevention of myocardial infarction suggested by the Preventive Services Task Force (USPSTF) report[42]. The reduced risk of a thrombotic event was seen in a cross-sectional study of aPL positive patients with connective tissue disease and APS treated with aspirin and/or HCQ[43].

Role of HCQ in unexplained recurrent early miscarriage (RM)

Recurrent miscarriages have an incidence of 1 - 3%, and an aetiology is never established in approximately 50% of those. As demonstrated by the HEPASA study[44], there is no effective treatment to date, even if RM is associated with risk factors, such as aPL positive status, which is detected in 5 - 15% of women with RM. Mekinian *et al* (2016) found that there was currently no data on the clinical efficacy of HCQ in women with recurrent unexplained miscarriages[37].

Role of HCQ in COVID-19

The US Food and Drug Administration issued an Emergency Use Authorisation (EUA) on March 28, 2020, allowing HCQ and CQ to be used for certain hospitalised patients with COVID-19. HCQ was widely used for SARS-CoV-2 infections during the Coronavirus pandaemic, although data does not support its efficacy in the treatment of COVID-19[45].

Role of HCQ in Artificial Reproductive Therapy

Recent studies showed the association between various autoantibodies (antinuclear antibody, anti-RO/SSA antibody, and anti-dsDNA antibody) with poor reproductive outcomes by affecting embryo implantation, maternal pregnancy, the placenta, and the foetus[46]. In a recent retrospective study, a total of 128 patients who were positive for autoantibodies were included. The study was conducted between October 2017 and December 2022 in patients undergoing Frozen Embryo Transfer (FET) for 65 cycles. HCQ was administered 2 months before embryo transfer and continued till the end of the first trimester while a control group consisted of 63 cycles without HCQ. There were improved clinical pregnancy outcomes and a reduced rate of first-trimester abortion with HCQ use in patients who were positive for autoantibodies during Frozen Embryo Transfer (FET) cycles[47]. There were significantly higher implantation rates (IR), CPR, and ongoing pregnancy rates (OPR) in the treatment group than those in the control group. The results showed clinical pregnancy rate (CPR) OR: 3.106; 95% confidence interval (CI):1.458 - 6.616; P = 0.003. The biochemical pregnancy rate (BPR) and early

miscarriage rate (EMR) were also significantly lower in the treatment group than in the control group ($p = .029$, $p < .001$).

Role of HCQ in Rheumatoid Arthritis

Rheumatoid Arthritis is an immune system disorder just like SLE, Systemic Sclerosis. In nearly 50 - 70% of women with rheumatoid arthritis (RA), the disease improves during pregnancy and half of them will have moderate-to-severe RA activity through pregnancy. HCQ is a disease-modifying anti-rheumatic drug[5], and it is widely used as an anti-rheumatic agent in RA. HCQ interferes with immunological reactions through antigen-related biological events and the cytokines as mentioned earlier. It is thought to suppress and inhibit rheumatoid factor and acute-phase reactants in RA[13].

The use of HCQ in pregnant women with RA is a safe and effective therapy for early and mild to moderate RA, but it is used as an effective component of combination therapy for aggressive RA. Additional benefits of HCQ in patients with RA are the reduced risk of diabetes mellitus and its favourable effects on lipids[48].

Role of HCQ in chronic placental inflammation

Chronic placental inflammation is characterised by disrupted healthy placental tissue, which can only be confirmed by a post-delivery histopathological examination. It has been linked to severe complications of pregnancy, such as foetal growth restriction, premature labour, and miscarriage[49]. The value of adding HCQ to pregnant women with a positive history of chronic placental inflammation was studied by Brady *et al*, showing a decrease in disease severity and a trend for a higher live birth rate[50]. Hence, HCQ is a potential therapeutic option for such cases with chronic placental inflammation. Currently, there is no prospective controlled trials on the efficacy of HCQs in these settings, which emphasizes the need for further investigations to verify HCQ's efficacy in chronic placental inflammation.

Side-effects of HCQ

HCQ has multiple adverse effects, which require vigilance as mentioned in Table II. The common side-effects are nausea, vomiting, diarrhoea, and abdominal pain, which generally subside after a few days of treatment. Other adverse effects include retinopathy, hyperpigmentation, myopathy, and skin reactions[51]. Haemolysis has been reported in individuals with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. The most discussed and studied HCQ side-effect in SLE is retinopathy. The important risk factors for HCQ-related retinopathy are the duration of treatment, chronic kidney disease, and pre-existent retinal disease.

Table II: Side-effects of hydroxychloroquine[51].

System	HCQ's side-effects Short-term	HCQ's side-effects Long-term
Cardiovascular	Hours-days: prolonged QT (attention to the association with other drugs that affect the QT interval) Overdose: cardiovascular shock, collapse	Weeks-months: Conduction troubles, cardiomyopathy, vacuolar myopathy, valvular disorders
Dermatologic	Days-weeks: pruritus, rashes, urticaria exanthematous pustulosis, toxic epidermal necrolysis, Stevens-Johnson syndrome	Years: hyperpigmentation
Digestive intolerance	Days: nausea, vomiting, diarrhoea, bloating	
Haematological	Days to weeks: bone marrow toxicity, cytopenia (neutropenia)	Weeks-months: bone marrow toxicity, cytopenia (neutropenia)
Metabolic	Days: hypoglycaemia	
Neuromuscular	Days: increase of creatine kinase	Months: myositis, muscle weakness
Otorhinolaryngology	Days-weeks: ototoxicity, tinnitus	
Ophthalmologic	Days-weeks: eye accommodation troubles	Months-years (5-20 years): retinopathy (maculopathy)
Only case reports	Fulminant hepatic failure; toxic myopathy with respiratory failure; podocytopathy mimicking Fabry disease; rare cutaneous side-effects (erythroderma, dark rash, gray skin, erythema multiforme)	

Ophthalmologic screening is mandatory. In cases with pre-existing risk factors, yearly screening starting from baseline is required. In cases without retinopathy risk factors, the first screening at 5 years on HCQ, and yearly thereafter[52,53]. The current 2020 Joint Statement on HCQ recommended using sensitive testing modalities such as optical coherence tomography (OCT) and automated visual fields that could detect early retinal toxicity.

The most common long-term adverse effects (use over five years) include retinopathy, which can lead to retinal damage and permanent loss of sight, and cardiotoxicity, which results in damage of the heart and potentially lethal cardiac arrhythmias[54]. The risk of HCQ-induced retinopathy is 0.3% among patients on standard dosage[55], while cardiomyopathy is rare. Irreversible retinopathy with retinal pigmentation changes (bull's eye appearance), visual field defects (paracentral scotomas) and visual disturbances (visual acuity), maculopathies (macular degeneration), decreased dark adaptation, and colour vision abnormalities have been reported.

HCQ is not indicated in patients who have pre-existing retinopathy or other retinal diseases; conduction block or other arrhythmias; and/or severe liver or kidney disease. The

recommended dose limit is reduced from 6.5 mg/kg of ideal body weight to no more than 5.0 mg/kg of actual body weight.

Ongoing trials on the role of HCQ in recurrent miscarriage and pre-eclampsia

Two phase-3 multicentre double-blind randomised clinical trials are ongoing and are investigating the preventive effect of HCQ on foetal loss in women with a history of Recurrent Miscarriage[56]. One trial is "HCQ for prevention of RM or BBQ" (ClinicalTrials.gov: NCT03165136; estimated study completion date: February 2023). It is a French study, which is comparing HCQ to a placebo in women with RM (three or more losses in the first trimester of pregnancy) regardless of their thrombophilia status. HCQ was started before conception in a daily dose of 400 mg till the end of 10 weeks gestation, with the primary outcome of a live and viable birth. The other trial is "HCQ for Recurrent Pregnancy Loss", of women with RM without APL antibody positivity (ClinicalTrials.gov: NCT03305263; estimated study completion date: January 2023). It is a Danish study. Research is ongoing in three upcoming trials (not yet recruiting) on women with autoimmune diseases, with the aim to evaluate the impact of HCQ in addition to conventional therapy in the prevention of obstetrical complications (ILIFE trial: NCT03671174; HYDROSAPL[57]; and HYPATIA[58] as mentioned earlier.

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CASE REPORT

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Cold Agglutinin Syndrome Secondary to Acute Hepatitis A Infection in an Adult

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Abstract

Cold agglutinin syndrome (CAS) is a rare condition characterised by formation of cold agglutinins which cause destruction of erythrocytes. CAS is associated with other clinical conditions like infections, malignancies, lymphomas or autoimmune disorders. We describe a young patient who presented with jaundice and anaemia for two weeks. On evaluation, he was found to be having cold agglutinin related haemolytic anaemia secondary to acute hepatitis A infection. He was treated successfully with blood transfusion and a short course of steroids. This case highlights an unwonted extrahepatic manifestation of hepatitis A infection.

Key words: Coomb's test, haemolytic anaemia, steroids.

Introduction

Autoimmune haemolytic anaemia (AIHA) is an acquired disorder characterised by production of antibodies directed against red blood cells (RBCs) surface antigen causing their destruction[1]. AIHA is further classified into two major types based on the optimal temperature at which antibodies react with erythrocyte antigen: warm AIHA (usually IgG) optimal around 37^0 C and cold agglutinin (usually IgM) optimal at 4^0 C. Cold-antibody AIHA is relatively uncommon, accounting for 15 - 30% of AIHA. Cold-antibody AIHA is termed as cold agglutinin disease (CAD) when it is primary and is called cold agglutinin syndrome (CAS) when it is secondary to other clinical diseases like infections, autoimmune disorders, lymphomas or other malignancies[2]. Infections associated with CAS include *Mycoplasma pneumoniae*, Epstein-Barr Virus, Cytomegalovirus, Human Immunodeficiency Virus, Varicella Zoster, SARS-COV-2 and influenza virus[3]. Herein, we present a rare case of CAS secondary to acute Hepatitis A Virus (HAV) infection in an adult.

Case report

A 32-year-old male presented in the month of December with complaints of yellowish discoloration of eyes, weakness and fatigue for the last two weeks. On general physical examination, he had pallor and icterus. Systemic examination revealed moderate hepato-splenomegaly. Blood investigations showed low haemoglobin of 7.2 g/dL, raised MCV - 105 fl, low RBC count - $1x10^6$, haematocrit of 11.7% and MCHC - 61 g/dL with normal total leucocyte and platelet counts. Peripheral smear showed anisocytosis, nucleated RBCs, polychromatophils and RBC agglutination (Fig. 1); RBC agglutination disappeared on pre-warming the sample to 37^0 C for 20 minutes (Fig. 2). Direct Coomb's test was positive at 4^0 C with raised cold agglutinin titres and complement levels (C3 and C4) were low. Serum Lactate DeHydrogenase (LDH) level was high 507 IU/L (Normal <250 IU/L), serum haptoglobin was undetectable and corrected reticulocyte count was high (5%). Vitamin B12 and serum folate levels were normal. Liver function test was deranged with serum total bilirubin of 3.7 mg/dL (Direct bilirubin - 1 mg/dL, Indirect bilirubin - 2.7 mg/dL), aspartate transaminase of 135 U/L and alanine transaminase of 152 U/L. Hepatitis B surface antigen, Anti Hepatitis C Virus antibody and Anti Hepatitis E Virus IgM tests were negative; however, Anti Hepatitis A Virus IgM test was positive. Serum protein electrophoresis, Human immunodeficiency virus (HIV) test and *Mycoplasma*

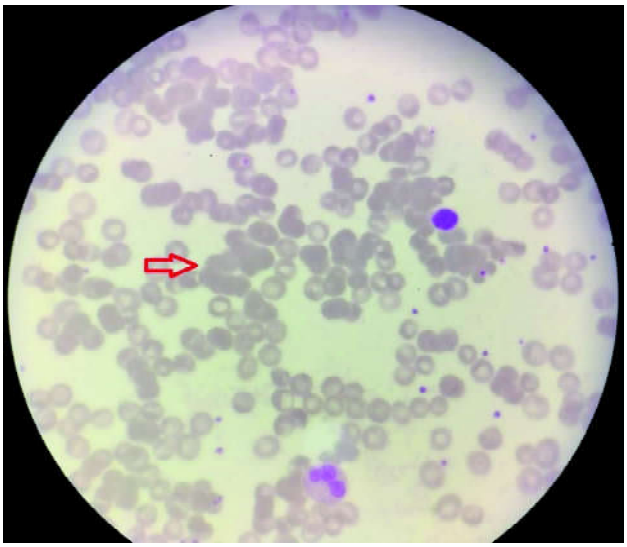

Fig. 1: *Peripheral smear showing clumping of RBCs (red arrow).*

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pneumoniae IgM and IgG was negative.

A diagnosis of Cold agglutination syndrome due to acute Hepatitis A Virus infection was made. He was advised to avoid cold exposure and one-unit warm packed RBCs was transfused. He was started on oral prednisolone 30 mg once a day for a week followed by gradual taper over the next two weeks. A repeat haemogram, liver function tests and LDH level done after three weeks of treatment showed normalisation of all parameters.

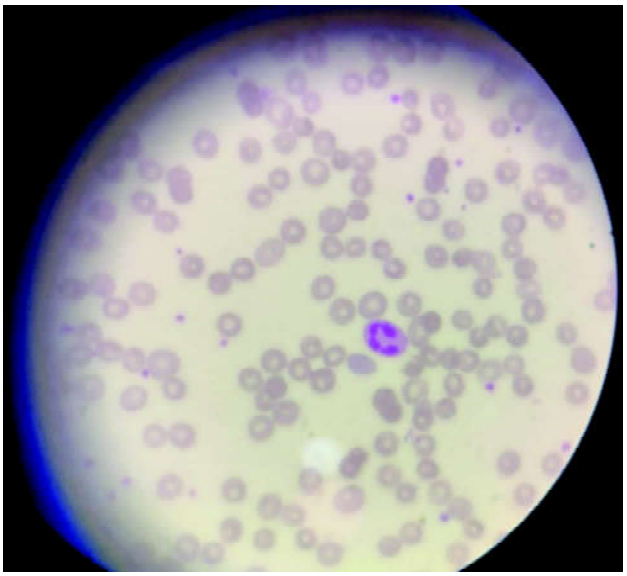

Fig. 2: *Complete resolution of clumping on prewarming the sample at 37°C.*

Discussion

Cold agglutinin syndrome (CAS) occurs secondary to autoimmune disorders, lymphomas, solid malignancies and various bacterial and viral infections. Post-infectious cold agglutinins are seen with *Mycoplasma pneumoniae*, Hepatitis B and C, Human Immunodeficiency Virus, Influenza Virus, Varicella, Epstein-Barr Virus and SARS-COV-2. HAV infection is the most common cause of acute hepatitis in developing countries with low socio-economic condition and poor sanitation. Extra-hepatic manifestations like nephritis, pancreatitis, pericarditis, pneumonitis, and haemolysis occur rarely. Acute HAV infection associated warm type AIHA has been reported earlier, but CAS is very rare with just one prior reported case in a child[4-5]. To the best of our knowledge, this is the first reported case of hepatitis A virus associated CAS in an adult.

CAS is characterised by formation of cold agglutinins (IgM antibodies) against I antigen on the surface of erythrocytes, which readily bind to RBCs as blood passes through the cooler peripheral circulation. Once bound, IgM cold agglutinins activate the complement cascade resulting in binding of C3b to the cell surface. Upon reaching the central circulation at 37^0 C, cold agglutinins detach from the erythrocyte, whereas C3b remains bound. This C3b-coated cells are further sequestered by the macrophages of the reticuloendothelial system resulting in extravascular haemolysis. Also, activation of C5 complement leads to formation of membrane attack complex and intravascular haemolysis in severe cases[6]. The clinical features include symptoms of primary disease along with non-specific symptoms like fatigue, malaise and weakness. Diagnosis is made by presence of haemolytic anaemia with positive direct antiglobulin test (DAT) and high titres of cold agglutinins in the blood.

Management of CAS includes non-pharmacological measures like avoiding cold exposure, warm clothing, and blood transfusion with in-line blood warmer in severe cases. No definite therapy has been established except treatment of the underlying disease[7]. CAS secondary to infection is generally self-limiting; however, corticosteroids have been used in CAS secondary to *Mycoplasma* and various other viral infections with varying success[8-10]. Definite evidence regarding benefit of steroids is lacking due to the rarity of this condition. We gave a short course of moderate dose prednisolone as the patient had severe symptomatic anaemia and a favourable outcome was observed. Thus, clinicians should be aware of this rare association, and Hepatitis A Virus screening should be done in suspected CAS cases.

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CASE REPORT

JIACM 2024; 25 (1-2): 63-66

A Rare Case of Sjögren's Syndrome with Lupus Anticoagulant and Factor VIII Inhibitor Antibodies Presenting as Thrombocytopenic Purpura

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Abstract

A 27-year-old lady presented with complaints of menorraghia for 28 days and purpuric rashes on both upper and lower limbs. On evaluation, initial investigations showed thrombocytopenia and prolonged activated partial thromboplastin time (aPTT). Other routine investigations were normal. She was further evaluated for thrombocytopenia and prolonged aPTT; her ANA profile and factor inhibitor test were sent, and the patient was diagnosed with Sjögren's syndrome along with the presence of concomitant Lupus anticoagulant and factor VIII inhibitor antibodies. She was started on steroids, and became better with rising platelet numbers and no further bleeding.

Key words: Antinuclear antibody, factor VIII inhibitor, lupus anticoagulant, activated partial thromboplastin time, antiphospholipid syndrome.

Introduction

Antinuclear antibody (ANA) is a distinct characteristic of connective tissue diseases (CTD's), and a positive ANA has a high sensitivity for CTD's. Autoimmunity involves the adaptive immune system. The T- and B-cell-mediated effects play a central role in the complex pathophysiology of CTDs. These diseases can present with arthralgia, malaise, myalgia, low-grade fever, or any specific organ system manifestation. They may also present as thrombocytopenia, often due to antibody-mediated platelet destruction. Some common CTDs are SLE, Sjögren's, and Scleroderma, Sjögren's syndrome (SS) is an autoimmune disease evidenced by broad organ-specific and systemic manifestations, the most prevalent being decreased lacrimal and salivary gland function, xerostomia, keratoconjunctivitis sicca, and parotid gland enlargement[1]. It has also been recognised that patients with thrombocytopenia[2] might have lupus anticoagulant positivity[3,4]. Antiphospholipid syndrome (APS) may be associated with autoimmune diseases, rarely with Sjögrens syndrome, and can also present as isolated primary APS[5]. Patients presenting with thrombocytopenia along with Lupus anticoagulant positivity can present with prolonged activated partial thromboplastin time (aPTT). Another cause of prolonged aPTT is the presence of factor-VIII inhibitor antibodies.

Case report

A 27-year-old lady presented with complaints of menorrhagia for one month and purpuric rashes on both upper and lower limbs. There was no recent history of any fever or infection. There was no history of any drug intake and any prior medical comorbidity. Her complete blood count (CBC) report revealed total leucocyte counts of 5,500/mm^3, thrombocytopenia with platelet counts of 9,000/mm^3 and Hb of 10 g/dL. Peripheral blood film showed normocytic normochromic anaemia with no evidence of schistocytes or tear drop cells. Reticulocyte counts and lactate dehydrogenase (LDH) were within normal limits. The direct and indirect Coombs tests were negative. Ultrasound did not show splenomegaly or hepatomegaly. Serum iron studies were within normal range.

Her coagulation profile revealed a prolonged activated partial thromboplastin time (aPTT) of 72 seconds (normal: <27 seconds). The patient was further evaluated for prolonged aPTT, and a mixing study was done, which came out to be 52 seconds (normal: <27 seconds), hence still prolonged. Evaluating prolonged aPTT in a stepwise approach, her Lupus anticoagulant and factor inhibitor were sent; her Lupus anticoagulant was positive, and factor inhibitor screening was also positive, suggesting a high-risk of connective tissue disorder. Anticardiolipin IgM, IgG,

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and anti-Beta2 glycoprotein IgM, IgG were not elevated. The patient had no prior history of any thrombotic events. In light of the mixing study and her clinical history, the presence of a factor VIII inhibitor was suspected. To confirm that, a Bethesda assay was done and the result was 85.2 Bethesda units (normal <50.4), thus confirming factor VIII inhibitor antibody.

Table I: Relevant investigations.

Lab tests	Values
Haemogram (Hb/TLC)	10 g/dl, 5500/mm^3
Platelet Count	Day 1: 9,000/mm^3 Day 3: 70,000/mm^3 (after SDP transfusion) Day 5: 30,000/mm^3 Day 9: 1,25,000/mm^3 (After starting on steroids)
PT/INR/aPTT	14/1.3/ 72.6 (Normal reference range: <27 sec)
aPTT with mixing study	56.5 sec (Normal ref. range: <27)
Vitamin B12	450 pg/mL (Normal ref. range: 240 - 930)
ESR	23 mm 1st hour
Serum Electrolytes (Na+/K+/Cl)	140/4.1/109 meq/L
Fibrinogen	339 mg/dL (Normal ref. range: 220-496)
Reticulocyte Count	1.7% (Normal ref. range: 0.5 - 2.5)
LDH (Lactate Dehydrogenase)	208 u/L (Normal ref. range: 120 - 246)
ANA by IFA	Positive 1:80 Speckled
PBF	Normocytic Normochromic anaemia
Viral Markers (HBsAG, HIV1 and 2, HCV)	Negative
TSH, LFT, URINE R/E, RFT (Renal Functions)	Within normal limits (WNL)
ANA Profile	SS-A/RO60 KD +++SS-A/RO52 KD +++
Lupus Anticoagulant DRVV Screen (Test)	Detected 106.9 (Normal ref. range: 35 - 39 sec)

TLC: Total leucocyte count, PT/INR: Prothrombin time, international normalised ratio, aPTT: Activated partial thromboplastin time, LFT: Liver functon test, RFT: Renal function test, ANA: Antinuclear antibody.

Anti-Nuclear Antibody (ANA) by Indirect Immunofluorescence Assay (IFA) was positive, and it was (2++) of speckled appearance. ANA immunoblot revealed SS-A/Ro60/52 strong positive (3+++). The patient had no history of any joint pain, arthralgia, dry mouth, or any other sicca symptoms. The patient was further evaluated for Sjögren's syndrome. The ophthalmologist's opinion was taken, and Schirmer's test was done, which was conclusive in favour of dry eye disease. Her left eye showed no signs of tears (a severe form of dry eye), and her right eye revealed moderate dry eye (<6 mm). Her tear film break-up test (TFBT) revealed dryness in both eyes. In view of active bleeding and thrombocytopenia, 1 unit of SDP was transfused. The patient was started on tablet Hydroxychloroquine (HCQ) 200 mg twice a day and oral steroids at 1 mg/kg, and eventually her platelets increased, with no further active bleed, and she was discharged on oral steroids and tablet HCQ. On follow-up after 1 week, her platelets were 4,00,000/mm^3, and she was asymptomatic. The patient is on regular follow-up, with regular CBC profile monitoring. After 3 months of follow-up, her CBC revealed platelet count of 3,50,000/mm^3 and she is asymptomatic, on a tapering dose of steroids.

Discussion

Connective tissue disorders (CTDs), such as SLE, Sjögren's syndrome, antiphospholipid syndrome (APS), and undifferentiated connective tissue diseases (UCTD), are characterised by positive ANA tests and can sometimes present as thrombocytopenia.

One study showed[7] that the ANA-positive group's platelet count at diagnosis was lower than the ANA-negative group. The two primary autoantibodies detected in the study responsible for causing thrombocytopenia were anti-SSA and anti-Ro52, which is similar to our case but with no other presenting history of any sicca symptoms or arthralgias made this a bit unusual and also the presence of persistently raised aPTT was not explained by this syndrome; hence, further evaluation of prolonged aPTT was needed.

The unusual combination of the presence of an FVIII inhibitor and a Lupus anticoagulant (LA) in a patient who presented with bleeding manifestations with no prior thrombotic event poses difficulty in determining the cause of a prolonged aPTT[8] as aPTT can be prolonged by both FVIII inhibitors and a Lupus anticoagulant. Even though these autoantibodies are rare, it is possible to identify the underlying autoantibodies through a stepwise approach and manner. It is quite uncommon for a lupus anticoagulant and an acquired FVIII inhibitor to coexist together, and very few cases have been reported worldwide[8]. Along with that, the presence of an underlying autoimmune disease like Sjögren's syndrome makes this case ever rarer.

An acquired clotting factor inhibitor is a possibility when large ecchymoses or bleeding manifestations suddenly appear in a person without major trauma or a known bleeding condition, along with a prolonged aPTT. Antiphospholipid syndrome (APS) patients also exhibit prolonged aPTT, although their symptoms are thrombotic rather than bleeding most of the time. Disseminated intravascular coagulation (DIC) is also a differential for prolonged aPTT, but our patient did not fit this because she had a normal Prothrombin (PT) time as well as no sepsis, trauma, malignancy, or obstetric complications.

Normal liver function tests and a normal prothrombin time excluded liver disease as a possibility for her clinical picture.

The most common auto-antibody that affects clotting-factor activity is an antibody against factor VIII, leading to a bleeding disorder. A prolonged aPTT is the hallmark feature of acquired FVIII deficiency. The Bethesda assay measures the inhibitor titre and confirms the diagnosis. The Bethesda assay measures the quantity of factor VIII that the patient's plasma inactivates when it is mixed with normal plasma under specific circumstances[9]. One Bethesda unit (BU) is equal to the quantity of antibody that will neutralise 50% of factor VIII in a 1:1 mixture of the patient's plasma and normal plasma after a 2-hour incubation at 37° C. Our patient had an assay of 85.2 Bethesda unit (normal range <50 units).

Both FVIII inhibitors and LA prolong the aPTT, and each autoantibody interferes with the methods designed to detect the presence of the other. LA can interfere with PTT-based factor activity assays, resulting in a falsely decreased FVIII activity level and an erroneous diagnosis of congenital or acquired haemophilia A. Antiphospholipid antibody syndrome may be misdiagnosed due to presence of FVIII inhibitor-associated false positive results for LAs, especially when the silica clotting time (SCT) test is used. The diluted Rusell viper venom time test (dRVVT), which is unaffected by the presence of the other autoantibody, is useful for differentiating between the two[13] which was also the case in our patient, hence LA was tested by dRVVT method.

Lupus anticoagulants are a heterogeneous class of immunoglobulins that bind to glycoprotein I and, more rarely, prothrombin or other proteins in complex with negatively charged phospholipids. Lupus anticoagulants prolong phospholipid-dependent coagulation tests, including the aPTT[10]. The presence of lupus anticoagulants can be incidental or associated with an increased risk of thrombosis. Rarely, the presence of lupus anticoagulants is associated with an increased risk of bleeding.

A high-risk antiphospholipid antibody testing profile is defined by the presence of a positive lupus anticoagulant test[11], whereas the definitive diagnostic criteria include triple positivity for antiphospholipid antibodies (lupus anticoagulants, anticardiolipin IgM and IgG, and beta-2-glycoprotein IgM and IgG antibodies)[12].

In our patient with Sjögren's syndrome with thrombocytopenia and prolonged aPTT, on doing a mixing study to determine the factor inhibitor or factor deficiency, aPTT failed to normalise with the mixing study, and our patient was detected to have a concomitant Lupus anticoagluant and factor VIII inhibitor antibody with the presence of an underlying autoimmune aetiology, hence making this case a rare entity. The patient was started on steroids, and her platelets increased. She became symptomatically better, was then discharged, and is on regular follow-up.

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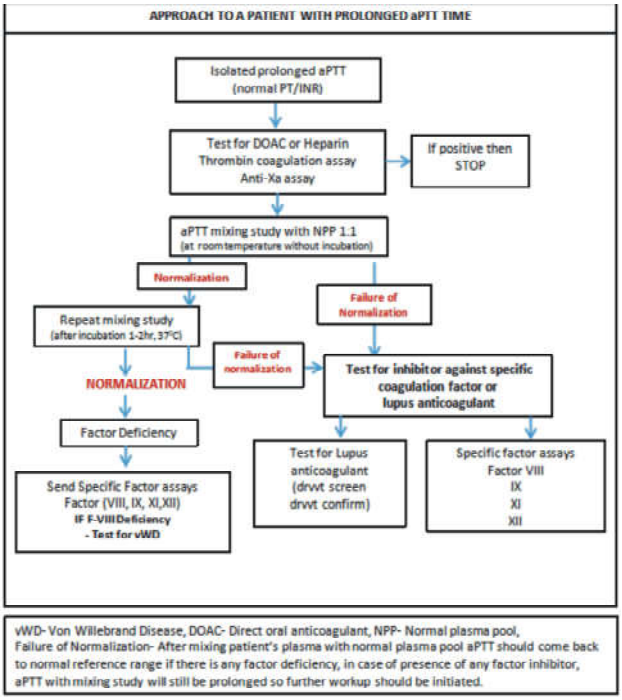

Fig. 1: *Approach to a patient with prolonged aPTT*[14].

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CASE REPORT

JIACM 2024; 25 (1-2): 67-69

Acute Paraplegia: A Rare Presentation of Askin Tumour

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Abstract

Background: Askin tumour is a rare, highly malignant chest wall neoplasm, most commonly observed in children and adolescents. It is a rapidly growing tumour with varied clinical manifestations and is associated with a poor prognosis. Given the non-specific clinical manifestations and aggressive nature of the disease, it is important to diagnose and treat early with a multi-disciplinary team involvement. In our case, a 14-year-old male presented with progressive left-sided chest pain and developed paraplegia due to compressive myelopathy, which is a rare presentation in this case. He was diagnosed with Askin tumour on histopathology and started on chemotherapy.

Key words: Askin tumour, paraplegia, compressive myelopathy.

Introduction

Askin tumour is a rare, aggressive malignant neoplasm of neuroectodermal origin, that arises from the soft tissues of the chest wall. It belongs to the Ewing sarcoma and primitive neuroectodermal tumour (PNET) family sharing histopathological characteristics of small round cells with variable degrees of neuroectodermal differentiation. The tumour occurs mainly in children and adolescents with a male preponderance (1.5:1). It is associated with a poor prognosis with a reported survival of 60% at 5 years[1,2,3].

The presentation can be variable, and symptoms range from being asymptomatic to prominent respiratory complaints such as chest pain, fever, cough, pleural effusions, and weight loss; making the diagnosis challenging[4]. Askin tumour causing acute paraplegia due to compressive myelopathy is extremely rare. Herein, we report a case of a 14-year-old male presenting with chest pain and acute paraparesis who was diagnosed with Askin tumour.

Case report

A 14-year-old male presented to our hospital emergency department with increasing left-sided chest pain for 20 days. He had no history of fever, cough, breathlessness. A chest X-ray showed left upper and mid-zone homogeneous rounded opacity (Fig. 1). A contrast computed tomography (CT) scan of the chest showed a large well-defined heterogeneously enhancing left apical mass lesion, eroding the posterior aspect of 2nd rib, measuring 8.6 x 7.2 x 9.3 cm (Fig. 2).

The patient was admitted to the ward for pain management and evaluation. His routine blood tests were within normal range apart from mild anaemia. A bronchoscopy and bronchoalveolar lavage (BAL) were performed from the left upper lobe. There was no endobronchial growth and BAL sample was negative for routine culture, acid-fast bacilli (AFB) smear, Gene-xpert and cytology. He developed sudden onset progressive bilateral lower limb weakness for 4 days and loss of sensation below the umbilicus and

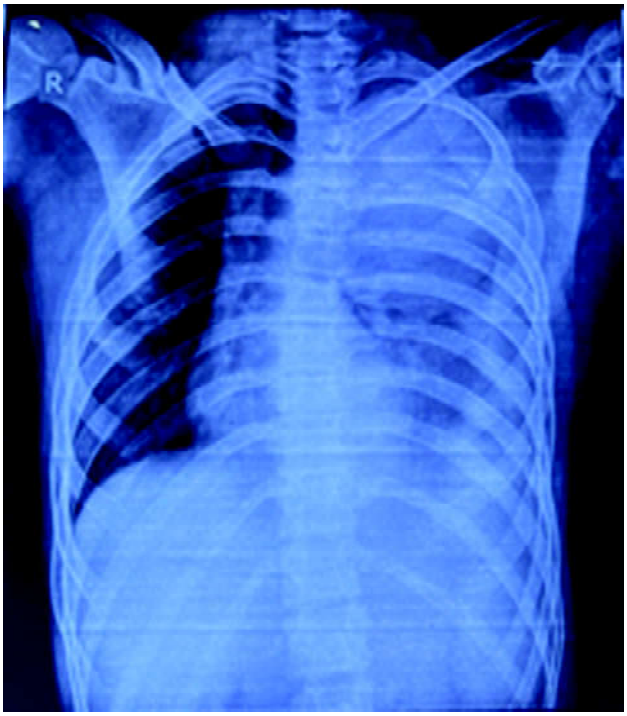

Fig. 1: *Chest X-ray showing round opacity in left upper and midzone.*

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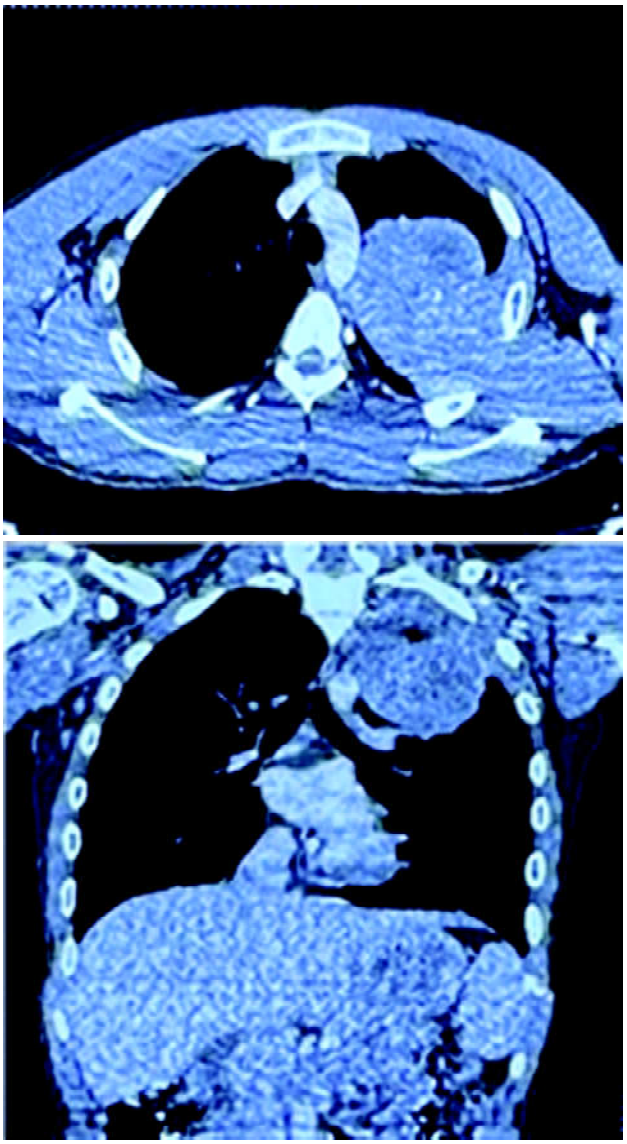

Fig. 2: *CT-chest demonstrating a heterogeneous left apical soft tissue mass eroding the posterior aspect of 2nd rib.*

urinary incontinence for 3 days. On neurological examination, his power was 5/5 in bilateral upper limbs and 0/5 in bilateral lower limbs along with brisk reflexes and loss of touch, vibration and joint position sense in bilateral lower limbs. Neurological consult was taken and the patient was started on intravenous methylprednisolone 500 mg, for suspected transverse myelitis. A magnetic resonance imaging (MRI) of the spine was performed that demonstrated a heterogeneous mass in the left upper thoracic cavity causing compressive myelopathy from D2 to D4, erosion of 2nd rib and infiltration into paraspinal muscles (Fig. 3).

Methylprednisolone was stopped and the patient was electively intubated for airway protection. Ultrasonography

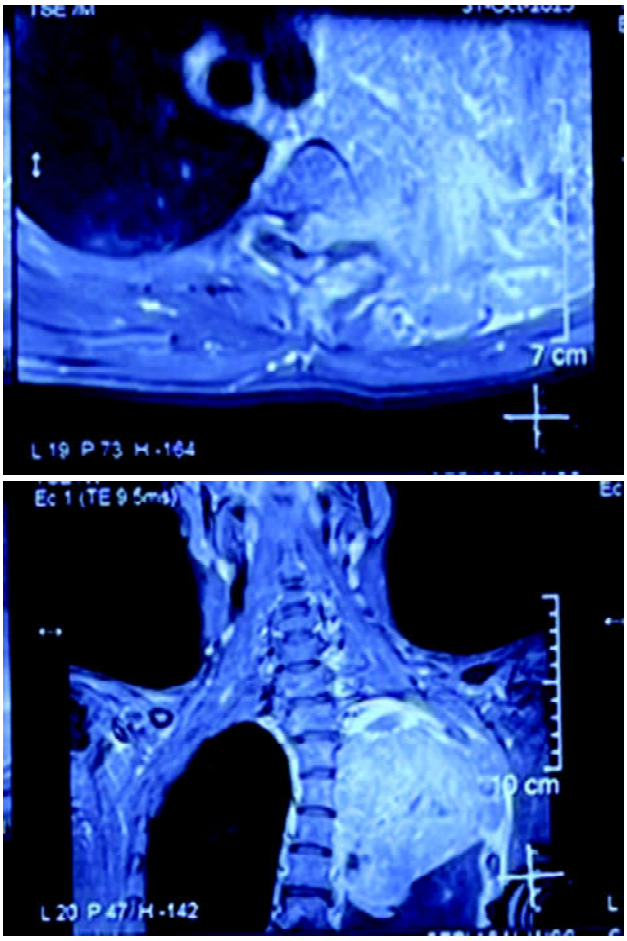

Fig. 3: *MRI showing heterogeneous hyperintense mass lesion in the left upper thoracic cavity causing compression from D2-D4.*

(USG)-guided tru-cut biopsy of the mass was performed via posterior approach. The histopathology reported the presence of a small round cell tumour (Fig. 4A). The immunohistochemistry was positive for CD99 suggestive of Askin tumour (Fig. 4B).

The patient was referred to oncology and initiated on chemotherapy with a Etoposide, Carboplatin and dexamethasone with a reassessment of tumour size after three cycles for radiotherapy and consideration for surgical resection.

Discussion

Askin tumours are small round blue cell tumours of soft tissues of chest wall that belong to the Ewing sarcoma family of tumours (ESFT). It is a highly malignant neoplasm with potential for loco-regional spread and recurrence, associated with poor prognosis. The clinical presentation can be non-specific including an incidentally detected mass on chest X-ray to a rapidly growing painful, palpable large mass[1,5]. However, a rapidly growing mass causing

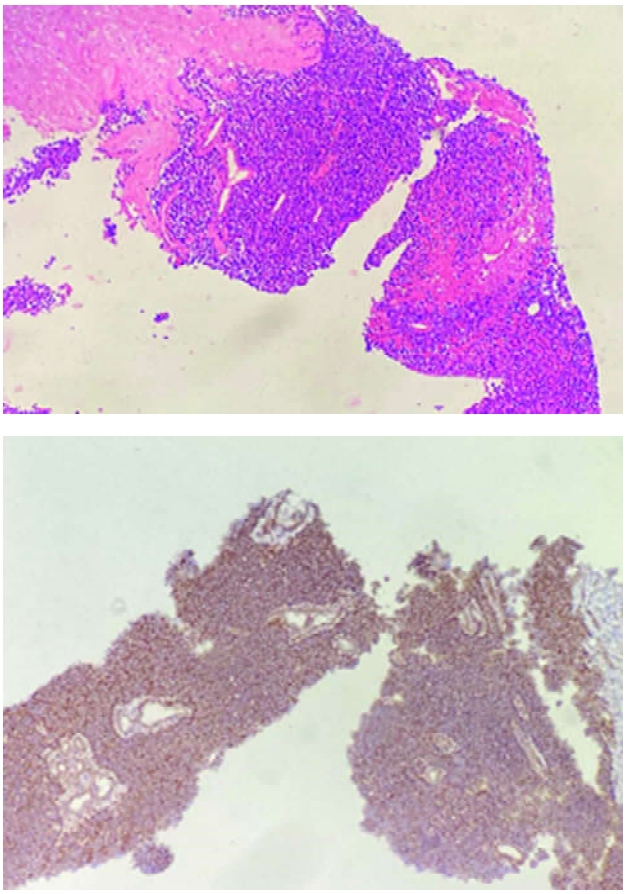

Fig. 4A: *Sheets of round to oval cells with* ***(B):*** *CD99-strong membranous positivity scant cytoplasm.*

compressive myelopathy and acute paraparesis are rare presentations, and to our knowledge, only two cases in the literature have been reported so far. The differential diagnosis that was considered in this case were acute transverse myelitis, and Gullian Barre syndrome (GBS).

These tumours appear as heterogeneous masses on MRI and CT scan with areas of cystic degeneration, necrosis, haemorrhage and pleural effusions. Rib destruction is observed in 25 - 63% of cases[6].

Primary chest wall tumours constitute less than five per cent of thoracic neoplasms, with a malignancy rate of fifty per cent. Fifty-five per cent arise from bone or cartilage and forty-five per cent arise from soft tissues. About twenty per cent are discovered incidentally. The most common primary chest wall malignant tumour is chondrosarcoma; other differential causes include rhabdomyosarcoma, plasmacytoma, neuroblastoma, lymphoma, neurofibroma and metastatic disease[4,7]. Our case was diagnosed based on the aggressive nature of the disease, biopsy findings of small round blue cells and positive CD 99 stain on IHC.

There are limited clinical trials to provide a definite consensus on management. A multimodality treatment approach of chemotherapy followed by *en bloc* resection and adjuvant chemoradiation is associated with a 5-year overall survival rate of 60.7%. Poor prognostic factors include age >18 years, poor response to induction chemotherapy, and presence of pleural effusion[8].

Conclusion

Askin tumour is a rare cause of a chest wall mass with variable and non-specific clinico-radiological presentation. It is an aggressive tumour that can cause acute paraplegia due to compressive myelopathy and should be kept as a differential in a young patient with a chest wall mass presenting with paraparesis. Hence, timely diagnosis and prompt multidisciplinary team involvement can prolong the overall survival significantly.

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CASE REPORT

JIACM 2024; 25 (1-2): 70-72

Severe Hypercalcaemia and Hepatosplenic Granulomas: A Rare Presentation of Multisystemic Sarcoidosis

Gurinder Mohan, Hargurdas Singh**, Ranjeet Kaur****

Abstract

Sarcoidosis is an orphan disease characterised by non-caseating granulomas with predominant pulmonary involvement, heterogeneous presentations, and variable incidence and prevalence. Here we are presenting the case of a 60-year-old female with multisystemic sarcoidosis who presented with chronic gastrointestinal manifestations and severe hypercalcaemia. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) from subcarinal and paratracheal lymph nodes revealed non-caseating epithelioid cell granuloma which was negative for acid-fast bacilli and tuberculosis PCR. The diagnosis of sarcoidosis is difficult, especially in tuberculosis-endemic countries.

Key words: Sarcoidosis, EBUS-TBNA, hypercalcaemia, non-caseating granuloma.

Introduction

Sarcoidosis is a systemic granulomatous disease of unknown aetiology with different phenotypic as well as biochemical presentations[1]. It is a global disease with a variable prevalence of 3.68 cases per 1,00,000 people in Eastern Europe to 40 cases per 1,00,000 people in Northern Europe[2]. The incidence seems to be higher among Blacks than Whites. In India, sarcoidosis incidence is estimated to be 10 to 12 cases/1,000 new registrations annually at the respiratory unit at Kolkata and 61.2/1,00,000 new cases seen at Vallabhbhai Patel Chest Institute, Delhi[3]. The exact prevalence is not well studied in India due to inadequate epidemiological data and under-reporting due to lack of awareness, scarce invasive diagnostic tests, and frequent misdiagnosis as tuberculosis due to strong clinico-radiological resemblance[1]. The exact cause is unknown and multiple factors like genetics, environmental, and infectious triggers leading to immune-mediated inflammatory response have been postulated. Around 25 - 30% of patients have extrapulmonary involvement in the skin, eyes, musculoskeletal system, kidneys, heart, central nervous system, and exocrine glands. But hepatosplenic involvement is around 3 - 4%[4].

Case report

A known diabetic, hypertensive, hypothyroid 60-year-old lady presented with pain abdomen, loss of appetite, constipation, weight loss, and grade 1 - 2 breathlessness according to Modified Medical Research Council grading from the last 3 years which got aggravated in the last 2 months. On examination, bilateral fine crackles were present in both infra-scapular areas, and hepatosplenomegaly was also present. Laboratory investigations are depicted in Table I. Abdominal ultrasonography revealed hepatosplenomegaly with multiple hypoechoic areas in the spleen. Contrast-enhanced computed tomography (CECT) of abdomen (Fig. 1a) confirmed ill-defined nodules in the spleen and liver with retroperitoneal lymphadenopathy suggestive of granulomatous disease. CECT chest (Fig. 1b) also suggested multiple nodules in all lobes of both lungs with tree-in-bud appearance and mediastinal lymphadenopathy. Bronchoscopy showed no endobronchial lesions; and EBUS-guided transbronchial needle aspiration (EBUS-TBNA) from subcarinal and paratracheal lymph nodes showed non-caseating epithelioid cell granuloma which was negative for acid-fast bacilli and tuberculosis PCR. Complete blood counts, renal function tests, serum glutamic-pyruvic transaminase, and serum glutamic-oxaloacetic transaminase, serum albumin, and ECG were normal. Viral markers, sputum for Cartridge Based Nucleic Acid Amplification Test (CBNAAT), urine, and blood culture were negative. She responded well to fluid resuscitation, salmon calcitonin, and oral steroids along with supportive care. The corticosteroid-sparing medication methotrexate with folic acid were added as it was difficult to taper steroids and associated co-morbidities. The patient is doing well on follow-up at 18 months.

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Table I: Laboratory investigations.

Parameters	Results	Reference range
CRP	12 mg/L	0 - 5.0 mg/L
ESR	32 mm/hr	4 - 12 mm/hr
Alkaline phosphatase	602.4 U/L	46 - 116 U/L
Corrected Calcium	15 mg/dL	8.4 - 10.4 mg/dL
Serum Phosphate	2.32 m/dL	2.5 - 4.5 mg/dL
25-Hydroxy-Vitamin D	18.3 ng/mL	30 - 100 ng/mL
Se. Parathyroid Hormone Intact	7.40 pg/mL	14 - 72 pg/mL
Se. Angiotensin Converting Enzyme	208 U/L	8 - 52 U/L
HbA1C	7.1%	6.5%
Thyroid profile	FT3 2.76pg/mL, FT4 1.24 ng/dL, TSH 7.91 mIU/L	2.45 - 5.93 pg/mL 0.78 - 2.19 ng/dL 0.46 - 4.68 mIU/L
Anti-thyroid peroxidase antibody	>1,300 U/mL	<60.00 U/mL

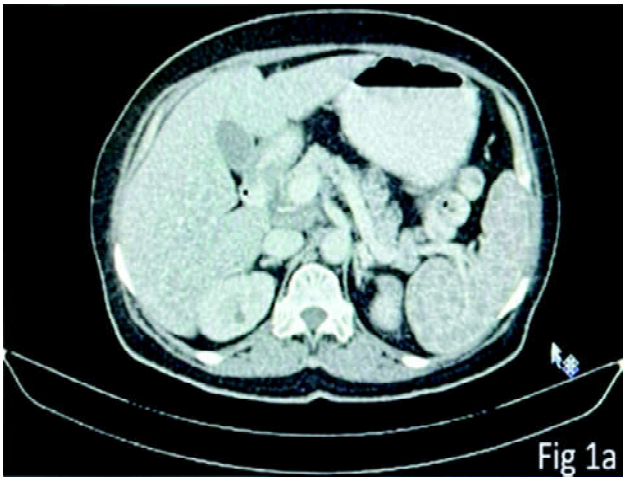

Fig. 1.a: *CECT abdomen showing Ill-defined nodules in spleen and liver.*

Discussion

Sarcoidosis incidence is more in the 4th decade with a second peak occurring around 65 years of age[2]. Female predominance is well documented with more ocular and neurological manifestations. Some Indian studies have found no gender predominance[4]. Non-caseating granulomas are the hallmark of this disease. Immunopathogenetic mechanisms triggering T-cell antigen stimulate a cascade of events leading to non-caseating granuloma formation. First-degree relatives have an increased risk of developing the disease by five-fold. Certain HLA alleles are associated with increased susceptibility like HLA-DRB1*03, *11, *12, *14, *15, and with certain phenotypes like HLA-DRB1*1101 with cardiac sarcoidosis[2].

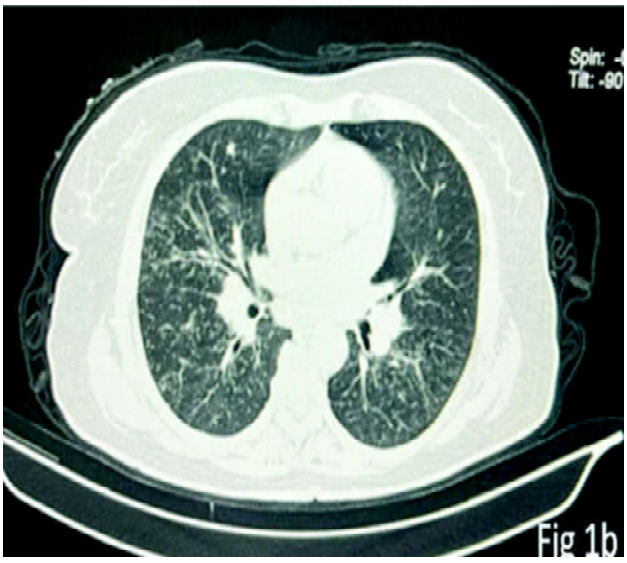

Fig. 1b: *CECT thorax showing perilymphatic micronodular opacities.*

Nath *et al* 2019 did a retrospective study from January 2014 to December 2018 and found gastrointestinal involvement in eight patients (6.67%) out of 120 with only 4 having hepatosplenomegaly with hypodense lesions[5]. Graf *et al* (2021) found hepatic sarcoidosis in 4.2% patients, 62 out of 1476 sarcoidosis patients diagnosed between 2004 to 2020 in 5 German centres, and cirrhosis was found in 9 patients[6]. The most common presentation is the cholestatic pattern with raised alkaline phosphatase and gamma-glutamyl transferase as seen in our patient. If untreated and not diagnosed in time, can lead to portal hypertension, end-stage liver disease, and cirrhosis. Madan *et al* (2022) found only 1.5 - 3% hepatosplenic involvement and 3.8 % hypercalcaemia on ambispective analysis of 327 sarcoidosis patients at AIIMS, New Delhi diagnosed between 2013 to 2019[4]. Also, 12.2% had hypothyroidism and nearly 30% had received anti-tubercular treatment[4]. Autoimmune thyroid disease with positive autoantibodies has been associated with sarcoidosis and hypothyroidism being more common as in our patient[7]. There can be direct granulomatous infiltration of the thyroid gland or an associated autoimmune process. Sarcoidosis patients have higher levels of thyroid peroxidase antibodies and/or thyroglobulin antibodies. It is a major co-morbidity that should be diagnosed and treated in time. Serum ACE levels are raised in around only 50% of cases as in our patient and normal levels do not rule-out sarcoidosis. The ACE levels can also be raised in tuberculosis, lymphoma, or atypical mycobacterial infection. As hypercalcaemia can be due to infective or non-infective granulomatous disease or malignancy, it becomes a diagnostic challenge to rule out these. The patient also had severe hypercalcaemia with a corrected calcium level of 15 mg/dL. As hypercalcaemia

can be due to infective or non-infective granulomatous disease or malignancy, it becomes a diagnostic challenge to rule-out these, especially in developing countries like India. Anand *et al* 2015 reported a case of a 35-year-old lady with isolated abdominal sarcoidosis presenting with hypercalcaemic crisis[8]. Although asymptomatic hypercalcaemia is more common. The index patients had primarily gastrointestinal symptoms for a long time due to sarcoidosis as well as hypothyroidism which remained undiagnosed and later aggravated leading to severe hypercalcaemia. Even though bronchoscopy, BAL, EBUS-TBNA, and lung biopsy are invasive and costly, but very helpful to delineate the exact aetiology and rule out neoplasm as well as other infective aetiologies, especially tuberculosis. Because of its clinical heterogeneity, learning about varied presentations is crucial to avoid missed or delayed diagnoses. Pulmonary involvement is the most common cause of morbidity and mortality in sarcoidosis patients. The true burden of sarcoidosis is not known because of underreporting, varied presentation, and inaccurate diagnosis. The treatment goal is to decrease granuloma formation and progression, thus decreasing the risk of morbidity, mortality and improving quality-of-life[9]. Many patients undergo spontaneous remission on their own but some follow a more chronic progressive course. Mortality increases with time due to disease or treatment complications. Treatment is considered for those with high symptom burden and/or organ damage with more aggressive approach in case of hypercalcaemia, neurological, cardiac, or ophthalmic involvement. The first-line treatment is corticosteroids; 20 - 40 mg/day prednisolone maintained over 1 to 3 months and then gradually tapered to 5 - 10 mg/day over 6 months to 1 year. Corticosteroid-sparing medication like methotrexate, azathioprine, leflunomide, and mycophenolate mofetil is used when inability to taper steroids below 10 mg/day or relapse or increased complications or side effects[9]. The biologics like Tumour Necrosis Factor-alpha (TNF-a) inhibitors infliximab, adalimumab, and rituximab are given in case of non-remitting disease or relapse according to the systemic involvement[10].

Take home message

Sarcoidosis is not as rare as earlier thought in tuberculosis-endemic countries like India but still not much reported and diagnosed in time. Bronchoscopy and EBUS-TBNA play an important diagnostic role. Extrapulmonary and gastrointestinal manifestations can be the first presenting features. Autoimmune thyroid disease should be ruled-out.

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CASE REPORT

JIACM 2024; 25 (1-2): 73-77

Vasculitic Neuropathy Secondary to Disseminated Brucellosis Manifesting as Bilateral Foot Drop

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Abstract

Brucellosis is a bacterial zoonosis of global concern prevalent in countries having major shares in the livestock segment. It is often underdiagnosed due to its misleading clinical picture. Half-a-million cases are estimated globally, with population at risk of 2.4 billion. The disease encompasses a wide spectrum of clinical manifestations involving many organ systems. Neurological involvement occurs in up to 10% of cases and is a rare sequelae of brucellosis. We present the case report of a 19-year-old lady with disseminated brucellosis who developed bilateral foot drop as a manifestation of vasculitic polyneuropathy.

Key words: Neurobrucellosis, foot drop, vasculitic neuropathy.

Introduction

Brucellosis is a zoonotic infection caused by bacteria of the genus *Brucella* and is a major public health concern in many parts of the world, including India where it is endemic in several states. It has a diverse range of clinical manifestations depending upon the organs involved. Common symptoms include fever, night sweats, chills, headache and musculoskeletal symptoms. Neurobrucellosis is a rare complication of Brucellosis that occurs in less than 5% of the patients with disease[1]. It is a severe and potentially life-threatening condition that affects both central and peripheral nervous systems affecting the brain, spinal cord, and nerves. Bacteria invade the nervous system through bloodstream or by direct extension from an adjacent infected area. Common symptoms include headache, fever, lethargy, depression, meningoencephalitis, intracerebral abscess, cranial nerve deficits, myelitis, and radiculitis. In severe cases, patients may develop seizures, coma or permanent neurological deficits.

The transmission of brucellosis occurs through direct or indirect contact with infected animals such as cattle, goats and pigs, or their derived products including milk, meat, cheese, or ice cream. Brucellosis is acquired by ingestion, inhalation, mucosal or percutaneous exposure. In India, where livestock sector is a significant contributor to the economy, prevalence of brucellosis remains high[2]. Close proximity of humans and animals, poor hygiene practices, and lack of awareness contribute to the spread of the disease.

As healthcare personnel, it is essential to recognise the clinical manifestations of brucellosis and to consider it in the differential diagnosis, especially in patients with a history of exposure to animals or their products. Pancytopenia, polyneuropathy, and foot drop, as observed in this case report, are rare presentations of brucellosis and require prompt evaluation and management.

Case report

A 19-year-old lady, presented to the emergency department with a history of fever and joint pains for two months associated with weakness of both lower limbs for 20 days. The fever was insidious in onset, intermittent in nature, initially low grade, which subsided with medication. However, for the past one month, the patient experienced high grade continuous fever (102° - 103° F) associated with chills, night sweats, and non-projectile vomiting. She also developed a reddish-pink maculopapular exanthem predominantly over the trunk. There was a history of generalised weakness, fatigue, headache, vomiting and shortness of breath on exertion. She also reported a four to five kilogram weight loss in the last two months. Joint pains predominantly involved both large and small joints symmetrically and were not relieved by rest. Weakness of both lower limbs developed insidiously, making it difficult for the patient to walk and perform daily household activities for the last 10 days. It was also associated with numbness in both feet. The patient had no significant past medical history or family history. The patient reported a history of exposure to domestic animals, which included cattle and she was actively involved in the care of these animals.

On physical examination, the patient was febrile (102° F) with pallor, tachycardia and level II, III, IV group of cervical

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lymphadenopathy. Her body mass index (BMI) was significantly low (15.6 kg/m^2). Musculoskeletal examination revealed acute, bilaterally symmetrical polyarthritis involving both large and small joints, predominantly hip and knee joints and flexion contracture of the lower limbs at hip and knee with bilateral foot drop (Fig. 1 and 2). On neurological examination, higher mental functions were normal. Motor examination revealed a flexion attitude at bilateral hip and knee joints with reduced bulk and tone in the bilateral lower limbs. Power was assessed around all joints and found to be in the range of 0/5 to 3/5 in all movements at the hip, knee and ankle joints. Sensory system examination revealed loss of both superficial and deep sensations in bilateral foot in a non-dermatomal fashion pointing towards polyneuropathy. All the sensations above the ankle joints were normal. There was no evidence of cerebellar, autonomic or meningeal involvement. Abdominal examination revealed mild epigastric tenderness. The liver was enlarged, non-tender, with a liver span of 15 cm, smooth surface, rounded margins and soft in consistency. The spleen was not palpable. The cardiovascular and respiratory systems were normal on examination.

Laboratory investigations (Table I) revealed severe anaemia with a haemoglobin level of 5.5 g/dL, leukocytosis with a total leukocyte count of 12.80 x $10^3/\mu L$, and a platelet count of 108 x $10^3/\mu L$. The reticulocyte production index was

Fig. 1: *Bilateral foot drop.*

Fig. 2: *Flexion contracture and deformity at bilateral hip and knee joints.*

calculated at 0.45, indicating reduced erythropoiesis. Tests for viral markers including HIV, HBsAg, and anti-HCV were negative, while serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were found to be significantly elevated. Smear for malarial parasite, dengue serology, typhoid antibodies, anti-streptolysin O titres were negative and were done to rule out the sequelae of common tropical infections prevalent in our area. Liver and kidney function tests were unremarkable. A chest radiograph revealed areas of increased opacity in bilateral upper and middle lung zones. Ultrasound abdomen showed hepatomegaly (liver size 16.5 cm) and splenomegaly (spleen size 12.5 cm). She was started on intravenous ceftriaxone 1 gm 12 hourly, intravenous paracetamol 1 gm 8 hourly, proton pump inhibitors (PPIs) and intravenous fluids.

Her haemoglobin remained consistently low even after transfusing two units of packed cell volume with no improvement in fever spikes, and hence antibiotics were upgraded to intravenous piperacillin and tazobactam 4.5 gm 6 hourly on day four of admission, followed by the addition of intravenous vancomycin 1 gm 12 hourly on the sixth day. The patient developed blackish discoloration of the right great and second toes for which Doppler ultrasonography of the lower extremity arteries and coagulation profile were done and found normal except for D-dimer, which was significantly elevated (1,321 ng/mL, normal reference range: <250 ng/mL). The patient was treated along the lines of disseminated intravascular coagulation (DIC). Blood cultures and 2D echocardiography were done to rule out infective endocarditis and were unremarkable. By day 11, there was no progression in toe discoloration, and the coagulation profile was normal.

The patient continued to have fever spikes despite antibiotics. A contrast-enhanced computed tomography

(CECT) scan of the chest and abdomen was done to rule-out any collection or other sources of infection. CECT chest showed bilateral mild-to-moderate pleural effusion with underlying linear areas of atelectasis and ground-glass opacities in the posterior segment of bilateral upper, superior, and basal segments of bilateral lower lobes, along with multiple subcentimetric sized lymph nodes in the pre and paratracheal regions (Fig. 3 and 4). Bone marrow aspiration and biopsy were also conducted to investigate the possibility of tuberculosis, lymphoma, or haemophagocytic lymphohistiocytosis. However, the results were inconclusive, showing erythroblastopenia and a hypocellular marrow. The patient was continued on the same antibiotics.

Table I: Laboratory investigations of the patient on presentation.

Lab parameter	Observed value	Normal reference range
Haemoglobin	5.5 g/dL	11.0 - 16.0 g/dL
Total leukocyte count	12.80 x 10^3/μL	4.00 - 10.00 x 10^9/L
Absolute platelet count	108 x 10^3/μL	100 - 300 x 10^9/L
ESR	132 mm/1st hour	≤20 mm/hr
CRP	76.09 mg/L	<5 mg/L
Blood urea	57 mg/dL	10 - 50 mg/dL
Serum creatinine	0.5 mg/dL	0.7 - 1.3 mg/dL
Aspartate amimotransferase	41 U/L	Upto 40 U/L
Alanine amiontransferase	27 U/L	Upto 40 U/L
Alkaline phosphatase	67 U/L	39 - 117 U/L
Serum Protein	6.4 g/dL	6 - 8 g/dL
Serum Albumin	3.3 g/dL	3.8 - 4.4 g/dL
Total Bilirubin	0.7 mg/dL	0.2 - 0.8 mg/dL
Direct Bilirubin	0.2 mg/dL	0 - 0.2 mg/dL
Indirect Bilirubin	0.5 mg/dL	0.2 - 0.7 mg/dL
Anti-Streptolysin O titre	60 IU/ml	Less than 200 IU/mL

The patient's fever improved subsequently and touched baseline on day 21 of admission, and a repeat neurological examination showed improvement in power around bilateral knee and hip joints. But the patient still experienced difficulty walking without support. Further, a high stepping gait was observed in the right lower limb more than the left lower limb. A magnetic resonance imaging (MRI) scan of the spine and bilateral sacroiliac joints was done to rule out sacroiliitis or compressive neuropathy, which were unremarkable. Nerve conduction studies were performed and revealed prolonged latency and reduced amplitude of compound motor action potentials in bilateral tibial and peroneal nerves. Sensory nerve action potentials showed

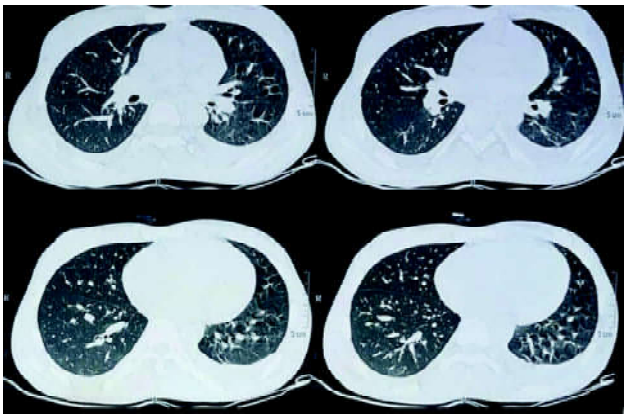

Fig. 3: *Bilateral mild-to-moderate pleural effusion with underlying linear areas of atelectasis and ground-glass opacities in the posterior segment of bilateral lower lobes.*

decreased amplitude and velocity with prolonged peak latency in bilateral sural nerves. F-wave latencies were prolonged in bilateral tibial and peroneal nerves. The results were consistent with bilateral sensorimotor polyneuropathy involving deep peroneal, sural, and tibial nerves.

Sural nerve biopsy was performed which revealed a florid acute axonal breakdown with perivascular and interstitial inflammation suggestive of inflammatory neuropathy consistent with vasculitic neuropathy. Based on her history and a strong clinical suspicion, Brucella serology titres were sent which revealed positive Brucella IgM antibodies with a value of 13.62 (reference positive was >11.0), and the patient thereafter was started on streptomycin 750 mg intramuscular (IM) once daily, oral doxycycline 100 mg twice daily and oral rifampicin 600 mg once daily. The patient was also started on oral prednisolone 40 mg once daily for one month and gradually tapered over the next two months. She remained afebrile and took discharge on request on oral rifampicin 600 mg once daily, oral doxycycline 100 mg twice daily, oral acetaminophen 650 mg once daily and oral iron supplementation. Antibiotics were continued for the next three months and regular physiotherapy was advised along with customised braces for foot drop.

Subsequently, cytopenias improved dramatically. The patient could walk without support after two months. The power of the muscles around bilateral ankle joints improved from 1/5 to 3/5 two months post-treatment. She continued to have right-sided foot drop after six months of therapy for which she was on regular physiotherapy. After one year of therapy, the patient completely recovered with no residual weakness or deformity. Hence, a final diagnosis of disseminated brucellosis was made. Various complications secondary to brucellosis were seen in our patient which included hepatosplenomegaly, lymphadenopathy

(reticuloendothelial), anaemia, leucocytosis, lymphopenia, thrombocytopenia, DIC (haematological), polyarthritis, flexion contracture (musculoskeletal), pleural effusion (pulmonary), foot drop and sensorimotor polyneuropathy (neurological).

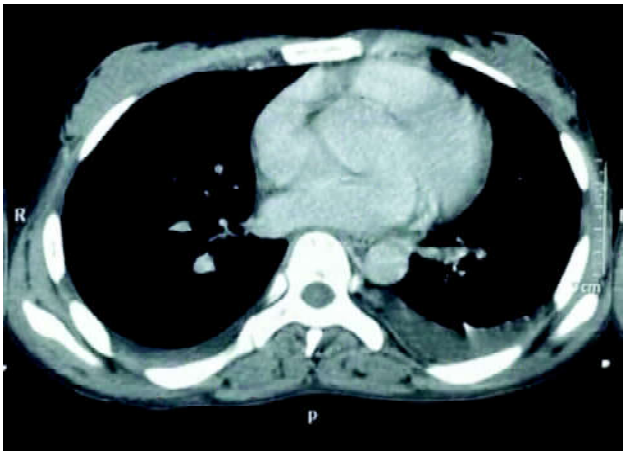

Fig. 4: *Multiple sub-centimetric sized lymph nodes in the pre and paratracheal regions.*

Discussion

Brucellosis is considered a difficult and deceptive disease in India, with musculoskeletal symptoms commonly observed and reported. Our patient showed signs and symptoms of disseminated brucellosis, including pleural effusion. There were haematological manifestations secondary to bone marrow suppression leading to anaemia, leucocytosis, thrombocytopenia, and DIC. The patient also showed signs of hepatosplenomegaly and lymphadenopathy with cutaneous involvement. Despite various case studies on brucellosis, neurobrucellosis remains a rarer manifestation of the disease.

The pathophysiology of neurobrucellosis, though not well studied, has three hypotheses. The first hypothesis suggests that the bacterium directly damages the nervous system. The second hypothesis proposes that the release of harmful cytokines or endotoxins by the immune system in response to the infection causes damage of nerves. The third hypothesis proposes that the inflammatory response mounted by the immune system to the Brucella antigen within the nervous system causes nerve damage[3]. In a large European case series, 82 patients had neurological involvement among 648 confirmed cases of brucellosis, with the most common manifestations being radiculopathies of the legs (41.46%), neck rigidity (46.34%), agitation (25.6%), behavioural disorders (18.3%), disorientation (19.5%) and stroke (1.22%). Cranial nerve involvement was also reported (24.4%)[4].

Foot drop and polyneuropathy are exceptionally rare presentations of neurobrucellosis. In a Turkish study by Inayat *et al*, foot drop was observed in only 0.09% of cases[5]. There are also case reports of permanent paralysis or hemiparesis secondary to brucellosis. Early diagnosis and prompt treatment play crucial roles in determining the prognosis of the disease in a patient. Neurological manifestations are likely to be reversed if diagnosed at an early stage. Doxycycline, rifampicin, and third-generation cephalosporins should be considered both standard and first choice medications for neurobrucellosis.

The diagnosis of brucellosis requires both clinical and serological aids. Common diagnostic tests include antibody detection against lipopolysaccharide, such as standard tube agglutination tests (SAT) and enzyme-linked immunosorbent assays (ELISA). Other tests include Brucella DNA detection by polymerase chain reaction, indirect immunofluorescence, the Wright agglutination test, the Rose Bengal test and bone marrow culture. Cerebrospinal fluid (CSF) Brucella antibody titre is an important diagnostic modality besides culture. CSF Brucella titres >1:8 demonstrated a sensitivity of 94% and a specificity of 96%[5].

The recommended treatment for uncomplicated brucellosis in adults is a combination of doxycycline and an aminoglycoside, with doxycycline-rifampicin and doxycycline- cotrimoxazole serving as alternative regimens. Quinolones may also be considered. For children under eight years old, cotrimoxazole plus rifampicin administered for six weeks may be the optimal treatment choice. For complicated cases or neurobrucellosis, a triple drug regimen of ceftriaxone-rifampicin-doxycycline is given in non-pregnant adults, while in pregnant women, ceftriaxone-rifampicin-cotrimoxazole is used. The duration of therapy is extended for four to six months in cases of meningitis or endocarditis. The use of corticosteroids can be a double-edged sword since the pathogenesis of polyneuropathy can be multifactorial, including sepsis, multiorgan failure, vasculitis, systemic inflammatory response syndrome (SIRS), malnutrition, prolonged immobilisation, critical illness polyneuropathy, or a deranged metabolic profile. In this case, the patient responded well with an improvement in disability.

The relapse rate after treatment for brucellosis ranges from 5 to 15 per cent[6]. Typically, relapse occurs within the first six months after the completion of treatment, although it can occur up to 12 months later. There are various causes for the same, like an inadequate antibiotic regimen or duration of therapy, a lack of adherence, or localised foci of infection. Hence, regular follow-up, at least for two years from the time of diagnosis is crucial.

Various ways to prevent brucellosis include avoiding

unpasteurised dairy products, wearing protective clothing, washing hands thoroughly after handling animals or animal products and vaccinating animals, particularly livestock against brucellosis. Thus, by educating individuals who are at risk of contracting the disease, the disease burden can be reduced thereby limiting its spread. The response to treatment can take time, as seen in this case, but nonetheless with appropriate testing and treatment, this uncommon complication was managed.

Conclusion

India comprises one of the largest livestock population in the world and brucellosis is a common and often neglected zoonotic disease. It must be considered as an important differential diagnosis in pyrexia of unknown origin and polyarthralgia. It often mimics the signs and symptoms of tuberculosis and hence often missed by the physicians. Importantly, neurobrucellosis is a rare but a lethal complication of brucellosis, manifestations ranging from cranial nerve palsies and neuropathies to fatal strokes.

Timely identification, swift diagnosis and rapid intervention can prevent irreversible manifestations of brucellosis. It is recommended to encourage active collaboration between health and veterinary services. At the same time, it is crucial to be aware of its clinical manifestations, modes of transmission and treatment options. Improving awareness among the general population, implementing effective control measures in the livestock sector and strengthening diagnostic and treatment facilities can help reduce the burden of brucellosis in India.

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PICTORIAL CME

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Homozygous Familial Hypercholesterolaemia with Severe Aortic Stenosis

*Prabhat Kumar**

A 24-year-old male patient presented with complaints of multiple nodular lesions on the body since the age of 5 years and exertional dyspnoea for 1 year. He was born to non-consanguineous parents and his developmental milestones were normal. His parents and one brother were healthy with no skin lesions or cardiac conditions. On examination, his BMI was 24 kg/m^2 and he had multiple tendinous/tuberous xanthomas on elbow, knuckles and achilles tendon, with polydactyly (Fig. 1-3). He also had cutaneous xanthomas over the body, xanthelasma palpebrarum and arcus juvenilis (Fig. 4-5). Systemic examination revealed grade 4 ejection systolic murmur in aortic area which was radiating to the carotids.

Blood investigations showed normal haemogram, blood glucose levels, thyroid, renal and liver function tests. However, lipid profile was grossly deranged with total cholesterol level of 730 mg/dL and LDL cholesterol level of 565 mg/dL. Echocardiography revealed severe supravalvular aortic stenosis. A diagnosis of homozygous familial hypercholesterolaemia was made and he was started on tablet rosuvastatin 40 mg, ezetimibe 10 mg, bempedoic acid 180 mg and aspirin 75 mg daily. Repeat lipid profile done after two months showed marginal change with total cholesterol level of 573 mg/dL and LDL-C of 483 mg/dL. He was advised lipoprotein apheresis, but could not be done due to financial constraints. His parents and sibling were also screened and all of them had LDL-C level of greater than 200 mg/dL without any skin manifestation, suggesting heterozygous familial hypercholesterolaemia.

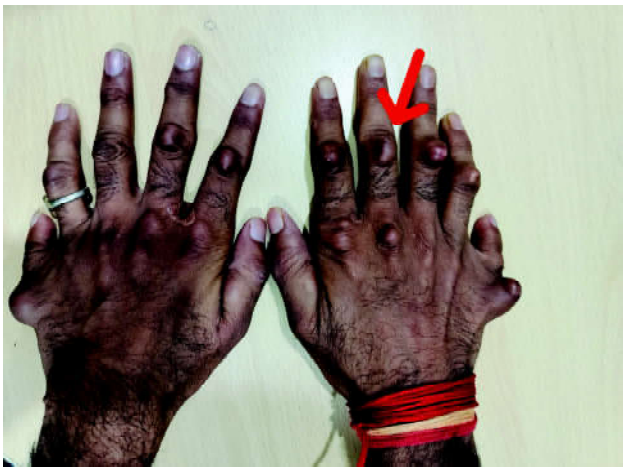

Fig. 1: *Tendinous xanthomas on knuckles with polydactyly.*

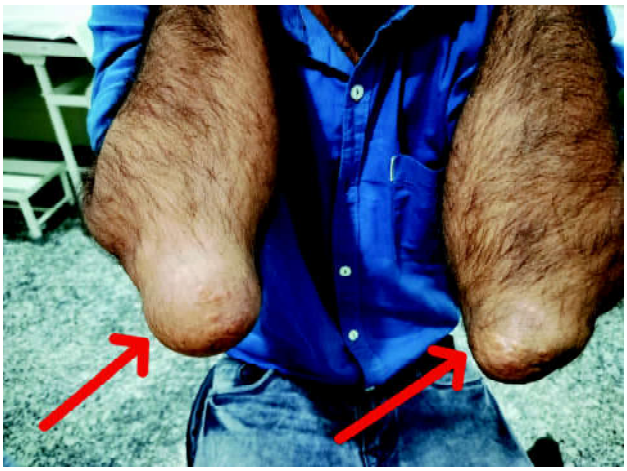

Fig. 2: *Tuberous xanthomas on elbow joints.*

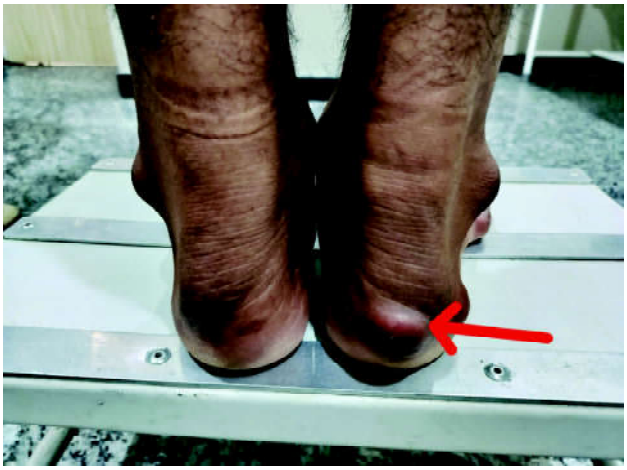

Fig. 3: *Tuberous xanthomas on achilles tendons.*

Familial hypercholesterolaemia (FH) is an inherited disorder characterised by severe elevation of serum LDL levels due

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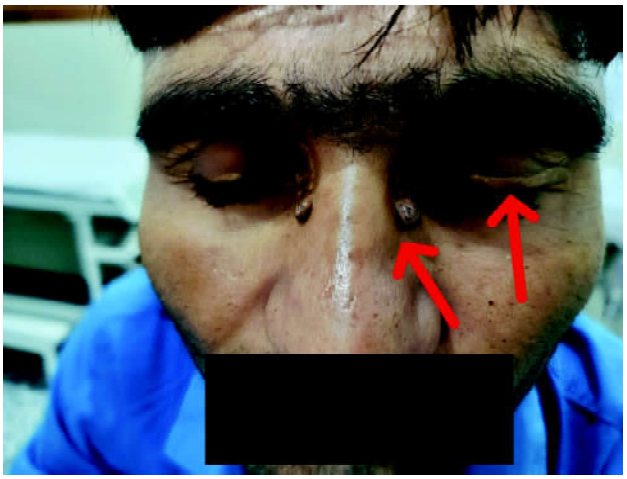

Fig. 4: *Xanthelasma palpebrarum on eyelids.*

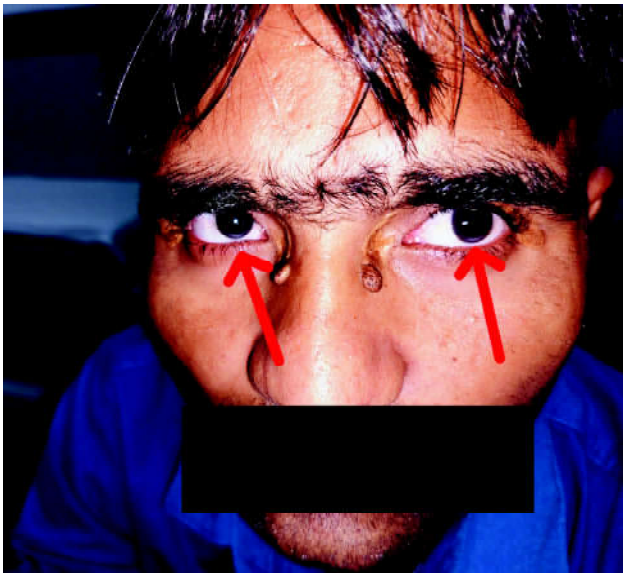

Fig. 5: *Arcus juvenilis.*

to mutations of the genes involved in the LDL receptor-mediated pathway for uptake of LDL[1]. There are three main genetic mutations in FH; defect in the LDL receptor (most common), apolipoprotein B (ApoB), or proprotein convertase subtilisin/Kexin type 9 (PCSK9). The severity of the disease and the age of onset of cardiovascular disease is determined by a homozygous or a heterozygous defect. Heterozygous FH (HeFH) patients have plasma LDL cholesterol (LDL-C) levels double the normal or higher and carry the mutated gene in a single allele. Homozygous FH (HoFH) exhibits LDL-C levels greater than five times of normal and have mutations in both alleles.

HoFH is a rare condition with prevalence of 1 in 1 million and is characterised by triad of very high LDL-C, cutaneous and/or tendon xanthomas and premature atherosclerotic cardiovascular disease (ASCVD). The LDL-C in HoFH is generally beyond 500 mg/dL, causing premature coronary artery disease and valvular/supravalvular aortic stenosis. Cutaneous xanthomas develop during infancy and are found on the extensor surfaces of elbow, knee, wrist and gluteal region. Tendon xanthomas manifest due to accumulation of cholesterol within macrophages in connective tissue of tendons[2]. Cholesterol deposition around corneal rim causes corneal arcus juvenilis and deposition on eyelids is called xanthelasma palpebrum.

Diagnosis of HoFH can be made by genetic or clinical criteria. An untreated LDL-C plasma concentration of ≥500 mg/dL, or a treated LDL-C concentration of ≥300 mg/dL and the presence of cutaneous or tendon xanthomas before the age of 10 years, or the presence of untreated elevated LDL-C levels consistent with HeFH in both parents is the clinical criteria for diagnosis of HoFH. The medical management of HoFH include lifestyle modifications with high dose statins, ezetimibe, bempedoic acid and PCSK9 inhibitors[3]. These medicines act by enhancing LDL receptor activity and are often ineffective due to near complete loss of LDL receptor activity in HoFH. Lipoprotein apheresis is the core therapy for HoFH as it directly removes LDL from plasma through selective absorption or filtration of LDL using an extra-corporal circulation system[4]. The prognosis of untreated HoFH is extremely poor as patients seldom survive beyond 30 years. The LDL-C accumulation increases risk of myocardial infarction and aortic stenosis, which may become the cause of death in these patients[5].

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