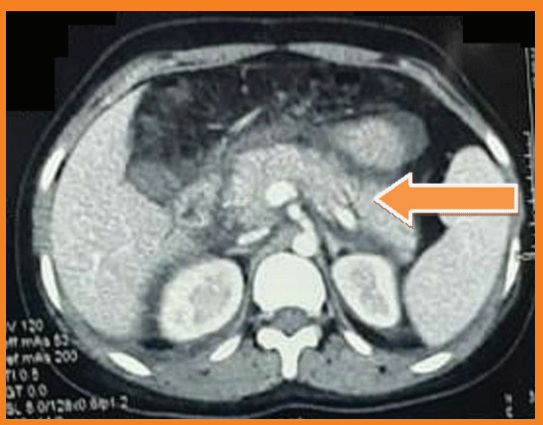
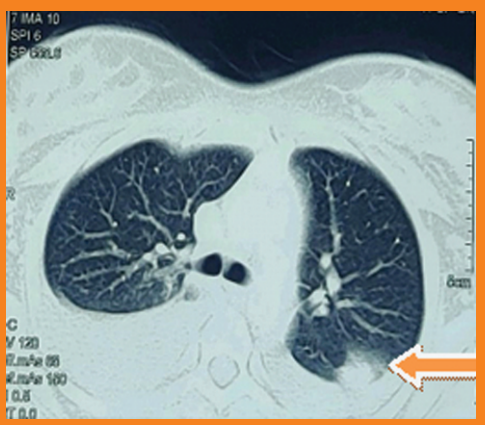
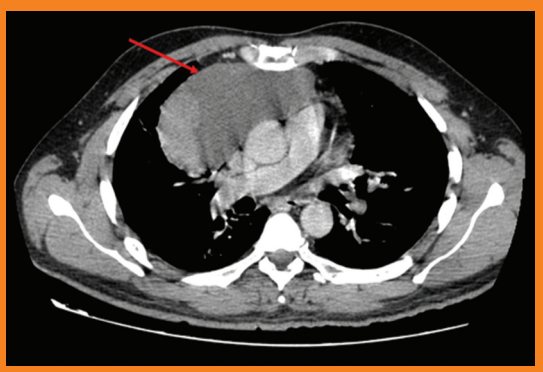
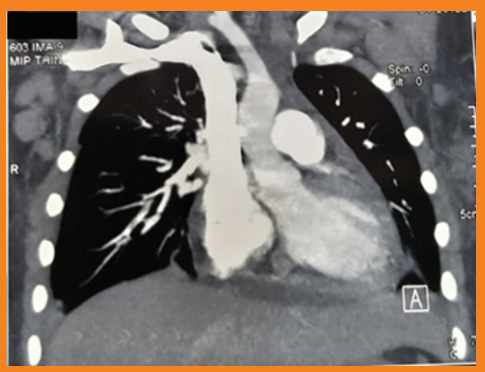
Journal, Indian Academy of Clinical Medicine

Volume 24 • Number 3-4 July – December, 2023









JIACM

An Official Publication of the Indian Association of Clinical Medicine

ISSN 0972-3560

Indexed in Scopus, IndMED

Website:www.jiacm.in
Email: iacmjournal@gmail.com

Unistar Biotech Limited

Recharge Nerves
With Matchless Accuracy

NERVISTAR™-CD3

Methylcobalamin 1500 mcg + Calcium Carbonate 625 mg + Vitamin D3 1000 I.U.+ Benfotiamine 150 mg + Folic Acid 1.5 mg + Zinc Sulphate Monohydrate 7.5 mg Tablet

- **Promotes the synthesis and regeneration of myelin.[1]**
- **Improves the symptoms of diabetic neuropathy.[2]**

Prevent Neuro
Degenrarting Disorders

NERVISTAR™-OD

Methylcobalamin 1500 mcg + Alpha Lipoic Acid 100 mg + Thiamine Mononitrate 10 mg + Pyridoxine Hydrochloride 3 mg + Folic Acid 1.5 mg Capsule

- **Protective effect on peripheral neuronal cell damage generated with DM.[3]**
- **Maintains healthy nervous system.[4]**

1. Zhang M, Han W, Hu S, Xu H. Methylcobalamin: a potential vitamin of pain killer. Neural Plast. 2013;2013:424651. doi: 10.1155/2013/424651
2. Vallianou N, Evangelopoulos A, Koutalas P. Alpha-lipoic Acid and diabetic neuropathy. Rev Diabet Stud. 2009 Winter;6(4):230-6. doi: 10.1900/RDS.2009.6.230
3. Tasci I, Demir CF, Kuloglu T. Effects of Alpha Lipoic Acid on Loss of Myelin Sheath of Sciatic Nerve in Experimentally Induced Diabetic Rats. Med Arch. 2018 Jun;72(3):178-181. doi: 10.5455/medarh.2018.72.178-181.
4. Calderón-Ospina CA, Nava-Mesa MO. B Vitamins in the nervous system: Current knowledge of the biochemical modes of action and synergies of thiamine, pyridoxine, and cobalamin. CNS Neurosci Ther. 2020 Jan;26(1):5-13. doi: 10.1111/cns.13207.

NERVISTAR CD3
COMPOSITION: Each film coated tablet contains: Methylcobalamin 1500 mcg, Folic Acid 1.5 mg, Calcium Carbonate 625 mg, Vitamin D3 1000 I.U., Benfotiamine 150 mg, Zinc Sulphate Monohydrate 7.5 mg. THERAPEUTIC INDICATIONS: Treatment and prevention of vitamin B12 deficiency, Treatment of peripheral neuropathy, Treatment of diabetic neuropathy, Treatment of alcoholic neuropathy, Treatment of cognitive impairment, Treatment of bell's palsy, Treatment of calcium deficiency, Support for bone health. DOSE: The usual adult dosage for oral use is 1 tablet daily. CONTRAINDICATIONS: It is contraindicated in patients who are hypersensitive to any component of this product. PREGNANCY AND LACTATION: Instruct patients to notify their healthcare provider before taking Nervistar-CD3 if they are pregnant or breastfeeding. ADVERSE REACTIONS: Instruct patients to notify their healthcare provider if they experience any of the following symptoms: weakness, headache, back pain, muscle pain, indigestion, nausea, and/or vomiting.

NERVISTAR OD
COMPOSITION: Each hard gelatin capsule contains: Methylcobalamin 1500 mcg, Alpha Lipoic Acid 100 mg, Thiamine Mononitrate 10 mg, Pyridoxine HCL 3 mg, Folic Acid 1.5 mg. THERAPEUTIC INDICATIONS: Treatment of drug induced neuropathy, Treatment of diabetic neuropathy, Treatment of peripheral neuropathy, Treatment of neuralgia, Treatment of fatigue, weakness, constipation, and appetite loss associated with vitamin B12 deficiency. DOSE: The usual adult dosage for oral use is 1 capsule daily. CONTRAINDICATIONS: It is contraindicated in patients who are hypersensitive to any component of this product. PREGNANCY AND LACTATION: Instruct patients to notify their healthcare provider before taking Nervistar-OD if they are pregnant or breastfeeding. ADVERSE REACTIONS: Instruct patients to notify their healthcare provider if they experience any of the following symptoms: nausea, vomiting, diarrhoea, abdominal pain headache, dizziness, rash.

For the use of registered medical practitioner or hospital or laboratory only.

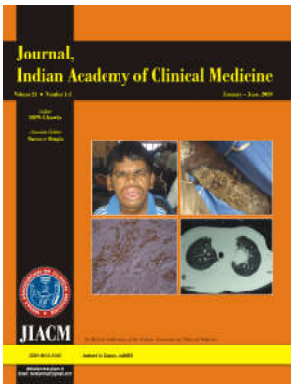
For any therapeutic area or product related information please contact: info@ublindia.com

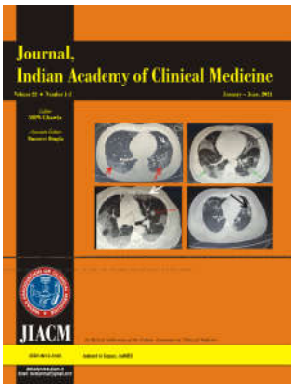
For full prescribing information, please write to: Unistar Biotech Ltd. 5/6, Calico Nagar, Narol, Ahmedabad, Gujarat - 382405.

From the Editor

"The only good is knowledge
and the only evil is ignorance."

– Socrates.





It has been my proud privilege and honour to edit widely read *JIACM*. I have been associated with the Journal in various capacities for the past 20 years or so. It has been a unique experience and has been helpful in my professional growth. With this issue, as my second 3-year term as Editor of this esteemed Journal comes to an end, it is time to thank profusely all our contributing authors and readers who have made this journey a memorable and enriching experience. The *potpourri* of contributions to the Journal have enhanced the richness of its pages by adding to the pool of practical and clinical knowledge in all areas of internal medicine. The *JIACM* has always maintained its unique style of presentation – reader friendly and easy on the eye while catering to the clinically relevant academic needs of our esteemed internist colleagues. Since each issue deserves to be preserved for future reference – whether clinical research or practice – we have been uploading issues on our website from the Editor for free access by one and all. This has been a boon for post-graduate students, teachers and practicing internists.

As of today, there are very few journals in the Indian subcontinent which are dedicated exclusively to the art and science of clinical medicine. With a sense of satisfaction, joy, and professional pride, I can say that the *Journal, Indian Academy of Clinical Medicine (JIACM)* is one such unique instrument which has inspired and whetted the academic appetite of thousands of internists – whether engaged in the clinical departments of medical institutions or practicing independently in private setups. The last few decades have seen the *JIACM's* footprint reach the length and breadth of our country, in effect guiding physicians by updating their knowledge and clinical skills. Each and every offering by the contributing author(s) never goes in vain as there is always a new and novel take-home point for the readers. Knowledge thus gained eventually translates into better, optimal, and safer management strategies for patients, thus enhancing the quality of healthcare services available to society.

Globally, print editions of medical journals are facing the challenge of rising production, postage, and handling costs – especially since the COVID-19 pandemic. The *JIACM* is no exception. At times, we too have been left with no option, but to club 2 issues. Nevertheless, this has never impacted our editorial and production standards. We have managed to stay out of the commercial angle of taking money and accepting articles for publication and have tried to maintain high academic standards.

I thank and congratulate Dr Sumeet Singla and Dr Vipin Mediratta and wish them the very best as they assume the charge as the next Editor and Associate Editor respectively. I am thankful to Dr Amit Aggarwal for all his hard work as Joint Secretary. I am ever grateful to Members of the Editorial Board for their untiring efforts. I am indebted to the IACM President Dr KK Pareek, and all office bearers and members for guidance and support at all times.

I wish to thank Dr AK Agarwal, my Guru for all his support and guidance.

I wish to thank my family members – my wife, Gurwinder, my son, Hardrisht and my daughter, Jaimeet for their patience, support and assistance at all hours during these challenging and hectic years.

I shall be failing in my duty if I don't mention the names of Technical Team – Mr Yashpal Satmukhi (Circulation and Advertising), Mr Vijay Shankar Vashist (Typesetting) and Mr Avinash Kumar (Production) for their untiring and selfless work.

Long live *JIACM*, Jai Hind

– Dr MPS Chawla
drmpschawla@gmail.com

CONTENTS

Journal, Indian Academy of Clinical Medicine • Vol. 24, Number 3-4, July-December, 2023

Contains 80 pages from 161 to 240 (inclusive of all advertisements)

CONTENTS

Journal, Indian Academy of Clinical Medicine • Vol. 24, Number 3-4, July-December, 2023

Contains 80 pages from 161 to 240 (inclusive of all advertisements)

Journal, Indian Academy of Clinical Medicine

JOURNAL, INDIAN ACADEMY OF CLINICAL MEDICINE

is edited by

Dr. MPS Chawla

for the

Indian Association of Clinical Medicine

Headquarters :

Post-Graduate Department of Medicine, Sarojini Naidu Medical College, Mahatma Gandhi Road, Agra - 282 002 (U.P.)

Editorial/Mailing Address

4/19 B, Jangpura B, New Delhi - 110 014
Tel.: (011) 23361252

E-mail: iacmjournal@gmail.com

ISSN 0972-3560

RNI Regn. No. : DELENG/2000/1686

Indexed in Scopus, IndMED

Listed in UGC Approved List of Journals

"Bibliographic details of the journal available in ICMR-NIC's database – IndMED (http://indmed.nic.in). Full-text of articles (from 2000 onwards) available on medIND database (http://medind.nic.in)."

Published by Dr. MPS Chawla
for and on behalf of the Indian Association of Clinical Medicine
from 4/19 B, Jangpura B, New Delhi - 110 014
and printed by him at Sumit Advertising, 2 DLF (Part) Industrial Area, Moti Nagar, New Delhi - 110 015.

Indian Association of Clinical Medicine

Headquarters:
Post-Graduate Department of Medicine, Sarojini Naidu Medical College,
Mahatma Gandhi Road, Agra - 282 002 (U.P.)

Founder-President: MC Gupta (Agra)

GOVERNING BODY

President
KK Pareek (Kota)

President-Elect
HS Pathak (24 Parganas)

Immediate Past-President
Subhash C Gupta (Agra)

Vice-Presidents
BL Bhardwaj (Patiala)
Smarajit Banik (Siliguri)

Hony. General Secretary
Suresh Kushwaha (Agra)

Hony. Treasurer
MP Singh (Agra)

Hony. Editor, *JIACM*
MPS Chawla (New Delhi)

Associate Editor, *JIACM*
Sumeet Singla (New Delhi)

Members
Arun Chaturvedi (Agra)
YB Agarwal (Agra)
Vikas Loomba (Ludhiana)
GD Ramchandani (Kota)
Vipin Mediratta (New Delhi)
Udai Lal (Hyderabad)
Debasis Chakrabarti (Siliguri)
RPS Sibia (Patiala)

Zonal Members

North Zone
Tarun Satija (Ludhiana)

South Zone
Naval Chandra (Hyderabad)

East Zone
P Pratim Chakraborty (Midnapore)

West Zone
YN Verma (Udaipur)

Central Zone
Parbhat Kumar Agrawal (Agra)

Organising Secretary
(IACMCON-2023)
Debaparsad Chakraborty (Agartala)

Organising Secretary
(IACMCON-2022)
Sujit Kumar (Biharsharif)

Joint Secretaries
SS Dariya (Jaipur)
Ajeet Singh Chahar (Agra)
Amit Aggarwal (New Delhi)

ORIGINAL ARTICLE

JIACM 2023; 24 (3-4): 167-70

A Study of Endothelial Dysfunction Amongst Medical Professionals and Para Medical Staff in Pre- and Post-COVID-19 Pandemicity

SH Talib, Manjiri R Naik**, Pranita Barapatre***, Sachin Patel***, Abdulla Ibji*****

Introduction

Though endothelial dysfunction is often a long-standing chronic process, in acute infection endothelial cell injury may result in premature multiorgan system manifestations leading to severe morbidities[1]. This mechanism is the unifying underlying pathological process responsible for widespread long-term complications of SARS-CoV2 infection. Early recognition of endothelial dysfunction using non-invasive means like "Angio-defender" for assessing flow mediated dilatation (FMD) of brachial artery is desirable in younger age group – for recognising and treating modifiable risk factors of endothelial dysfunction. This denotes advanced vascular age as compared to their chronological age. For the purpose, we intended to record endothelial dysfunction status and vascular age among medical professionals of MGM medical college (a tertiary care hospital) who have served with heavy duties in COVID-19 pandemic.

Aim

To study endothelial dysfunction and vascular age status of medical resident doctors and paramedical personnel at MGM medical college and hospital, Chhatrapati Sambhaji Nagar, Maharashtra, India who were exposed to COVID-19 wards/ OPD/ICU, using Angio-defender.

Objectives

To record and analyse various modifiable and non-modifiable risk factors observed in younger age group with higher vascular age vs biological age and compare the data with non-exposed medical/paramedical subjects.

Research design

Study area: Department of Medicine, MGM Medical College, Chhatrapati Sambhaji Nagar, Maharashtra, India.

Study period: 8 months.

Study design: Comparative analytical study.

Sample size: The study was done in two phases.

A. Phase I: 205 non-exposed medical/paramedical personnel (2018 - 2019).

B. Phase II: 200 medical/paramedical personnel exposed to COVID-19 pandemic while working in COVID OPD/ wards/ICU.

Institutional ethics committee approval: Obtained.

Material and Methods

Medical personnel of age > 18 yrs who had engaged with COVID-19 patients' medical care in the hospital and who were ready to participate were included. Subjects irrespective of hypertension, dyslipidaemia, diabetes, obesity status were included for detailed records.

Endothelial dysfunction was considered when there was a change in flow mediated dilatation of artery using angio-defender. The vascular age was determined by using angio-defender device (Everist) which is CE certified and has been proven to be equivalent to the gold standard-BAUS imaging. The system comprises of inputs such as FMD, smoking habit, hypertension, HbA1C, total cholesterol and serum HDL levels for calculating the vascular age. The device used hyperaemia induced flow mediated vasodilatation for calculating FMD. Measurement of dilation of brachial artery was recorded at rest and after cut-off deflation after supra systolic compression (30 mm above systolic blood pressure for 5 mins) of either arm. Maximum flow velocity was measured in all subjects at rest and later within 15 sec of the cuff deflation. Vasodilation was assessed and calculated as percentage change in the arterial diameter compared to baseline value. Impaired FMD was defined as a value less than 10%, severe dysfunction was considered when value was less than 6% and moderate when values were between 6 - 10%. FMD value < 6% was considered a good predictor of presence of coronary artery disease.

For the purpose of this project, hypertension was defined as systolic pressure >140 mm Hg and diastolic pressure > 90 mm Hg for persons on anti-hypertensive medications. ADA criteria were used for defining type II diabetes

**Professor Emeritus, **Professor and Head, ***Senior Resident, ****Junior Resident, Department of Medicine, MGM Medical College, Chhatrapati Sambhaji Nagar - 431 003, Maharashtra.*

Corresponding Author: Dr SH Talib, Emeritus Professor, Department of Medicine, MGM Medical College and Hospital, Chhatrapati Sambhaji Nagar - 431 003, Maharashtra. Tel: 91 7875127786, E-mail: sftalib@gmail.com.

mellitus. Cases of diabetes treated or on treatment having fasting blood glucose levels >126 mg% or HbA1C >6.4% were included. WHO criteria for Asian population were considered for defining body mass index {normal (18.5 - 23 kg/m^2), overweight (23 - 27.5 kg/m^2) and obese (>27.5 kg/m^2)}. Dyslipidaemia was considered when total cholesterol value exceeded >200 mg/dL and HDL < 40 mg/dL. Smoking records were taken when the person smoked at least 5 cigarettes per day in the last month.

Results

The study result comprised analysis on pre-COVID phase and post-COVID phase in different age groups analysed for endothelial dysfunction using 'Angio-defender', calculating percentage change in arterial diameter compared to baseline. Results were statistically analysed and recorded.

Table I: Endothelial dysfunction in different age groups.

Age groups (years)	Post-COVID – phase II Pre-COVID – phase I	Normal (>10%)	Moderate (6 - 10%)	Severe (< 6%)	Total	P-value
16 - 25	Post-COVID-19	19	29	16	64	
	Pre-COVID-19	3	26	11	40	
	Total	22	55	27	104	**0.02 (S)**
26 - 35	Post-COVID-19	28	48	14	90	
	Pre-COVID-19	5	117	16	138	
	Total	33	165	30	228	**0.00 (S)**
36 - 45	Post-COVID-19	10	17	5	32	
	Pre-COVID-19	3	10	2	15	
	Total	13	27	7	47	0.66 (NS)
>45	Post-COVID-19	0	8	6	14	
	Pre-COVID-19	0	8	4	12	
	Total	0	16	10	26	**0.00 (S)**

Endothelial dysfunction in 36 - 45 years age group, was non-significant and as the age advance to more than 45 years of age group, the endothelial dysfunction was significant. However, the younger age group of 16 - 25 – 26 - 35 years were also having statistically significant endothelial dysfunction. Severity of the disease was statistically significant with increasing age.

Table II shows that greater endothelial dysfunction was noted in subjects having risk factors (< 2). The values shown are statistically significant. 22 subjects had severe endothelial dysfunction in pre-COVID-19 stage and 7 subjects in post-COVID-19 phase. More number of subjects were affected in pre-COVID-19 phase, which could be attributable to modifiable and non-modifiable risk factors.

Table II: Showing relation between endothelial dysfunction and risk factor.

FMD (%)	Post-COVID – Phase II Pre-COVID – Phase I	< 2 Risk factors	≥2 Risk factors	Total	P-value
Normal (>10%)	Post-COVID-19	32	25	57	
	Pre-COVID-19	11	0	11	
	Total	43	25	68	**0.01 (S)**
Moderate (6 - 10%)	Post-COVID-19	89	13	102	
	Pre-COVID-19	89	72	161	
	Total	178	85	263	**0.00 (S)**
Severe (< 6%)	Post-COVID-19	34	7	41	
	Pre-COVID-19	11	22	33	
	Total	45	29	74	**0.00 (S)**

Table III: Showing relation with endothelial dysfunction and gender.

FMD (%)	Post-COVID – Phase II Pre-COVID – Phase I	Male	Female	Total	P-value
Normal (>10%)	Post-COVID-19	17	40	57	
	Pre-COVID-19	7	4	11	
	Total	24	44	68	**0.03 (S)**
Moderate (6 - 10%)	Post-COVID-19	41	61	102	
	Pre-COVID-19	86	75	161	
	Total	127	136	263	**0.04 (S)**
Severe (< 6%)	Post-COVID-19	26	15	41	
	Pre-COVID-19	17	16	33	
	Total	43	31	74	0.3 (NS)

Out of 68 persons having normal FMD value, 11 (16%) were in pre-COVID-19 period and remaining 57 (83.82%) were in post-COVID-19 period. Similar changes were noted for severe endothelial dysfunction (< 6%) in pre- and post-COVID-19 period (Table III).

Table IV: Showing relation between risk factors and gender.

Risk factors	Post-COVID – Phase II Pre-COVID – Phase I	Male	Female	Total	P-value
< 2	Post-COVID-19	76	108	184	
	Pre-COVID-19	66	45	111	
	Total	142	153	295	**0.00 (S)**
≥ 2	Post-COVID-19	8	8	16	
	Pre-COVID-19	44	50	94	
	Total	52	58	110	0.81 (NS)

Females had more affliction than males in post-COVID-19 phase with risk factors (< 2), for reasons of more female nursing staff employment for COVID-19 care in the hospital (Table IV).

Table V: Showing relation between age and risk factors.

Age group	Post-COVID – Phase II Pre COVID – phase I	< 2	≥2	Total	P-value
16 - 25	Post-COVID-19	61	3	64	
	Pre-COVID-19	24	16	40	
	Total	85	19	104	**0.00 (S)**
26 - 35	Post-COVID-19	77	13	90	
	Pre-COVID-19	76	62	138	
	Total	153	75	228	**0.00 (S)**
36 - 45	Post-COVID-19	26	6	32	
	Pre-COVID-19	7	8	15	
	Total	33	14	47	**0.02 (S)**
>45	Post-COVID-19	11	3	14	
	Pre-COVID-19	4	8	12	
	Total	15	11	26	**0.02 (S)**

Statistically significant findings were noted in the post- and pre-COVID-19 period was respect to age with both < 2 and ≥2 risk factors affection. ≥ 2 risk factors were seen in 94 subjects in pre-COVID-19 period and 25 subjects in post-COVID-19 period. < 2 risk factors were seen in 111 subjects in pre-COVID-19 and 175 subjects in post-COVID-19 (Table V).

Discussion

Endothelial dysfunction has been recognised as a vital and critical component of COVID-19 disease. Since the vascular endothelial cells cover the entire circulatory system from heart to small capillaries, their study bears great prognostic significance as altered endothelial function presents with varied clinical complications and adverse outcomes. The importance of endothelial dysfunction has often been discussed in the setting of acute COVID-19 infection, with disparities observed in the extent of endothelial dysfunction/FMD lowering[2].

Endothelial dysfunction is a chronic process and may result in premature multiorgan system manifestations as 'long COVID-19 disorder'[2,3]. We have attempted to record endothelial dysfunction status and vascular age amongst medical/paramedical professionals of MGM medical college who have served arduous duties in the COVID-19 pandemic 2019 - 2021 (phase II study). The results were compared with phase I study wherein FMD values of medical professionals/paramedical personnel unexposed to this pandemic during 2018 - 2019 was carried-out. The present phase II study was carried-out with certain modifiable and non-modifiable risk factors like age, BMI, diabetes mellitus-II and smoking, assessed using flow mediated vasodilation (FMD) of brachial artery, similar to study done in phase I. It was matched with age, gender and risk factors as cited.

The maximum number of subjects in the phase II study belonged to age 16 - 25 yrs. In apparently young (< 35 yrs), healthy individuals with abnormal values of endothelial dysfunction (< 10%) suggested subclinical/premature atherogenicity. In the phase II study with advancing age (>45 yrs), the severity of endothelial dysfunction was also noted to be higher. FMD values < 6% are considered valid predictors of the presence of coronary artery disease. However, discriminations are noted in the percentage of FMD and presence or absence of coronary artery disease (CAD) in study reported by Enderle *et al* in 1998[4]. Similar observations are found in the present study. A higher number of subjects (64/200), between 16 - 25 yrs, and despite receiving vaccination had FMD < 10% as compared to phase I study (40/200). The difference observed was statistically significant (Table I). A higher number of subjects with >10% FMD values could be attributed to good herd immunity in them and/or good development of immunity post-vaccination. Vaccination protection only provide a limited reference for immune status. Abnormalities of vascular disease, notably CAD, can possibly be modified over weeks to months with risk reduction therapy.

As regards association between endothelial dysfunction and risk factors, it was noted that in subjects having ≥ 2 risk factors, more subjects were affected in pre-COVID-19 than post-COVID-19. Reasons could be attributed to modifiable and non-modifiable risk factors (Table II and III). It was also observed in the post-COVID-19 phase II study that females had more affliction than males having risk factors < 2. The reasons to could be attributed more employment of female nursing staff in pandemic period (Table IV).

Higher affliction with < 2 risk factors was seen in post-COVID-19 period and may be attributed to presence of COVID-19 infection in either subclinical or symptomatic subjects. Further, ≥2 risk factors showed more number of subjects in pre-COVID-19 period as they had no exposure to COVID-19 pandemic. The probable reasons for less number of subjects in post-COVID-19 with ≥2 risk factors can be presumed to be strict confinement of these subjects at home who had minimal chances of street exposure during pandemic (Table V).

FMD serves as an important marker for premature atherogenesis. Age recognition of normal FMD values in post-COVID-19 phase in young when noted, may speak of lower vascular age to their chronological age. Such individuals are also advised supplementary vaccination with optimum time interval between doses to strengthen their

immune system. Though vaccination protection can only be assessed indirectly by detecting neutralising antibody level, has otherwise limited value. It is therefore, imperative, to have FMD assessment and the measures to intervene and prevent overt vascular disease by adopting timely risk reduction therapy.

Conclusion

COVID-19 infection continues to evolve since the beginning of the pandemic. The risk factors for endothelial dysfunction include history of CVD, history of COVID-19 in medical personnel and residents/paramedical staff who were on heavy duties in pandemic, could be regarded as risk factors for others and their own future endothelial dysfunction. Therefore, focus should be on assessment of endothelial function and identification of high-risk subjects through non-invasive endothelial function testing for finding their vascular age. Other biomarkers evaluation is also needed, viz., diabetes mellitus, hypertension, obesity, CVD, to recognise high-risk individuals. In our study, higher groups were significantly low having ≥2 risk factors. Reasons attributable to this fact could be strict confinement and better care of modifiable risk factors at home. Use of angio-defender for FMD could prove as a useful tool in screening test for recognising early anticipated problems and long COVID derangements, especially in young age group.

References

1. Prasad M, Leon M, Lerman L *et al.* Viral Endothelial Dysfunction: A Unifying Mechanism for COVID-19. *Mayo Clin Proc* 2021; 96 (12): 3099-3108.
2. Evans PC, Rainger GE, Mason JC *et al.* Endothelial dysfunction in COVID-19: a position paper of the ESC Working Group for Atherosclerosis and Vascular Biology, and the ESC Council of Basic Cardiovascular Science. *Cardiovascular Research* 2020; 116: 2177-84.
3. Jin Y, Ji W, Yang H *et al.* Endothelial activation and dysfunction in COVID-19: from basic mechanisms to potential therapeutic approaches. *Sig Transduct Target Ther* 2021; 5: 293.
4. Enderle MD, Schroeder S, Ossen R *et al.* Comparison of peripheral endothelial dysfunction and intimal media thickness in patients with suspected coronary artery disease. *Am Heart J* 1998; 80: 349-54.

ORIGINAL ARTICLE

JIACM 2023; 24 (3-4): 171-76

Clinical Profile of Posterior Circulation Stroke

Vaibhav Bhat, Poonam Ashok Kamath*, BA Shastry***

Abstract

***Background:** The vascular territory associated with posterior circulation supplies a compact region of the brain which controls vital body functions, hence a stroke in this area can lead to significant morbidity and mortality. Due to overlapping symptomatology, it is often misdiagnosed as a peripheral cause of vertigo. Our study was aimed at studying the risk factors, symptomatology, anatomical localisation, artery involved, and outcomes related to posterior circulation stroke (PCS). We believe this study can lead to earlier diagnosis and prompt management which is very crucial in deciding outcomes of posterior circulation strokes.*

***Methods:** A tertiary care hospital-based cross-sectional time bound study was conducted among patients attending OPD or admitted in ward in from September 2021 to October 2022 meeting the inclusion-exclusion criteria. 43 patients admitted with PCS under departments of General Medicine and Neurology in Kasturba Hospital, Manipal were analysed for the study.*

***Results:** 22 patients were older than 65 years. 14 were aged 45 to 65 years. 28 were males. Among risk factors, diabetes and hypertension were found to be present in 23 and 21 patients, respectively. 21 subjects had significant smoking history. 26 subjects presented with ataxia or vertigo. 26 subjects had cerebellar signs on examination. Vertebral artery and posterior cerebral artery were the most common implicated vessel (12 and 6 subjects respectively). As per TOAST classification, small artery type was found in 14 subjects and large artery stroke was present in 11 subjects.*

***Conclusions:** Diabetes mellitus was the most common risk factor for PCS in our study followed by hypertension. Ataxia and vertigo were the most common presenting features of PCS in the present study. Cerebellum was the most common anatomical area involved. In our study, vertebral artery was most commonly affected. Small vessel disease was the main aetiological factor followed by large vessel disease.*

Introduction

Cerebrovascular accident (stroke) is a major cause of morbidity and mortality affecting the neurological system. Strokes can be classified based on the involved circulation into anterior and posterior circulation strokes. Posterior circulation of the brain supplies the brainstem, cerebellum, occipital lobe, thalamus, parts of parietal and temporal lobe. As posterior circulation supplies a compact of area of structure controlling important functions and containing neurological pathways, strokes involving this territory often result in significant morbidity and mortality with catastrophic outcomes. They account for 9.2% of all the strokes[1]. PCS presentation can be misdiagnosed as a peripheral cause; it mimics vestibular disease, thereby causing significant delay in diagnosis and treatment[2]. These factors also add on to the morbidity associated with the disease. PCS can also mimic anterior circulation stroke[3]. The clinical presentation and risk factor stratification for PCS have not been extensively studied in the Indian population for PCS. The aim of our study was to study the risk factors, clinical presentation and anatomical areas involved in PCS.

Material and Methods

A tertiary care hospital-based, cross-sectional, time bound study was conducted among patients attending OPD or admitted in ward in from September 2021 to October 2022 meeting the inclusion-exclusion criteria. Ethical clearance was obtained from the Institutional Ethics Committee (IEC) of KMC (Kasturba Medical College) and Hospital, Manipal (IEC 255/2021). The study has been registered with Clinical Trials Registry of India (CTRI/2022/09/045676). Written informed consent was taken.

Patients aged above 18 years of age presenting with clinical features and radiological evidence of PCS were included. Patients having radiological evidence of haemorrhage or infarct in anterior circulation or pre-existing infarcts were excluded from the study.

Detailed questionnaires were filled regarding clinical features, co-morbidities, risk factors, and radiological imaging. Data were entered in MS Excel and analysis was done using SPSS 21.0 version. Data was presented as mean and standard deviation for continuous variables and as percentages for categorical variables. Histograms were used

**Senior Resident, **Professor, Department of General Medicine, Kasturba Medical College, Manipal Academy of Higher Education, Manipal - 576 104, Karnataka.*

Corresponding Author: Dr Poonam Ashok Kamath, Senior Resident, Department of General Medicine, Kasturba Medical College, Manipal Academy of Higher Education, Manipal - 576 104, Karnataka. Tel: 8317402192, E-mail: kamath.poonam@manipal.edu

to plot the continuous data, whereas bar diagrams and pie charts for qualitative data.

Sample size was estimated at 9%prevalence of PCS to be 68. In our centre in that year there were 804 stroke patients, out of which 68 had PCS. However, 19 had simultaneous anterior circulation involvement as well hence were excluded. 6 patients got discharged against medical advice hence investigations and detailed assessment could not be done, and they were not included in analysis. Since it was a time bound study, 43 subjects were studied.

Results

43 patients admitted with PCS under departments of General Medicine and Neurology in Kasturba Hospital, Manipal were analysed for the study. Hence n = 43.

Table I: Baseline characteristics.

Characteristic		Total
Age (years) Mean: 61.3 ± 14	< 45	7
	45 - 65	14
	Above 65	22
Gender	Male	28
	Female	15
Co-morbidities	Diabetes	23
	Hypertension	21
	Dyslipidaemia	11
	BMI > 30 kg/m^2	11
	Ischemic heart disease	5
	Hypothyroidism	4
	Rheumatic heart disease	1
Modifiable risk factors	Smoking	21
	Alcoholism	7

Among the cranial nerves involved, 10 subjects had IX and X nerve palsy. 4 subjects each had III nerve and VII nerve (UMN and LMN) palsy. 2 patients had optic (II) pathway involvement (visual field loss). No involvement of abducent

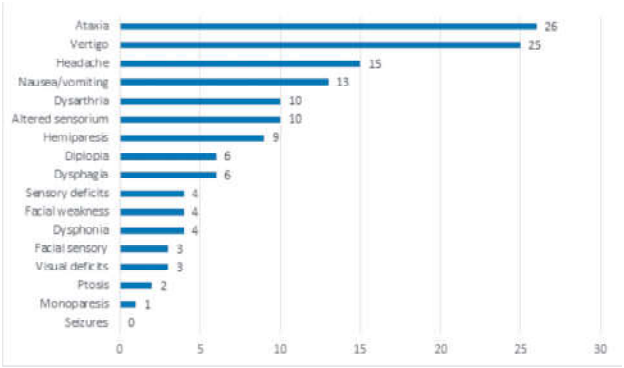


Fig. 1: *Bar graph showing presenting symptoms in posterior circulation stroke.*

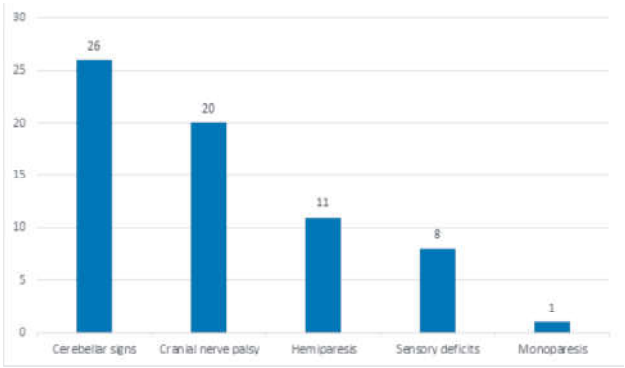


Fig. 2: *Bar graph showing clinical signs on examination.*

(IV) or hypoglossal (XII) nerves were noted in the study.

MRI brain was conducted for all patients in the study. It showed ischemic stroke in 40 subjects and haemorrhage in 3 patients. Out of the three, 2 had pontine bleed and 1 subject had cerebellar bleed.

Among the anatomical areas involved, cerebellum was most commonly implicated, in 19 subjects. Occipital lobe was involved in 14 subjects and 12 had medulla involvement. Pons was involved in 9 patients. 6 patients each had midbrain and temporal lobe involvement. 23

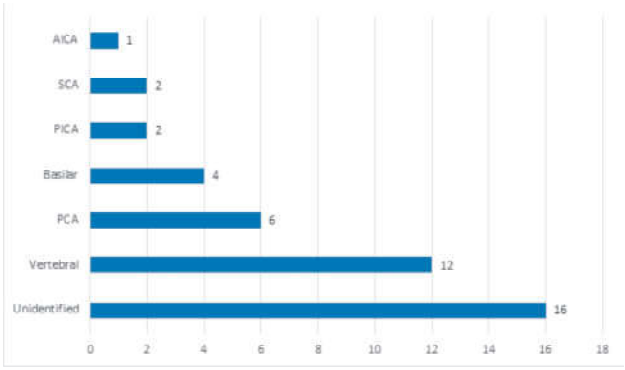


Fig. 3: *Bar graph showing arteries involved in PCS. AICA – anterior inferior cerebellar artery, SCA – superior cerebral artery, PICA – posterior inferior cerebellar artery, PCA – posterior cerebral artery.*

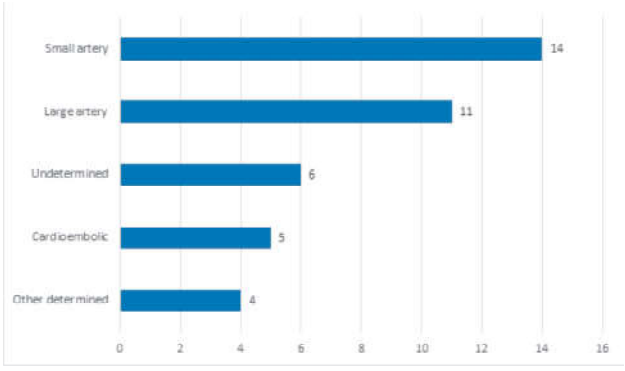


Fig. 4: *Bar graph showing aetiology of stroke as per TOAST classification.*

individuals had multiple territories involved in posterior circulation in the form of lacunar stroke.

Discussion

Prevalence

In our hospital, 8.6% of all strokes in the study period were PCS. It was similar to other Indian studies (Manmohan *et al*)[4] that showed 11.3% of PCS among all strokes. But these were comparatively lesser when compared to Western population studies in Europe and USA, where PCS were ranging from 26 - 39.8%[5,6]. Europe and USA have a higher average life expectancy when compared to India. In older adults, diabetes mellitus, hypertension, dyslipidaemia, metabolic syndrome and other risk factors have a higher chance of causing atherosclerotic vessel wall damage. These metabolic diseases-induced atherosclerotic disease causes hardening and narrowing of arteries which is prominent in posterior circulation system[7].

Age and gender

In the current study, 51% (22) patients were over the age of 65 years with an average age of 61 years and SD of 14 years. The predominance of PCS in older age groups is due to calcium deposition and metabolic disease like diabetes mellitus, dyslipidaemia, hypertension causing atherosclerotic damage and plaque formation. The results are similar to another study by Joshi *et al*[8] with an average age of 59.8 years. In the study by Manmohan *et al*[4], the average age was 51 years as this study had included patients from paediatric age groups. Male predominance was seen in the current study with 65.1% (25) being males. Stroke pathology is influenced by gender in numerous ways and understanding the same still remains incomplete. In females, Oestrogen reduces atherosclerosis by its action on intravascular adhesion process, tone of the smooth muscle and monocyte differentiation[9]. Also, in males, testosterone levels act variably in association with stroke risk. There is a correlation of increased risk in older men with decreased testosterone and younger men with elevated levels of testosterone[10]. Male predominance is also seen in closely associated risk factors like diabetes mellitus and hypertension which predispose male gender to a higher risk of stroke. Among other studies, Manmohan *et al*[4] and Joshi *et al*[8] showed a male predominance. It was also comparable to the New England PCS registry[11] which also showed a male predominance of 65% (256).

Risk factors

In the present study, diabetes mellitus was the predominant risk factor for PCS seen in 23 patients. Diabetes mellitus being a metabolic disease, plays a role in different mechanisms for cardiovascular disease. Long-standing DM can cause early onset arteriosclerotic changes with endothelial dysfunction leading to adhesion defect and thickening of capillary basement membrane. These factors lead to non-compliance of the vessel and atherosclerotic plaque formation due to turbulent flow and systemic inflammation. This predisposes patients with diabetes mellitus to stroke[12]. In the current study, diabetes mellitus was predominant when compared to Manmohan *et al*[4] (30%) and Joshi *et al*[8] (28%), as the present study was done in South Indian population where incidence and prevalence of diabetes mellitus is higher when compared to North Indian population[13].

Hypertension was the second most common risk factor in this study with 21 patients being previously diagnosed with the same. Long-standing hypertension causes accelerated atherosclerosis. These structural modifications in the arterial vessel wall protect the microcirculation from pressure change related injury. However, these changes lower the vessel's response to vasodilation related changes and are seen more in tortuous vessels with higher turbulent flow like vertebral artery. This response associated with intraluminal plaque plays a major role in stroke[13]. It was the predominant risk factor in Manmohan *et al*[4] and Joshi *et al*[8] studies. These studies were done in metropolitan cities. Environmental factors and lifestyle changes may have a role in hypertension which is not fully understood at present[14].

In the current study, 11 subjects had dyslipidaemia at presentation, which is one of the established factors for ischaemic stroke. Dyslipidaemia causes increased fatty acid oxidation. This causes elevated generalised inflammation which also affects arteries. Inflammation with elevated LDL and altered ApoB levels leads to intravascular plaque formation[15]. Role of dyslipidaemia in haemorrhagic strokes remains inconclusive and no significant association is established. Serum triglyceride levels are associated with higher neurological decline post-CVA and poorer recovery. The exact mechanism and role of serum triglyceride in this process is still under evaluation, but significant association has been established[16]. In the Manmohan *et al* study[4], 21.5% of the patients had dyslipidaemia, which is similar to the current study.

Obesity is an independent risk factor for stroke[17]. In this study, 11 patients had obesity while the Manmohan *et al* study[4] had 10% patients with obesity. Inclusion of paediatric strokes may have resulted in this difference as obesity is seen more commonly in adults in Indian population when compared to the Western world where paediatric obesity is significantly present.

In our study, 5 patients had ischaemic heart disease, which

is known to contribute to stroke by various pathophysiological means. It causes endo-myocardial ischaemia which alters surface adhesion process and causes decreased contractility, due to myocardial ischaemia[18]. These factors provide an environment for formation of microthrombi in the intramural surface. Ischaemic heart disease causing atrial fibrillation, leads to an intra-atrial clot which embolises and causes stroke[19]. But coronary artery disease and stroke are more of an association rather than risk factors for each other. In the Manmohan *et al* study, a higher prevalence of ischaemic heart disease was seen at 22.5% when compared to the current study. This can be due to epidemiological variation occurring with different study populations, as stroke is associated with numerous risk factors and confounders.

In the study we conducted, 21 patients were smokers. Stroke – first presentation and recurrent stroke, both are associated with smoking. Vessel elasticity and compliance is altered in smokers[20]. Smoking raises haematocrit, which increases blood viscosity. It causes damage to the endothelial lining, which stimulates platelet aggregation and hence encourages thrombosis. The persistent endothelial inflammation induced by smoking and secondary polycythaemia predispose chronic smokers to recurrent CVA. 31% patients were chronic smokers in the Manmohan *et al* study[4] and 34% patients in the Joshi *et al* study[8]; there is a difference which was attributed to socio-demographic variations. 2 patients in the current study had secondary polycythaemia (in known chronic smokers).

Alcoholism is the next factor in substance abuse that is an established risk factor for CVA. In this study, 7 patients were diagnosed with alcohol abuse as per alcohol use disorder criteria[18]. Alcohol in moderation (1 - 2 drinks/ week) was associated with decreased hazard ratio for stroke. At higher levels of consumption, alcohol cases were positively correlated with stroke incidence. Direct correlation between alcohol consumption and stroke is not known. 6.25% patients in the Manmohan *et al* study were diagnosed as alcohol abusers as per CAGE criteria. The data are similar between the current study and the Manmohan *et al* study.

In our study, 3 patients were diagnosed as chronic kidney disease. A higher risk of ischaemic and haemorrhagic stroke is linked to chronic kidney disease (CKD) as it can lead to platelet dysfunction, coagulation abnormality, endothelial dysfunction, and inflammation in addition to common risk factors like hypertension caused by reno-parenchymal disease[21]. In the Manmohan *et al* study[4], 3.75% of the patients had CKD. This difference is due to the increased prevalence of diabetes in the current study.

1 patient in the current study had anti-phospholipid antibody (APLA) syndrome – a 20-year-old female with recurrent abortions presenting with features of cerebellar CVA. APLA although rare, is a significant risk factor for CVA. APLA leads to formation of anti-phospholipid antibodies like lupus anticoagulant and anticardiolipin antibody that causes decreased formation of prostacyclin. This process causes increased aggregation of platelets leading to plaque or thrombus, hence causing endothelial injury.

Symptomatology

Most common presentation was with features of acute vestibular syndrome, presenting as sudden onset ataxia in 26 and vertigo in 25 patients. In PCS, stroke involving cerebellar peduncles, cerebellum and vestibular nuclei causes ataxia with vertigo[22]. It was also the predominant complaint in the Manmohan *et al*[4] and Joshi *et al*[8] studies. It was noted that in this study, 9 patients were primarily evaluated under ENT for peripheral vertigo and later referred to medicine for further evaluation of acute vestibular syndrome, which was further diagnosed as PCS. This delay in diagnosis and gap in knowledge in PCS presentation leads to delayed initiation of anti-thrombotic agents and poorer neurological outcomes. Headache with nausea/vomiting was the second most predominant complaint in PCS in our study. Headache was predominantly posterior, characterised by a dull aching sensation. This occurs due to irritation of trigeminovascular neurons located in brainstem arteries[23]. If headache is present in acute vestibular syndrome presentation, PCS must be ruled out. The other differential diagnosis for such a presentation is vestibular migraine, a rare entity. In PCS, nausea/vomiting are attributed to 2 mechanisms. First is involvement of vestibular nuclei or fasciculus, this is usually accompanied with vertigo. Second mechanism is involvement of CTZ vascular supply, where no significant vertigo or ataxia is seen[24]. Dysarthria was the next common symptom of presentation in the current study, observed in 10 subjects. It was noted in facial nerve nuclear/ fascicular lesions and cerebellar lesions. 10 patients also had altered sensorium at presentation, which can be attributed to involvement of RAS (reticular activating system) centre in brainstem strokes. Hemiparesis was present in 9 patients. It was mainly seen in brainstem strokes involving basal pons and pyramids of medulla. 1 case of hemiparesis was noted in midbrain stroke as a part of Weber's syndrome. In the Manmohan *et al* study, the predominant presenting symptomatology was vertigo and ataxia in 56% and 48% of the patients respectively. It was followed by vomiting and headache in 33% and 25% of the patients. In the Joshi *et al* study, 70% patients had vertigo and 62% patients had ataxia, followed by 58% patients with headache and 54% patients with vomiting. These findings are similar to the current study.

Anatomical localisation

All the studies had localised infarcts with MRI Brain-DWI sequence and ICH by NCCT brain imaging. 40 patients had ischaemic lesions in the current study. Joshi *et al* study showed increased haemorrhagic strokes in 37% (n = 15) patients. In this study, 4 patients with haemorrhagic stroke were discharged against medical advice, therefore they could not be included in the analysis. This might have led to decreased representation of haemorrhagic strokes in our study. Our study showed predominance of cerebellar strokes(19 cases). In PCS studies, cerebellar strokes were predominant, but the exact mechanism of this predominance remains unknown. Possible hypotheses include branches of multiple arteries from the posterior circulation supply various parts of cerebellum and involvement of these gives a higher chance of involvement of cerebellum. In the Joshi *et al* study, cerebellum was predominantly involved at 37.5% of all strokes. Occipital lobe involvement was the second most common stroke in the present study seen in 14 patients. They most commonly present with headache. In the Joshi *et al* study, 24% of the patients had occipital strokes, which is comparable and similar to our study. 12 patients had medullary involvement in the present study. Among them 8 patients had "lateral medullary syndromes" with 4 of them having hemiparesis or extension into pyramids causing "Babinski-Naegotte Syndrome". 1 patient had "hemi-medullary syndrome" involving complete left half of the medulla. 9 patients presented with pontine lesions in the present study. 2 of them had pontine haemorrhage with others having ischaemic lesions. Most common presentation was with 7th LMN cranial nerve involvement and hemiparesis as a part of multi-infarct status. 1 patient with pontine lacunar infarct presented with "Dysarthria-Clumsy Hand syndrome". 1 patient with pontine haemorrhage was diagnosed as "Locked-in Syndrome" presented with quadriparesis with preserved vertical eye movements and loss of other conjugate vision. 6 patients had midbrain strokes. 2 patients presented with involvement of 3rd cranial nerve nuclei causing ptosis with one patient being diagnosed as Weber's Syndrome. A total of 53.5% (23) of the patients had brainstem involvement in the present study and 23 patients also had multi-infarct presentation due to artery-to-artery embolisation (in large artery disease) or by cardio-embolic phenomena.

Artery involved

CT angiography was used for diagnosis of arterial involvement, measure of degree of occlusion and status of the plaque. Occlusions of >50% were considered as clinically significant. In this study, vertebral artery was predominantly involved, in 12 patients. The tortuous extracranial course of the vertebral artery along with commonly occurring hypoplasia predispose them for endothelial damage and large artery disease in older adults. Our study had a higher representation of older adults, hence showed a higher predominance for vertebral artery involvement. This is followed by PCA in 6 patients. However, in the Manmohan *et al* study, 53% patients had involvement of PCA with only 2.5% of the patients showing vertebral artery involvement. In the Manmohan *et al* study, extracranial vertebral artery lesions were excluded. As extracranial course is predominantly involved, the Manmohan *et al* study showed significantly low incidence of vertebral artery involvement.

TOAST Classification

Our study had predominantly small artery disease/lacunar strokes in 14 patients, followed by large artery disease in 11. In the Manmohan *et al* study, majority of the patients had large artery disease in 61% followed by cardio-embolic phenomena in 10%. Higher age is associated with small artery disease due arterial decreased compliance that progresses with age. This can be noted, as predominant small vessel disease was observed. New England PCS registry[11] showed a predominance of large artery disease.

Outcome

Mortality due to PCS were similar in the present study compared to national and international studies. Predominant causes of death were secondary hospital acquired infections like ventilator associated pneumonia in 4 patients. 1 patient suffered concomitant myocardial infarction followed by cardiogenic shock. 1 patient with cerebellar bleed who had delayed presentation to hospital, had features of brainstem herniation on CT imaging, and eventually led to cardiopulmonary compromise. Posterior circulation infarcts have been generally considered to have a poor outcome with high mortality and morbidity[25], but several studies have conflicting results. The comparative functional outcome of patients with posterior *versus* anterior circulation stroke has been little studied, especially that of the subset of patients with minor initial deficits. The current evidence suggests that minor PCS exhibited more frequent disability at 3 months than minor ACS. Especially, the presence of vertebrobasilar large vessel disease in minor PCS had a substantially higher risk of disability when compared to anterior circulation strokes[24].

Conclusion

Diabetes Mellitus was the most common risk factor for PCS in our study followed by hypertension. Ataxia and vertigo, with clinical features of "Acute Vestibular Syndrome" were

the most common presenting features of PCS in the present study. Cerebellum was the most common anatomical area involved. Vertebral artery was most commonly affected and small vessel disease was the main aetiological factor.

Limitations

Our study had a relatively smaller sample size compared to other studies. Large number of PCS had prior or concomitant anterior circulation involvement, hence could not be included as per our criteria. Hence, few variables like cardioembolic phenomenon, large artery disease could not be assessed adequately and might have affected the results. In the COVID pandemic, subtle or self-limiting acute vestibular syndromes may not have been diagnosed adequately or may not have sought healthcare.

References

1. Vasculature of the Central Nervous System and the Cerebrospinal Fluid. In: Martin JH. eds. Neuroanatomy: Text and Atlas, 5e. McGraw Hill; 2021. Accessed October 16, 2023.
2. Kim JT, Park MS, Choi KH *et al*. Clinical outcomes of posterior versus anterior circulation infarction with low national institutes of health stroke scale scores. *Stroke* 2017; 48 (1): 55-62.
3. Tao WD, Liu M, Fisher M *et al*. Posterior versus anterior circulation infarction: how different are the neurological deficits? *Stroke* 2012; 43 (8): 2060-5.
4. Mehndiratta M, Pandey S, Nayak R. Posterior circulation ischaemic stroke-clinical characteristics, risk factors, and subtypes in a north Indian population: a prospective study. *Neurohospitalist* 2012; 2 (2): 46-50.
5. Kim H, Kim JT, Lee JS *et al*. Stroke of Other Determined Aetiology: Results From the Nationwide Multicenter Stroke Registry. *Stroke* 2022; 53 (8): 2597-2606.
6. Ng AC. Posterior Circulation Ischaemic Stroke. *Am J Med Sci*. 2022; 363 (5): 388-98.
7. Shuaib A, Hachinski VC. Mechanisms and management of stroke in the elderly. *CMAJ* 1991; 145 (5): 433-43.
8. Rawat KJ, Korde BS, Joshi KS. Clinical profile and prognosis of patients with posterior circulation stroke. *Inter J Res Med Sci* 2016; 4 (12): 5159-64.
9. Haast RA, Gustafson DR, Kiliaan AJ. Sex differences in stroke. *J Cereb Blood Flow Metab* 2012; 32 (12): 2100-7.
10. Bhadra J, Seth S, Kulshrestha M *et al*. Testosterone and estradiol in men with acute ischaemic stroke: A North Indian case control. *Curr J Neurol* 2021; 20 (4): 202-7.
11. Caplan L, Chung CS, Wityk R *et al*. New England medical center posterior circulation stroke registry: I. Methods, data base, distribution of brain lesions, stroke mechanisms, and outcomes. *J Clin Neurol* 2005; 1 (1): 14-30.
12. Tun NN, Arunagirinathan G, Munshi SK. Diabetes mellitus and stroke: A clinical update. *World J Diabetes* 2017; 8 (6): 235-48.
13. Kuriakose D, Xiao Z. Pathophysiology and Treatment of Stroke: Present Status and Future Perspectives. *Int J Mol Sci* 2020; 21 (20): 7609.
14. Valham F, Mooe T, Rabben T *et al*. Increased risk of stroke in patients with coronary artery disease and sleep apnea: a 10-year follow-up. *Circulation* 2008; 118 (9): 955-60.
15. Dong H, Chen W, Wang X *et al*. Apolipoprotein A1, B levels, and their ratio and the risk of a first stroke: a meta-analysis and case-control study. *Metab Brain Dis* 2015; 30 (6): 1319-30.
16. Deng Q, Li S, Zhang H *et al*. Association of serum lipids with clinical outcome in acute ischaemic stroke: A systematic review and meta-analysis. *J Clin Neurosci* 2019; 59: 236-44.
17. Vicente VS, Cabral NL, Nagel V *et al*. Prevalence of obesity among stroke patients in five Brazilian cities: a cross-sectional study. *Arq Neuropsiquiatr* 2018; 76 (6): 367-72.
18. Kranzler HR, Soyka M. Diagnosis and Pharmacotherapy of Alcohol Use Disorder: A Review. *JAMA* 2018; 320 (8): 815-24.
19. Smith WS, Johnston S, Hemphill III J. Ischaemic Stroke. In: Loscalzo J, Fauci A, Kasper D *et al*. eds. *Harrison's Principles of Internal Medicine*, 21e. McGraw Hill; 2022.
20. Kool MJ, Hoeks AP, Struijker Boudier HA *et al*. Short- and long-term effects of smoking on arterial wall properties in habitual smokers. *J Am Coll Cardiol* 1993; 22 (7): 1881-6.
21. El Husseini N, Kaskar O, Goldstein LB. Chronic kidney disease and stroke. *Adv Chronic Kidney Dis* 2014; 21 (6): 500-8.
22. Choi JH, Kim HW, Choi KD *et al*. Isolated vestibular syndrome in posterior circulation stroke: Frequency and involved structures. *Neurol Clin Pract* 2014; 4 (5): 410-8.
23. Vestergaard K, Andersen G, Nielsen MI. Headache in stroke. *Stroke* 1993; 24 (11): 1621-4.
24. Stroke and Cerebrovascular Diseases. In: Ropper AH, Samuels MA, Klein JP, Prasad S. eds. *Adams and Victor's Principles of Neurology*, 11e. McGraw Hill; 2019.
25. Kim JT, Park MS, Choi KH *et al*. Clinical outcomes of posterior versus anterior circulation infarction with low national institutes of health stroke scale scores. *Stroke* 2017; 48 (1): 55-62.

ORIGINAL ARTICLE

JIACM 2023; 24 (3-4): 177-81

Cardiovascular Manifestations in Moderate-to-Severe COVID-19 Patients and their Correlation with Inflammatory Markers

Garima, Mridul Chaturvedi**, Nitu Chauhan***, Ajeet Singh Chahar****, Suryakamal Verma*****, Akanksha Semawal*, Niharika Agarwal**

Abstract

Introduction: SARS-COV-2 induced novel coronavirus disease (COVID-19) associated high morbidity and mortality was the most threatening medical challenge in this century. COVID-19 induces multiple cardiovascular complexities such as myocarditis, pericarditis, acute myocardial injury, cardiogenic shock, arrythmias, cardiac arrest and subsequently heart failure. Early diagnosis could help to discern at-risk patients to facilitate early treatment.

Aim: To study the cardiovascular manifestations in moderate-to-severe COVID-19 patients and their correlation with inflammatory markers.

Methods: This was an observational study done in a tertiary care institute of Northern India in the state of Uttar Pradesh on moderate and severe COVID-19 patients. Detailed history and clinical examination were done along with laboratory work-up to look for cardiovascular involvement in patients with COVID-19 disease.

Results and Conclusion: Out of 100 cases, 54% were moderate and 46% were severe; 50% males and 50% females in severe group, most of them aged above 40 years with hypertension (50%) and diabetes (27%) as leading associated co-morbidities. Inflammatory markers like CRP, LDH and ferritin were significantly raised and correlated with the severity of the disease ($p < 0.05$). ECG revealed sinus tachycardia (44%) as the most common finding. In echocardiography, the most common finding was LV diastolic dysfunction (30%), followed by LV systolic dysfunction (23%), RV systolic dysfunction (15%). Most common valvular abnormality was tricuspid regurgitation (38%) followed by mitral regurgitation (30%). Pulmonary artery hypertension (14%), pericardial effusion (6%) and regional wall motion abnormalities (8%) were also seen.

Conclusion: COVID-19 disease is associated with significant involvement of the cardiovascular system and is the second most common cause of mortality after respiratory system. Also, increased levels of inflammatory markers correlate with the severity of the disease.

Introduction

The COVID-19 pandemic, caused by SARS-COV-2 virus had a crippling effect on global health. Emerging from Wuhan province in China, this virulent virus soon took almost every country in the globe under its grasp with 649,896,619 confirmed patients and 6,654,860 deaths reported as of Dec. 12, 2022[1].

Patients infected with SARS-CoV-2 present with a spectrum of clinical severity varying from asymptomatic to fatal conditions. Immune system disturbance has been considered as one of the hallmarks of COVID-19, especially cytokine release syndrome, lymphopenia along with endothelial dysfunction via Angiotensin-Converting Enzyme 2-receptor (ACE-2) and myocardial damage[2]. Inflammatory markers such as C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, interleukin-6 (IL-6), D-dimer and procalcitonin are drastically increased during cytokine storm creating parenchymal lesions in vital organs. COVID-19 is a disease that involves multiple body systems of which manifestations of the cardiovascular system were the main concern in our study. These can be acute heart failure, ischaemic heart disease, acute myocarditis, arrhythmias, venous thromboembolism, and pericardial diseases.

The aim of the study was to study the cardiovascular manifestations in moderate-to-severe COVID-19 patients and their correlation with inflammatory markers.

Material and Methods

This was an observational study conducted on 100 patients with moderate and severe COVID-19 disease admitted in the Medicine department of Sarojini Naidu Medical College, Agra during the period December 2020 to June 2022. Only patients >18 years of age were enrolled. All the 100 patients

**Junior Resident, **Professor and Head, ****Associate Professor, *****Assistant Professor, Department of Medicine, ***Associate Professor and Head, Department of Transfusion Medicine,Sarojini Naidu Medical College, Mahatma Gandhi Road, Agra - 282 002, Uttar Pradesh.*

Corresponding Author: Dr Ajeet Singh Chahar, Associate Professor, Department of Medicine, Sarojini Naidu Medical College, Mahatma Gandhi Road, Agra - 282 002, Uttar Pradesh. Tel: 8923414151, E-mail: drajeetchahar@gmail.com.

were subjected to detailed clinical examination and investigations: CBC, SGOT/SGPT, bilirubin, creatinine, urea, electrolytes, lipid profile, CRP, LDH, ferritin, troponin T, pro-BNP, chest X-ray postero-anterior view, electrocardiography and 2D echocardiography.

Results

A total of 100 patients with moderate (54%) and severe (46%) COVID-19 formed the study population. All the clinical details, progress of disease, and outcome were recorded and following observations were made:-

1. Demographic features:

Age of patients included in the study varied from 18 to 83 years. The majority of patients belonged to age > 40 yrs (72%) and percentage of severe COVID-19 patients was more in the age group of > 60 yrs (34.78%).

Table I: Age distribution.

Age group	Moderate COVID-19		Severe COVID-19		Total	
(years)	No.	%	No.	%	No.	%
18-20	3	5.55	2	4.34	5	5.00
21-40	11	20.37	12	26.08	23	23.00
41-60	22	40.74	16	34.78	38	38.00
>60	18	33.33	16	34.78	34	34.00
Total	54	100.00	46	100.00	100	100.00
Mean ± SD	52.22 ± 18.0		51.28 ± 16.91			

The percentage of male and female genders was 58.18% and 40% in the moderate COVID-19, 50%, and 50% in the severe COVID-19 group.

Table II: Comparison of gender frequencies between moderate and severe COVID-19 patients.

Gender	Moderate (n = 54)		Severe (n = 46)	
	N	%	N	%
Male	32	59.25	23	50.00
Female	22	40.74	23	50.00

2. Associated comorbidities

In the present study, hypertension was the leading comorbidity for COVID-19 disease in 50%, followed by diabetes mellitus (27%), dyslipidaemia (20%), obesity (12%), chronic obstructive pulmonary disease (6%), asthma (4%), pulmonary tuberculosis (6%), chronic kidney disease (4%), carcinoma (2%) and other (14%) with no associated comorbidities.

Table III: Distribution of patients according to comorbidity between moderate and severe COVID-19 patients.

Comorbidity	Moderate COVID-19 (n = 54)		Severe COVID-19 (n = 46)		Chi sq.	p-Value	Total	
	N	%	N	%			N	%
Hypertension	20	37.03	30	65.21	6.804	**0.009**	50	50%
T2DM	9	16.66	18	39.13	5.213	**0.02**	27	27%
Dyslipidaemia	5	9.26	15	32.61	7.08	**0.008**	20	20%
Obesity	2	3.70	10	21.74	6.04	**0.014**	12	12%
COPD	2	3.70	4	8.60	181	0.178	6	6%
Asthma	1	1.85	3	6.52	162	0.11	4	4%
Pulmonary Tuberculosis	5	9.26	1	2.17	1.13	0.287	6	6%
CKD	2	3.70	2	4.35	0.03	0.870	4	4%
Carcinoma	2	3.70	0	0.00	0.36	0.547	2	2%
None	6	11.11	8	17.39	0.38	0.540	14	14%

3. Investigations

It was noted that the level of inflammatory markers viz. CRP, LDH, and ferritin was significantly higher in severe COVID-19 group patients and correlated with severity of the disease.

Table IV: Mean values of inflammatory markers in moderate and severe COVID-19 patients.

	Moderate COVID-19 (n = 54)		Severe COVID-19 (n = 46)		T	p-Value
	Mean	±SD	Mean	±SD		
CRP (mg/L)	36.56	46.35	100.6	40.60	-10.439	**0.002**
LDH (mg/dL)	376.29	220.83	1037.73	399.67	-6.399	**0.001**
Ferritin (ng/mL)	443.67	274.24	962.95	517.38	-3.169	**0.002**

Raised levels of Troponin T were seen in 20 patients of COVID-19, which included 15 severe patients and 5 moderate patients signifying cardiac injury. Pro-BNP levels were also significantly increased in 29 COVID-19 patients, of which 15 were severe and 14 were moderate.

Table V: Cardiac biomarkers in moderate and severe COVID-19 patients.

Troponin T (ng/mL)	Value	Moderate COVID-19	Severe COVID-19	Total
	0-14	37	15	52
	14-99	17	11	28
	>99	5	15	20
Pro-BNP (pg/mL)	<300	42	29	71
	>300	14	15	29

4. Electrocardiography:

Sinus tachycardia was present in 44% of patients with ST-T changes in 10%. Right ventricular hypertrophy, right atrial enlargement, and right bundle branch block together constituted 18% whereas left ventricular hypertrophy, left atrial enlargement, and left bundle branch block constitute 13%. Atrial prematore complexes and Ventricular prematore complexes were present in 4% and 6%, respectively. Low voltage complexes were seen in 6%. Diffuse ST segment elevation with concavity upwards suggesting pericarditis was seen in 7%. Atrial fibrillation (6%) and atrial flutter (2%) were also seen. Changes representing Acute Coronary Syndrome were also noted in 4%. Ventricular tachycardia and complete heart block were also seen in 3% and 1% each, respectively. Normal electrocardiography was seen in 59% of patients.

Table VI: Various electrocardiogram changes seen in patients.

Electrocardiography findings	No. (%)
Sinus tachycardia	44%
LA enlargement	3%
RA enlargement	5%
APC	4%
VPC	6%
RVH	9%
LVH	8%
RBBB	4%
LBBB	2%
Complete heart block	1%
Wide QRS with A-V dissociation	3%
Atrial flutter	2%
AF	6%
ST elevation V1-V4	1%
ST elevation V1-V6	1%
ST elevation II, III, avF	1%
ST-T changes	10%
Diffuse ST elevation with concavity upwards	7%
Low voltage complexes	6%

5. Echocardiographic abnormalities

Diastolic dysfunction (DD) of the left ventricle was the most common abnormality detected in echocardiography and accounted for 30% of total patients, in which 20% of the patients had grade 1 DD, 8% had grade 2 DD and 2% had grade 3 DD. LV systolic dysfunction was seen in 23% of patients. 4% patients had severely reduced ejection fraction (LVEF) (< 30%), 9% had moderately reduced LVEF (30% - 40%) and 10% had a mild reduction in LVEF (40% - 50%). RV systolic dysfunction was seen in 15% of patients who had abnormal TAPSE scores of < 17 mm.

14% patients developed pulmonary artery hypertension in which 10% had PASP in the range of 30 - 50 mmHg whereas 4% had PASP in the range of 70 - 90 mmHg. Among valvular abnormalities, tricuspid regurgitation was seen in 38% of total patients followed by mitral regurgitation (30%), pulmonary regurgitation (12%) and aortic regurgitation (5%). Pericardial effusion (6%) and regional wall motion abnormalities (8%) were also seen.

Table VII: Summary of findings on echocardiography in moderate and severe COVID-19 patients.

Echocardiography findings	No. (%)
Normal	59%
LV Diastolic dysfunction	30%
LV Systolic dysfunction	23%
RV Systolic dysfunction	15%
Concentric LVH	10%
Regional wall motion abnormalities	8%
Pulmonary artery hypertension	14%
Mitral regurgitation	30%
Tricuspid regurgitation	38%
Pulmonary regurgitation	12%
Aortic regurgitation	5%
Pericardial effusion	6%

6. Outcome of Moderate and Severe COVID-19 patients

The total number of patients who died were 32. Among them, 22 patients were severe COVID-19 patients and 10 patients were moderate COVID-19. The maximum number of patients who died were in the age group of ≥ 60 years which was 17 in number, 11 patients died in the age group 40 - 60 years followed by 4 patients who died in the age group 18 - 40 years. 18 patients were male and 14 were female. Among them, 25 patients had some form of cardiovascular involvement.

Discussion

The effect of COVID-19 disease on cardiovascular system is not fully understood currently. This study was undertaken to study the cardiovascular manifestations in moderate-to-severe COVID-19 patients. We enrolled 100 patients with moderate and severe COVID-19 disease admitted in Medicine Department of Sarojini Naidu Medical College, Agra. Hypertension and diabetes mellitus were the leading comorbidities in our study which was also noticed by Line Kabi[3] and Sumon Ganguli[4] in their study who also reported

that the most frequent comorbidities were hypertension (46%), and diabetes (40%).

In our study, the mean levels of inflammatory markers like CRP (100.6 mg/L), LDH (1037.73 mg/dL), and ferritin (962.95 ng/mL) with a p-value of 0.002, 0.001, and 0.002, respectively, were significantly higher in the severe COVID-19 group and correlated with the severity of the disease. Dysregulation of immune response by SARS-COV-2 virus, when it invades the host is likely mediated by inflammatory cytokine storm, evidenced by an increase in the serum levels of LDH, ferritin, and CRP. This is consistent with the results of Huang, Wang, Lin *et al*[5], who found LDH, CRP, and ferritin level was significantly elevated in COVID-19 patients, which required intensive care unit care compared to patients that did not require ICU care.

Raised levels of Troponin-T and Pro-BNP were seen in 20 and 29 patients of moderate and severe COVID-19, respectively. The mechanisms explaining myocardial injury in those with COVID-19 infection include direct ("non-coronary") myocardial damage by ACE2 – the binding site for the SARS-CoV-2 – in cardiomyocytes, some have postulated that myocarditis might explain the rise of high-sensitivity cardiac Troponin in some patients. Lastly, acute myocardial infarction (MI) is always possible. Biomarkers of myocardial stress, i.e., natriuretic peptide is frequently elevated among patients with heart failure and are associated with an unfavorable course among patients with ARDS. Shahzad Khan[6] and Hahramani *et al*[7], also concluded that increased levels of cardiac biomarkers correlates with the severity the disease and with worse outcomes.

In our electrocardiographic study, sinus tachycardia (44%) was the most frequent finding, followed by right side changes (18%), left-sided changes (10%), ACS (4%) along with rhythm abmormalities like AF, VT, etc. Our results were in accordance with a study by Brit Long[8] where the commonest ECG abnormality was sinus tachycardia followed by ST-T segment changes, atrial fibrillation, ventricular arrythmias and QTc prolongation. They opined that ECG abnormalities may be due to cytokine storm, hypoxic injury, electrolyte abnormalities, plaque rupture, coronary spasm, microthrombi or direct endothelial or myocardial injury.

Left ventricular diastolic dysfunction (30%) was the most common abnormality detected in echocardiography followed by LV systolic dysfunction (23%) of patients, RV systolic dysfunction (15%) and 14% develop pulmonary artery hypertension. Among valvular abnormalities, TR (38%), MR (30%), PR (12%) and AR (5%) were seen. Regional wall motion abnormalities and pericardial effusion were seen in 8% and 6% of patients respectively. Marcelo Luiz Campos Vieira[9] found that echocardiography was normal in 46% of patients, 31% had left ventricular diastolic dysfunction, 17.1% presented with right ventricular dysfunction, 18% with decreased left ventricle ejection fraction, 16.2% had abnormal left ventricle global longitudinal strain, and 28% had pericardial effusion.

A total of 32 patients died in our study – 22 of these patients were severe COVID-19 and 10 patients were moderate COVID-19. Male: female ratio was 18:14 predominantly in the age group of ≥60 years. It was staggering to note that 25 out of 32 mortalities had some form of cardiovascular involvement. 68 patients out of 100 improved and discharged from the hospital. Laura A Bienvenu *et al*[10] found that records from China, South Korea, Italy and Germany suggested that males accounted for 59 - 75% of COVID-19 deaths in comparison to females. Williamson EJ *et al*[11] found that older age is a classical cardiovascular disease risk factor and is most profoundly implicated in COVID-19 related deaths. Rishi K. Wadhera[12] in his study concluded that there was an increase in deaths caused by ischaemic heart disease and hypertensive diseases in some regions of the United States during the initial phase of the COVID-19 pandemic. These findings suggest that the pandemic may have had an indirect toll on patients with cardiovascular disease.

Conclusion and Summary

In our study, hypertension (50%) was the leading comorbidity with COVID-19 disease, followed by diabetes mellitus (27%), dyslipidaemia (20%), and were significantly associated with the severity of the disease. It was noted that the levels of inflammatory markers like CRP ($p = 0.002$), LDH ($p = 0.001$), and ferritin ($p = 0.002$) were significantly higher and correlated with the severity of the disease. Levels of Troponin-T and Pro-BNP levels were also significantly increased in 20 patients and 29 COVID-19 patients, respectively signifying cardiac injury. In electrocardiography, sinus tachycardia (44%) was the most common finding with ST-T changes in 10%. RVH, RAE, and RBBB together constituted 18%, whereas LVH, LAE, and LBBB constituted 13%. Left ventricular diastolic dysfunction (30%) was the most common abnormality followed by LV systolic dysfunction (23%) and RV systolic dysfunction (15%). Fourteen per cent (14%) of the total patients developed pulmonary artery hypertension. Among valvular abnormalities TR (8%), MR (30%), PR (12%) and AR (5%) were seen. Pericardial effusion (6%) and regional wall motion abnormalities in (8%) were also seen. The total number of patients who died were 32. Among them, 25 patients had some form of cardiovascular involvement in moderate and severe COVID-19 patients.

In our study, cardiac dysfunction was seen in 35% patients of moderate and severe COVID-19 patients, which was

associated with high morbidity and mortality. Cardiac mortality was the second most common cause of death after respiratory failure in COVID-19 in our study. Thus, cardiac screening of all moderate and severe COVID-19 patients, especially, hypertensive, diabetics, and old age, and earlier treatment may reduce cardiac mortality and morbidity. The level of inflammatory markers CRP, LDH, and ferritin were significantly higher in the severe group. Inflammatory markers have a prognostic significance in patients with COVID-19 with higher levels being associated with worse outcomes so they could help to discern at-risk COVID-19 patients to facilitate early treatment.

Reference

1. WHO.https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation- reports/. (Accessed 15 December 2020).
2. Tan L, Wang Q, Zhang D *et al*. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. *Signal Transduct Target The* 2020; 5 (1): 33.
3. Kaabi L, Louhaichi S, Khalfallah I *et al*. *Euro Res J* 2021; 58: PA3807. DOI: 10.1183/13993003.congress-2021.PA3807.
4. Ganguli S, Howlader S, Dey K *et al*. Association of comorbidities with the COVID-19 severity and hospitalisation: A study among the recovered individuals in Bangladesh. *Int J Health Sci (Qassim)* 2022; 16 (4): 30-45.
5. Huang, lin, Wang. predictive value of hematological markers of systemic inflammation for managing COVID. *Oncotarget* 2017; 8 (27): 44824.
6. Khan S, Rasool ST, Ahmed SI. Role of Cardiac Biomarkers in COVID-19: What Recent Investigations Tell Us? *Curr Probl Cardiol* 2021; 46 (10): 100842.
7. Hahramani S, Tabrizi R, Lankarani KB *et al.* Laboratory features of severe vs. non-severe COVID-19 patients in Asian populations: a systematic review and meta-analysis. *Eur J Med Res* 2020; 25: 30.
8. Long B, Brady WJ, Bridwell RE *et al*. Electrocardiographic manifestations of COVID-19. *Am J Emerg Med* 2021; 41: 96-103.
9. Vieira MLC, Afonso TR, Oliveira AJ *et al*. In-hospital COVID-19 infection echocardiographic analysis: a Brazilian, tertiary single-center experience. *Cardiovasc Ultrasound* 2021; 19: 34.
10. Bienvenu LA, Noonan J, Wang X. Higher mortality of COVID-19 in males: sex differences in immune response and cardiovascular comorbidities, *Cardiovascular Research* 2020; 116 (14): 2197-2206.
11. Williamson EJ, Walker AJ, Bhaskaran K *et al*. Open SAFELY: factors associated with COVID-19 death in 17 million patients. *Nature* 2020; 584: 430-6.
12. Wadhera RK, Shen C, Gondi S *et al. J Am Coll Cardiol* 2021; 77 (2): 159-69.

ORIGINAL ARTICLE

JIACM 2023; 24 (3-4): 182-87

Clinical Profile and Outcome of Sepsis Patients on Mechanical Ventilation in A Tertiary Care Medical Intensive Care Unit

Rajnish Kaushik, Devyani Thakur**, Rohit Saini***, Himanshu Sikri****, MPS Chawla******

Abstract

Background: In a hospital, the highest-risk patients are managed in Intensive Care Unit (ICU). Of these, the subgroup of patients with sepsis and on mechanical ventilation has a high mortality rate. And yet, research exclusive to this cohort is sparse.

Method: In this study, the data of 309 consecutive patients was analysed retrospectively, who were admitted throughout one year in a non COVID, medical ICU of a tertiary care hospital in central Delhi. Out of these 309, our study group was of 223 sepsis patients on mechanical ventilation who were analysed for their clinical profile and outcome.

Results: We found that the mean age of the sample was 46.5years which ranged from 18 years to 97 years. There were 93 (41.7%) females and 130 (58.3%) males and 67.7% of our participants had no co-morbidities at baseline. 39.01% (n = 87) of patients had septic shock and 48.88% (n = 109) had MODS at admission to the ICU. 13.5% (n = 30) developed Ventilator Associated Pneumonia and Acinetobacter baumanii was the most common isolate. 128 patients (57.4%) survived whereas 95 (42.6%) succumbed to their illness.

Conclusion: The deadly combination of sepsis and mechanical ventilation is fairly common but grossly under-researched in Indian ICUs. They lead to a high mortality and the factors affecting mortality need to be further researched and reported.

Key words: Sepsis, mechanical ventilation, ICU, mortality rate.

Introduction

Sepsis, classically defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection, is an important cause of hospitalisation and a major cause of death in the Intensive Care Units (ICUs) worldwide[1]. Additionally, it has been found that patients on mechanical ventilation form a major subgroup among those admitted to the ICU with a very high mortality. Thus, this intersecting group of patients with sepsis on mechanical ventilation has been associated with a high mortality rate by several studies[2,3].

Most epidemiological data that is available is from Western literature, which is drawn from their central registries and national healthcare database. Indian data is sparse and there is a glaring lacuna in information from Indian Intensive Care Units. One of the reasons is due to heterogeneous policies regarding admission to ICUs in the public sector, private hospitals and smaller nursing homes, leading to non uniform trends in admission, management and mortality[4]. It is undeniable that patients with sepsis and mechanical ventilation put a large burden on the intensive care resources and individually as well as collectively influence the outcomes of survival and mortality. Therefore there is an imperative need to study them and the factors which influence the outcomes.

Ours is a tertiary care public sector hospital with very pressing requirements for rapid turnover of beds. Through this study we aim to analyze one of the most dreaded combinations that we face in our ICU – sepsis and mechanical ventilation.

Objective

To study the clinical profile and outcome of patients on mechanical ventilation complicated by sepsis, in a Non-Covid Medical ICU of a tertiary care hospital in Delhi.

Material and Methods

It was a retrospective, observational, cross-sectional descriptive study conducted by reviewing the data of 309 consecutive patients admitted in a tertiary care medical ICU throughout a one-year duration from Jan 2020 to Dec

Assistant Professor, Department of Pulmonary Medicine, VMMC and Safdarjung Hospital, New Delhi - 110 029, **Medical Specialist, Department of Internal Medicine, 171 Military Hospital, Samba - 184 121, J & K, ***Senior Resident, *****Professor and Head, Department of Medicine, ****Senior Medical Officer, Department of Emergency Medicine, ABVIMS and Dr Ram Manohar Lohia Hospital, Baba Kharak Singh Marg, New Delhi - 110 001.

Corresponding Author: Dr Himanshu Sikri, Senior Medical Officer, Department of Emergency Medicine, ABVIMS and Dr Ram Manohar Lohia Hospital, Baba Kharak Singh Marg, New Delhi - 110 001. Tel: 8285506075, E-mail: drhimanshu.sikri@gmail.com.

2020. Of these, our study group was of 223 sepsis patients on mechanical ventilation, in a non Covid, medical ICU of a tertiary care hospital in central Delhi.

Patients included in the study were: 1) > 18 years of age, 2) On mechanical ventilation, 3) COVID-19 negative, 4) Fulfilling the criteria of sepsis wherein Sepsis was defined as systemic inflammatory response syndrome (SIRS) with suspected or proven microbial aetiology. SIRS includes the presence of at least two of the following: (1) Body temperature >38° C or <36° C, (2) Heart rate >90/min, (3) Respiratory rate >20 breaths/min or hyperventilation with a PaCO2 <32 mmHg, (4) White blood cell count >12,000/mm^3 or <4,000/mm^3, or with >10% immature neutrophils[5].

We excluded the following patients: 1) <18-year-old, 2) Not on mechanical ventilation, 3) With diagnoses other than sepsis at presentation such as acute left ventricular failure, myocardial infarction, stroke, etc., and 3) Had incomplete or missing data.

Other definitions that were used were: 1) *Septic shock*- sepsis with persisting hypotension requiring vasopressors to maintain Mean Arterial Pressure ≥ 65 mmHg and having a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation[6], and, 2) *Multiple organ dysfunction syndrome (MODS)* - critical illness characterised by simultaneous dysfunction of two or more organs. This organ dysfunction was assessed using the sequential organ failure assessment (SOFA) score which includes scores from 0 - 4 for six major organ systems (pulmonary, haematologic, hepatic, cardiovascular, central nervous, and renal)[7].

Statistics

The data entry was done in Microsoft EXCEL spreadsheet and final analysis was done using Statistical Package for Social Sciences (SPSS) software, ver 25.0. The association of qualitative variables was analysed using Chi-Square test with Fisher's exact test, where necessary. A p-value of less than 0.05was considered statistically significant.

Results

Data of 309 patients consecutive patients admitted to the ICU was analysed; of these 223 patients were included in our analysis. They were divided into two major groups as per the outcome-survivors and non survivors (Fig. 1). And then further divided into subgroups for analysis as per age defined in the APACHEII scoring system, gender, number of co-morbidities, duration of ICU stay and prevalence of Ventilator-associated pneumonia (VAP).

We found that most of our patients (47.53%) were young

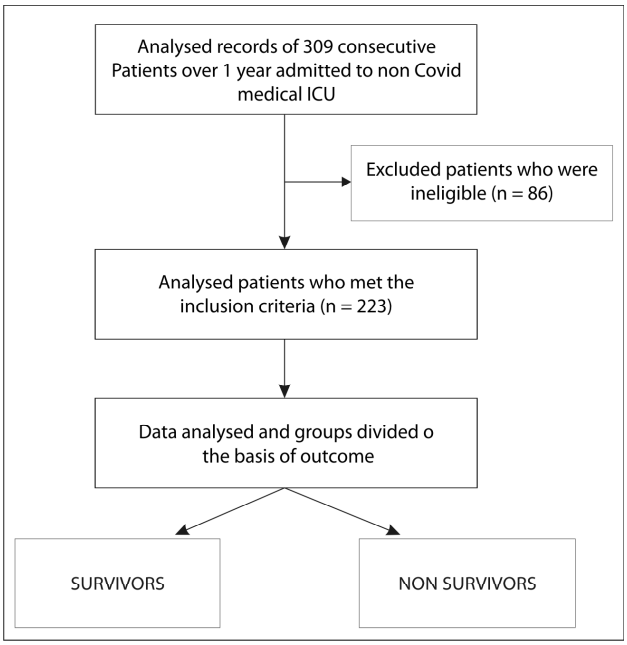


Fig. 1: *Line diagram of research method.*

and in the <44 yrs age group. Mean age of the study population was 46.5 years which ranged from 18 years to 97 years and median 45 years. There were 93 (41.7%) females and 130 (58.3%) males. 67.7% of our participants had no comorbidities whereas, 22.8% had a single, 8% had two, 1% had three and 0.5% of our sample had more than three comorbidities as per Charlson Comorbidity Index[8]. Diabetes mellitus was the most common comorbid condition we encountered. 87 (39.01%) patients had septic shock and 109 (48.88%) patients had MODS at the time of admission to the ICU. 89 patients (39.91%) had an ICU stay of a week or less and 134 (60.09%) stayed on for more than 7 days. This ranged from the shortest stay of 1 day to the longest of 93 days with a median stay of 10 days (5 - 16 days).

When we broadly divided the focus of sepsis into six groups, we found that 59% (n = 132) of our patients had a pulmonary aetiology. This was followed by 14.8% in whom no focus could be identified and 12% who were admitted with CNS infections (Fig. 2).

Although, all our patients were on invasive mechanical ventilation and admitted with sepsis, 13.5% (n = 30) developed VAP diagnosed as per the Clinical pulmonary infection score (CPIS)[9]. *Acinetobacter baumanii* was the most common isolate in the culture of secretions sent. The overall survival rate was 57.4% such that 128 patients survived and were transferred out to the wards in a stable condition and 95 patients, i.e., 42.6% succumbed to their illness in the ICU (Table I).

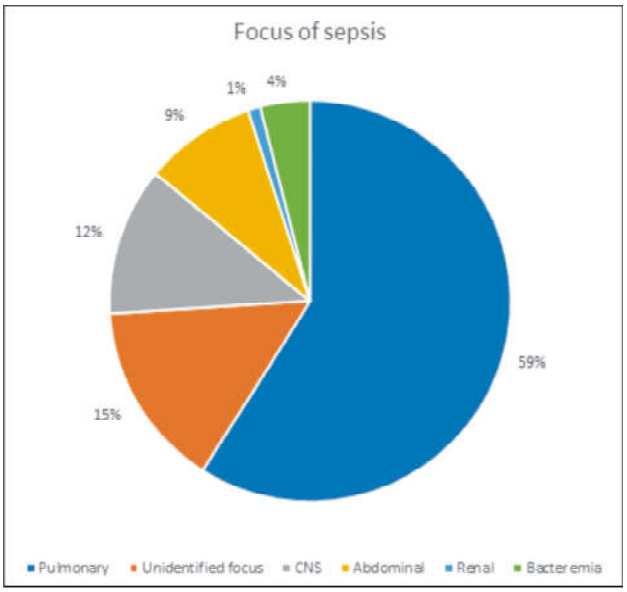


Fig. 2: *Pie chart showing distribution of foci of sepsis.*

Table I: Demographic profile and clinical outcome of studied patients.

Parameters	Frequency	Percentage
Age (years)		
< = 44 years	106	47.53%
45 - 54 years	36	16.14%
55 - 64 years	35	15.70%
65 - 74 years	27	12.11%
> = 75 years	19	8.52%
Mean ± SD	46.54 ± 18.8	
Median (25th - 75th percentile)	45 (30 - 60)	
Range	18 - 97	
Gender		
Female	93	41.70%
Male	130	58.30%
Number of co-morbidities		
0	151	67.71%
1	51	22.87%
2	18	8.07%
3	2	0.90%
4	1	0.45%
Duration of stay (days)		
< = 7 days	89	39.91%
> 7 days	134	60.09%
Mean ± SD	12.45 ± 11.85	
Median (25th - 75th percentile)	10 (5 - 16)	
Range	1 - 93	
VAP		
Not present	193	86.55%
Present	30	13.45%
Outcome		
Non Survivors	95	42.60%
Survivors	128	57.40%

In the final analysis, it was found that advancing age was associated with co-morbidities ($p < 0.0001$) and increasing age was also associated with higher frequency of VAP (p - 0.034).

Though most patients had an ICU stay of greater than a week, yet it was found that increasing age was associated with a prolonged ICU stay of over a week (p - 0.041). However, we did not find any significant relation between advancing age and the outcome of survival and demise (p - 0.883) or between gender and outcome (p - 0.704) or number of co-morbidities and outcome (p - 0.188). The presence of septic shock or MODS, also did not correlate with the outcome (p - 0.697 and p - 0.395 respectively). Similarly, there was no relation between frequency of VAP and duration of ICU stay (p - 0.111). It was found with statistical significance that those with an ICU stay of one week or less (56%) succumbed, whereas most of those who survived beyond one week, i.e., 66%, were transferred out of the ICU (p - 0.0008) (Table II).

Table II: Correlation between clinical parameters and outcome.

Parameter	Survivors	Non-survivors	p-value
Gender			0.704
Male	76	54	
Female	52	41	
Number of co-morbidities			0.188
0	81	70	
1	32	19	
2	13	5	
3	2	0	
4	0	1	
Age			0.883
< 44 years	61	45	
45 - 54 years	23	13	
55 - 64 years	18	17	
65 - 74 years	15	12	

> 75 years	11	8	
Days in ICU			**0.0008**
< 7 days	39	50	
>7 days	89	45	
Septic shock			0.395
Present at admission	53	34	
Absent at admission	75	61	
MODS			0.697
Present at admission	64	45	
Absent at admission	64	50	
Site of infection			0.376
Pulmonary	79	53	
Abdomen	9	10	
Renal	3	0	
CNS	12	15	
Bacteremia	5	4	
Unidentified focus	20	13	

Discussion

A hospital's highest risk patients are managed in the ICU. Sepsis patients on mechanical ventilation are one such high risk group. We found several studies on patients with sepsis and patients on mechanical ventilation, however, sparse literature was found which exclusively studied patients with both sepsis and mechanical ventilation.

It is well established that advancing age is an independent risk factor for severe sepsis and co-morbidities. Most studies also found an average age of 60 years but a younger cohort was reported in certain ICU studies with a mean age of 53.8 years. Contrary to the majority, our study had a much younger mean age group of 46.5 years which ranged between 18 to 97 years.

A few arguments could be made to explain this younger patient subset. Research suggests that given the poor prognosis, physicians do not readily admit older individuals > 80 years to ICUs, and those admitted to the ICU often do not receive mechanical ventilation[10,11]. And more importantly, India has one of the youngest demographic dividends in an ageing world.

In gender distribution, our findings of 41.7% females and 58.3% males, were similar to most reports but quite different from Mohamed *et al* who studied 71.25% males and 28.75% females in their ICU[2].

Only 32.3% of our participants had co-morbidities at baseline, whereas most ICU studies report a much higher prevalence, even as much as 79%[12]. This could be because of the younger mean age of admitted patients or possibly as the Charlson Comorbidity Index is itself criticised to be insufficiently discriminative[13].

In our study, patients had a median ICU stay of 10 days (5 - 16 days). Comparable figures of ICU patients with severe sepsis were 8 (4 - 12) days, as reported by Chatterjee *et al* and 10 (5 - 15) days in another study[14,15].

Septic shock and MODS, both are reportedly associated with a high mortality rate in several studies. Our data revealed a mortality rate of 39% (n - 34) among patients with septic shock, which was slightly less than studies reporting mortality in excess of 40%[6]. Similarly, there are studies from various medical and surgical ICUs that report a higher mortality rate among patients with MODS ranging from 27 to 100%. Our mortality rate was 41.3% (n - 45), even though the setting of septic shock and MODS was with the additional factor of mechanical ventilation[7]. Although this mortality rate of patients with septic shock and MODS was comparable with others, there was no statistically significant association between mortality and the presence of septic shock or MODS in our studied population.This could be due to mechanical ventilation itself compounding the calculated mortality rate.

All patients in our study were on mechanical ventilation, of which 30 (13.5 %) developed VAP. This falls within the known range of VAP incidence of 5 - 40% reported by previous studies[16]. It is much lower than 57.14%, reported from an Indian research. However, similar to us, they also found *Acinetobacter* as the most common pathogen in their ICU[17]. There are large variations in incidence rates depending upon the country, ICU type and clinical criteria used to define VAP in studies[16].

There is extensive data reporting high mortality rates in ICU patients and patients with sepsis. A mortality rate of 35% was found in the INDICAPS II and 26.5% in the multicentric ANZICS. Other studies show that mortality rate in patients given Mechanical Ventilation in the ICU ranges from 23% to 51%[18-21]. The mortality rate in our study was also a comparable 42.6%. The only similar study group was a subset of mechanically ventilated patients in severe sepsis (n = 56) studied by Vincent *et al* who have reported a mortality rate of 85.72% (n = 48)[22].

We found no significant association between age, female gender, number of co-morbidities and mortality. This was in agreement with the results of Mohamed *et al*, Liang *et al* and Prabhdev *et al*[2,23-24]. Contrary to these, are Koleef *et al*, who have found in their ICU setting that female gender had a higher mortality on mechanical ventilation[25].

The most common focus of infection we found was pulmonary, in as high as 59% of the admitted patients. This is much like the results of Patel *et al* (49.3%) , Artero *et al* (24.1%) and Watanbe *et al*, who found most of their studied patients to have pulmonary focus of infection. Jain *et al* have reported their prevalence of 70% pulmonary infections from a primarily Respiratory ICU. In congruence with our results, all of them have reported no association of the outcome with source of infection[26-29].

There are several limitations of our study and larger quantum of data is required to make any definitive generalisations. This is a single centre study over the period of one year, analysed in retrospect and the patients transferred out could not be followed up. As this is a very high volume centre, no uniform policy of admission to the medical ICU could be practiced to channel the influx of patients in sepsis alone and no step down unit with intensive monitoring was available for faster transit of patients.

The strength of this study is in the large sample size of a relatively under-reported subgroup. Patients with sepsis and mechanical ventilation usually form just a subset of study groups and due to their high mortality rates, remain an under reported cohort. The lack of such a comparative group in literature makes drawing conclusions from results difficult and we hope that more such studies are reported to trace further patterns for reducing mortality benefit in such patients.

References

1. Rhodes A, Evans LE, Alhazzani W *et al*. Surviving sepsis campaign: International guidelines for management of sepsis and septicshock: 2016. *Intensive Care Med* 2017; 43: 304-77.
2. Mohamed AK, Mehta AA, James P. Predictors of mortality of severe sepsis among adult patients in the medical Intensive Care Unit. *Lung India: Official Organ of Indian Chest Society* 2017; 34 (4): 330.
3. Urner M, Jüni P, Hansen B *et al*. Time-varying intensity of mechanical ventilation and mortality in patients with acute respiratory failure: a registry-based, prospective cohort study. The *Lancet Respiratory Med* 2020; 8 (9): 905-13.
4. Prayag S. ICUs worldwide: critical care in India. *Critical Care* 20026; 6 (6): 479.
5. Bone RC, Balk RA, Cerra FB *et al*. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest* 1992; 101 (6): 1644-55.
6. Singer M, Deutschman CS, Seymour CW *et al*. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016; 315 (8): 801-10.
7. Mascarenhas RM, D'souza RC, Shafeel Ibrahim K *et al*. Assessing mods in ICU – A critical appraisal. *Head Neck Brain IP Indian J Anat Surg* 2019; 5 (2): 61-3.
8. Austin SR, Wong YN, Uzzo RG *et al*. Why summary co-morbidity measures such as the Charlson co-morbidity index and Elixhausers core work. *Medical Care* 2015; 53 (9): e65.
9. Zilberberg MD, Shorr AF. Ventilator-associated pneumonia: the clinical pulmonary infection score as a surrogate for diagnostics and outcome. *Clinical Infectious Diseases* 2010; 51 (Suppl_1): S131-5.
10. Garrouste-Orgeas M, Boumendil A, Pateron D *et al*. Selection of intensive care unit admission criteria for patients aged 80 years and over and compliance of emergency and intensive care unit physicians with the selected criteria: anobservational, multicenter, prospectivestudy. *Critical Care Medicine* 2009; 37 (11): 2919-28.
11. Boumendil A, Aegerter P, Guidet B. CUB Rea Network. Treatment intensity and outcome of patients aged 80 and old erinintensive care units: a multicenter matched cohort study. *J Amer Geriatrics Soc* 2005; 53 (1): 88-93.
12. Aronsson Dannewitz A, Svennblad B, Michaëlsson K *et al*. Optimised diagnosis-based co-morbidity measures for all-cause mortality prediction in a national population-based ICU population. *Critical Care* 2022; 26 (1): 1-1.
13. Gedeborg R, Sund M, Lambe M *et al*. An aggregated co-morbidity measure based on history of filled drug prescriptions: development and evaluation in two separate cohorts. *Epidemiology* 2021; 32: 607-15.
14. Chatterjee S, Bhattacharya M, Todi SK. Epidemiology of adult-population sepsis in India: a single center 5 year experience. *Indian Journal of Critical Care Medicine: Peer-reviewed, Official Publication of Indian Society of Critical Care Medicine* 2017; 21 (9): 573.
15. Divatia JV, Amin PR, Ramakrishnan N *et al*. Intensive care in India: The Indian intensive care case mix and practice patterns study. *Indian Journal of Critical Care Medicine: Peer-reviewed, Official Publication of Indian Society of Critical Care Medicine* 2016; 20 (4): 216
16. Ranjan N, Chaudhary U, Chaudhry D. Ventilator-associated pneumonia in a tertiary care intensive care unit: Analysis of incidence, risk factors and mortality. *Indian Journal of Critical Care Medicine: Peer-reviewed, Official Publication of Indian Society of Critical Care Medicine* 2014; 18 (4): 200.
17. Papazian L, Klompas M, Luyt CE. Ventilator-associated pneumonia in adults: a narrative review. *Intensive Care Medicine* 2020; 46 (5): 888-906.
18. Mani RK. INDICAPSII: A Bird's Eye View of the Indian Intensive Care Landscape. *Indian Journal of Critical Care Medicine: Peer-reviewed, Official Publication of Indian Society of Critical Care Medicine* 2021; 25 (10): 1087.
19. Finfer S , Bellomo R, Lipman J *et al*. Adult-population incidence of severe sepsis in Australian and New Zealand intensive care units. *Intensive Care Medicine* 2004; 30: 589-96.
20. Kurek CJ, Dewar D, Lambrinos J. Clinical and economic outcome of mechanically ventilated patients in New York State during 1993: Analysis of 10,473 casesunder DRG475. *Chest* 1998; 114 (1): 214-22.
21. Chelluri L, Rotondi AJ, Sirio CA. 2-month mortality and functional status of critically ill adult patients receiving prolonged mechanical ventilation. *Chest* 2002; 121 (2): 549.
22. Vincent JL, Rello J, Marshall J *et al*. International study of the prevalence and outcomes of infection in intensive care units. *JAMA* 2009; 302 (21): 2323-9.
23. Liang J, Li Z, Dong H. Prognostic factors associated with mortality in mechanically ventilated patients in the intensive care unit: A single-center, retrospective cohort study of 905 patients. *Medicine* 2019; 98 (42).
24. Prabhudev P, Ramamoorthi K, Acharya RV. A Clinical and Demographic Profile of Elderly (>65 Years) in the Medical

Intensive Care Units of a Tertiary Care Center. *Indian Journal of Critical Care Medicine: Peer-reviewed, Official Publication of Indian Society of Critical Care Medicine* 2023; 27 (3): 166.

25. Kollef MH, O'Brien JD, Silver P. The impact of gender on outcome from mechanical ventilation. *Chest* 1997; 111 (2): 434-41.
26. Artero A, Zaragoza R, Camarena JJ *et al*. Prognostic factors of mortality in patients with community-acquired bloodstream infection with severe sepsis and septic shock. *J Critical Care* 2010; 25 (2): 276-81.
27. Jain S, Sinha S, Sharma SK *et al*. Procalcitonin as a prognostic marker for sepsis: a prospective observational study. *BMC Research Notes* 2014; 7 (1): 1-7.
28. Watanabe Y, Oikawa N, Hariu M. Ability of procalcitonin to diagnose bacterial infection and bacteria types compared with blood culture findings. *Inter J General Med* 2016; 30: 325-31.
29. Patel RR, Karagatharavm VH, Dudhrecha B. Outcome of Patients with Sepsis Admitted in Intensive Care Unit of a Tertiary Care Hospital in India. *National J Med Res* 2022; 12 (02).

ORIGINAL ARTICLE

JIACM 2023; 24 (3-4): 188-92

Serum Vitamin B12 Levels in Patients of Ischaemic Stroke: A Cross-Sectional Study

Preeti, RP Saini**, SN Ambedkar***, Samita Saluja*****

Abstract

***Background:** Ischaemic stroke is the most common cerebrovascular disease and is one of the leading causes of death and long-term disability in the world. Vitamin B12 (B12) deficiency, by virtue of causing hyperhomocysteinaemia may be implicated as an acquired risk factor of ischaemic stroke, which is also easily modifiable. There is a scarcity of data from India regarding the prevalence of B12 deficiency and hence the correlation with ischaemic stroke patients. The objective of this study was to evaluate the relationship between serum vitamin B12 levels and ischaemic stroke, including folic acid and homocysteine levels.*

***Material and methods:** The study was a matched case-control study. 50 cases of ischaemic stroke were compared with an equal number of age and gender matched controls. Serum vitamin B12, folate and homocysteine levels were analysed as continuous data (Student's t test) as well as categorical data (Chi square test) using Statistical Package for Social Sciences (SPSS) version 21.0. Correlation of serum B12, folate and homocysteine in ischaemic stroke was studied using Pearson's co-efficient.*

***Results:** Mean levels of vitamin B12, folic acid and homocysteine in cases were 187.25 pg/mL, 7.95 ng/mL and 31.12 µmol/L respectively while in controls it was 463.84 pg/mL, 13.42 ng/mL and 6.63 µmol/L respectively and the differences were statistically significant, pvalue < 0.001. There was a negative correlation of vitamin B12 (-0.424) and folic acid (-0.355) levels and positive correlation of homocysteine (0.304) with ischaemic stroke.*

***Conclusions:** Vitamin B12 and folic acid deficiency and hyperhomocysteinaemia appear to be important risk factors for cerebrovascular accidents. It is therefore important to assess vitamin B12 folate and homocysteine levels in all cases of cerebrovascular accidents.*

Introduction

Stroke is defined as a clinical syndrome of sudden onset rapidly developing symptoms or signs of focal, and at times global, loss of cerebral function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin[1]. Acute ischaemic stroke is the most common cerebrovascular disease and is one of the leading causes of death (10.55%) and long-term disability (daily 4.88%) throughout the world[2].

Management of the disease is largely conservative. Several risk factors for stroke have been identified which are the target of both primary and secondary preventive strategies[3]; these risk factors include hypertension, diabetes mellitus, cardiac diseases, sickle cell anaemia, cigarette smoking, other emerging risk factors include hyperhomocysteinaemia, hypovitaminosis B12, and low folic acid levels, etc.[4-7].

Vitamin B12 is a water-soluble vitamin with a key role in the normal functioning of the brain and nervous system, and for the formation of erythrocytes. Vitamin B12 deficiency leads to abnormality in methylene-tetrahydrofolate reductase resulting in impaired ability to form methyl-tetrahydrofolate from methylene-tetrahydrofolate. This causes functional folate deficiency, resulting in failure to remethylate homocysteine to methionine leading to hyperhomocysteinaemia[8-10]. Hyperhomocysteinaemia is a known risk factor for ischaemic stroke.

However there are no clear cut recommendations for supplementing vitamin B12 for the prevention of stroke. A recent metaanalysis by David J A indicated that B vitamin combinations and folic acid reduced the risk of stroke; the authors recommended folic acid for this purpose in countries where folate fortification does not exist[8].

Hence, this study was undertaken to evaluate the serum level of vitamin B 12 in patients of ischaemic stroke.

Aims and objectives

Aim

The aim of this study was to evaluate the relationship between serum vitamin B12 levels and ischaemic stroke.

**PG Student, **Consultant and Associate Professor, ***Associate Professor, Department of Medicine, ****Director Professor and HOD, Department of Haematology, VMMC and Safdarjung Hospital, New Delhi - 110 029.*
Corresponding Author: Dr RP Saini, Consultant and Associate Professor, Department of Medicine, VMMC and Safdarjung Hospital, New Delhi - 110 029. Tel: 9868885579, E-mail: dr.rpsaini@yahoo.com.

Objective

To determine levels of serum vitamin B12 in patients of ischaemic stroke.

Material and Methods

Study setup: The study was conducted in the Department of Medicine, Haematology and Biochemistry, VMMC and Safdarjung Hospital, New Delhi.

Collaborative department: Department of Haematology and Biochemistry, Safdarjung Hospital, New Delhi.

Study period: 18 months.

Study design : Case-control study.

Sample Size: Considering the prevalence of vitamin B12 deficiency in general population as 6%[9] and in stroke patients 40%[10], keeping confidence interval 95% and power of study 80% sample size selected was 50 cases, with 50 healthy age and sex-matched controls by using software Open Epi version 3.0.

Sample collection : 10 mL venous blood sample was taken for investigation. Vitamin B12 including folate and homocysteine levels were done by automated chemiluminiscent immunoassay in Beckman coulter access 2 machine.

Study population: 50 ischaemic stroke patients attending, the department of Internal Medicine and Neurology after fulfilling inclusion and exclusion criteria with 50 age and sex-matched controls, who gave consent, after fulfilling inclusion and exclusion criteria.

Stastistical analysis: The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0. Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non-parametric tests were used.

Statistical tests were applied as follows:-

1. Quantitative variables were compared using unpaired t-test/Mann-Whitney Test (when the data sets were not normally distributed) between the two groups.
2. Qualitative variables were compared using Chi-square test/Fisher's exact test.
3. Logistic regression was used to find the risk factors of vitamin B12 deficiency in ischaemic stroke patients.

A p value of < 0.05 was considered statistically significant.

Consent and ethical clearance

Written and informed consent was taken from all subjects participating in the study. Ethics clearance was taken from the Ethics Committee of Safdarjung Hospital, before conducting the study. The study was performed according to the principles of Declaration of Helsinki.

Inclusion criteria

Patients presenting with ischaemic stroke aged 18 - 70 years within 7 days of onset.

Exclusion criteria

1. Patient on vitamin B12 or folic acid supplementation within last 3 months.
2. Patients with haemorragic stroke and previous history of ischaemic stroke.
3. Patient with chronic illness, liver or renal disease.
4. Chronic alcoholic.
5. Patients with major gastrointestinal surgery or malabsorption syndrome.

Results

Most patients were in the age group of 40 - 60 years; 33 (66%) in cases and 34 (68%) in controls. Males were 32 (64%) in cases and 35 (70%) in controls, while females were 18 (36%) and 15 (30%) respectively. Smoking was present in 32 (64%) cases and 31 (62%) controls. There were 14 (28%) diabetic patients in cases and 12 (24%) in controls. Dyslipidaemia was present in 17 (34%) cases and 11 (22%) controls. Hypertension were present in 18 (36%) patients in both the groups. In cases, 21 (42%) patients were vegetarian while 12 (24%) patients in controls were vegetarians (Table I).

Table I: Demographic profile of patients.

Factors		Cases	Controls	Total	p value
Age (years)	1) <= 40	6 (12%)	7 (14%)	13 (13%)	
	2) 41 - 50	15 (30%)	18 (36%)	33 (33%)	0.881
	3) 51 - 60	18 (36%)	16 (32%)	34 (34%)	
	4) >60	11 (22%)	9 (18%)	20 (20%)	
Gender	F	18 (36%)	15 (30%)	33 (33%)	0.523
	M	32 (64%)	35 (70%)	67 (67%)	
Smoking	Y	32 (64%)	31 (62%)	63 (63%)	0.836
	N	18 (36%)	19 (38%)	37 (37%)	
Diabetes	N	36 (72%)	38 (76%)	74 (74%)	0.648

	Y	14 (28%)	12 (24%)	26 (26%)	
Dyslipidaemia	N	33 (66%)	39 (78%)	72 (72%)	0.181
	Y	17 (34%)	11 (22%)	28 (28%)	
Hypertension	N	32 (64%)	32 (64%)	64 (64%)	1
	Y	18 (36%)	18 (36%)	36 (36%)	
Diet	M	29 (58%)	38 (76%)	67 (67%)	0.056
	V	21 (42%)	12 (24%)	33 (33%)	

Mean value of serum vitamin B12 in cases was 187.26 ± 138.74 pg/mL whereas in controls it was 463.84 ± 251.75 pg/mL. Median value was 145.5 pg/mL in cases and 368 pg/mL in controls, (p value < 0.0001) (Fig. 1).

Mean value of serum folic acid in cases was 7.95 ± 5.1 ng/mL and 13.42 ± 6.59 ng/mL in controls. Median value was 6.8 ng/mL in cases and 12.5 ng/mL in controls. (p value < 0.0001) (Fig. 2).

Mean value of serum homocysteine in cases was 31.12 ± 14.98 µmol/L and 6.63 ± 3.86 µmol/L in controls. Median value was 32.23 µmol/L in cases and 6.14 µmol/L in controls (Fig. 3).

Risk factors like diabetes, hypertension, smoking, vitamin

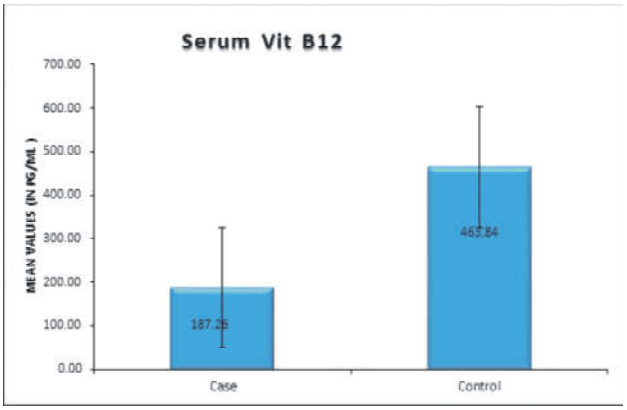


Fig. 1: *Levels of serum vitamin B12 in study population.*

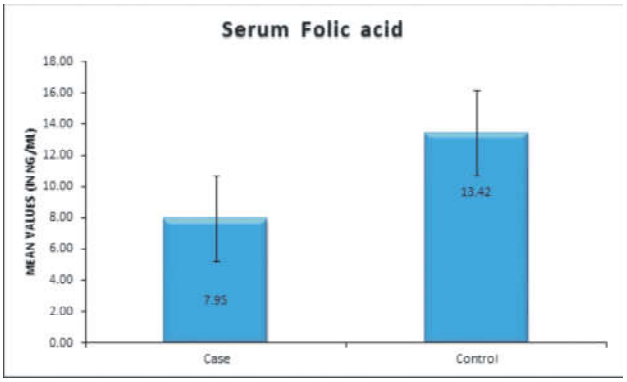


Fig. 2: *Levels of serum folic acid in study population.*

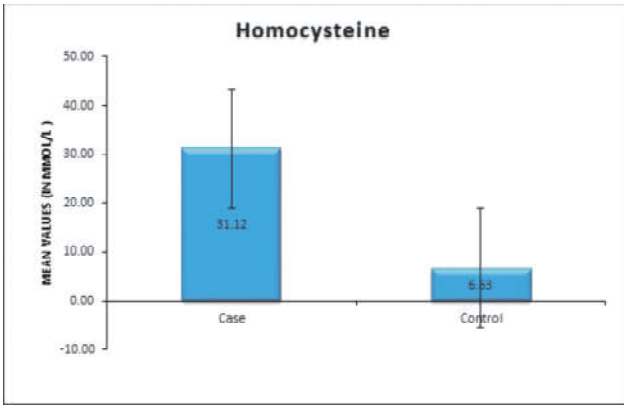


Fig. 3: *Levels of serum homocysteine in study population.*

B_{12} and folic acid levels were low and serum homocysteine levels were high (Table II).

Table II: Association of serum vitamin B12, folic acid and homocysteine in cases and controls with risk factors.

		Vitamin B12		Folic Acid		Homocysteine	
		Mean Values (in pg/mL)	P value	Mean Values (in ng/mL)	p value	Mean Values (in µmol/L)	p value
Diabetes	Cases	205.14 ± 158.78	**<0.001**	7.93 ± 4.62	**<.0001**	45.56 ± 11.79	**<.0001**
	Control	370.58 ± 131.93		13.71 ± 5.33		8.64 ± 2.11	
Hypertension	Cases	164.61 ± 151.99	**<0.005**	7.27 ± 4.42	**<.0001**	37.29 ± 16.41	**0.034**
	Control	462.67± 131.5		12.82 ± 5.47		7.33 ± 3.13	
Smoking	Cases	166.11 ± 147.71	**<0.001**	6.59 ± 3.32	**<.0001**	39.85 ± 13.82	**0.001**
	Control	452.53 ± 134.36		12.27± 5.78		7.4 ± 3.44	
Dyslipidaemia	Cases	154.53 ± 91.84	**<0.001**	7.63 ± 4.9	**<.0001**	45.24 ± 8.56	**<.0001**
	Control	420.27 ± 156.19		12.5 ± 5.26		9.72 ± 2.1	
Diet	Cases	153 ± 20.28	**<0.0001**	8.07 ± 5.39	**<.0001**	22.54 ± 11.34	**<.0001**
	Control	337.6 ± 138.03		13.28 ± 4.8		9.7 ± 1.75	

There were 36 vitamin B12 deficient patients (vitamin B12 < 211 pg/mL), 19 folic acid deficient patients (folic acid < 5.38 ng/mL) and 42 hyperhomocysteinaemic patients (homocysteine >15 µmol/L). There were 14 vitamin B12 and folic acid deficient patients; 19 folic acid deficient and hyperhomocysteinaemic patients; 34 vitamin B12 deficient and hyperhomocysteinaemic patients. There were 15 vitamin B12 and folic acid deficient and

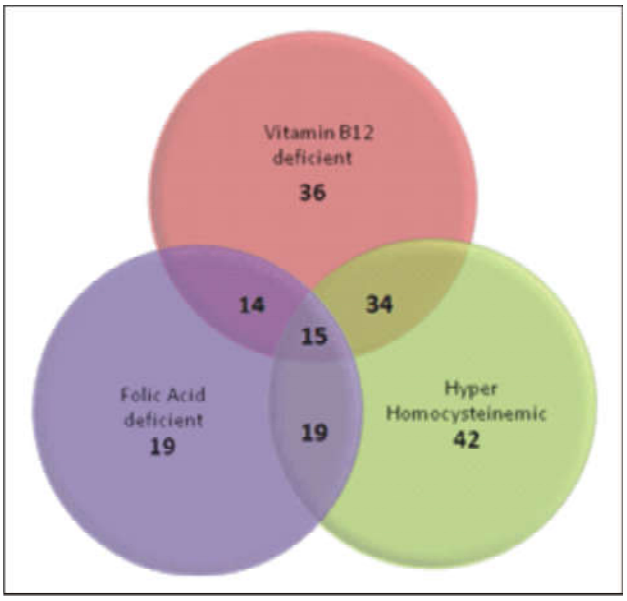


Fig. 4: *Combined result of vitamin B12 and folic acid deficient and hyperhomocysteinaemic patients.*

hyperhomocysteinaemic patients (Fig. 4). There was positive correlation between vitamin B12 and folic acid (pearson co-efficient value 0.355, logistic regression -0.077); and both of them had negative correlation with homocysteine (pearson co-efficient value -0.343, logistic regression value 0.025). It showed that lower levels of vitamin B12 and folic acid are associated with hyperhomocysteinaemia.

Discussion

Stroke is the major cause of death and disability worldwide. Each year, about 4.4 million people die of stroke globally, of whom almost three million are from developing countries. Decreased level of vitamin B12 and folic acid in blood may be an important factor associated with ischaemic stroke. There are very limited number of studies which compare the levels of vitamin B12, folate and homocysteine and their combined or independent effects on the risk of acute ischaemic stroke in India.

Our findings were similar to the findings of Gajbhare *et al*[11], Narang *et al*[12], Biswas *et al*[13] and Modi *et al*[14] who concluded that hyperhomocysteinaemia as an important risk factor for ischaemic stroke. But in contrast to these studies, relatively higher values of homocysteine was observed in both cases and controls in our study. These findings might be reflective of a higher prevalence of hyperhomocysteinaemia in the population our hospital caters to. This assumption can however, only be confirmed by a large scale community based study in this particular part of the country. Wadia *et al*[15] also concluded that vitamin B12 deficiency leads to raised serum homocysteine levels which is common in India and is a major risk factor for strokes. Ahmed *et al*[16] also showed vitamin B12 deficiency and hyperhomocysteinaemia in patients of stroke or transient ischaemic attack.

Limitations

Our study had the following limitations. First, the design was cross-sectional, done in a tertiary care hospital based population. Second, though study duration was long, relatively small number of patients were included in this study. Third, metabolic deficiency of vitamin B12 was not taken into account along with various genetic factors for vitamin B12 and folic acid deficiency and hyperhomocysteinaemia. Fourth, iatrogenic vitamin B12 deficiency like patients on proton pump inhibitors metformin was not excluded. Fifth, number of vegetarian patients were more in cases which could be the confounding factor. Sixth, patients with cardio-embolic stroke were not excluded. Hence, further large scale studies are required including a large number of cases and control in a normal based population, taking into account various environmental, iatrogenic, confounding and genetic factors.

Conclusion

We conclude that in patients of ischaemic stroke levels of vitamin B12 were low, along with low levels of folic acid and high homocysteine levels. This showed negative correlation of vitamin B12 and folic acid levels and positive correlation of homocysteine levels in patients of ischaemic stroke. However, there were few limitations of this study. Further large scale studies including various other risk factors like environmental and genetic factors are needed to confirm the findings.

References

1. Prasad K, Vibha D, Meenakshi. Cerebrovascular disease in South Asia – Part I: A burning problem. *JRSM Cardiovasc Dis* 2012; 1 (7): 20.
2. Towfighi A, Saver JL. Stroke declines from third to fourth leading cause of death in the United States: historical perspective and challenges ahead. *Stroke* 2011; 42: 2351-5.
3. Omrani HQ, Shandiz EE, Qabai M *et al*. Hyperhomocysteinaemia, folate and B12 vitamin in Iranian patients with acute ischaemic stroke. *ARYA Atheroscler* 2011; 7 (3): 97-101.
4. Robertson J, Iemolo F, Stabler SP *et al*. Increased importance of vitamin B12 for total homocysteine and carotid plaque in the era of folate fortification of the brain supply. *CMAJ* 2005; 172: 1569-73.
5. Kalita J, Kumar G, Bansal V, Misra UK. Relation of homocysteine with other risk factors and outcome of ischaemic stroke. *Clin Neurol Neurosurg* 2009; 111: 364-67.
6. Neogi SS, Thomas M, Sharma A *et al*. Early markers of occult

megablastosis for low cost detection of hyperhomocysteinaemia in patients with ischaemic strokes: prevention approach for primary healthcare. *Can J Physiol Pharmacol* 2014; 92: 713-6.

7. Kirtania K, Ahmed S, Sultana N *et al*. Study on serum vitamin B12 and folic acid in patients of ischaemic stroke. *J Dhaka Med Col* 2010; 19 (2): 115-7.
8. Spence JD, Bang H, Chambless LE *et al*. Vitamin intervention for stroke prevention trial. *Stroke* 2005; 36: 2404-9.
9. Mahajan SK, Aundhakar SC. A study of the prevalence of serum vitamin B12 and folic acid deficiency in Western Maharashtra. *J Fam Med Primary Care* 2015; 4: 64-8.
10. Maheshwari D, Sardana V, Mohan S *et al*. A Study of Vitamin B12 Level as a Risk Factor for Ischaemic Stroke. *Int J Med Res Prof* 2017; 3 (1): 84-8.
11. Gajbhare PT, Juvale NI. The study of plasma homocysteine level as a risk factor for ischaemic strokes in young patients. *Int J Adv Med* 2017; 4 (4): 1019-25.
12. Narang AP, Verma I, Kaur S *et al*. Homocysteine – risk factor for ischaemic stroke. *Ind J Physiol Pharmacol* 2009; 53 (1): 34-8.
13. Biswas A, Ranjan R, Meena A *et al*. Homocystine Levels, Polymorphisms and the Risk of Ischaemic Stroke in Young Asian. *J Stroke Cerebrovasc Dis* 2009; 18 (2): 103-10.
14. Modi M, Prabhakar S, Majumdar S *et al*. Hyperhomocysteinaemia as a risk factor for ischaemic stroke: An Indian scenario. *Neurology India* 2005; 53 (3): 297-301.
15. Wadia RS, Edul NC, Bhagat S *et al*. Hyperhomocysteinaemia and vitamin B12 deficiency in ischaemic strokes in India. *Ann Ind Acad Neurol* 2004; 7: 387-92.
16. Ahmed S, Bogiatzi C, Hackam DG *et al*. Vitamin B12 deficiency and hyperhomocysteinaemia in outpatients with stroke or transient ischaemic attack: A cohort study at an academic medical centre. *BMJ Open* 2019; 9 (1): e026564.

ORIGINAL ARTICLE

JIACM 2023; 24 (3-4): 193-98

Effect of Quality of Health Services and Cost of Treatment on Healthcare Utilisation Among Geriatric Patients of Respiratory Diseases – An Indian Perpective – Ghaziabad, Delhi NCR

Sonisha Gupta, Smita Asthana**, Atul Kumar Gupta***, Pawan Kumar Basarwadia*****

Abstract

Background: Aging refers to inevitable, irreversible decline in organ function.

Methods: Cross-sectional study of elderly aged 60 yrs and above was conducted in urban and rural area of NCR and Ghaziabad district of Uttar Pradesh. Elderly with respiratory diseases were asked questionnaire regarding healthcare utilisation.

Results: In Government sector good behaviour of healthcare provider had significantly positive effect on healthcare utilisation by urban elderly (p value - .001). But not in rural elderly population. In Government, while availability of specialist was significant factor for healthcare utilisation by urban elderly (p value = .040), for rural elderly it was availability of free medicines (.036). But satisfaction with doctor positively affected healthcare utilisation of both urban as well as rural elderly (p value = .020 and < .001). As the cost of treatment decreased, healthcare utilisation improved. But this effect did not achieve statistical significance in either urban or rural area. Both in urban and rural area most elderly who were utilizing health services found private health services 'very expensive'.

Conclusion: Majority of elderly (more than 80%) feel that Government healthcare services are very crowded and they have to wait very long to get consultation. Availability of free medicines is particularly poor at rural health facilities. Healthcare policy makers need to be aware of the heterogeneity of Indian elderly and plan healthcare systems suited to local expectations and needs.

Key words: Elderly, quality, cost of treatment, healthcare utilisation, respiratory diseases, geriatric.

Introduction

Every organ system during youth has sufficient homoeostatic reserve. Progressive constriction of this reserve, "Homoeostenosis", starts in 3rd decade of life[1].

Elderly population is progressively increasing worldwide. Global old age population was 784 million in 2011. India's old population accounts for 10% of the World's old age population (784 million) in 2011. Also its population in India is much greater than the total population of many developed and developing countries.

Improvement in healthcare along with development has brought a demographic transition. It has resulted in increased proportion of elderly in population. Respiratory disorders are an important cause of morbidity and mortality in old age. Inadequate treatment or no treatment of these disorders leads to increased morbidity, complications, poor quality of life and increased risk of dying from these disorders.

Finance is an important factor in healthcare utilisation. Healthcare utilisation is directly related to financial status. Access to free quality healthcare (either through employer or some kind of health insurance) also positively influences healthcare utilisation. Less than 20% of Indians have some form of health insurance. According to one study, 36 million people in India fall below the poverty line each year due to expenditure on healthcare[2]. Despite all this, a large portion of the population choose to bypass free public services to pay out-of-pocket in private institutions[3,4]. This fact reflects poor quality and accessibility of government healthcare services.

Recognising the special needs of elderly, reasons for non-utilisation of available healthcare services and problems faced by them in utilizing these services is the first step in formulating health policies for them.

Methodology

A descriptive survey of geriatric population aged 60 yrs and above was conducted in urban and rural area of NCR and Ghaziabad district of Uttar Pradesh. Urban colonies and rural villages which were conglomerated in close areas were

Professor, Department of Respiratory Medicine, SMSR, Sharda University, Greater Noida - 201 308, Uttar Pradesh.
*****Scientst E, ICMR NICPR, Noida - 201 301, Uttar Pradesh.***
******Associate Professor, Department of Surgery, Government Institute of Medical Sciences, Greater Noida - 201 308, Uttar Pradesh.***
*******Chest Physician, Department of Pulmonary Medicine, ABVIMS and Dr Ram Manohar Lohia Hospital, Baba Kharak Singh Marg, New Delhi - 100 001.***
Corresponding Author: Dr Sonisha Gupta, Professor, Department of Respiratory Medicine, SMSR, Sharda University, Greater Noida - 201 308, Uttar Pradesh. Tel: 8527214749, E-mail: sonishagupta@gmail.com.

selected based on convenience. A systematic random sampling was done from each urban and selected rural units. Interview of elderly in every alternate household was taken to achieve adequate sample size.

Population Setting: Urban area – Nandgram is a locality in Ghaziabad city with more than 10,000 houses with 7 blocks and free households, inhabited mainly by lower middle class families. Rural area – Six selected villages were – Chipiyana Buzurg and Shah beri from Greater Noida, Chhaprauala and Shahpur Bamheta from one side while Iliachipur and Khanpur from other side of Ghaziabad.

Sample of 51 elderly from Shah Beri village, 343 from Chipyana, 405 from Chhapraula, 136 from Shahpur Bamheta, 495 Ilaichipur and 73 was collected from Khanpur village. Total rural sample was 1503. Total urban sample of 1522 was collected from Nandgram. Total combined sample was 3025.

Period of study: January 2015 to January 2018.

Sample size: For qualitative data, formula used to derive sample size was: $n = 4\ pq/L^2$. (p – prevalence) available literature on prevalence of respiratory illness among elderly was assumed as 20% with an allowable error of 3%. For 95% confidence level, by simple random sampling, a sample size of 682 was required. By adding 10% attrition, the sample size was fixed at 750. As sample procedure was systematic, we doubled the size and fixed it at 1500 each in rural and urban groups. It was predicted to give an average of 300 respiratory cases of elderly in each group.

Tools and Methodology: Door-to-door survey was conducted using a pre-designed, pre-tested questionnaire having 2 parts. First part included socio-demographic characteristics, self-reported co-morbidities and physical disabilities. Medical records of patients were seen. Three healthcare workers were trained for this purpose. After analyzing screening proforma, elderly with suspected respiratory disease were selected. In second stage, screening proformas of suspected cases were verified. General and respiratory system examination was carried-out. These patients with respiratory diseases were asked about quality of health services and cost of treatment on healthcare utilisation.

Statistical Analysis

Data were entered using Microsoft Excel 2010 and statistical analysis was done using IBM SPSS v 20.0.0. and 23.0.0 both. Categorical variables were analysed using proportions and percentages. In the first stage, a descriptive analysis was performed for all records (n = 3025), both urban and rural seperately. Association between categorical variables was studied by two-way cross-tabulations and the significance established by Chi square test. The level of statistical significance was assessed at (P - values less than 0.05) 5% probability.

Effect of quality of Government health services, cost of treatment of Government health facility, quality of private health services, cost of treatment at private healthcare facility on healthcare utilisation was analysed in both urban and rural groups separately. It was assessed by chi-square test. Association between these two groups among all above mentioned variables was also established by chi-square test.

Odds ratio at 95% confidence intervals were used for strength of association and interpretation of bivariate analysis. If differences found were significant on univariate analysis, then further analysis of the data was conducted by controlling for demographic and health characteristics. Multiple regression analysis was used to analyse various factors for assessing their independent contribution after adjusting for various factors in the model.

Table I: Quality of healthcare services vs healthcare utilisation.

		Government Healthcare utilisation														
		Urban					Rural					Combined				
		Inade-quate	No	Yes	Total 100.0%	P value	Inade-quate	No	Yes	Total 100.0%	P value	Inade-quate	No	Yes	Total 100.0%	P value
Long wait	Yes	1466 0.3%	145 0.8%	8233 0.9%	242 100%	.708	161 69.1%	411 7.6%	311 3.3%	233 100%	.334	307 64.6%	551 1.6%	113 23.8%	475 100%	.067
	No	207 1.4%	27 0.1%	62 1.4%	28 100%		397 8%	91 8%	24 0%	50 100%		597 5.6%	111 4.1%	81 0.3%	78 100%	
Very crowded	Yes	143 60.1%	15 6.3%	80 33.6%	238 100%	.659	177 70.2%	42 16.7%	331 3.1%	252 100%	.151	320 65.3%	571 1.6%	1132 3.1%	490 100%	.299
	No	236 9.7%	13 0%	92 7.3%	33 100%		267 4.3%	92 5.7%	00 0%	35 100%		497 2.1%	101 4.7%	91 3.2%	68 100%	
Behaviour good	Yes	114 62.6%	73 0.8%	613 3.5%	182 100%	**.001**	123 74.1%	231 3.9%	201 2.0%	166 100%	.293	237 68.1%	308 0.6%	812 3.3%	348 100%	**.012**
	No	486 2.3%	45 0.2%	253 2.5%	77 100%		766 5.5%	272 3.3%	131 1.2%	116 100%		124 64.2%	311 6.1%	381 9.7%	193 100%	

Specialist available	Yes	1195 9.5%	94 0.5%	723 6.0%	200 100%	**.040**	137 71.7%	281 4.7%	261 3.6%	261 3.6%	.201	256 65.5%	37 9.5%	982 5.1%	391 100%	**.004**
	No	427 0%	46 0.7%	142 3.3%	60 100%		636 8.5%	222 3.9%	77 0.6%	92 100%		1056 9.1%	261 7.1%	211 3.8%	152 100%	
Doctor satisfaction	Yes	925 8.2%	74 0.4%	593 7.3%	158 100%	**.020**	104 75.9%	96 0.6%	241 7.5%	137 100%	**<.001**	1966 6.4%	165 .4%	832 8.1%	295 100%	**<.001**
	No	617 0.1%	44 0.6%	222 5.3%	87 100%		797 0.5%	272 4.1%	65 0.4%	112 100%		1407 0.4%	311 5.6%	281 4.1%	199 100%	
Free med available	Yes	995 8.9%	127 0.1%	573 3.9%	168 100%	.455	457 3.8%	58 0.2%	111 8.0%	61 100%	.036	1446 2.9%	177 .4%	682 9.7%	229 100%	**<.001**
	No	646 8.1%	33 0.2%	272 8.7%	94 100%		1497 1.3%	401 9.1%	209 0.6%	209 100%		213 70.3%	431 4.2%	471 5.5%	303 100%	
Pvt.																
Long wait	Yes	585 6.9%	87 0.8%	363 5.3%	102 100%	.681	748 6.0%	55 0.8%	78 0.1%	86 100%	**.003**	132 70.2%	136 0.9%	432 2.9%	188 100%	.118
	No	1096 4.5%	84 0.7%	523 0.8%	169 100%		1226 4.2%	452 3.7%	231 2.1%	190 100%		2316 4.3%	531 4.8%	752 0.9%	359 100%	
Very crowded	Yes	485 2.2%	99 0.8%	353 8.0%	92 100%	.130	648 4.2%	67 0.9%	67 0.9%	76 100%	**.033**	1126 6.7%	158 0.9%	412 4.4%	168 100%	.551
	No	1196 6.5%	73 0.9%	532 9.6%	179 100%		1306 5.7%	442 2.2%	241 2.1%	198 100%		2496 6.0%	511 3.5%	772 0.4%	377 100%	
Behaviour good	Yes	1566 1.9%	135 0.2%	833 2.9%	252 100%	.318	1426 8.3%	391 8.8%	271 3.0%	208 100%	.380	2986 4.8%	521 1.3%	1102 3.9%	460 100%	**.020**
	No	550 0%	220 0%	330 0%	10 100%		377 2.5%	112 1.6%	35 0.9%	51 100%		426 8.9%	132 1.3%	69 0.8%	61 100%	
Specialist available	Yes	1426 2.8%	83 0.5%	763 3.6%	226 100%	**.003**	1077 5.9%	128 0.5%	221 5.6%	141 100%	**<.001**	2496 7.8%	205 0.4%	982 6.7%	367 100%	**<.001**
	No	165 7.1%	621 0.4%	621 0.4%	28 100%		487 1.6%	152 2.4%	46 0%	67 100%		646 7.4%	212 2.1%	101 0.5%	95 100%	
Doctor satisfaction	Yes	1606 2.0%	135 0%	853 2.9%	258 100.0%	**.002**	1646 9.2%	471 9.8%	261 1.0%	237 100%	.570	3246 5.5%	601 2.1%	1112 2.4%	495 100%	.330
	No	342 0.9%	342 0.9%	114 .3%	710 0.0%		197 0.4%	414 0.8%	414 0.8%	27 100%		226 4.7%	720 0.6%	514 0.7%	34 100%	

Table II: Cost of treatment of healthcare services *versus* healthcare utilisation.

Cost of treatment at Government	**Health Care utilisation**											
Health services	**Urban**				**Rural**				**Combined**			
	Inadequate	**No**	**Yes**	**Total 100.0%**	**Inadequate**	**No**	**Yes**	**Total 100.0%**	**Inadequate**	**No**	**Yes**	**Total 100.0%**
Very expensive	6 (66.7%)	0 (0%)	3 (33.3%)	9 (100%)	17 (77.3%)	4 (18.2%)	1 (4.5%)	22 (100%)	23 (74.2%)	4 (12.9%)	4 (12.9%)	31 (100)
Expensive but affordable	38 (67.9%)	1 (1.8%)	17 (30.4%)	56 (100%)	123 (74.5%)	25 (15.2%)	17 (10.3%)	165 (100%)	161 (72.9%)	26 (11.8%)	34 (15.4%)	221 (100%)
Not expensive	118 (61.1)	13 (6.7%)	62 (32.1%)	193 (100%)	45 (62.5%)	14 (19.4%)	13 (18.1%)	72 (100%)	163 (61.5%)	27 (10.2%)	75 (28.3%)	265 (100%)
NA	12 (50%)	3 (12.5%)	9 (37.5%)	24 (100%)	25 (64.1%)	11 (28.2%)	3 (7.7%)	39 (100%)	37 (58.7%)	14 (22.2%)	12 (19%)	63 (100%)
Total	174 (61.7%)	17 (6%)	91 (32.3%)	282 (100%)	210 (70.5%)	54 (18.1%)	34 (11.4%)	298 (100%)	384 (66.2%)	71 (12.2%)	125 (21.6%)	580 (100%)
P value		.514				.184				**.003**		
Cost of treatment of Private Health services	**Inadequate**	**No**	**Yes**	**Total 100.0%**	**Inadequate**	**No**	**Yes**	**Total 100.0%**	**Inadequate**	**No**	**Yes**	**Total 100.0%**
Very Expensive	44 (55%)	8 (10%)	28 (35%)	80 (100%)	70 (59.3%)	32 (27.1%)	16 (13.6%)	118 (100%)	114 (57.6%)	40 (20.2%)	44 (22.2%)	198 (100%)

Expensive but affordable	113 (66.5%)	4 (2.4%)	53 (31.2%)	170 (100%)	52 (76.5%)	7 (10.3%)	9 (13.2%)	68 (100%)	165 (69.3%)	11 (4.6%)	62 (26.1%)	238 (100%)
Not expensive	6 (50%)	2 (16.7%)	4 (33.3%)	12 (100%)	35 (77.8%)	7 (15.6%)	3 (6.7%)	45 (100%)	41 (71.9%)	9 (15.8%)	7 (12.3%)	57 (100%)
NA	11 (55%)	3 (15%)	6 (30%)	20 (100%)	53 (79.1%)	8 (11.9%)	6 (9%)	67 (100%)	64 (73.6%)	11 (12.6%)	12 (13.8%)	87 (100%)
Total	174 (61.7%)	17 (6%)	91 (32.3%)	282 (100%)	210 (70.5%)	54 (18.1%)	34 (11.4%)	298 (100%)	384 (66.2%)	71 (12.2%)	125 (21.6%)	580 (100%)
P value		**.048**				**.024**				**<.001**		

Table III: Group wise regression analysis.

Urban				
Quality of Government healthcare service				
Factor	**Sig. (p value)**	**Odds ratio**	**(95% CI)**	
Gender	**.033**	2.141	1.05	4.38
Age	.122	1.904	.83	4.38
Educational status	.574	.812	.39	1.71
S – E class	**.002**	2.700	1.41	5.15
Satisfaction with Govt. doctor	**.022**	2.219	1.11	4.44
Constant	.106	.490	.20	1.18
Quality of Private healthcare service				
Factor	**Sig. (p value)**	**Odds ratio**	**(95% C I)**	
Gender	.065	1.832	.95	3.53
Age	.357	1.407	.67	2.95
Educational status	.447	.775	.40	1.51
S – E class	**.011**	2.061	1.17	3.64
Distance to Pvt. service	**.008**	.394	.20	.79
Constant	.074	2.840	.88	9.15
Rural				
Quality of Government healthcare service				
Factor	**Sig. (p value)**	**Odds ratio**	**(95% CI)**	
Age	.137	.208	.03	1.72
Educational status	.154	1.979	.76	5.16
S – E class	.599	1.266	.51	3.11
Gender	.598	.792	.33	1.91
Govt. crowding	.998	.000	.00	
No satisfaction with Govt. doctor	**.002**	5.745	1.84	17.92
Constant	.998	3317993102.965	.00	
Quality of Private healthcare service				
Factor	**Sig. (p value)**	**Odds ratio**	**(95% C I)**	
Age	.413	.405	.04	3.69
Educational status	.164	2.338	.69	7.92
S – E class	.207	1.912	.68	5.34
Gender	.699	.820	.30	2.28
Awareness of pvt. service	**.035**	.294	.09	.94
No good behaviour of Pvt.	**.049**	7.978	.96	66.09
Constant	**.023**	14.025	1.36	44.17

Combined (Urban and Rural data)				
Quality of Government healthcare service				
Factor	**Sig. (p value)**	**Odds ratio**	**(95% CI)**	
Location	.000	3.087	1.85	5.16
Age	.468	1.291	.64	2.61
Educational status	.347	1.304	.74	2.30
S – E class	.003	2.165	1.29	3.63
Gender	.181	1.435	.84	2.46
Long waiting time	.050	.422	.17	1.02
No satisfaction with Govt. doctor	.000	2.750	1.55	4.88
Constant	.258	.492	.14	1.72
Quality of Private healthcare service				
Factor	**Sig. (p value)**	**Odds ratio**	**(95% CI)**	
Location	.182	1.523	.81	2.86
Age	.262	1.471	.74	2.93
Educational status	.531	1.197	.67	2.13
S – E class	.027	1.751	1.06	2.90
Gender	.126	1.523	.88	2.64
Awareness of pvt. service	.007	.287	.11	.72
No satisfaction with Pvt. Doctor	.014	2.600	1.19	5.66
Constant	.432	1.784	.41	7.78

In Urban, among Government health service quality variables - group, gender (p = .033), socio-economic status (p = .002) and non-satisfaction with Government doctor (p = .022), were found to be significant, i.e., (p < 0.05). Among Private care service quality, factors which were found to be significant, were socio-economic status (p = .011) and distance to private facility (p = .008), denoting (p <0.05).

In Rural, in analysis of Government quality group, non-satisfaction of Government doctor (p = .002) were found to be significant, i.e., (p < 0.05). After analysis of Private care service group, factors which were found to be significant, were private awareness (p = .035), not good behaviour of private doctors (p = .049) denoting (p <0.05).

In combined, in analysis of Government quality group, economic status (p = .003), long wait in Government sector (p = .050), non-satisfaction of Government doctor (p = .000) were found to be significant, i.e., (p < 0.05). After analysis of Private care service group, factors which were found to be significant, were economic status (p = .027), private awareness (p = .007), not satisfaction with doctor (p = .014) denoting (p <0.05).

Discussion

Quality of available healthcare services is an important

determinant of healthcare utilisation. In our study we enquired respondents about the quality of government as well as private healthcare facilities on the basis of past experience and perception. Quality of healthcare services has got many components, i.e., infrastructure and organisation of facility, availability of expertise and equipments as per requirements, behaviour of healthcare providers, their ability to address concerns of patients, giving them enough time and satisfy them, convenience in getting the service in the form of crowding, waiting time. In case of government services availability of free medicines and levying of user charges are also significant factors. We studied response of elderly regarding quality of healthcare services for six factors, viz., crowding, waiting time, availability of specialist, behaviour of healthcare providers, satisfaction with doctor and cost of treatment at facility. For government facility availability of free medicines was also asked. In our study among urban elderly 85.8% (242/282) and 84.4% (238/282) respectively complained of long waiting time and overcrowding at government health facilities. Among rural elderly 78.2% (233/298) and 84.6% (252/298) respectively complained of these two problems in seeking government health services. These problems regarding government health facilities in India is a well known fact. These factors make accessing healthcare services especially difficult for elderly considering their poor physical condition. Majority of elderly reported behaviour of healthcare provider as good. Satisfaction with Government doctor was 56 (158/282) and 46 (137/298) per cent respectively for urban and rural areas but this difference was not significant ($p = .053$). Availability of free medicines was significantly better in urban facilities as compared to rural area. While in urban area 59.6% (168/282) elderly said that free medicines were available at Government health facility only 20.5% (61/298) rural elderly reported so. It is understandable due to better monitoring, as well as awareness of users in urban areas. Partly due to availability of free medicines, there was also significant difference regarding cost of treatment at Government facility perceived by urban and rural elderly ($p = .000$). While majority of elderly (68.4% - 193/282) in urban area found Government health services as not expensive, majority of rural elderly (55.4% - 165/298) perceived them as expensive but affordable. Other reason for this perceived difference could also be due to difference in financial affordability between two populations. Quality of private healthcare services for all these factors was better than Government facilities except for cost.

Many studies have found poor quality of healthcare services as a significant impediment to healthcare utilisation. In an American study, lack of responsiveness of doctor was most often cited (33%) than physical barriers such as cost or transportation. An elderly person's perception of the physician's lack of responsiveness was a greater disincentive to seeking care than more tangible barriers[5]. In Dharan, Nepal study, elderly cited the following reasons for avoiding Government healthcare facility. A large number (16% - 41%) complained about the poor attitude of healthcare workers towards their health needs and treatment and 107 (26.8%) found facility too crowded and avoided due to lengthy process to get treated[6]. In this study, the above said facility was a big Government medical institute (BPKIHS) with availability of high-end equipment and specialists, still many elderly did not find it good. This data underlines special needs of elderly.

Another study from Bangladesh also emphasized importance of provider behaviour. It found most powerful predictor for client satisfaction with Government services was provider behaviour especially respect and politeness. Reduction of long waiting time was more important to the clients than prolongation of short consultation time[7]. An AIIMS study found carelessness (31.6%) and disillusionment (23.5%) due to previous unsatisfactory experience as second and third most important reasons for avoiding treatment by elderly for their self-reported problems[8]. Various other studies have reported out-of-pocket costs, long queues, disrespectful treatment by facility staff, medication stock-outs and perceived ineffective care as barriers to healthcare utilisation[9-11].

In our study, satisfaction with doctor affected healthcare utilisation significantly both by rural and urban elderly ($p < .001$ and $< .05$ respectively). Behaviour of provider and availability of free medicines had differing effect on urban and rural elderly. While provider behaviour affected healthcare utilisation by urban elderly only ($p = .001$), rural elderly only were affected by availability of free medicines ($p = .036$). Higher sense of self pride in urban population due to better socio-economic status, thus making them more sensitive to perceived bad behaviour by healthcare provider may be the reason of this factor affecting healthcare utilisation in urban elderly only. Difference in financial status could also be the reason for differing effect of availability of free medicines on healthcare utilisation by two population. As majority of urban elderly found Government healthcare facility as non-expensive, non availability of free medicines did not affect their healthcare utilisation. Better awareness may be the reason for availability of specialist affecting healthcare utilisation by urban elderly only ($p = .040$). While healthcare cost at Government facility had no effect on utilisation by either urban or rural elderly, cost at private facility affected utilisation by both these population ($p = .048$ and .024). This difference may be due to much higher cost of healthcare services at private as compared to Government facility.

In 2021 an analysis by Banerjee has been done using the unit level data of Social Consumption: Health (Schedule number 25.0) of the 75th round of the National sample Survey conducted during July 2017 – June 2018. Preference for a trusted doctor/hospital (29.17% in rural and 40.73% in urban) and unsatisfactory quality of services in public facilities (27.79% in rural and 22.77 % in urban) were the two most commonly cited reasons for not availing healthcare services from Government sources in both urban and rural areas albeit constituting a varying proportion. The third most common reason for not availing healthcare services from Government sources, even if it the quality was satisfactory was that it involves long waiting which accounted 17.47% in rural and 21.55% in urban[12].

A study by Gnanasabai *et al*, when asked about the reasons for not seeking treatment, around 30.3% reported that it was a minor illness, 21% were not taking treatment due to financial constraints[13].

Conclusion

The Indian Government is unable to cover the full spectrum of healthcare needs due to persistently low public investment in health, poor health infrastructure, which increases the cost and the financial burden of care resulting in out-of-pocket catastrophic expenditure on health. The expansion in insurance coverage and the provision of good-quality, subsidised, public health facilities will both improve access to healthcare and protect the poor elderly against financial catastrophe[14].

References

1. Sharma OP. Geriatric care; A textbook of geriatrics and gerontology 2008/3rd Ed/1-6 published by Vinod Vasishtha for viva books private limited.
2. Balarajan Y, Selvaraj S, Subramanian S. India: towards universal health coverage 4, healthcare and equity in India. *The Lancet* 2011; 377 (9764): 505-15.
3. Cohen M. Community based health insurance shows promise in India.[http://www.prb.org/Articles/2006/CommunityBased HealthInsuranceShowsPromiseinIndia.aspx].
4. Devadasan N, Ranson K, Van Dammie W, Criel B. Community health insurance in India: an overview. *Economic and Political Weekly* 2004. [http://www.srtt.org/downloads/communityhealth.pdf].
5. Fitzpatrick AL, Powe NR, Cooper LS *et al*. Barriers to Healthcare Access Among the Elderly and Who Perceives Them. *Am J Public Health* 2004; 94 (10): 1788-94.
6. Adhikari D, Rijal DP. Factors affecting health seeking behaviour of senior citizens of Dharan. *J Nobel Med Coll* 3, no. 1, (5): 50-7.
7. Aldana JM, Piechulek H, Ahmed AS. Client satisfaction and quality of healthcare in rural Bangladesh. *Bull WHO* 2001; 79 (6): 512-7.
8. Goswami A, Reddaiah VP, Kapoor SK *et al*. Health Problems and Health Seeking Behaviour of the Rural Aged. *Ind J Gerontolo* 2005: 19 (2): 163-80.
9. Harris B, Goudge J, Ataguba JE *et al*. Inequities in access to healthcare in South Africa. *J Public Health Policy* 2011; 32: S102-S123.
10. Gilson L, McIntyre D. Post-apartheid challenges: household access and use of healthcare in South Africa. *Int J Health Serv* 2007; 37 (4): 673-91.
11. Burger R, Bredenkamp C, Grobler C. Have public health spending and access in South Africa become more equitable since the end of apartheid? *Dev South Afr* 2012; 29 (5): 681-703.
12. Determinants of rural-urban differential in healthcare utilisation among the elderly population in India Banerjee BMC Public Health 2021; 21939.
13. Gnanasabai G, Kumar M, Boovaragasamy C *et al*. Health seeking behaviour of geriatric population in rural area of Puducherry- a community based cross-sectional study. *Int J Community Med Public Health* 2020; 7: 3665-8.
14. Sahoo H, Govil D, James KS *et al*. Health issues, healthcare utilisation and healthcare expenditure among elderly in India Thematic review of literature. *Aging and Health Research 1* 2021; 100012.

ORIGINAL ARTICLE JIACM 2023; 24 (3-4): 199-203

Knowledge and Perspectives of Undergraduate Medical Students Towards the Introduction of Electives in the Undergraduate Medical Curriculum: A Cross-sectional Study from a Medical College in India

Nitin Sinha, Annie Singh**, Ishaan Singh**, Piyush Jain**

Abstract

Background: An Elective is an area or a stream in a speciality which can be chosen by an undergraduate student to work for a stipulated duration to learn something over and above to what is normally taught by that speciality in undergraduation. Electives as a teaching module has been introduced for the first time in Indian undergraduate medical curriculum from the year 2019. This study was done among MBBS students before Electives were opted by the very first MBBS students batch. This study was done to ascertain their knowledge regarding Electives, their choice of Electives and reasons for choosing the Electives they wanted to pursue. Such a study on Electives has not been undertaken as Electives had been introduced for the first time in Indian undergraduate medical curriculum.

Methods: A pilot tested and self-designed questionnaire was administered to consenting undergraduate students studying in different phases in our Institute. Analysis was done using SPSS Software (version 16, IBM).

Results: Awareness regarding electives was less even in the batch that was supposed to pursue Electives. Knowledge regarding different guidelines-related to Electives was also lacking. Varied perceptions of students related to various aspects of Electives were noted.

Discussion: Electives is a new concept. Hence, appropriate knowledge regarding the same must be imparted to students so that they can choose their Electives wisely. Institutes also have to formulate Electives based on perception of students. Onus is also on the Institutes to allocate Electives in an appropriate manner.

Keywords: Electives, competency based undergraduate curriculum India, perceptions of undergraduate students on Electives, knowledge regarding electives.

Introduction

The term "Elective" translates to being an option, i.e., having a choice. In the context of medical education, the term "Elective" implies an area/stream in which a student himself/herself opts to work/undergo training for a defined period in a particular speciality. National Medical Commission (NMC), India is a body that frames curriculum for the undergraduate medical students of India. A new Competency Based Undergraduate Medical Curriculum has been launched by NMC from the year 2019. In this new curriculum, NMC has introduced Elective module for the first time in India. The purpose of Elective module is mentioned as "a learning experience created in the curriculum to provide an opportunity for the learner to explore, discover and experience areas or streams of interest[1]."

As per the NMC guidelines, an Elective is an area or a stream that a speciality will offer which will help the students to learn and explore something new. Even Superspeciality departments (which are not involved in undergraduate teaching) can offer Electives. The total duration for Electives is one month divided into two Blocks (Block 1 and Block 2) each having a duration of fifteen days. Students will have to choose from Electives offered by Pre- and Para-Clinical departments (Anatomy, Physiology, Biochemistry, Pathology, Microbiology, Pharmacology and Forensic Medicine and Toxicology) in Block 1 and from Clinical (Broad Speciality), Superspeciality departments and Community Clinics (rural/urban) in Block 2. Each student is supposed to do two Electives, one in each block. Presently, MBBS students move through four Phases while undergoing their training. Phase I (Pre-Clinical) starts with entry to the Medical College followed by Phase II (Phase II), Phase III (Part I) and finally Phase III (Part II). Electives are conducted at the end of Phase III (Part I) and before the beginning of Phase III (Part II). The entire list of Electives being offered by the Institute is provided to all the students well in advance. Every Elective needs to have specified learning objectives, well defined

Professor, **MBBS Student (Phase III, Part I), Department of Medicine, Atal Bihari Vajpayee Institute of Medical Sciences, Baba Kharak Singh Marg, New Delhi - 110 001.

Corresponding Author: Dr Nitin Sinha, Professor, Department of Medicine, Atal Bihari Vajpayee Institute of Medical Sciences and Dr Ram Manohar Lohia Hospital, Baba Kharak Singh Marg, New Delhi - 110 001. Tel: 9818046274, E-mail: drnitinsinha26@yahoo.co.in.

plan of its execution, a logbook and an assessment at the end. Every Elective can have only a fixed number of students that can be trained in that Elective. This number is to be decided by the speciality offering that Elective. Students have to choose Electives from the list provided. The further method of allocating Electives to the students is to be decided by the Institute. Electives can also be chosen in an outside Institution[1].

In the United States of America, after the initial two-year course in pre and para clinical sciences, the final 2 years are divided into two parts, Required sequence blocks and Optional sequence blocks (synonymous to Elective). Required sequence blocks are those stipulated as necessary to be done by every student to meet the minimum expectations, while the optional sequence blocks allow students to self-elect[2].

Mihalyunk *et al* in their study conducted in University of British Columbia, found that many medical students view career choice decisions as a process to be undertaken in medical school. The free choice clerkship was reported not only as a positive, highly regarded learning experience, but also as a key feature of the educational process of decision-making, including clarifying decisions about both future education and career choices[3].

Reed *et al* in their extensive review of medical education noted[4]:

"Exploring the complex, developmental nature of the specialty choice process is key to both understanding how specialty decisions are made and ultimately improving the decision-making process. Because this is an area that has not been researched widely, there is ample opportunity for researchers to fill this gap in our knowledge."

This study was undertaken before the Electives were allotted for the first time in our Institute. As a new module had been introduced and students of MBBS were naïve, we thought it was necessary to know about the awareness and knowledge among the MBBS students regarding the NMC guidelines on Electives. Also, it was prudent that the perceptions of students towards Electives was assessed and understood. The results obtained from this study would be helpful in refining the approach of Institutions towards imparting knowledge regarding Electives and designing Electives as per the perceptions of the students.

Methods

A questionnaire based cross-sectional study was conducted among undergraduate medical students between 1st and 10th October 2022 after obtaining the Institutional Ethical Committee Permission. There were three batches of MBBS students with 100 students in each batch at the time the study was conducted. A self-designed, structured, pilot-tested questionnaire was administered to the consenting participants. The initial part of the questionnaire required the participant to fill demographic details and answer a question on the awareness regarding Electives. Only those who were aware regarding introduction of Electives in the curriculum were required to complete the further questionnaire. The first serial numbered question was regarding how the student became aware regarding Electives. The questions from serial number 2 to 6 assessed the knowledge among the students regarding the guidelines on Electives by NMC. The remaining nine questions (Question number 7 to 15) assessed the perceptions of the students regarding various aspects of Electives. The time allotted was 5 minutes. The data obtained from the questionnaire was recorded and analysed using IBM SPSS (Statistical package for Social Sciences) ver 16.0 (Chicago, USA) software.

Results

At the time this study was conducted, three batches of MBBS students were studying in our Institute. One batch each comprising of 100 students was in Phase III (Part I), Phase II and Phase I. Forty six, fifty and sixty students from Phase III (Part I), Phase II and Phase I, respectively consented to be a part of the study.

Awareness regarding Electives

Out of 46 consenting students of Phase III (Part I), 12 (26.08%) students had no idea regarding Electives being a part of the latest MBBS Curriculum. Among the 34 students who were aware, 15 got awareness from the Foundation Course conducted in the beginning of MBBS Part I, 14 got awareness from friends studying in other medical colleges, three got awareness from seniors and one got awareness from his batchmate. One student did not mention the source of awareness about Electives.

Out of the 50 consenting students in Phase II, only twelve (24%) were aware regarding Electives being a part of MBBS Curriculum. Among these 12, three came to know about Electives from their seniors, 2 each from the Foundation Course conducted in MBBS Phase I and friends from other Medical Colleges and five from 'Other' sources (Three students became aware from Faculty lectures, one from the Dean's address and one from the NMC website).

Among the sixty students who consented to be part of the study, only three (5%) students were aware regarding Electives being part of MBBS Curriculum. Two of these became aware about Electives from their seniors and one from YouTube.

In view of only a total of 15 students of MBBS Phase II and MBBS Phase I having awareness regarding Electives, the further results are presented cumulatively for both the Phases.

Knowledge regarding Electives

Among Phase III (Part I) students, correct knowledge regarding the timing of Electives in the curriculum was known to only 14 (41.17%) students. Twenty students answered wrongly regarding the timing of Electives. Out of these twenty, fourteen students had knowledge that Electives are scheduled to be conducted at the end of MBBS Phase III (Part II) and three students each had knowledge that Electives are scheduled to be conducted at the end of MBBS Phase II and MBBS Phase I, respectively. Out of total 15 Phase II and Phase I students, six (40%) had correct knowledge regarding timing of Electives. Out of remaining nine students, five had knowledge that Electives are to be conducted at the end of MBBS Phase II and two each had knowledge that Electives are to be conducted at end of Phase I and during Internship, respectively.

Correct response about the departments that are supposed to conduct Electives in Block 1 was marked by 11 (32.35%) Phase III (Part I) students and Five (33.33%) Phase II and Phase I students. Correct response to the question on the departments that are supposed to conduct Electives in Block 2 was marked by 12 (35.29%) Phase II (Part I) students and eight (53.33%) Phase II and Phase I students.

With regards to duration of Electives in Block 1, 18 (52.94%) students of Phase II (Part I) and six (40%) students of Phase II and Phase I marked the correct answer of 4 weeks. Correct response of 4 weeks duration of Electives in Block 2 was marked by 14 (41.17%) Phase III (Part I) students and five (33.33%) Phase II and Phase I students.

Perceptions

Regarding perceptions of students towards the purpose of introducing Electives in the curriculum, the results are displayed in Table I (Students could select more than response to this question).

Responses to agreement upon introduction of Electives in the MBBS Curriculum are depicted in Fig. 1. It is evident that maximum students of any Phase agreed of Electives being part of MBBS Curriculum.

Among the Phase III (Part I) students, on being asked to choose the best method that should be adopted by our Institute to select a student for an Elective being offered, 10 students (47.61%) chose 'interview by the Teacher In charge for an Elective' as the best method for selection. 13 (38.23%) students, however, did not answer this question (Table II). Out of 15, six students (46.15%) of MBBS Phase II and MBBS Phase I also chose the same option. Two students (13.33%) did not respond to the question.

Twenty-five MBBS Phase III (Part I) students (73.52%) responded to the question regarding indicating their preferred departments for Electives in Block 1. Twelve out of these 25 students (48%) had not decided upon any preferences at the time of filling the questionnaire. Only two students filled the names of departments that are

Table I: Perceptions of students regarding purpose of introduction of Electives in the MBBS Curriculum.

Perceptions	MBBS Phase III (Part I) (Total = 34)	MBBS Phase II and MBBS Phase I (Total = 15)
Help in choosing a career stream later	12 (35.29)	5 (33.33)
Gain in depth knowledge on something not normally taught in detail in routine teaching	22 (64.70)	7 (46.66)
Understand concepts of research	7 (20.58)	7 (46.66)
Provide an edge to students planning to go to foreign universities after MBBS	6 (17.64)	2 (13.33)
Develop self-directed learning skills	8 (23.52)	4 (26.66)
Any other perception	Nil	Nil

Values in cells are expressed as Number Observed(%).

Table II: Best method that should be adopted by Institute to select students for an Elective.

Method	MBBS phase III (Part I) (Total = 21)	MBBS phase II and MBBS phase I (Total = 13)
Based on cumulative marks of all Internal Assessments and University Examinations held prior to choosing an Elective	5 (23.80)	4 (30.76)
Interview by Teacher In charge of an Elective	10 (47.61)	6 (46.15)
An MCQ based examination	6 (28.57)	3 (23.07)
Any Other Method Proposed	Nil	Nil

Values in cells are express as Number Observed (%)

supposed to offer Electives in Block 1. Rest all wrote names of departments that are not supposed to offer Electives in Block 1. However, maximum students chose the Department of Medicine (20%) as their first preference for Electives in Block 1. Three (20%) of the fifteen MBBS Phase II and Phase I students had not decided upon the departments they would choose for Electives in Block 1. Seven (46.66%) did not respond to the question. Three students (20%) wrote the correct departments that are supposed to offer Electives in Block 1. In response to the question on preferred departments for Electives in Block 2, 24 students of MBBS Phase III (Part I) (70.58%) wrote their preferences. Fourteen (56%) had not decided upon their preferences at the time of filling the questionnaire. Out of the ten remaining students, maximum (two students each) gave first preference to Medicine and Orthopaedics. Surgery received maximum number of second preferences (three students). Three students out of 15 (20%) of MBBS Phase II and Phase I gave their preferences. One student wrote names of departments that are not supposed to offer Electives in Block 2. The remaining two students chose Neurology and Medicine, respectively as their first preference for Electives in Block 2. Four (26.66%) had not decided regarding their preferences. Remaining eight did not answer the question.

In response to the question asking for reasons (students could select multiple responses) for choosing a subject as their first preference in an Elective, the results are displayed in Table III.

Fourteen students (41.17%) of MBBS Phase III (Part I) contemplated opting Elective in an outside institution. Fifteen students (44.11%), however, were not willing for an Elective in another institution. Five students did not respond to the question. Among those willing, the main reason for thinking to choose an Elective in another institution was that the subject in which Elective is planned to be chosen is better in another Institute. Nine students (60%) of MBBS Phase II and Phase I contemplated to opt for Electives in another institution. Four students were not contemplating choosing Elective in another institution. Two students did not answer the question. Table IV highlights the various reasons for contemplating choosing Electives in another Institution.

Discussion

The results clearly highlight that awareness and knowledge about Electives was seriously lacking among the students.

Among the MBBS Phase III (Part I) students, who were supposed to start their Electives within the next three months of participating in this study, 26.08% were surprisingly unaware about the electives. The awareness among the students in other phases was even poorer. Also, the source of awareness varied. Knowledge regarding the timing of Electives in the curriculum, Electives being conducted in two blocks, duration of each block and subjects/departments offering Electives in each block was also lacking among most of the students in all the three

Table III: Reasons for choosing a subject as First Preference for an Elective.

Reasons	MBBS Phase III (Part I) (Total = 13)	MBBS Phase II and Phase I (Total = 5)
Interest in that subject	9 (69.23)	2 (40)
Want to pursue career in that subject later on	4 (30.76)	1 (20)
Elective in this subject will give me an edge over others while obtaining admission in foreign universities after the MBBS is completed	0	3 (60)
You are already doing a research project in that subject	1 (7.69)	1 (20)
Your research project is approved already and will be done in Electives	0	
Your best friend is likely to select that project	2 (15.38)	
Any Other reason apart from above	2 (15.38) —Money	

Values in cells are written as Number Observed (%)

Table IV: Reasons for contemplating choosing Elective in another Institution.

Reasons	MBBS phase III (Part I) (Total=14)	MBBS phase II and phase I (Total=9)
Subject in which Elective is planned to be taken is better in another institution	8 (57.14)	4 (44.44)
Department where Elective is planned to be taken is not available in parent institute	3 (21.42)	3 (33.33)
Family member/Relative/Family Friend is present in the outside institute	3 (21.42)	1 (11.11)
The outside institute is in your hometown	Nil	1 (11.11)
Any Other Reason apart from these	Nil	Nil

Values in cells are written as Number Observed (%)

batches. Awareness and knowledge was more in Phase III (Part I) students as compared to Phase II and Phase I students. This is possibly due to the reason that Phase III (Part I) students were supposed to start their Electives within next three months. Also, Phase III (Part I) students had spent more time in the college and in the clinical postings. Hence, their chances of becoming aware and knowledgeable about the Electives were more. Overall less awareness and knowledge clearly highlights that steps need to be taken to make the students aware and knowledgeable regarding the Electives. This can be done by taking separate session on Electives in the Foundation Course (at present there is no separate session on Electives and only passing references are made by Faculty) where Institute can not only introduce the concept, purpose and intricate details regarding Electives to the students but also let them know the Electives that are routinely offered by the Institute. As Electives are to be conducted in Pre and Para Clinical subjects also, it is imperative that student is made aware of Electives well before Phase I starts (in Foundation Course). Further sessions can be taken in the beginning of Phase II and middle of Phase III (Part I), respectively.

Maximum students studying in any Phase had welcomed the introduction of Electives. Most common reason perceived by students to introduce Electives in the curriculum was "gaining in depth knowledge on something not normally taught in detail". They perceived that Elective in a particular department will help them to learn something extra in a particular field, learn nuances of research, give an edge in getting selection in foreign universities and develop self-learning skills. These perceptions are quite in sync with the objectives of Electives as stated by NMC.

The responses of students were divided when it came to choosing a process for allocation of Electives. The perceptions in this regard have to be seen in light of feasibility of conducting a particular method. Also, an Institute/NMC has to devise such a method to allocate Electives so that the students get a chance "to Elect" rather than being "Forced to Opt" an Elective. This can be a combination of methods as shown in Table II.

Department of Medicine and Surgery were the most preferred departments for pursuing Electives. Pre and Para Clinical departments were chosen by a select few. This reflects that students should be made aware of the specialised areas and research in Pre- and Para-Clinical departments so that their interest can develop in these departments. Clinical departments offer more interest probably because they involve lot of patient interaction.

As NMC guidelines allow a student to opt for elective in another Institution, many students were willing to opt Elective in another Institution. The main reason chosen was that the subject they wished to pursue Elective is better in another institution. The reason for this perception was not asked in the questionnaire but it can be reasoned that students of different medical institutions interact among each other and it is here that students get to know about various specialities in other Institutions. Parents or relatives of some students might be in other Institutions creating a perception of better specialities in another Institution. Another reason chosen by some students on wishing to opt Elective in an outside Institution was non-availability of an Elective in our institute. This was surprising because at the time this study was conducted, list of Electives was yet to be disclosed to the students.

Despite best of our efforts, we could not find any similar study on Electives. Hence, it was not possible to compare our results with the results from other Institutes.

Electives have been introduced by NMC with a positive ideation and onus is now on the Institutes to offer Electives to the students in an appropriate manner and in sync with the perceptions of the students.

References

1. UG curriculum. Org.in. Available from: https://www.nmc.org.in/information-desk/for-colleges/ug-curriculum/
2. Curriculum inventory. AAMC. Available from: https://www.aamc.org/about-us/mission-areas/medical-education/curriculum-inventory.
3. Mihalynuk T, Leung G, Fraser J *et al*. Free choice and career choice: Clerkship Electives in medical education. *Med Educ* 2006; 40 (11): 1065-71.
4. Reed VA, Jernstedt GC, Reber ES. Understanding and improving medical student specialty choice: a synthesis of the literature using decision theory as a referent. *Teach Learn Med* 2001; 13 (2): 117-29.

ORIGINAL ARTICLE

JIACM 2023; 24 (3-4): 204-8

Evaluating the Effectiveness of a Tailored Intervention on Medication Adherence among CABG Patients at a Tertiary Care Hospital in Delhi

Harvinder Kaur Vaid, Jyoti Sarin**, Kalpana Lodhi****

Abstract

Introduction: Cardiovascular diseases (CVDs) pose a significant global health challenge, with coronary artery bypass grafting (CABG) being a common surgical intervention for advanced coronary artery disease. In India, CVDs account for a substantial burden, with CVD-related deaths occurring a decade earlier than in the West. Medication adherence is crucial for post-CABG care, but non-adherence remains a concern due to multifaceted factors. Tailored interventions offer promise but lack research in the Indian context.

Methodology: This study employed a one-group pre-test, post-test design to assess a tailored intervention's impact on CABG patients' medication adherence in a Delhi Tertiary Care Hospital. Sixty-six patients participated, receiving tailored interventions addressing individual adherence barriers. Medication adherence was assessed using the Morisky Medication Adherence Scale, with data collected before and three months after CABG.

Results: After the intervention, medication non-adherence rates significantly decreased, with improvements in adherence levels. Significant changes were observed in cholesterol levels, reflecting better medication adherence.

Conclusion: Tailored interventions have significant potential to improve medication adherence among CABG patients, offering personalised support and education. These findings emphasize the importance of a patient-centered approach to cardiac care and hold promise for reducing the burden of cardiovascular disease on healthcare systems.

Key words: Medication adherence, tailored intervention, CABG patients, Morisky medication adherence scale, post-CABG care, cardiovascular diseases.

Introduction

Cardiovascular diseases (CVDs) remain a significant global health challenge; with coronary artery bypass grafting (CABG) being one of the most common surgical interventions for patients with advanced coronary artery disease. CVDs such as ischaemic heart disease and cerebrovascular accidents account for 17.7 million deaths and are the leading cause[1]. As per Global Burden of disease study the age-standardised CVD death rate of 272/1,00,000 population in India which is much higher than the global average of 235. CVD occurs in Indians a decade earlier than the Western population[2]. In India, data shows that in 2016, CVDs contributed to 28.1% of total deaths and 14.1% of total disability-adjusted life years (DALYs) compared with 15.2% and 6.9%, respectively in 1990[3]. While CABG surgery can effectively alleviate symptoms and improve overall cardiac health, optimal post-operative care is essential for successful outcomes. A critical aspect of this care is medication adherence, which plays a pivotal role in preventing post-CABG complications and promoting long-term cardiovascular health.

Medication non-adherence is a pervasive issue in healthcare, affecting patients across diverse medical conditions, including those who have undergone CABG surgery. Non-adherence to prescribed medications after CABG can lead to an increased risk of adverse events, including recurrent cardiac events, hospital readmissions, and decreased quality of life[4]. However, the reasons behind medication non-adherence are multifaceted and complex, encompassing individual patient factors, healthcare system barriers, and medication-related issues[5].

Tailored interventions have emerged as a promising approach to address medication adherence challenges among post-CABG patients. These interventions are designed to account for individual patient characteristics, preferences, and specific barriers to adherence, thereby enhancing the likelihood of success. However, despite the growing interest in tailored interventions, there is a noticeable research gap, particularly in the Indian healthcare context.

The existing literature on medication adherence among CABG patients predominantly originates from Western healthcare systems, which may not fully capture the unique

**Ph.D Scholar, **Principal and Dean, College of Nursing, MMDU, Mullana, Ambala - 133 203, Haryana.*
****Faculty, College of Nursing, Dr Ram Manohar Lohia Hospital, Baba Kharak Singh Marg, New Delhi - 110 001.*
Corresponding Author: Dr Harvinder Kaur Vaid, Ph.D Scholar, MMDU, Mullana, Ambala - 133 203, Haryana. Tel: 9868171550, E-mail: harvinder.kaur.rml@gmail.com.

cultural, socio-economic, and healthcare delivery aspects prevalent in India. Furthermore, there is a dearth of studies evaluating the effectiveness of tailored interventions specifically tailored to the needs of CABG patients in India. While general insights into medication adherence exist, the nuances and complexities of the Indian healthcare system and patient population require tailored approaches that have yet to be comprehensively explored.

The objective of this research study is to address this notable research gap by evaluating the effectiveness of a tailored intervention aimed at improving medication adherence among CABG patients receiving care at a tertiary care hospital in Delhi. This research is not only important from a clinical perspective but also holds significant implications for healthcare policy and practice in India, where cardiovascular diseases continue to be a major public health concern. The findings of this study can inform healthcare providers, policymakers, and researchers about the feasibility and impact of tailored interventions to enhance medication adherence among CABG patients in a tertiary care hospital setting in Delhi.

Methodology

This research employed a one-group pre-test post-test research design to assess the effectiveness of a tailored intervention in improving medication adherence among coronary artery bypass grafting (CABG) patients at a tertiary care hospital in Delhi.

The study was undertaken in two in-patient units at Dr RML hospital, a leading Government healthcare facility specializing in cardiovascular care in Delhi, India. This hospital serves a diverse patient population and provides comprehensive post-CABG care. Prior approval from the institutional ethics committee was taken. A total of 66 patients were included in the study that were posted for elective CABG, based on inclusion and exclusion criteria. Patients who were willing to participate in the study, aged more than 18 years, able to communicate in Hindi or English were included and patients with cognitive impairments or communication barriers that could affect their ability to provide accurate information were excluded. Purposive sampling technique was employed. Sample size calculation was done on an estimated prevalence of medication non-adherence among post-CABG patients, with a margin of error of 5% and a confidence level of 95%. Additionally, to account for attrition during the follow-up period, the sample size increased by 10%.

Medication adherence was assessed on first day of hospitalisation using structured interviews with patients. Data on socio-demographic characteristics, physiological and biochemical parameters were obtained; medical history, prescribed medications, and other relevant variables were collected through medical records and patient interviews. A validated Morisky Medication Adherence Scale (MMAS), was used to quantify adherence levels. Thereafter patients received a multifaceted tailored intervention designed to address individual barriers to medication adherence. Implementation of intervention was done by a trained nurse who was working in the CTVS Ward. Pre-test, post-test assessment, data collection and administration of interventions were done by the same nurse to each patient, individually.

Components of the intervention were medication counselling in which Individualised counselling sessions with a nurse to discuss the importance of medication adherence, potential side-effects, and strategies to overcome adherence challenges. Medication regimen simplification in which simplification of complex medication regimens to enhance patient understanding and compliance. Patient education which includes tailored educational materials and discussions to improve patients' understanding of their medications and their role in post-CABG recovery. Medication reminders includes implementation of reminder systems (alarm in mobile phone). Individualised discharge counselling, clarification of doubts and reinforcement in order to ensure the medication adherence was done. Weekly telephonic contacts were made to address their questions, concerns, or issues related to their medications and positive reinforcement was done. After 3 months, post-CABG adherence was reassessed using the same scale employed on the day of hospitalisation before CABG. Data was collected from May 2022 to February 2023. There were 6 patients unable to follow-up due to mortality; a total of 60 patients were included in the final analysis. All the data were entered into an Excel sheet. Statistical analysis was performed using software (SPSS version 26). Descriptive statistics was used to summarise patient demographics, physical and clinical parameters, and medication adherence levels. t-tests, Chi-squared tests, Fisher's exact test, McNemar test, were used to assess associations between variables. In the present study, past smoking, tobacco use, and alcohol intake means they stopped taking these since the last 6 month. Scoring of MGL score was 0 to Yes and 1 to No. For low adherence 0, moderate adherence score 1 - 2, and for high adherence scoring was 3 - 4.

Result

In this study, initially comprising 66 patients, 6 individuals were excluded due to attrition, resulting in a final sample size of 60 participants. The mean age of the included patients was 57.42 ± 9.23 years (as shown in Table I), and there was a notable male predominance. The majority of the participants identified as Hindu, were married, and resided in nuclear families. A significant proportion had received

education up to the primary school level and were engaged in skilled occupations. Furthermore, most participants belonged to the upper-lower socio-economic class and lived in urban areas. Notably, data revealed that 51.7% of patients had a history of past smoking, 40% had a history of past alcohol intake, and 32.5% had used tobacco in the past (Table II). Significant association was found with education of the patient ($p < 0.001$), (Table III).

Table I: Sample characteristics of CABG patients N = 60.

Variable	Mean	SD
Age (years)	57.42	9.23
Duration of illness (years)	8.89	8.71
Weight (Kg)	64.40	10.02
Height (cms)	162.89	9.20
BMI (Kg/m^2)	24.39	4.36
Heart rate (per minute)	78.98	12.36
SBP (mm Hg)	127.53	19.95
DBP (mm Hg)	77.78	7.92
Ejection fraction (%)	42.59	8.86
Total cholesterol (mg/dL)	204.43	26.54
LDL (mg/dL)	127.35	19.16
HDL (mg/dL)	33.92	3.31
TG (mg/dL)	188.42	29.25

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

S.No.	Variable	Categories	n	%
1.	Gender	Male	100	83.3
		Female	20	16.7
2.	Religion	Hindu	94	78.3
		Muslim	18	15
		Christian	1	0.8
		Sikh	7	5.8
3.	Marital Status	Single	1	0.8
		Married	119	99.2
4.	Type of Family	Joint Family	49	40.8
		Nuclear Family	71	59.2
5.	Education of the patient	Profession	7	5.8
		Honors Graduate	10	8.3
		Intermediate or Diploma	7	5.8
		High school certificate	28	23.3
		Middle school certificate	25	20.8
		Primary school certificate	33	27.5
		Illiterate	10	8.3
6.	Occupation of the patient	Legislators, Senior Officials and Managers	1	0.8
		Professionals	8	6.7
		Technicians and Associate Professionals	1	0.8
		Clerks	0	0
		Skilled Workers and Shop & Market Sales Workers	29	24.2
		Skilled Agricultural and Fishery Workers	29	24.2
		Craft and Related Trade Workers	3	2.5
		Plant and Machine Operators and Assemblers	2	1.7
		Elementary Occupation	16	13.3
		Unemployed	31	25.8
7.	Total monthly income (Rupees)	≥123,322	0	0
		61,663 - 123,321	1	0.8
		46129 - 61,662	1	0.8
		30,831 - 46,128	8	6.7
		18,497 - 30,830	25	20.8
		6,175 - 18,496	43	35.8
		≤6174	42	35
8.	Socio-Economic Status	Upper Middle Class	9	7.5
		Lower Middle Class	31	25.8
		Upper Lower Class	71	59.2
		Lower	9	7.5
9.	Residence	Urban	68	56.7
		Rural	52	43.3
10.	Smoking	Past	62	51.7
		Current	5	4.2
		Never	53	44.2
11.	Alcohol Intake	Past	48	40
		Current	4	3.3
		Never	68	56.7
12.	Tobacco use	Past	39	32.5
		Current	5	4.2
		Never	76	63.3
13.	Family history of CAD	Yes	31	25.8
		No	89	74.2
14.	Type of investigation undergone	Angiography	0	0
		Echocardiography	0	0
		TMT	0	0
		ECG	2	1.7
		Echocardiography, ECG and Angiography	118	98.3
15.	Type of treatment undergone	Medication	109	90.8
		Thrombolytic therapy	1	0.8
		Coronary Angioplasty	8	6.7
		Intra coronary stent	1	0.8
		Any other, specify	1	0.8
16.	Comorbidity history	Diabetes mellitus	30	25
		Hypertension	18	15
		Diabetes mellitus and Hypertension	25	20.8
		Bronchial asthma	0	0
		Any other chronic illness	0	0
		No comorbidity history	47	39.2
17.	Dietary habits	Non-Vegetarian	74	61.7
		Vegetarian	46	38.3

It was observed that 53.3% of patients had a lapse in medication adherence, primarily due to forgetfulness, while 81.7% displayed carelessness, and 45% discontinued their medication when they perceived an improvement in their condition. Furthermore, 8.3% ceased medication intake if they experienced a worsening of symptoms after administration. However, following the implementation of a tailored intervention, these rates significantly decreased to 0%, 10%, 1.7%, and 0%,

respectively (p < 0.001), (Table IV). This intervention yielded an overall enhancement in medication adherence, transitioning from a moderate level (2.05 ± 1.17) to a high level (3.88 ± 0.32) (p < 0.001), (Table V).

Table III: Association of pre-test and post-test medication adherence of CABG patients with selected variables N = 60.

Variable	Pretest		Post-test	
	Test Value	p-value	Test Value	p-value
Age	-0.100	0.278	0.084	0.360
Gender	-0.097	0.294	-0.115	0.213
Religion	0.123	0.182	-0.009	0.919
Marital status	0.015	0.870	-0.092	0.319
Type of family	0.038	0.680	-0.074	0.423
Education of the patient	0.086	0.350	-0.291	**0.001***
Occupation of the patient	-0.209	**0.022***	-0.059	0.525
Total monthly income	-0.041	0.659	-0.133	0.146
SES	-0.038	0.684	-0.172	0.061
Residence	0.244	0.007&	-0.049	0.598
Smoking	0.036	0.700	0.082	0.373
Alcohol Intake	-0.008	0.929	-0.124	0.177
Tobacco use	0.017	0.853	-0.044	0.636
Family history of CAD	-0.087	0.345	-0.077	0.405
Type of investigation undergone	-0.158	0.084	0.173	0.059
Type of treatment undergone	0.006	0.949	-0.107	0.244
Co-morbidity history	0.185	**0.044***	0.051	0.582

Table IV: Comparison of change in MGL pre-post scores in the experimental group N = 60.

MGL	Baseline		Day 75			
	Yes	No	Yes	No	Test value	p-value
MGL 1	32 (53.3)	28 (46.7)	0	60 (100)	30.031	**<0.001***
MGL 2	49 (81.7)	11 (18.3)	6 (10)	54 (90)	41.023	**<0.001***
MGL 3	27 (45)	33 (55)	1 (1.7)	59 (98.3)	22.321	**<0.001***
MGL 4	5 (8.3)	55 (91.7)	0	60 (100)	-	0.063

*McNemar test: *indicates a significant difference at p ≤0.05.*

Table V: Post-hoc Bonferroni test for comparison of medication adherence scores of CABG patients between pre-test and post-test N = 60.

Time point	Mean and SD	p-value
Pre-test	2.05 ± 1.17	0.245
Post-test (3 months)	3.88 ± 0.32	**<0.001***

**Level of significance P <0.05.*

The difference in serum total Cholesterol levels was significant at the end of 3 months in the post-test group (p <0.0001). There were substantial reductions observed in LDL cholesterol and triglyceride levels (p <0.0001), alongside a significant enhancement in HDL cholesterol by the end of the 3-month follow-up within the post-test group (p <0.0001), (Table VI).

Table VI: Comparison of Biochemical parameters before and after the intervention in experimental group N = 60.

Biochemical parameters	Mean ± SD		p-value
	Day-1	Day – 75	
T Cholesterol (mg/dL)	196.10 ± 20.56	149.13 ± 22.87	**<0.0001$**
LDL Cholesterol (mg/dL)	120.82 ± 14.05	92.97 ± 9.05	**<0.0001$**
HDL Cholesterol (mg/dL)	34.47 ± 2.68	54.40 ± 3.52	**<0.0001$**
TG (mg/dL)	180.52 ± 28.62	144.02 ± 25.95	**<0.0001$**

**Chi-square test, **Fisher's exact test.*

Discussion

The findings of this study provide compelling evidence that tailored interventions have a positive impact on medication adherence among patients recovering from cardiovascular events. This aligns with the idea that comprehensive, patient-centered care provided by nurses can extend beyond physical rehabilitation and extend to medication management. The discussions with participants revealed that the personal connection and ongoing support offered by nurses played a pivotal role in fostering adherence to prescribed medications.

Previous studies have also shown the effects of tailored intervention on the reduction of hospital readmission, and its positive effects such as the improved control of the patients' BP and drug adherence. Our results are similar to the accumulated evidence of the efficacy of such interventions on clinical outcomes[6,7]. Many studies that have evaluated the effectiveness of nonpharmacological CAD prevention interventions have shown that individual counselling had significant impact on the control of BP[8,9]. There was a significant change in the biochemical profile such as serum TC, TG, and LDL were found to be significantly reduced in the patients at 3 months' follow-up (p <0.01) whereas HDL was significantly increased in the patients (p <0.01); it was in contrast to the study which has shown the significant increase in the HDL in control group[10,11]. The reduction in the lipid level in this study might be attributed to the effect of medication along with the tailored support and education[12]. This argument is supported by the result of previous studies' findings which demonstrated significantly better adherence to the medication in the experimental group which showed a successful reduction in TG, TC, and LDL at 3 months (p < 0.01)[12,13]. Few studies have shown the significant reduction in the total cholesterol and LDL level at

the end of 6 months follow-ups ($p < 0.025$)[14,15].

This we believe is the effect of tailored intervention and improved drug adherence as shown previously[16,17]. We found superior medication adherence in the post-test. It is pivotal as non adherence of anti-platelet drugs can cause thrombosis.

Implications for Future Research and Clinical Practice: The findings of this study underscore the importance of tailored interventions in improving medication adherence among patients who underwent CABG. Future research in this area should explore the long-term effects of these interventions, assess cost-effectiveness, and examine their applicability across diverse healthcare settings. Furthermore, healthcare institutions should consider the integration of tailored interventions into standard cardiac rehabilitation protocols.

Limitations: It is essential to acknowledge the limitations of this study. Limitations of the study were the absence of a control group, and the sample size may not fully represent the diversity of CABG patients, and self-reporting of medication adherence can be subject to recall bias. Additionally, the study was conducted in a specific healthcare setting, which may limit the generalisability of the findings. Only some predefined parameters were assessed for the effect of an intervention. Short duration of 3 months follow-up could be a major limitation.

Conclusion

Uses of tailored interventions demonstrate significant potential in enhancing medication adherence among individuals recovering from cardiovascular events.

The success of tailored interventions in promoting medication adherence can be attributed to the personalised support and education provided to patients. Nurses, as trusted healthcare professionals, were able to address patients' concerns, explain the importance of medications, and clarify any misconceptions. This tailored approach increased patients' understanding of their medications and motivated them to adhere to their prescribed regimens.

This research highlights the importance of a patient-centered, multidisciplinary approach to cardiac care and provides valuable insights for healthcare providers and policymakers aiming to optimise outcomes in cardiovascular rehabilitation programs. Antiplatelet therapy, beta blockers, nitrates, ACE-inhibitor, and lipid lowering therapy plays a pivotal role in improving the condition and preventing occurrence of future cardiac events, Further investigation and implementation of these strategies holds the promise of improving the overall well-being of cardiac patients and reducing the burden of cardiovascular disease on healthcare systems.

References:

1. WHO . World Health Organisation; Geneva: 2016. Global Health Estimates 2015: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2015. [Google Scholar].
2. Prabhakaran D, Jeemon P, Roy A. Cardiovascular diseases in India. *Circulation* 2016; 133: 1605-20.
3. Ruhil R. India has reached on the descending limb of tobacco epidemic. *Ind J Community Med* 2018; 43: 153-6.
4. Kar A, Ahamad N, Dewani M *et al*. Wearable and implantable devices for drug delivery: Applications and challenges. *Biomaterials* 2022; 283: 121435.
5. Brown MT, Bussell JK. Medication adherence: WHO cares? *Mayo Clin Proc* 2011; 86 (4): 304-14.
6. Kamath DY, Xavier D, Gupta R *et al*. Rationale and design of a randomised controlled trial evaluating community health worker based interventions for the secondary prevention of acute coronary syndromes in India (SPREAD). *Am Heart J* 2014; 168: 690-7.
7. Ghannem M, Ghannem L, Ghannem L. Cardiac rehabilitation after myocardial infarction. *Ann Cardiol Angeiol (Paris)* 2015; 64: 517-26.
8. Santiago DA, Chaves GS, Davies P *et al*. Interventions to promote patient utilisation of cardiac rehabilitation. *Cochrane Database Syst Rev* 2019; 2: CD007131.
9. Wittlinger T, Schwaab B, Völler H *et al*. Efficacy of lipid lowering therapy during cardiac rehabilitation in patients with diabetes mellitus and coronary heart disease. *J Cardiovasc Dev Dis* 2021; 8: 105.
10. Premkumar S, Ramamoorthy L, Pillai AA. Impact of nurse-led cardiac rehabilitation on patient's behavioural and physiological parameters after a coronary intervention: A pilot randomised controlled trial. *J Family Community Med* 2022; 29 (1): 17-23.
11. Kotseva K, De Backer G, De Bacquer D *et al*. Lifestyle and impact on cardiovascular risk factor control in coronary patients across 27 countries: Results from the European Society of Cardiology ESC EORP EUROASPIRE V registry. *Eur J Prev Cardiol* 2019; 26: 824-35.
12. Carlsson R, Lindberg G, Westin L. Influence of coronary nursing management follow-up on lifestyle after acute myocardial infarction. *Heart* 1997; 77: 25-69.
13. Nakano M, Yahagi K, Otsuka F *et al*. Causes of early stent thrombosis in patients presenting with coronary syndrome: An *ex vivo* human autopsy study. *J Am Coll Cardiol* 2014; 63: 2510-20.
14. Piepoli MF, Hoes AW, Agewall S *et al*. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): Developed with the special contribution of the European Association for Cardiovascular Prevention and Rehabilitation (EACPR). *Eur J Prev Cardiol* 2016; 23: NP1-96.
15. Mach F, Baigent C, Catapano AL *et al*. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020; 41: 111-88.
16. Hansen VB, Maindal HT. Cardiac rehabilitation with a nurse case manager (GoHeart) across local and regional health authorities improves risk factors, self care and psychosocial outcomes. A one year follow up study. *JRSM Cardiovasc Dis* 2014; 3: 1-11.
17. Kubilius R, Jasiukevieiene L, Gripas V *et al*. The impact of complex cardiac rehabilitation on manifestation of risk factors in patients with coronary heart disease. *Medicine (Kaunas)* 2012; 48: 166-73.

ORIGINAL ARTICLE

JIACM 2023; 24 (3-4): 209-13

Role of Pulmonary Rehabilitation in Fully Treated Cases of Pulmonary Tuberculosis on Exercise Capacity and Quality of Life

Shivam Upadhyay, Prashant Prakash**, Balvir Singh***, Gajendra Vikram Singh****, Kanika Agarwal**

Abstract

Background: Pulmonary Rehabilitation may have a key role in improving the functional capacity and overall quality of life in patients having post-tubercular sequelae despite being declared completely cured.

Aims: To study the role of pulmonary rehabilitation in fully treated cases of pulmonary tuberculosis.

Material and Methods: The study was carried-out in the Post-Graduate Department of Medicine and Super Speciality Department of Pulmonary Medicine, SN Medical College and Hospital, Agra. We evaluated physiologically and bacteriologically confirmed patients of healed pulmonary tuberculosis who had completed their anti-tubercular treatment according to their categories.

Results: When compared pre- and post-rehabilitation, the change in decline in mean modified Borg's scale rating (Pre 6-MWT) observed between the case and control groups was significant (p = 0). The change in mean 6-MWT distance observed between the case and control groups was significant (p = 0.01). The change in decline in mean SGRQ score observed between the case and control groups was significant (p = 0).

Conclusion: It can be concluded that pulmonary rehabilitation is an effective adjunct to standard medical treatment for management of patients of fully treated pulmonary tuberculosis having functional limitation. When given along with standard medical treatment, it can be assumed that pulmonary rehabilitation can increase the exercising capacity of fully treated cases of pulmonary tuberculosis so as to lessen their functional limitations.

Key words: Pulmonary rehabilitation, pulmonary tuberculosis, 6-minute walk test.

Introduction

ATS/ERS defines pulmonary rehabilitation as: "A comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies which include, but are not limited to, exercise training, education and behaviour change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviours[1]."

In the management of obstructive pulmonary disorders, pulmonary rehabilitation is a well-established technique and is now a standard of care for patients with moderate-to-severe illness.

Three crucial components of effective recovery are the emphasis of this approach. First off, the programme is multidisciplinary and draws on knowledge from a range of healthcare areas to create a thorough and well-rounded curriculum. Second, the programme is customised to meet the demands of every person. Patients with incapacitating lung illness require individualised assessments that take into account the disease's complexity, severity, and co-morbidities as well as their needs. Then, a programme that is tailored to each patient's needs can be created. Thirdly, the programme strives to produce a comprehensive set of results, including enhanced social, psychological, and physical abilities as well as effective use of healthcare resources. Pulmonary rehabilitation aims to reduce symptom load, improve exercise performance, foster autonomy, increase involvement in daily activities, improve (health-related) quality of life, and create long-lasting behaviour changes that will improve health.

It is well known that rehabilitation can help patients with chronic lung disorders manage their symptoms, improve their functional capacity, and supplement routine pharmacologic and other treatments[2]. Any rehabilitation programme's main objective is to return the patient to the highest level of independent function. Rehabilitation focuses on reducing disease-related disability rather than just trying to reverse the disease process. In the past, patients with Chronic Obstructive Pulmonary Disease (COPD) have been the main target of pulmonary rehabilitation strategies development and application. However, pulmonary rehabilitation has also been

PG Resident, Department of Medicine, **Professor and Head, Department of Pulmonary Medicine, ****Professor and Head, Department of Tuberculosis and Chest Diseases, Sarojini Naidu Medical College, Agra - 282 002, Uttar Pradesh.
******Principal and Dean, Autonomous State, Medical College, Ferozabad - 283 203, Uttar Pradesh.***
Corresponding Author: Dr Kanika Agarwal, PG Resident, Department of Medicine, Sarojini Naidu Medical College, Agra - 282 002, Uttar Pradesh. Tel: 9105458898, E-mail: drkanika2102@gmail.com.

successfully used with patients who have interstitial lung disorders, cystic fibrosis, bronchiectasis, and anomalies of the thoracic cage[3]. The recovery of patients from acute processes, such as acute lung injury or exacerbations of chronic lung disease necessitating mechanical ventilation or urgent hospital care, has been aided by pulmonary rehabilitation. If the right individuals are chosen and attainable goals are established, pulmonary rehabilitation may even be beneficial for patients with advanced lung illness. In our study, we used pulmonary rehabilitation in the patients who, despite being deemed entirely healed of pulmonary tuberculosis, still had functional pulmonary limitations according to their respective classifications. In patients with post-tubercular sequalae, it may show to be a highly useful tool for enhancing functional capacity and overall quality of life.

Material and methods

We evaluated physiologically and bacteriologically confirmed patients of healed pulmonary tuberculosis who had completed their anti-tubercular treatment according their categories presenting to PG Department of Medicine, Agra of any age who were stable and interested in participating in our study filling into inclusion criteria, irrespective of present "smoking status" and having none of exclusion criteria, were enrolled into the study.

Inclusion criteria

1. Known or diagnosed cases of pulmonary tuberculosis who had taken full course of anti-tubercular treatment according to his/her category on the basis of clinical history, physical examination, chest radiographs and were sputum negative and follow-up culture negative were enrolled into the study.

Exclusion criteria

1. Any patient having history of pulmonary impairment not as a sequel of pulmonary tuberculosis.
2. Any patient who during the course of the study comes out to be sputum positive.
3. Any patient who during the course of the study comes out to be culture positive.
4. On LTOT (Long-term oxygen therapy).
5. Respiratory failure.
6. Pleural effusion.
7. Oxygen saturation < 88% at rest (room air).
8. History of receiving any supervised respiratory rehabilitation programme within previous 2 years.
9. Those who did not consent to participate in our study.

Methods

Each patient was evaluated as follows:-

a. Clinical history

b. General, systemic and physical examination

c. Anthropometric examination

d. Laboratory investigations.

Baseline evaluation

Every patient enrolled into our study was evaluated before pulmonary rehabilitation programme for the following aspects:-

1. Exercising capacity
2. Quality of life assessment.
   A. Tools for assessing exercising capacity: 6 m-walk test, modified Borg's scale
   B. Tools for quality-of-life assessment: Saint George Respiratory Questionnaire (SGRQ).

The comprehensive pulmonary rehabilitation programme given to the case group was formulated according to the various recommendations given by standard evidence-based guidelines[4].

Pulmonary rehabilitation programme

Programme structure

Home Exercise Programme (HEP)[5] which was partially supervised.

Exercise prescription – Individually tailored exercise formula based on maximum symptom – limited levels after the baseline tests.

Duration of this rehabilitative programme was 10 weeks.

Components of the Pulmonary Rehabilitation Programme:

The programme consisted of:

A. Physical reconditioning: Various types of sustained aerobic exercises and strength training exercises were included:-
   1. Brisk walking
   2. Stretching and relaxation exercises
   3. Cycling exercises

B. Breath retaining: We taught pursed lip breathing to the patients. Breathing pattern training enhanced with

visual feedback has been shown to increase the FEV1 and FVC in patients with COPD[6].

C. Exercise for Bronchial Hygiene: An individualised programme of secretion removal technique was taught to the patient of rehabilitation group in form of:-

   1. Postural drainage
   2. Huffing and controlled coughing

D. Dietetics

E. Health education

F. Psychosocial counselling.

Patients in both groups underwent a second evaluation of their nutritional condition, symptoms, lung function, exercise capacity, and health-related quality of life at the conclusion of the rehabilitation programme using the same standard methods. Before drawing any conclusions, the obtained data were utilised to compare any pre- and post-rehabilitation improvements in the case group and their advantages over those in the control group (if any).

Observation and results

Table I: Modified Borg's scale rating (Pre 6-MWT).

	Pre-programme		Post-programme		% change	t-value	p-value
	Mean	SD	Mean	SD			
Case	5.25	0.84	3.25	0.84	-38.10	9.5238	**<0.0001**
Control	5.39	0.88	5	0.86	-7.24	2.334	**0.0271**
Group	**Difference in Mean (Borg's scale Pre 6-MWT)**					**t-value**	**p-value**
Cases (n = 32)				-2.00	-11.51	0	
Controls (n = 28)				-0.39			

Table II: 6-MWT distance (m).

	Pre-programme		Post-programme		% change	t-value	p-value
	Mean	SD	Mean	SD			
Case	369.63	29.59	479.25	33.24	29.66	-13.9342	**<0.0001**
Control	360.89	28.76	416.79	32.34	15.49	-6.8347	**<0.0001**

Table III: Modified Borg's scale rating (Post 6MWT)

	Pre-programme		Post-programme		% change	t-value	p-value
	Mean	SD	Mean	SD			
Case	5.91	0.73	3.56	0.84	-39.76	11.9452	**<0.0001**
Control	6.25	0.89	5.75	0.7	-8.00	2.3366	**0.0116**
Group	**Difference in mean (Borg's scale Post 6-MWT)**					**t-value**	**p-value**
Cases (n = 32)				-2.35		0.484	0.68
Controls (n = 28)				-0.50			

The change in decline in mean modified Borg's scale rating (Pre 6-MWT) observed between the case and control groups was significant ($p < 0.05$)

The change in mean 6-MWT distance observed between the case and control groups was significant ($p = 0.01$)

The change in decline in mean SGRQ score observed between the case and control groups was significant ($p < 0.05$).

The change in decline in mean Modified Borg's scale rating (Post-6-MWT) observed between the case and control groups was significant ($p < 0.05$).

Table IV: SGRQ score.

	Pre-programme		Post-programme		% change	t-value	p-value
	Mean	SD	Mean	SD			
Case	15.51	2.46	14.3	2.32	-7.80	2.0242	**0.0472**
Control	16.61	1.96	16.49	1.81	-0.72	0.238	**0.5936**
Group	**Difference in mean (SGRQ)**					**t-value**	**p-value**
Cases (n = 32)			-1.21			-6.844	**<0.05**
Controls (n = 28)			-0.12				

Discussion

Due to structural changes brought on by the disease, patients with pulmonary tuberculosis (PTB) frequently experience deterioration in pulmonary function. Numerous survivors undergo long-term anatomical alterations. Studies on the patterns and severity of impairment in people with pulmonary tuberculosis were inconsistent[7]. Studies on pulmonary function[7] range from normal to severely impaired and can demonstrate restrictive, obstructive, or mixed patterns. Variously severe structural and functional lung sequelae are frequently seen by pulmonary TB survivors and have recently received more thorough description.

In our study, we evaluated 60 patients of fully treated pulmonary tuberculosis having functional limitation for the effects of pulmonary rehabilitation on exercising capacity.

In our study, pulmonary rehabilitation was found to significantly enhance exercise tolerance compared to routine medical care modified Borg's scale Pre-6-MWT ($p < 0.05$) and modified Borg's scale Post-6-MWT ($p < 0.05$). The case group's mean Pre 6-MWT modified Borg's scale value changed by 38.10%, nearly five times as much as the control group, where it changed by 7.24%. In the case group, the mean value of the Post 6-MWT modified Borg's scale had changed by 39.76%, nearly five times more than in the control group, where it had changed by 8.00%. Francesca Gibellino *et al*[8] (2014) discovered a comparable outcome in their investigation on the effect of pulmonary

rehabilitation in COPD, where they discovered a substantial improvement in exercise tolerance (mMRC scale p0.02). Osamu Nishiyama *et al*[9] (2008) reported a very same outcome in their investigation on the effects of pulmonary rehabilitation in IPF patients, where they discovered a substantial improvement in exercise tolerance ($p = 0.05$). Similarly, exercise tolerance afforded by pulmonary rehabilitation in chronic lung illnesses was significantly improved by O'Neill *et al*[10] (2001) and Oh EG[11] (2003). In restrictive lung disorders, pulmonary rehabilitation significantly improved exercise tolerance, according to Salhi *et al*[12] (2010. However, Donna de Grass *et al*[13] (2014) did not find any such improvement in exercise tolerance in pulmonary TB patients.

In our study on patients of fully treated pulmonary tuberculosis having functional limitation, when the 6-MWT distance was compared between the case and control groups pre- and post-rehabilitation, significant improvement was found conferred by pulmonary rehabilitation in the case group (369.63 ± 29.59 m before rehabilitation vs 479.25 ± 33.24 m after rehabilitation) over control group (360.89 ± 28.76 m before rehabilitation vs 416.79 ± 32.34 m after rehabilitation) ($p = 0.01$). The percentage change in the 6-MWT distance in the case group (29.66%) was almost double of that observed in the control group (15.49%). Similar results were found by Mara Popescu-Hagen *et al*[14] (2014) and Francesca Gibellino *et al*[8] (2014), both of their studies being on role of pulmonary rehabilitation in patients of COPD (6-MWT $p < 0.004$). O'Neill *et al*[10] (2001) and Oh EG[11] (2003), observed similar results in chronic lung diseases. Salhi *et al*[12] (2010) found significant improvement in exercising capacity provided by PR in restrictive lung diseases. Osamu Nishiyama *et al*[9] (2008) found significant improvements in 6-MWD provided by PR in IPF patients. Al Moamary[15] (2012) found significant improvement in 6-MWT distance conferred by PR in patients of ILD and Bronchiectasis.

Finally, when the quality of life was compared between the case and control groups before and after rehabilitation in our study on patients with fully treated pulmonary tuberculosis who had functional limitations, pulmonary rehabilitation was again found to have significantly improved the case group's quality of life over the control group ($p < 0.05$), according to the SGRQ. When compared to the control group, where it was -0.72%, the case group's mean SGRQ score changed by a percentage of -7.8%, which is over 10 times more than that. Osamu Nishiyama *et al*[9] (2008) made a similar finding in their studies on the function of pulmonary rehabilitation in IPF. In terms of quality of life, they discovered a substantial improvement (SGRQ $p = 0.05$). In restrictive lung disorders, Salhi *et al*[12] (2010) discovered comparable outcomes. However, Donna de Grass *et al*[15] (2014) failed to discover any appreciable improvement in the patients with pulmonary TB brought on by pulmonary rehabilitation.

Conclusion

We evaluated 60 patients of fully treated pulmonary tuberculosis having functional limitation and tried to find out the advantage offered by pulmonary rehabilitation if any over standard medical treatment in terms of exercising capacity and quality of life.

Bearing in mind, the limitation of a small sample size, following conclusions may be drawn from the present study:

1. Pulmonary rehabilitation significantly improves the exercising capacity of patients of fully treated pulmonary tuberculosis having functional limitation when given along with standard medical treatment, significantly well and above that conferred by standard medical treatment alone, as indicated by the significant increase in the 6-MWT distance in the case group over control group ($p = 0.01$).
2. Pulmonary rehabilitation significantly increases the exercise tolerance and reduces the sensation of dyspnoea in patients of fully treated pulmonary tuberculosis having functional limitation when given along with standard medical treatment as indicated by the significant decline in modified Borg's scale rating pre-6-MWT ($p = 0$) and post-6-MWT ($p = 0$).
3. Pulmonary rehabilitation significantly improves the quality of life of patients of fully treated pulmonary tuberculosis having functional limitation when given along with standard medical treatment, i.e., the patients after rehabilitation have more symptom free days, better control over day-to-day activities and lesser impact of the disease sequelae on their life. This is indicated by the significant reduction in the mean value of SGRQ score in case group as compared to control group ($p = 0$).

References

1. Spruit MA, Singh SJ, Garvey C *et al*. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances inpulmonary rehabilitation. *Am J Respir Crit Care Med* 2014; 189 (12): 1570.
2. American association of cardiovascular and pulmonary rehabilitation. Guidelines for pulmonary rehabilitation programmes. 4th ed. Champaign, IL: Human Kinetics; 2011.
3. Ferreira A, Garvey C, Connors GL *et al*. Pulmonary rehabilitation in interstitial lung disease: benefits and predictors of response. *Chest* 2009; 135: 442-7.
4. Nici L, Donner C, Wouters E *et al*. On behalf of the ATS/ERS

Pulmonary Rehabilitation Writing Committee. American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. *Am J Respir Crit Care Med* 2006; 173 (12): 1390-1413.

5. Greening NJ, Williams JEA, Hussain SF *et al*. An early rehabilitation intervention to enhance recovery during hospital admission for an exacerbation of chronic respiratory disease: randomised controlled trial. *BMJ* 2014; 349.
6. Román M, Larraz C, Gómez A *et al*. Efficacy of pulmonary rehabilitation in patients with moderate chronic obstructive pulmonary disease: a randomised controlled trial. *BMC Family Practice* 2013; 14: 21.
7. Long R, Maycher B, Dhar A *et al*. Pulmonary tuberculosis treated with directly observed therapy: serial changes in lung structure and function. *Chest* 1998; 113: 933-43.
8. Gibellino F, Laura Mammana. The Effects of Pulmonary Rehabilitation on Lung Function in Patients With COPD. 2014; 146 (4) Meeting Abstracts.
9. Nishiyama O, Kondoh Y, Kimura T *et al*. Effects of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. *Respirology* 2008; 13: 394-9.
10. O'Neill BM, Johnston D, Burrell N *et al*. Effect of once weekly pulmonary rehabilitation on exercise tolerance in patients with chronic lung disease. *Irish J Med Science* 2001; 170 (4): 231-2.
11. Oh EG. The effects of home-based pulmonary rehabilitation in patients with chronic lung disease. *Int J Nurs Stud* 2003; 40 (8): 873-9.
12. Salhi B, Troosters T, Behaeqel M *et al*. Effects of pulmonary rehabilitation in patients with restrictive lung diseases. *Chest* 2010; 137 (2): 273-9.
13. Donna de Grass, Manie S, Amosun SL. Effectiveness of a home-based pulmonary rehabilitation programme in pulmonary function and health-related quality of life for patients with pulmonary tuberculosis: a pilot study. *Afr Health Sci* 2014; 14 (4): 866-72.
14. Popescu-Hagen M, Traistaru R, Marica C *et al*. An Eight Week Pulmonary Rehabilitation in COPD Patients: Observational Study. 2014; 146 (4): Meeting Abstracts.
15. Al Moamary MS. Impact of a pulmonary rehabilitation programme on respiratory parameters and healthcare utilisation in patients with chronic lung diseases other than COPD. *EMHJ* 2012; 18 (2). Eastern Mediterranean Health Journal La Revue de Santé dela Méditerranée orientale 120.

REVIEW ARTICLE

JIACM 2023; 24 (3-4): 214-20

Seizure Disorders in Pregnancy

Upasana Verma, Sandhya Jain***

Introduction

Epilepsy is a challenging neurological problem encountered during pregnancy. It is defined as occurrence of two or more unprovoked seizures which is the clinical manifestation of an abnormal, excessive, purposeless and synchronised electrical discharge in the brain cells called neurons[1]. Though the incidence of epilepsy in pregnancy is less than 1%, apart from risk of injury, it has substantial effect on mother and foetus from conception till post-partum period if not supervised effectively. Moreover, the rate of maternal mortality is 10 times higher than those without seizure disorder in pregnancy[2]. The management of Women With Epilepsy (WWE) requires the joint efforts of obstetrician, neurologist, anaesthetist, and neonatologist. Since antiepileptic drugs (AEDs) play a major role in treatment, the vast spectrum of interaction of these drugs with pregnancy and lactation and *vice versa* always keeps a clinician in dilemma. This article highlights the overview of epilepsy in women from the pre-conception period to the post-partum period and the associated management dilemmas.

Diagnosis of epilepsy

The diagnosis of seizure disorder in pregnancy is to be confirmed by a neurologist or the medical practitioner who has expertise in epilepsy. WWE should undergo complete neurological evaluation prior to conception. The type of epilepsy should be recognised as focal, generalised, combined or unknown onset and related to any epileptic syndrome like Lennox-Gastaut syndrome or Dravet syndrome as per revised classification of international league against epilepsy (ILAE)[3]. The enquiry regarding duration, frequency, and severity helps to determine prognosis in pregnancy and to identify and prevent the factors of seizure deterioration. Generalised tonic clonic seizure is considered to cause maximum adverse effect on mother and foetus. Choice of AEDs also depends on the type of seizure disorder. Occurrence of seizure episode first time during pregnancy after 20 weeks in association with high blood pressure is mostly diagnosed to be eclampsia in the absence of any previous history of epilepsy. However, there can be other causes too (Table I). Proper history, examination, blood biochemistry, antibody testing, ECG and cerebrospinal fluid investigations are helpful in ruling-out these conditions. Imaging modality like MRI is a safe investigation for assessment during pregnancy with minimal radiation exposure to the foetus.

Table I: Causes of epilepsy in pregnancy.

Pregnancy specific	
Eclampsia	
PRES*	
Post-partum angiopathy (RCVS)#	
Nonspecific to pregnancy	
Metabolic conditions	Intracranial space occupying lesion
Hypogycaemia,	Intracerebral tumour (primary or metastatic)
Hyponatraemia,	Meningioma
Hypocalcaemia,	Cardiac conditions
Hypergycaemia hyperosmolar syndrome	Arrythymia
Infections	Asystole
Encephalitis,	Drug withdrawl
Meningitis	Cocaine
Cerebral malaria	Alcohol
Cerebral abscess	Psychogenic
Neurocysticercosis	Pseudoseizure or
Herpes simplex	Dissociative
humani mmunodeficiency virus	Autoimmune
Cerebrovascular accidents/	Idiopathic
Haemorrhage	Genetic
Infarction	
Central venous sinus thrombosis	
Head trauma	

**Posterior reversible encephalopathy syndrome, # Reversible cerebral vasoconstrictive syndrome.*

Effect of pregnancy on epilepsy

Pregnancy may influence the course of seizure disorders. In majority (67%) of WWE, there is no deterioration of seizure frequency in pregnancy[4]. The seizure-free duration and type of seizure disorder are the most important factors in predicting the occurrence of seizure. Females with seizure free span for last 5 years without AEDs have almost no further risk of epilepsy in pregnancy. Studies have shown that women who remain seizure free for at least 9 months to 1 year prior to conception, have a 74 - 92% chance of being seizure free during pregnancy[5]. Pregnant women with idiopathic generalised epilepsies are more likely to remain seizure free (74%) than those with focal epilepsies (60%). Only 15 %

****Associate Professor, **Director Professor, Department of Obstetrics and Gynaecology, UCMS and Guru Teg Bahadur Hospital, Dilshad Garden, Delhi - 110 095.***

Corresponding Author: Dr Sandhya Jain, Director Professor, Department of Obstetrics and Gynaecology, UCMS and Guru Teg Bahadur Hospital, Dilshad Garden, Delhi - 110 095. Tel: 9958811946, E-mail: drsandy2015@gmail.com.

WWE have increased seizure frequency in pregnancy. Increased hepatic and renal clearance of AEDs, increased volume of distribution and changes in serum protein binding decrease the levels of AEDs in blood leading to increased seizure frequency. Stress and decreased sleep during pregnancy also lower the seizure threshold. Concerns regarding the teratogenic effects of AEDs on foetus, reduces compliance among WWE and further enhances the risk of seizure episode (Table II). Seizure frequency increases with rise in oestrogen and decrease in progesterone levels[6], therefore the risk of seizure is more seen during the last trimester. There is insufficient evidence to state the increasing incidence of status epilepticus in pregnancy. However, 10% maternal mortality is reported owing to sudden unexpected death (SUDEP) in epilepsy with poorly controlled seizures being the main contributory factor[7].

Table II: Causes of increased frequency of seizures in pregnancy (approximately 15%).

- Stress
- Sleep deprivation
- Decreased adherence to AEDs
- ⇧Hepato-renal clearance of AEDs
- ⇧Volume of distribution and changes in protein binding of AEDs due to physiological haemodilution
- Change in oestrogen and progesterone levels

Effect of epilepsy and AEDs on pregnancy

As compared to women without epilepsy, WWE have 1.7 times increased risk of adverse pregnancy outcomes like spontaneous abortions, antepartum haemorrhage, foetal growth restriction, hypertensive disorders, preterm birth, caesarean section and post-partum haemorrhage[8]. Direct effect of generalised tonic-clonic seizures can lead to hypoxia and lactic acidosis, which may harm the foetus via placental transfer causing intrauterine foetal death[9].

The risk of congenital malformation to foetus in WWE not on AEDs is comparable to women without epilepsy (2 to 3%). The risk is two-fold increased (4 to 6%) in WWE on AEDs and is dependent on the type, number and dose of AEDs[10]. Valproic acid, though being the most effective AED, has maximum teratogenic potential followed by phenytoin, phenobarbitone, primidone, topiramate and carbamazepine. Neural tube defect is the commonest anomaly found in foetus of WWE exposed to sodium valproate, in addition to craniofacial, cardiovascular, and urogenital anomalies[11]. Orofacial clefts, cardiac malformations, and genitourinary defects are the major malformations described with phenytoin. Topiramate exposure in pregnancy is associated with an increased risk of foetal growth restriction and low birth weight[12]. Long-term studies on neurological development show higher rates of abnormal electroencephalogram (EEG) findings, developmental delay, lower intelligence quotient (IQ) scores and autistic spectrum in children exposed to AEDs *in utero*, especially with sodium valproate[13]. Risk of congenital malformation is dose dependant and is more associated with polytherapy as compared to monotherapy. Various effect of AEDs in pregnancy are shown in Table III. Lamotrigine and levetiracetam monotherapy at lower doses have found to have the least risk of congenital malformation and cognitive abnormality[14-16]. They are broad spectrum AEDs, effective in almost all types of seizures and are best choices in preconceptional and antenatal period[17]. But, they need dose escalation as their plasma concentration falls in pregnancy[18]. There is no AED which fall in FDA category A or B for pregnancy.

Table III: Various antiepileptic drugs and their effects and implications in pregnancy.

AED	Risk of CM	Specific CM	Neurodevelopmental delay, outcome in children	Require dose adjustment (↑/↑↑), serum level of AED in pregnancy (↑/↑↑)	Comments	FDA category for pregnancy
1st Generation						
Carbamazepine	2.6 to 6.6%	Microcephaly	Cognitive delay, Attention deficit hyperactivity disorder, Autism	No	Caution	D
Phenobarbitone	5.5 to 13.7%	Cardiac, cleft palate, hypospadiasis	High cognitive, psychomotor delay	Yes ↑,(50 to 70% ↑↑)	Avoid in pregnancy	D
Phenytoin	2.3 to 8.8%	NTD, cardiac, cleft palate, club foot	Not specific	Yes ↑,(50 to 61%↑↑)	Caution	D
Valproate	6.7 to 10.3%	NTD, Orofacial, limb, skeletal malformation, hypospadiasis[11]	Low IQ, neurodevelopmental delay, cognitive delay, Autism[13]	No	Avoid in pregnancy	D
Ethosuximide	15.4%	Cleft palate	*	*	Avoid	C
Clobazam	9.4% - 22%	*	*	*	Avoid	C
2nd Generation						

Lamotrigine	1.9 to 2.6%	No	No[15] Autism#	Yes'!, 50 to 70% (56.1%)"!	First-line drug (focal and generalised seizure in pregnancy)	C
Levetiracetam	0.7 to 2.8%	No	No	Yes '!,40 to 60%"!(40%)[18]	First-line drug in pregnancy (focal, generalised and myoclonic seizure in pregnancy)	C
Oxcarbamazepine	2.39%	Hypospadiasis*	*autism, neonatal abstinence syndrome[16]	Yes'!,32% "!	'! risk of seizure, Caution	C
Eslicarbazepine	*	*	*	*	Avoid	C
Felbamate	*No	*	*	*	Avoid	C
Gabapentin	*22%	Cardiac (VSD),	SGA	Yes'!,"!*	Avoid	C
locasamide	*	*	*	Yes'!*,39%"!*	Avoid	C
Topiramate	4.4%	Cleft lip, microcephaly(18.5%)	No *	Yes'!,30-40% "!	Caution	D
Zonisamide	*	Anencephaly, ASD	SGA*	Yes'!,30%"!	Avoid 40% risk of breakthrough seizure	C
3rd Generation						
Perampenal	*	Low APGAR Score, cystic fibrosis, congenital deafness*	*	*	Avoid	C
Pregabalin	3.3%*	VSD	*	Yes*	Avoid	D

**Insufficient data/limited studies, #Rare studies, CM: Congenital malformation, VSD: Ventricular septal defect, SGA: Small for gestational age.*

Management in Preconception phase

Preconceptional counselling plays a very important role in managing WWE right from prior to conception to antenatal, intrapartum and post-natal period. Complete verbal and written information regarding the effect of pregnancy on seizure profile and effect of epilepsy and AEDs on pregnancy should be provided to the women and her relative. Pharmacotherapeutic issues regarding adherence to AEDs should be addressed[17]. Pregnancy *per se* should not be considered a contraindication to WWE. Selection of appropriate AED weighing the risk benefit ratio should be taken to obtain effective control of seizure episodes prior to pregnancy in consultation with a neurologist. Teratogenic drugs (e.g., sodium valproate) should be replaced with other drugs (levetiracetam and lamotrigine). AED polytherapy should be switched to monotherapy if possible. The lowest effective dose of the most appropriate AED should be used. The therapeutic range of AEDs should be established in the preconception stage to eliminate inter-individual variations. WWE should be warned against abrupt discontinuation of AEDs.

Folic acid deficiency in preconception period, is associated with development of various congenital malformation like neural tube defects, oesophageal atresia, conotruncal heart defect, cleft palate, urinary malformations and omphalocoeles. Therefore, levels of folic acid should be measured preconceptionally to detect folate deficiency[19]. Folic acid supplementation (5 mg/day) at least 3 months prior to conception and until at least the end of the first trimester is recommended. Folic acid also reduces the cognitive impairement in children exposed to AEDs in *utero*[20].

Antenatal care and management

WWE presenting with unplanned pregnancy should be discouraged to stop or change the antiepileptic drugs abruptly of their own. This can result in epileptic attack, resulting in foetal intracranial haemorrhage, transient foetal bradycardia, miscarriage, or even death of the mother and foetus. WWE should be managed jointly by an obstetrician and neurophysician. Proper evaluation is to be done in case seizure occurs first time in pregnancy to know the cause (Table I). AEDs levels should be monitored closely and the therapeutic range should be individualised. In case of controlled seizure on AED polytherapy an attempt should be made to reduce the number of drugs and dose to lowest therapeutic level[21]. Valproic acid should be avoided if possible. Levetiracetam, lamotrigine and carbamazepine are good choice AEDs.

ILAE, 2019 report has concluded that a decrease of more than 35% in AED levels is associated with worsening of seizure control[9]. Therefore, close monitoring of antiepileptic medication serum levels during pregnancy in each trimester is important because of the increased clearance of these during pregnancy and frequent requirement for dose escalation especially with lamotrigine and levetiracetam

(Table III). Frequency of drug level monitoring may vary with type and level of control of seizure. More frequent AED monitoring is required in females with active epilepsy (a seizure within the past 12 months), bilateral tonic-clonic seizures and having modifiable risk factors for SUDEP (non-adherence to medication, alcohol and drug misuse, having focal to bilateral tonic-clonic seizures or generalised tonic-clonic seizures, having uncontrolled seizures, living alone and sleeping alone without supervision)[17].

In case it there is no facility for monitoring drug levels, dose of AED can be increased if female is on lamotrigine, levetiracetam or oxcarbazepine; type of seizure is changed from focal to generalised; seizure control has been sensitive to change in AED levels before pregnancy[9].

AEDs also alter the pharmacokinetics of folic acid metabolism. Folic acid is a vitamin B involved in the synthesis of purines, which are required for DNA formation, and low levels are associated with reduced growth, risk of congenital malformation, and anaemia. Women taking enzyme-inducing AEDs (e.g., strong inducers: carbamazepine, phenytoin; weak inducers: topiramate, oxcarbazepine, eslicarbazepine acetate) have a greater risk of folic acid deficiency during pregnancy compared with the general population. Valproate, although not enzyme inducing, interferes with folate absorption and folate-related co-enzymes. Therefore, folic acid supplementation is essential in antenatal period too. High-dose supplementation is recommended for enzyme-inducing and older AEDs. The American College of Obstetricians and Gynaecologists (ACOG) and the United Kingdom guidelines[20] recommend a daily folic acid supplementation of 4 mg and 5 mg respectively. No clear guidelines for dosing folic acid with newer AEDs such as lamotrigine or levetiracetam are available. Certain studies recommend high-dose folic acid supplementation in high-risk cases like previous pregnancies with NTDs, unplanned pregnancy not supplemented with folic acid, and women with low intake or impaired adherence to daily folic acid supplementation. In addition, women with known genetic variations in the folate metabolic cycle, those exposed to medications with antifolate effects, smokers, diabetics, and the obese may benefit from higher doses of folic acid daily during the first trimester[22]. However, according to other authors, there is no reason to use higher dosages since there is no evidence that higher dosages are more useful and at least 0.4 mg/day is considered enough[9]. Therefore, the dose to be used is between 0.4 and 5 mg and should be evaluated in each specific clinical case[23].

Though, there is less, but significant obstetric risk like spontaneous abortion, pre-eclampsia, antepartum haemorrhage, preterm labour and foetal growth restriction, antenatal care should be imparted as high-risk pregnancy. Risk factors such as sleep deprivation, dehydration, fever and stress; seizure type and frequency; adherence to AEDs should be assessed in each antenatal visit. Early anomaly scan should be done at 11 to 14 weeks to detect neural tube defect. Option of aneuploidy screening should be given. Detailed anomaly ultrasound scan is recommended at 18 to 22 weeks to detect other congenital malformations and cardiac defects. Foetal echo may be also be advised in case of suspicion of cardiac anomaly. Serial growth scans are required for detection of small-for-gestational-age babies and to plan further management in WWE exposed to AEDs. Number of antenatal visits should be individualised taking the serum level of AEDs, clinical seizure control and associated obstetric complications into consideration.

If admission is required antenatally, WWE at reasonable risk of seizures should be kept in an environment that allows for continuous observation by a caretaker, partner, or nursing staff. There is no role for routine antepartum foetal surveillance with cardiotocography in WWE taking AEDs[20].

Intranatal care

Though there is increased risk of seizure frequency in labour, women should be assured as only 2% of WWE have been reported to have epilepsy during delivery[24]. Risk of seizure in labour varies with the AEDs (lamotrigine and carbamazepine – 2.6%, phenobarbitone – 1.9%, valproate – 1.4%). If seizure deterioration is anticipated in the peripartum period, delivery should take place where there are facilities for maternal and neonatal resuscitation and treatment of maternal seizures.

Adequate analgesia and appropriate care in labour should be provided to prevent occurrence of seizure. Pethidine, in higher doses, should be avoided or used with caution, as it is metabolised to norpethidine, which is epileptogenic. Epidural analgesia can be the option. Less number of visitors should be allowed in the vicinity. Patient should be kept in a calm environment so that she can take sleep in-between. Bed railing should be padded to avoid injury. One caregiver should always be present in the labour room along with the patient. Oral AED intake should be continued, but should be replaced with parenteral alternative in case of non-tolerance. Long-acting benzodiazepines, such as clobazam can be considered if there is a very high risk of seizures in the peripartum period. Seizures in labour should be terminated as soon as possible with benzodiazepines like lorazepam (drug of choice), diazepam, or midazolam to avoid maternal and foetal hypoxia and foetal acidosis. If seizures are not controlled, the loading dose of phenytoin (or fosphenytoin), 10 - 15 mg/kg should be administered by intravenous infusion, with the usual dosage for an adult of about 1,000 mg[25]. This should be followed by maintenance dose.

Seizure disorder in pregnancy is not the indication for induction of labour (IOL). But, the evidence suggests an increased incidence of IOL in WWE. AEDs do not have any interaction with drugs that are used for IOL. Hyperventilation and maternal exhaustion should be avoided because these conditions can exacerbate a seizure in the labouring women. Epilepsy is not an indication for a caesarean section but should be considered for obstetric reasons. Epidural anaesthesia is preferred as it allays pain and prevents seizure. In case of repeated seizures (status epilepticus), patient should be considered for mechanical ventilation and early termination by caesarean section. Uterotonic administration and CTG monitoring should be considered in case of uterine tonicity. Though few studies have reported risk of maternal and neonatal haemorrhage in WWE taking enzyme inducing AEDs. However, there is less evidence for the role of vitamin K prophylaxis, especially women on enzyme-inducing AEDs[26].

Post-partum care and breastfeeding

The frequency of seizure episodes decreases in post-partum period, but AEDs intake should not be stopped. The dose of AEDs should be reviewed by measuring the serum levels within 10 days of delivery to avoid toxicity. Lamotrigine, levetiracetam and oxcarbamazepine levels sharply rise in blood, therefore, doses need to be tapered. Dose reduction is also needed with eslicarbazepine, gabapentine, lacosamide, oxcarbazepine, pregabalin, rufinamide, topiramate, valproic acid and vigabatrin as the physiological renal and hepatic enzymatic changes (e.g., glucoronidation) associated with pregnancy resolves in 2 to 3 weeks. Whereas cytochrome P450 coenzymes may take 1 to 2 months to return to baseline clearance rate. As such, dose titration is less likely required in WWE taking enzyme-inducing drugs like carbamazepine, clobazam, ethosuximide, felbamate, phenytoin, phenobarbitone, primidone, tiagabine and zonisamide[9].

Secondly, trigger of epilepsy like sleep deprivation should be avoided. Caregiver should be advised to adopt shift approach so as to allow mother with epilepsy to have adequate sleep. Responsibility of baby should be shared with family. Emotional and mental support should be provided to avoid stress and postpartum depression. Various safety measures should be taken to avoid injury to mother and baby in case of unexpected epilepsy. Mother and baby should not be allowed to bathe alone in the early post-partum period as there is risk of drowning and injury in bathroom in case of sudden epilepsy. Baby carrier should be used while walking around with the baby. In patients with uncontrolled epilepsy, a safety strap is recommended while holding the baby.

WHO recommends breast feeding in WWE in post-partum period, as it provides many benefits for the infant including nutrition, immunoprotection, and cognitive development. ILAE 2019, advocated that the adaptation to bottle feeding may be allowed as per seizure sensitivity based on history and type of epilepsy; this permits uninterrupted sleep for at least 4 hours. Pumping breast milk during the day to maintain milk supply and a partner feeding the child during the night can assure both less sleep deprivation for the mother and the benefit of breast milk over formula nutrition for the child[23]. Though, potential transfer of AEDs through breast milk and their side-effect has been a matter of concern, but in breastfed infants the level of AEDs is much lower than the umbilical cord blood AEDs[27,28].

The safety and low levels of AEDs in breastfed infants depends on plasma protein binding, oral bioavailability, milk-to-plasma ratio (M/P ratio) and plasma half-life. These drugs are categorised in 5 lactation groups (ranging from L1- safest to L5- contraindicated) depending upon the safety profile (Table IV). Ethosuximide, zonisamide, benzodiazepines (though single dose does not alter the levels in infants) and felbamate are probably high-risk and contraindicated in breastfeeding[27].

Table IV: Safety profile of AEDs in lactation.

Catogory	AED	Dose adjustment(“!‘!)
L2-Safe*	Carbamazepine	Not required
	Phenytoin	
	Valproic acid	
L3-Moderately safe#	Levetiracetam	“!
	Pregabalin	
	Lamotrigine	
	Tiagabine	
	Vigabatrine	
	Topiramate	
	Oxcarbazepine	
L4-possibly hazardous”	Zonisamide	
	Primidone	-
	Phenobarbital	“!
	Clobazam	-
	Clonazepam	-
	Ethosuximide	-
Insufficient data	Eslicarbazepine-acetate	“!
	Perampanel	-
	Lacosamide,	“!
	Brivaracetam	-

**High degree of protein binding in plasma, low degree of penetration into breast milk, M/P ratio 0.01 to 0.7, #Low degree of protein-binding in plasma (from 15% of topiramate to 55% of lamotrigine and oxcarbazepine), low molecular weight, M/P ratio from 0.1 to 2.0" low degree of protein-binding, M/P ratio from 0.3 to 2.8, high excretion into breast milk.-Insufficient studies or data.*

The effect of AEDs in the baby can be reduced by appropriate timing of medication. Breastfeeding mothers on once-a-

day AED should be advised to take it at the beginning of baby's longest sleep, usually right after the bedtime feeding. In case when medication is to be taken more than once a day, mother should be advised to breast-feed the baby immediately before taking a dose. That's when the level is likely to be lowest.

Breastfed infants should be watched for diarrhoea, sleepiness, excessive crying, vomiting, decreased appetite, and appearance of rashes. Infant should be reviewed by the neonatologist and neurologist for untoward effect of AEDs. The risk of the child developing epilepsy in life depends mainly on the type of epilepsy in the mother, especially hereditary epilepsy syndrome. The risk increases with decreasing gestation age and birth weight[29].

Contraception

Contraception should be offered to WWE to avoid unplanned pregnancy[20]. Choice of contraception depends on various pharmacokinetic interactions between hormonal contraception (HC) and AEDs. Most combined oral contraceptives (COCs) are metabolised by cytochrome P450 enzymes. Enzyme inducing antiepileptic drugs like carbamazepine, phenytoin and phenobarbitone, induce these enzymes resulting in the decreased efficacy of COCs. Patients receiving these AEDs should take at least 50 mcg of ethinyl estradiol (high-dose COCs) or two tablets of 30 mccg ethinyl estradiol. Alternatively, one can switch to another method like IUCD (intrauterine devices). If the patient prefers only oral contraception, use of smartphone app (pill-reminder), digital tablet dispenser, or other measures are suggested to minimize number of missed pills. These women should also be provided with the option of drugs that have no interactions with HCs. Valproic acid, vigabatrin, gabapentin, tiagabine, levetiracetam, zonisamide, ethosuximide, and benzodiazepines – including clobazam and clonazepam – pose no risk of contraceptive failure. Progesterone-only pill, progestin/progesterone implants, combined contraceptive patches, and vaginal ring are not recommended because of reduced efficacy. If depot medroxyprogesterone injection is given, it should be given at more frequent intervals (10 week interval rather than 12 week interval)[30].

In contrast, the oestrogenic component of COCs can lower lamotrigine levels by 40% to 60%, by increasing uridine-diphosphate glucuronosyl transferase (UGT) mediated glucuronidation, thus enhancing the risk of breakthrough seizures. Therefore, lamotrigine levels should be carefully monitored before and after starting a COC, and doses adjusted accordingly, potentially by up to 50%. Options like IUCD, DMPA, implants should to suggested. Any hormonal contraception can be offered to patients receiving levetiracetam[31].

Concerns like alteration of milk production, cardiovascular and thromboembolic risk in post-partum women, COCs are contraindicated. Copper IUCD should be the choice for these patients.

WHO Medical Eligibility criteria (MEC), 2016 for use of different contraceptive methods in women with epilepsy and AEDs usage is shown in Table V[32].

Table V: Medical eligibility criteria (MEC) for contraception in epilepsy.

Medical eligibility	COCpill/ patch/ring	POP	Inj DMPA	Implant	Levonor-gesterol-IUCD	Copper IUCD
Epilepsy – no AED/on non EIAED	1	1	1	1	1	1
EIAED *	3	3	1	2	1	1
Lamotrigine	3	1	1	1	1	1
Breast feeding <6 weeks	4				3	1"
Breast feeding (6 weeks to 6 months)	3	1	1	1	1	1©

*EIAED = Enzyme inducing antiepileptic drug, *Phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine; Felbamate and topiramate,are less potent enzyme inducers but, selectively, induce metabolism of progesterone and oestrogen component of OCPs, respectively. COC: Combined oral contraception, POP: Progesterone only pills, DMPA: Depot medroxyprogesterone acetate, IUCD: Intrauterine contraceptive devices, MEC: 1. no restriction, 2. advantages of using the method outweigh the theoretical or proven risk, 3. theoretical or proven risks outweigh the advantages of using the method, 4. unacceptable health risk/contraindication" ruling-out contraindications for IUCD postpartum period, like post-partum haemorrhage, severe anaemia, prolonged leaking (>18 hrs) and preferably within 24 hrs of delivery, ©Post-menstrually,once the menses resumes or when its sure patient is not pregnant.*

Conclusion

Epilepsy is a common chronic neurological problem in pregnancy, associated with foeto-maternal morbidity and mortality. The management requires multidisciplinary team of obstetrician, neurologist and neonatologist. WWE should undergo proper preconception counselling and folic acid supplementation. Pregnancy should be planned after complete evaluation and adequate control of seizure episodes with safe AEDs. Lamotrigine, levetiracetam and oxcarbamazepine are safe and preferred in pregnancy. Patient should be monitored for obstetric complications and detailed anomaly scan is a must at 18 to 22 weeks. AED levels should be monitored closely. Advocating good safety precautions, along with appropriate choice and adherence to antiepileptic drugs avoids seizure episodes and risk of injury to mother and baby even during delivery. Caesarean section should be reserved for obstetric indication or in cases of status epilepticus. Breast feeding should be

advocated as much as possible. Counselling and administration of appropriate contraception, unaffected by antiepileptic drugs, like intrauterine contraceptive devices should be promoted in post-partum period.

References

1. Fisher RS, Acevedo C, Arzimanoglou A *et al*. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia* 2014; 55 (4): 475-82.
2. Edey S, Moran N, Nashef L. SUDEP and epilepsy-related mortality in pregnancy. *Epilepsia* 2014; 55: e72-4.
3. Fisher RS, Cross JH, French JA *et al*. Operational classification of seizure types by the International League Against Epilepsy: Position paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 2017.
4. Battino D, Tomson T, Bonizzoni E *et al*. EURAP Study Group. Seizure control and treatment changes in pregnancy: observations from the EURAP epilepsy pregnancy registry. *Epilepsia* 2013; 54: 1621-7.
5. Vajda FJ, Hitchcock A, Graham J *et al*. Seizure control in antiepileptic drug-treated pregnancy. *Epilepsia* 2008; 49: 172-6. 49-5.
6. Tauboll E, Sveberg L, Svalheim S. Interactions between hormones and epilepsy. *Seizure* 2015; 28: 3-11.
7. Shorvon S,Tomson T. Sudden unexpected death in epilepsy. *Lancet* 2011; 378: 2028-38.
8. Viale L, Allotey J, Cheong-See F *et al*. Epilepsy in pregnancy and reproductive outcomes:a systematic review and meta-analysis. *Lancet* 2015; 386: 1845-52.
9. Tomson T, Battino D, Bromley R *et al*. Management of epilepsy in pregnancy: a report from the International League Against Epilepsy Task Force on Women and Pregnancy. *Epileptic Disord* 2019; 21 (6): 497.
10. Shannon GD, Alberg C, Nacul L *et al*. Preconception healthcare and congenital disorders: systematic review of the effectiveness of preconception care programs in the prevention of congenital disorders. *Matern Child Health J* 2014; 18: 1354-79.
11. Tomson T, Battino D, Bonizzoni E *et al*. Comparative risk of major congenital malformations with eight different antiepileptic drugs: a prospective cohort study of the EURAP registry. *Lancet Neurol* 2018; 17 (6): 530.
12. Veiby G, Daltveit AK, Engelsen BA. Fetal growth restriction and birth defects with newer and older antiepileptic drugs during pregnancy. *J Neurol* 2014; 261 (3): 579-88.
13. Christensen J, Gronborg TK, Sorensen MJ *et al*. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *JAMA* 2013; 309 (16): 1696-703.
14. Bromley RL, Calderbank R, Cheyne CP *et al*. Cognition in school-age children exposed to levetiracetam, topiramate, or sodium valproate. *Neurology* 2016; 87 (18): 1943.
15. Veroniki AA, Rios P, Cogo E *et al*. Comparative safety of antiepileptic drugs for neurological development in children exposed during pregnancy and breast feeding: a systematic review and network meta-analysis. *BMJ Open* 2017; 7: e017248.
16. Weston J, Bromley R, Jackson CF *et al*. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. *Cochrane Database Syst Rev* 2016; 11: CD010224.
17. National Institute for Health and Care Excellence. Epilepsies in children, young people and adults. NICE clinical guideline 217: NICE; 2022.
18. Pennell PB, Karanam A, Meador KJ *et al*. Antiseizure medication concentrations during pregnancy: results from the Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) study. *JAMA Neurol* 2022; 79: 370-9.
19. Valentin M, Coste Mazeau P, Zerah M *et al*. Acid folic and pregnancy: a mandatory supplementation. *Ann Endocrinol* 2018; 79: 91-4.
20. Royal College of Obstetrians and Gynaecologists. Epilepsy in pregnancy: Green-top guideline No. 68. RCOG. 2016.
21. Meador KJ, Pennell PB, Harden CL *et al*. Pregnancy registries in epilepsy: a consensus statement on health outcomes. *Neurology* 2008; 71: 1109-17.
22. Chitayat D, Matsui D, Amitai Y *et al*. Folic acid supplementation for pregnant women and those planning pregnancy: 2015 update. *J Clin Pharmacol* 2016; 56: 170-5.
23. Nucera B, Brigo F, Trinka E. Treatment and care of women with epilepsy before, during, and after pregnancy: a practical guide. *Therapeutic Advances in Neurological Disorders* 2022; 15.
24. Sveberg L, Svalheim S, Taubøll E. The impact of seizures on pregnancy and delivery. *Seizure* 2015; 28: 35-8.
25. National Institute for Health and Care Excellence. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. NICE clinical guideline 137. [Manchester]: NICE; 2012.
26. Shahrook S, Ota E, Hanada N *et al*. Vitamin K supplementation during pregnancy for improving outcomes: a systematic review and meta-analysis. *Sci Rep* 2018; 8: 11459.
27. Davanzo R, Dal Bo S, Bua J *et al*. Antiepileptic drugs and breastfeeding. *Ital J Pediatr* 2013; 39: 50.
28. Tomson T, Battino D, Bromley R *et al*. Breastfeeding while on treatment with antiseizure medications: a systematic review from the ILAE Women Task Force. *Epileptic Disord* 2022; 24 (6): 1020-32.
29. Sun Y, Vestergaard M, Pedersen CB *et al*. Gestational age, birth weight, intrauterine growth and risk for epilepsy. *Am J Epidemiol* 2008; 167: 262-70.
30. Li Y, Meador KJ. Epilepsy and Pregnancy. *Continuum (Minneap Minn)* 2022; 28 (1): 34-54.
31. Penovich PE. Levetiracetam and Oral Contraceptives. *Epilepsy Curr* 2002; 2 (6): 182.
32. Thomas SV. Controversies in contraception for women with epilepsy. *Ann Indian Acad Neurol* 2015; 18: 278-83.

CASE REPORT

JIACM 2023; 24 (3-4): 221-23

Eltrombopag-induced Cortical Vein Thrombosis: A Case Report

Tarun Selvarajan, Vasudeva Acharya**, Cynthia Amrutha Sukumar***, Nandakrishna B***, Nagraj Kamath*, Rukmoni Balasubramanian**

Abstract

Eltrombopag, a thrombopoietin receptor agonist is widely used in the treatment of immune thrombocytopenic purpura (ITP), aplastic anaemia and post-transplant cytopenia. Eltrombopag is used as second-line treatment in ITP. We describe a rare and life-threatening complication of this drug namely cortical venous thrombosis in a patient with ITP. Pathogenetic mechanisms behind the thrombosis may vary from case to case. Thrombosis may be linked to the platelet count or additional thrombophilic states. Regular monitoring of patients on therapy with Eltrombopag is required to avoid these complications.

Introduction

Eltrombopag is an agonist of thrombopoietin receptors (TPO-RA) used in immune thrombocytopenic purpura (ITP) and aplastic anaemia. There have been few case reports which showed episodes of treatment concomitant thromboembolism with the reports of thrombosis in the venous and arterial circulation[1-4]. Here we describe the development of cerebral venous thrombosis involving the sigmoid and transverse sinus in a patient with immune thrombocytopenic purpura, who was being treated with Eltrombopag. We also discuss the possible pathophysiology behind the thrombotic events and steps to prevent the adverse event.

Case

A 34-year-old female patient had a three-year history of Immune thrombocytopenic purpura (ITP) being treated with oral prednisolone. Clinical remission was achieved for two years. Six months earlier she developed fever, purpura, epistaxis, and lab investigations revealed a platelet count of 6 x 16^3/μL. In view of the poor response to glucocorticoids, along with steroids, oral Eltrombopag 25 mg was started after the management of acute bleeding episodes with intravenous immunoglobulin. After two weeks of treatment, the patient experienced ongoing symptoms consistent with thrombocytopenia. Therefore, the dosage of Eltrombopag was escalated to 50 mg per day. Subsequently, the patient's platelet count showed improvement over the following week. She was discharged with a schedule for follow-up after 15 days for platelet measurement. But she failed to attend the scheduled follow-up. She received this medication for six weeks before presenting to us for emergency care for acute onset severe headache – which was throbbing in nature – and blurred vision.

Physical examination upon admission to the emergency care revealed normal vitals. The nervous system examination was unremarkable. Direct ophthalmoscopy revealed bilateral papilloedema. Laboratory investigations revealed elevated platelet counts, i.e., 658.0 x 10^3/μL, normal haemoglobin (13 g/dL), and normal coagulation studies. Peripheral smear showed features suggestive of reactive thrombocytosis and enlarged platelets. Magnetic Resonance venography (MRV) showed features suggestive of right sigmoid sinus thrombosis as shown in Fig. 1. Anti-nuclear antibodies and antiphospholipid antibodies were within normal limits.

Treatment

She was treated with low molecular-weight heparin and enoxaparin. The headache was managed symptomatically with Mannitol and oral analgesics. Eltrombopag was withheld in view of thrombosis. Subsequently, she was started on warfarin with a target INR of 2 - 3 which was achieved. The oral prednisolone dose was increased to 10 mg per day.

Outcome

At the time of discharge, the patient was stable with platelet count of 195 x 10^3/μL and the headache resolved. The most recent follow-up platelet count was 272 x 10^3/μL. MRV done during this time showed complete resolution of the thrombosis as shown in Fig. 2.

Discussion

Immune thrombocytopenic purpura is distinguished by

Junior Resident, **Professor, ***Associate Professor, Department of Medicine, Kasturba Medical College, Manipal Academy of Higher Education, Manipal- 576104, Karnataka.

Corresponding Author: Dr Nandakrishna B, Associate Professor, Department of Medicine, Kasturba Medical College, Manipal Academy of Higher Education, Manipal - 576 104, Karnataka. Phone: 9914201838, E-mail: nandaksb@gmail.com.

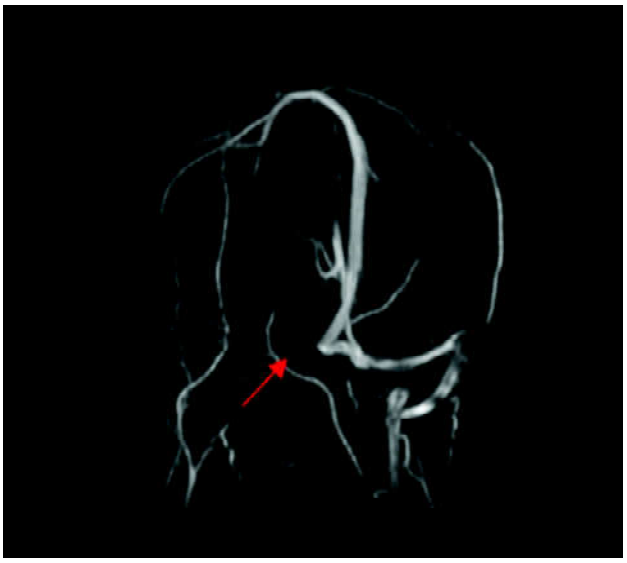


Fig. 1: *MRV showing absence of flow in the right sigmoid sinus, (red arrow) compared to left sigmoid sinus (white arrow).*

immune-mediated destruction of platelets and diminished production of platelets which leads to bleeding. Corticosteroids are the first-line drugs in the management of ITP. In the cases which are steroid-dependent or resistant, thrombopoietin receptor agonists like Eltrombopag are

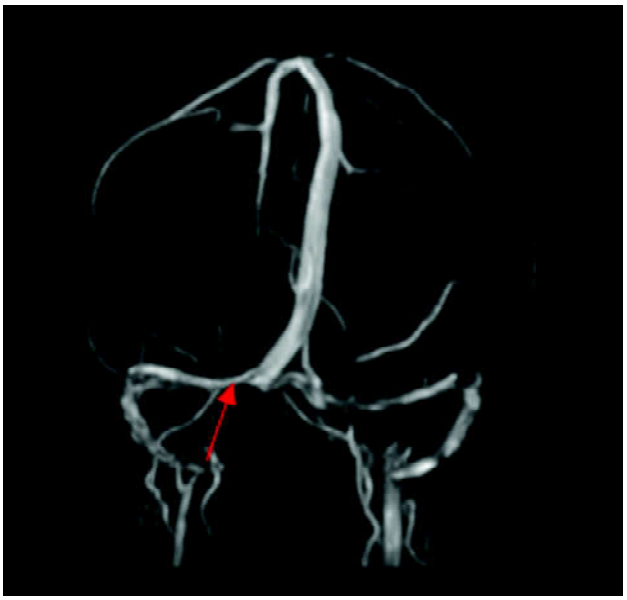


Fig. 2: *MRV showing flow established in the right sigmoid sinus, suggesting recanalisation (as pointed by arrow).*

used. It acts by its agonist action at thrombopoietin receptors leading to an increase in platelet counts compensating for increased destruction of platelets in ITP[5]. Eltrombopag has also been used for aplastic anaemia and post-transplant cytopenia.

Few adverse effects are reported with the use of Eltrombopag. The commonest of them is nasopharyngitis. Less common ones are thromboembolic episodes, transaminitis, and myelofibrosis. Sporadic cases of deep vein thrombosis[2], portal vein thrombosis[4], as well as myocardial infarction[6] due to thrombosis in those who have been taking Eltrombopag are reported. The incidence of thrombotic episodes was 6% in the EXTEND trial[7] which was aimed at long-term safety and efficacy of Eltrombopag in ITP whereas the RAISE trial by Cheng *et al*[8] had 2% thrombotic episodes. The relation between exposure to the drug and the development of thromboembolic has not yet been well described in the literature. In the EXTEND study, the rates of VTE did not increase beyond the first year of treatment. Similarly, in the majority of cases reported thromboembolic episodes occurred within the first 2 years.

The pathophysiological mechanisms behind thrombotic episodes with Eltrombopag use in ITP are manifold. First, is the relation of thrombotic events with increased platelet counts with therapy. Cheng *et al* in the RAISE trial reported that 2% of the patients receiving eltrombopag had episodes of thrombosis with a platelet count between 50 - 400 x $10^3/mm^3$. However, thrombocytosis was seen in 44.7% of cases with arterial thrombosis and 50% of venous thrombosis cases. Second is the presence of a concomitant thrombophilic state like protein C/S deficiency, or antiphospholipid antibody syndrome. Lastly, whether ITP predisposes to thrombosis inherently is a question to ponder as reported by several studies[8,9].

The onset of thrombus formation in the cerebral venous circulation may have been triggered by the eltrombopag administration induced thrombocytosis in our case. Other causes of thrombosis were ruled-out through appropriate tests. We immediately stopped the administration of Eltrombopag. Enoxaparin was used to achieve anticoagulation. Warfarin was initiated after the acute phase to prevent a recurrence.

Eltrombopag therapy requires regular monitoring. The initiation dose is 50 mg per day for the Western population. Whereas for the East Asian population recommended initiation dose is 25 mg/day. Recommended intervals for platelet monitoring:-

- One week after the initiation of treatment with TPO agonists.
- One week after the dose titration.
- One month after achieving a stable dose.

Table I below is a guide for dose adjustment of Eltrombopag as per platelet counts.

Table I:

Platelet Count Range	Action
>250 x 10^3/mm^3	Hold back the dose. Restart at 50% lower dose once platelet count is < 150 x 10^3
150 - 250 x 10^3/mm^3	Reduce the dose by 50% and monitor platelets 2 weeks after
50 - 150 x 10^3/mm^3	Continue with the same dose
< 50 x 10^3/mm^3 (after 2 weeks)	Increase the dose by 25 mg/day to a maximum of 75 mg/day

To summarize, albeit there have not been designated clinical trials, retrospective data have shown two to three times higher rates of thrombosis in adults treated with TPO-RA than in the population of ITP not administered TPO-RA, and even higher if compared to the general population.

Conclusion

Before initiating treatment with TPO-RA it is prudent to consider the individual's risk profile for thromboembolism. Also, thrombosis can occur following an increase in the dose of Eltrombopag.

Frequent observation of platelet count after start of Eltrombopag is an important aid in thwarting the episodes of thrombosis as they are associated with dramatic oscillation in the number of platelets, despite the platelet number remaining depressed.

Also it is important to individualise the dosing during the treatment using Eltrombopag. Attempts must be made to rectify the alterable risk factors.

If thrombosis is dose-dependent can we start the therapy at a lower dose? Further studies are required to check the beneficence/feasibility of this approach.

References

1. Saleh MN *et al*. Hepatobiliary and Thromboembolic Events during Long-Term EXTENDed Treatment with Eltrombopag in Adult Patients with Chronic Immune Thrombocytopenia (ITP). *Blood* 2016; 128 (22): 1368.
2. Wu C, Zhou X-M, Liu X-D. Eltrombopag-related renal vein thromboembolism in a patient with immune thrombocytopenia: A case report. *World J Clin Cases* 2021; 9 (11): 2611-8.
3. Spencer FA *et al*. Incidence rates, clinical profile, and outcomes of patients with venous thromboembolism. The Worcester VTE study. *J Thromb Thrombolysis* 2009; 28 (4): 401-9.
4. Kawano N *et al*. Portal vein thrombosis during eltrombopag treatment for immune thrombocytopenic purpura in a patient with liver cirrhosis due to hepatitis C viral infection. *J Clin Exp Hematop* 2013; 53 (2): 151-5.
5. Gómez-Almaguer D. Eltrombopag-based combination treatment for immune thrombocytopenia. *Ther Adv Hematol* 2018; 9 (10): 309-17.
6. Gunes H, Kivrak T. Eltrombopag-Induced Thrombosis: A Case with Acute Myocardial Infarction. *Curr Drug Saf* 2016; 11 (2): 174-6.
7. Wong RSM *et al*. Safety and efficacy of long-term treatment of chronic/persistent ITP with eltrombopag: final results of the EXTEND study. *Blood* 2017; 130 (23): 2527-36.
8. Cheng G *et al*. Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study. *Lancet* 2011; 377 (9763): 393-402.
9. Rodeghiero F. Is ITP a thrombophilic disorder? *Am J Hematol* 2016; 91 (1): 39-45.

CASE REPORT

JIACM 2023; 24 (3-4): 224-27

The Bug Story: Melioidosis with Candidaemia

Anusha Uddandam, Nandakrishna B**, Vasudev Acharya***, Cynthia Amrutha Sukumar***

Abstract

Candida infections, particularly Non-Albicans Candida (NAC) infections, are increasing in nosocomial settings. Catheter-related bloodstream infections (CRBSI) are fast becoming a significant risk to hospitalised patients. Of these, Candida parapsilosis is frequently isolated from blood cultures. In the context of increasing antimicrobial resistance, these infections have gained additional importance.

A 22-year-old woman with young-onset, uncontrolled diabetes presented with cough, fever, and dyspnoea for 1.5 months. Initial blood tests revealed anaemia, leukocytosis and significantly elevated HbA1C and CRP levels. Chest X-ray findings confirmed left lobar pneumonia, leading to the initiation of third-generation cephalosporins. She developed rapidly progressive hypoxia requiring intubation. Given her uncontrolled diabetes and pneumonia, a provisional diagnosis of Melioidosis, Staphylococcus and Tuberculosis was considered, and she was initiated on Meropenem. Following confirmation of Melioidosis, additional Trimethoprim/ Sulfamethoxazole was prescribed. Despite improvements in X-ray and ventilation, the patient continued to experience persistent fever spikes. Repeat blood cultures from both central and peripheral lines grew Candida species. Fluconazole was started while awaiting culture sensitivity reports. However, the patient did not respond to line removal and Fluconazole treatment. Her condition worsened, leading to severe hypotension and cardiac arrest within hours. Despite resuscitation efforts, she could not be revived and died. The blood culture sensitivity report revealed Candida parapsilosis with fluconazole resistance.

This case highlights the importance of monitoring critically ill patients for Candidaemia (CRBSI), especially in those with central and peripheral lines. Prompt identification, removal of infected lines, along with appropriate antifungal therapy, may prevent further morbidity and mortality in these patients.

Key words: Catheter-related bloodstream infections, Melioidosis, Candidaemia, Non-Albicans Candida, Candida parapsilosis.

Introduction

Melioidosis is an infectious disease caused by the bacteria *Burkholderia pseudomallei*, which is present in contaminated soil and water, and can be transmitted through direct contact. It is most commonly found in regions of South-eastern Asia and Northern parts of Australia. As the symptoms are similar to that of other tropical diseases, it is very often misdiagnosed or undiagnosed. According to a recently published article, the global annual infection rate could reach 1,65,000 individuals[1]. Along with this prediction, the study also suggests the disease is more prevalent in South Asia, predicting 44% of the total cases to be from there. A serosurveillance study conducted by Vandana *et al*, estimates a seroprevalence of 29%[2]. However, due to the limited awareness of this disease and the constraints of specific microbiology facilities and experienced microbiologists, the specific burden of this disease in India is unknown[3]. Melioidosis is associated with a global mortality of approximately 89,000 deaths per year. This mortality rate is comparable to other significant diseases such as Leptospirosis (50,000 deaths per year) and Dengue infection (9,100 - 12,500 deaths per year)[1].

On the contrary, another infection shows a recent in emergence, which could be attributed to improved identification methods microbiologically. Infections caused by *Candida species*, particularly *Candida albicans*, are responsible for a majority of nosocomial infections. Nevertheless, there has been a rise in infections caused by non-albicans *Candida* (NAC), including *Candida parapsilosis*, which is frequently isolated from blood cultures. The significant rise in Candida infections can be primarily attributed to various factors, such as the AIDS epidemic, a growing elderly population, increased numbers of immunocompromised patients, and the expanded utilisation of indwelling medical devices in hospitals[4]. Among the list of NAC infections, the most commonly seen species are *Candida glabrata*, *Candida parapsilosis*, and *Candida tropicalis*. Of which, *Candida tropicalis* is the most prevalent in India[5]. According to a recent article, the prevalence of *Candida parapsilosis* in India is thought to be approximately 8.36%[6]. Candidaemia can cause up to 46% mortality in immunocompromised patients as well[7]. Hospitalised patients also have increased morbidity and mortality due to Catheter-related bloodstream infections (CRBSI). Prompt identification and removal of infected lines,

****Intern, **Associate Professor, ***Professor, Department of Medicine, Kasturba Medical College, Manipal Academy of Higher Education, Manipal - 576104, Karnataka.***

Corresponding Author: Dr Cynthia Amrutha Sukumar, Associate Professor, Department of Medicine, Kasturba Medical College, Manipal Academy of Higher Education, Manipal - 576 104, Karnataka. Phone: 7259415415, E-mail: cynthiaamrutha@gmail.com.

along with appropriate antifungal therapy, may prevent further morbidity and mortality in critically ill patients.

Case report

A 22-year-old woman with young-onset, uncontrolled diabetes presented to our department with chief complaints of fever, dyspnoea on exertion, cough with expectoration, and left-sided chest pain for six weeks.

The patient was apparently asymptomatic six weeks ago when she developed a cough with a moderate amount of white, mucoid sputum. The cough was associated with left-sided chest pain during coughing bouts. There was no history of postural or diurnal variation in the cough. She also complained of fever during the same time. The fever was intermittent and high-grade and was also associated with chills. It was relieved on taking antipyretics. She also complained of shortness of breath since 6 weeks. This was insidious in onset and progressive in nature (progressing from MMRC Grade II to Grade III over this time).

Our patient did not have complaints of orthopnoea or paroxysmal nocturnal dyspnoea. There were no complaints of night sweats or recent weight loss in the patient.

While the patient was a home-maker hailing from coastal Karnataka, she was a known case of young onset Diabetes Mellitus since 2 years. Though she was taking oral hypoglycaemic agents, she was not compliant with the medications.

On clinical examination, the patient was found to be tachypnoeic and was noted to have hypoxia. She was started on oxygen supplementation. On general examination, she did not have pallor, icterus, cyanosis, clubbing, oedema, or lymphadenopathy. Respiratory examination showed bilaterally normal vesicular breath sounds heard with crepitations in the bilateral axillary areas. The cardiovascular, abdominal, and central nervous system examination were within normal limits. She showed no cerebellar or meningeal signs.

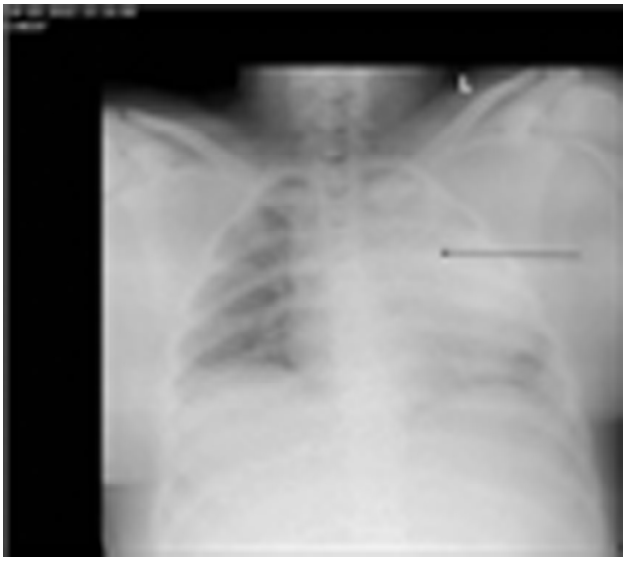


Fig. 1: *Chest X-ray on day 1 showing left upper lobe consolidation suggestive of left upper lobe pneumonia.*

The chest X-ray of the patient was suggestive of left upper lobe pneumonia (Fig. 1). Haematological tests revealed anaemia, increased total leucocyte count as well as increased glycated haemoglobin levels (Table I).

Table I: Haematological tests of the patient.

Haemoglobin	8.9 g/dL
Total leucocyte count	15.700/mm^3
Platelet count	3.27 x 10^3/mm^3
Liver function tests	Normal
Renal function tests	Urea - 18 mg/dL, Creatinine - 0.71 mg/dL, Sodium - 130 meq/L, Potassium - 4.4 meq/L
Glycated haemoglobin (HbA1C)	13.1%
CRP	250.69 mg/L
Procalcitonin	1.375 ng/mL

At this time, both sputum and blood cultures were ordered. She developed rapidly progressive hypoxia requiring intubation, within 24 hours of admission. Given her uncontrolled diabetes and pneumonia, a provisional diagnosis of Melioidosis/Staphylococcus/Tuberculosis was considered, and she was initiated on Meropenem. Blood culture reports showed growth of *Burkholderia pseudomallei* suggestive of Melioidosis. In view of this, the patient was given Co-trimoxazole along with Meropenem.

Despite being treated with Meropenem and Co-trimoxazole, she had persistent fever spikes and required continuous ventilatory support. Although chest X-rays and ventilation showed improvement (Fig. 2a and b).

Since the patient continued to have persistent fever spikes, blood cultures were repeated from both central and peripheral lines. Both of the cultures grew *Candida species* on Day 10, hence Fluconazole was started while awaiting culture sensitivity reports. On day 11, since the patient continued to need mechanical ventilation, tracheostomy was done. Patient continued to have fever spikes and blood cultures were sent again on Day 14 where they grew Gram-negative bacilli. In view of the worsening condition, Gram-negative bacterial sepsis was suspected and hence Tigecycline was added for the patient. After the addition of Tigecycline, the patient had further worsening of sepsis-Acute Kidney Injury with oliguria, hepatitis, and disseminated intravascular coagulation.

Despite removal of the lines along with Fluconazole treatment, the patient showed no improvement. Tragically, the patient's condition deteriorated rapidly within 12 hours, leading to a cardiac arrest that proved fatal, despite resuscitation efforts. The post-mortem blood culture sensitivity results indicated that the *Candida parapsilosis* isolated from her blood was sensitive to Amphotericin B and Caspofungin, while showing resistance to Fluconazole. Nonetheless, due to the timing of the report, it was not possible to implement the treatment change in time to impact the patient's clinical outcome.

Discussion

In this case report, we present the case of a young diabetic patient with disseminated melioidosis who developed candidaemia and subsequently succumbed due to the overwhelming infection. This case highlights the importance of CRBSI, which refers to catheter-related bloodstream infections in critically ill patients, particularly those with diabetes and other co-morbidities. CRBSI is a type of infection that develops when bacteria or fungi enter the bloodstream through an intravenous catheter.

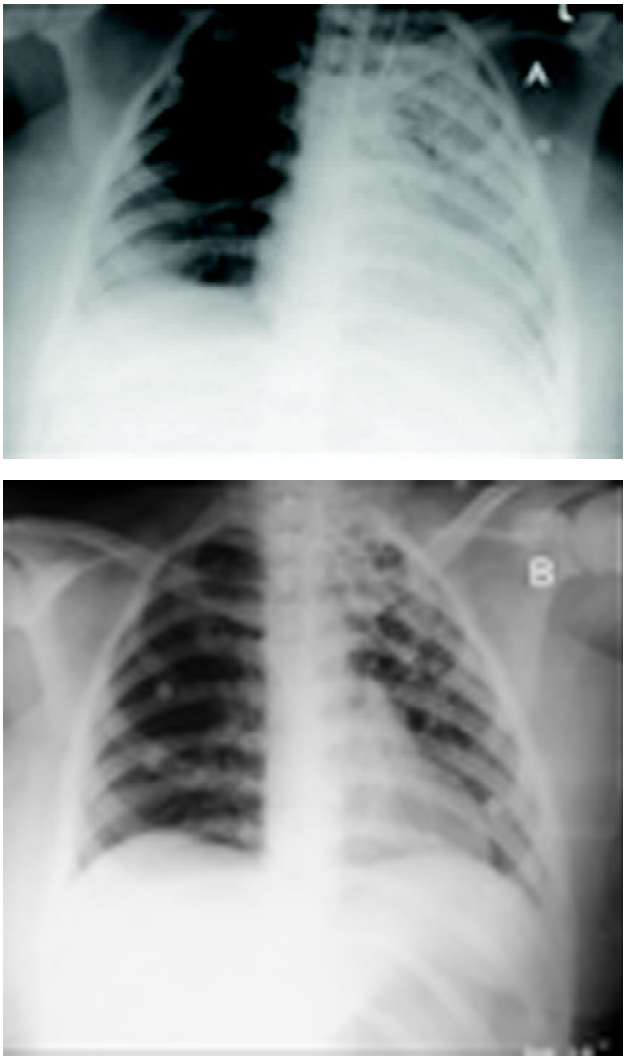


Fig. 2a: *Chest X-ray on day 4.* ***b:*** *Chest X-ray on day 13. The progression of these X-rays shows significant improvement of the patient's initial respiratory condition.*

In present-day medical care, the usage of intravascular catheters is crucial for delivering fluids, blood products, medications, nutritional solutions, as well as monitoring haemodynamic status. However, compared to other medical devices, central venous catheters (CVCs) carry an increased susceptibility to infections associated with medical devices, which can result in notable adverse effects on morbidity and mortality rates. Hospitalised patients are particularly susceptible to bacteraemia and septicaemia, with CVCs being a primary source of these infections. Research has indicated that the majority of catheter-related bloodstream infections (CRBSIs) are linked to CVCs, with CVCs carrying a relative risk for CRBSI that is up to 64 times higher compared to peripheral venous catheters[8].

The incidence rates of CRBSI varies between countries and even from hospital to hospital. In a study conducted by Singh *et al*, the infection rate for intravenous catheter-related bloodstream infections (IV-CRBSI) was determined to be 0.48 per 1,000 device days[9]. Furthermore, a study done at the Johns Hopkins University attributed the mortality rate for CRBSI to be between 12 - 25%[10]. According to a study conducted in our tertiary care centre, by Parameswaran *et al*, the incidence of CRBSI was 8.75 per 1,000 days of catheter use[11]. In a similar study conducted in a teaching hospital in Mumbai, providing specialised care at a tertiary level, the mortality rate in CRBSI was found to be 33.3% cases in patients having central venous catheters compared to the 20% mortality among cases of BSI in catheterised patients not associated with central venous catheters[12].

Candidaemia is a common cause of CRBSI in hospital patients with the most common species being *Candida albicans*. However, Non-Albicans Candida (NAC) have seen a significant increase in incidence rates over the years. *Candida tropicalis* is the most commonly seen species of NAC along with *Candida glabrata* and *Candida parapsilosis*[5]. In India, the overall incidence of candidaemia was observed to be 6.51 cases/1,000 ICU admissions[13]. When diagnosing Candidaemia, it is important to note that *C. parapsilosis* has mixed-morphology culture plates. However, diagnostically, the organism's ability to form pseudohyphae and adhesions is also very important. *Candida parapsilosis* forms adhesions and biofilms on the surface of intravascular devices, such as catheters, and this allows them to cause bloodstream infections via indwelling

catheters and TPN.

The sensitivity of *Candida parapsilosis* to commonly used antifungal agents such as Fluconazole and echinocandins (Example: Caspofungin) is high, making these agents the first-line treatment for candidaemia caused by *Candida parapsilosis*[14]. Fluconazole is commonly used as a first-line drug in the treatment of candidaemia for treating patients without any prior exposure to azoles and in situations where there is no indication of colonisation with a strain that exhibits decreased susceptibility to azoles[15]. Both of these situations were reasons for starting our patient on Fluconazole therapy while still awaiting the blood culture reports. However, when reports became available, the patient was noted to be resistant to Fluconazole. In this case, Caspofungin was planned to treat candidaemia in the patient.

Young onset diabetes and disseminated melioidosis are in itself, responsible for significant mortality[1] in patients. In this case, the patient developed candidaemia, which further complicated her condition and led to overwhelming infection. Candidaemia is a serious and potentially life-threatening complication, particularly in critically ill patients. The addition of candidaemia to the patient's existing condition likely contributed to her poor outcome and eventual death.

It is concerning to note that CRBSI cases are increasing annually[8]. Additionally, the use of central venous catheters, prolonged ICU stay, and underlying diseases such as diabetes mellitus have been associated with CRBSI. Prompt identification and removal of infected lines, along with appropriate antifungal therapy, may prevent further morbidity and mortality in critically ill patients.

Conclusion

CRBSI poses a substantial risk of morbidity and mortality in critically ill patients, with *Candida species* being a common cause. NAC is becoming a more widespread source of infections, especially in patients with central and peripheral lines.

Being aware of the potential risk factors and associations of CRBSI is crucial in the prevention of CRBSI. Regular monitoring of critically ill patients for CRBSI can help to identify and treat infections early, which can prevent further morbidity and mortality.

References

1. Limmathurotsakul, Direk *et al*. Predicted global distribution of *Burkholderia pseudomallei* and burden of melioidosis. *Nature Microbiolo* 2016; 1: 15008.
2. Vandana, Eshwara K *et al*. Seroprevalence of *Burkholderia pseudomallei* among Adults in Coastal Areas in Southwestern India. *PLoS Neglected Tropical Diseases* 2016; 10 (4): e0004610.
3. Global Burden of Melioidosis. Melioidosis.Info, www.melioidosis.info/info.aspx?pageID=104&contentID=1040102. Accessed 9 Apr. 2023.
4. Sónia S *et al*. *Candida glabrata*, *Candida parapsilosis* and *Candida tropicalis*: biology, epidemiology, pathogenicity and antifungal resistance. *FEMS Microbiolo Reviews* 2012; 36 (2): 288-305.
5. Arunaloke C *et al*. Recent experience with fungaemia: change in species distribution and azole resistance. *Scandinavian J Infectious Dis* 2009; 41 (4): 275-84.
6. Verma R *et al*. A systematic review on distribution and antifungal resistance pattern of *Candida species* in the Indian population. *Med Mycolo* 2021; 59 (12): 1145-65.
7. Abelson, Jonathan A *et al*. Frequency of fungaemia in hospitalised paediatric inpatients over 11 years at a tertiary care institution. *Paediatrics* 2005; 116 (1): 61-7.
8. Gahlot R *et al*. Catheter-related bloodstream infections. *International J Critical Illness and Injury Science* 2014; 4 (2): 162-7.
9. Singh S *et al*. Surveillance of device-associated infections at a teaching hospital in rural Gujarat, India. *Ind J Med Microbiolo* 2010; 28 (4): 342-7.
10. Maki Dennis G *et al*. The risk of bloodstream infection in adults with different intravascular devices: a systematic review of 200 published prospective studies. *Mayo Clinic Proceedings* 2006; 81 (9): 1159-71.
11. Parameswaran R *et al*. Intravascular catheter-related infections in an Indian tertiary care hospital. *J Infection Developing Countries* 2011: 5 (6): 452-8.
12. Chopdekar K *et al*. Central venous catheter-related blood stream infection rate in critical care units in a tertiary care, teaching hospital in Mumbai. Indian J Med Microbiolo 2011; 29 (2):169-71.
13. Moni M *et al*. A quality improvement initiative to improve the appropriateness of candidaemia management by the implementation of a comprehensive candidaemia care bundle at a tertiary care hospital in South India: Results of a quasi-experimental study. *Medicine* 2022; 101 (13): e28906.
14. Pappas Peter G *et al*. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clinical Infectious Diseases: An Official Publication of The Infectious Diseases Society of America* 2016; 62 (4): e1-50.
15. Bassetti M *et al*. The current treatment landscape: candidiasis. *The J Antimicrobial Chemotherapy* 2016; 71 (suppl 2): ii13-ii22.

CASE REPORT

JIACM 2023; 24 (3-4): 228-33

Acute Pancreatitis in Systemic Lupus Erythematosus: Rare Presentation of a not so Common Disease

Mahak Golani, Sanjay Pandit**, Vaishali Kathuria***, Iftekhar Ahmad*, Vineeta V Batra****, Kanishk Gupta******

Abstract

Introduction: Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder characterised by formation of autoantibodies, complement activation and altered cellular immunity, culminating in end organ damage. Acute pancreatitis in SLE is rare (0.4 - 1.1%) but carries high mortality (78.5%) if severe[1].

Case report: 16-year-old girl presented with Raynaud's phenomenon, skin lesions and polyarthralgia for 6 months, anasarca for 2 months and epigastric pain for one day. Investigations showed thrombocytopenia, raised serum lipase, low SAAG ascites, urine protein - 2.81 g/24 hours ANA+, anti-dsDNA+, pANCA+, anticardiolipin antibody and lupus anticoagulant+. CECT showed features of acute pancreatitis, hypoperfusion complex and shock bowel.

Skin biopsy showed Discoid Lupus Erythematosus (DLE), kidney biopsy revealed class II lupus nephritis. The patient was managed with pulse methylprednisolone and IVIg. She developed acute pulmonary thromboembolism after 2 weeks and was started on anticoagulants. In view of SLE/Lupus Nephritis/ Acute pancreatitis/Pulmonary thromboembolism/APS/? vasculitis, rituximab was started, to which she responded and is doing well.

Conclusion: Acute pancreatitis in SLE is a marker of disease activity. Autoimmune cause should be ruled-out in a young girl with pancreatitis. Patients with high SLEDAI score not showing adequate response with conventional treatment may be given a trial of B cell depletor therapy – like rituximab, especially in those with pANCA positivity and vasculitis.

Keywords: SLE, pancreatitis, rituximab.

Introduction

Systemic Lupus Erythematosus (SLE) is a multisystem autoimmune illness that classically affects women of childbearing age; is characterised by autoantibodies formation and deposition into tissues and complement activation culminating in end organ damage[1]. Although gastrointestinal manifestations are common and are seen in about 50% patients[2], pancreatic involvement is quite rare with an annual incidence of only 0.4 - 1.1%[3,4]. Acute pancreatitis is commonly seen in patients with high SLEDAI score and is associated with involvement of many organs and systems (liver, kidney, haematological), serositis, frequent fever, high CRP and anti-La antibodies[3]. Acute pancreatitis in SLE is responsible for morbidity as well as substantial mortality especially if severe (78.5% in severe vs 27.5% in all SLE related acute pancreatitis[3,5]. Various non-immune causes like mechanical obstruction, infection, toxic-metabolic and trauma need to be ruled out before attributing SLE as a cause of acute pancreatitis[3]. Pathogenesis of acute pancreatitis in SLE is multifactorial – characterised by autoantibody production, immune complex deposition, abnormal cellular immunity, complement activation, drug toxicity, vascular damage due to vascultis, intimal thickening and occlusion of arterioles and arteries by thrombosis[2,3].

This case report highlights pancreatitis as a presentation of SLE in a young girl who also had involvement of skin, joints, kidney, and Raynaud's phenomenon and showed remarkable improvement with steroids and rituximab. It emphasizes the fact that in a young patient without any obvious cause of pancreatitis, autoimmune cause should always be worked up for.

Case report

This 16-year-old girl, a resident of Delhi, had polyarthralgia since 6 months, involving PIP, MCP joints, but sparing DIP joints. There was associated history of pandigital Raynaud's phenomenon, on exposure to cold water, of similar duration. She developed anasarca with passage of frothy urine for 2 months. There was history of erythematous, non-pruritic, palpable rash on her left leg 1 month before

**Post-Graduate Resident, **Professor, Department of General Medicine, Maulana Azad Medical College, New Delhi - 110 002.*
****DNB Resident, Department of Nephrology, Medanta Medicity, Gurugram, Haryana.*
*****Director Professor, Department of Pathology, GIPMER and GB Pant Hospital, New Delhi - 110 002.*
******Consultant Histopathologist, Department of Pathology, Fortis Hospital, Vasant Kunj, New Delhi - 110 070.*
Corresponding Author: Dr Sanjay Pandit, Professor, Department of Medicine, Room No. 126, BL Taneja Block, Maulana Azad Medical College, Bahadur Shah Zafar Marg, New Delhi - 110 002. Phone: 9311656918, E-mail: spandit01@gmail.com.

presentation which had resolved completely over 1 week. She was having 6 - 7 episodes of watery loose stools since 1 day, associated with epigastric pain which relieved on stooping forward. This was also associated with non-bilious, non-projectile, non-blood tinged vomiting and abdominal distension. For this, she presented to the medicine emergency. She had 1 episode of fever on the day of presentation, documented to be 99.8° F. It was noticed by the patient that her urine output had decreased to approximately 200 - 300 mL in the last 24 hours. She had received her 1st dose of Covaxin 2 months before presentation. There was no history of haematuria, burning micturition, pain abdomen, jaundice, chest pain, cough or shortness of breath.

On presentation, her BP was 76/50 mmHg, PR was 110/min, all peripheral pulses were palpable and her SpO_2 was 97% on room air. There was facial and periorbital puffiness to the extent that the patient was unable to open her eyes. She was found to have signs of dehydration. On systemic examination, air entry was decreased and dull note on percussion was present in bilateral lower zones in chest. On abdominal examination, abdomen was distended with shifting dullness, epigastric tenderness, and absent bowel sounds. Rest of the clinical examination was found to be normal. The initial investigations are shown in Table I and Table II.

Table I: Investigations.

Date	17 days before presentation	6 days before presentation	On day of admission
Hb (g/dL)	10.1	9.9	11.6
TLC (cells/µL)	6530	5700	7000
DLC (Polymorphs%/ lymphocytes%/monocytes%/ eosinophils%)	71/27/1/1	61/31	59/37
PLC (cells/µL)	97k	97k	41,000
Chol (mg/dL)	115	110	97
TG (mg/dL)	247	242	274
LDL (mg/dL)	28.6	42	30
HDL (mg/dL)	37	33	28
Urea (mg/dL)	45	33	78
Creatinine (mg/dL)	1.0	0.9	1.2
TP/SA (g/dL)	7.0/3.2	7.2/3.4	6.2/2.9
Urine alb	2+	4+	
Urine RBC	Nil	3 - 5/hpf	
RBS (mg/dL)			110
CXR	WNL		
2D echo	WNL		
HIV	Non-reactive		
HBsAg	Non-reactive		
Anti-HCV	Non-reactive		
Amylase (U/L)			128
Lipase (U/L)			1507
LDH (U/L)			313
UA (mg/dL)			13.6

Table II: Investigations.

Date	On day of admission
ICT/DCT	Negative
P/S	Microcytic normochromic anaemia with thrombocytopenia, no toxic granules
Dengue serology	Negative
PSMP	Negative
Procalcitonin (ng/mL)	0.397
Blood culture	No growth
Urine examination	Inactive sediment with moderate proteinuria
Protein creatinine spot ratio	0.40
Ascitic fluid SAAG	0.85 (low SAAG)
Ascitic fluid protein (g/dL)	4.79 (high protein)
Ascitic fluid TLC (calls/mm^3)	10
Ascitic fluid DLC	All mononuclear
Renal artery Doppler	Normal
CECT chest and abdomen (Fig. 1)	Bilateral pleural effusion (R > L) with moderate ascites, reduced calibre of IVC and aorta with bulky pancreas and peripancreatic and perinephric fat stranding s/o CT hypoperfusion complex with shock bowel.

Patient was initially managed conservatively for pancreatitis by Ryle's tube decompression and Central Venous Pressure guided fluids. Further investigations are shown in Table III and Table IV. Since the autoimmune profile was suggestive of SLE with activity, and in view of autoimmune pancreatitis and lupus nephritis, she was started on methylprednisolone pulse therapy (1 g/day intravenous) for 5 days, followed by tablet prednisone 1 mg/kg/day.

On day 4, she developed 6 - 8 non-blanching, erythematous, palpable, non-pruritic, circular skin lesions on her leg and back, 0.5 - 0.8 cm in diameter. These lesions were biopsied, the findings of which are given in Table IV. Patient improved symptomatically and bowel sounds returned, hence she was allowed oral fluids. Her BP and PR stabilised, urine output improved and on investigations,

acute kidney injury settled. On day 8, triglyceride (TG) levels increased dramatically (780 mg/dL) despite statin therapy and platelet counts kept on dropping requiring multiple transfusions. In view of high TG levels, patient was started on D5 with insulin infusion 0.1 units/kg/hr on day 8 to maintain blood sugar levels between 150 - 200 with 12 hourly triglyceride monitoring. Triglycerides dropped to 337 mg/dL in 24 hours and insulin and D5 infusion were stopped. Patient was also given IVIg on day 8 for persistently low platelet counts for 2 days, suspecting ITP, but there was no improvement.

Table III: Further investigations.

24 hr urinary protein	0.81 g/day
ANA	homogeneous (+), speckled (1 to 2+), 1:80 dilution
AntidsDNA	1+
Nucleosomes	3+
Histones	1+
RPP/PO	4+
Anti-dsDNA by ELISA	> 400 IU/mL
P-anca	28 U/mL (positive)
C-anca	3 U/mL (negative)

Table IV: Skin biopsy and kidney biopsy.

Skin biopsy	Focal epidermal atrophy and spongiosis. Dermis showed mild chronic inflammatory infiltrate perivascular and periadnexal location with dermal fibrosis with paucity of skin adnexa. Direct Immunofluorescence for IgA and IgM were negative. (suggestive of Discoid Lupus Erythematosus).
Kidney biopsy (Fig. 2 and Fig. 3)	Enlarged glomeruli with mild increase in mesangial matrix and cellularity with no evidence of proliferative activity in the form of endocapillary proliferation or crescent formation. There was no basement membrane thickening or spike formation on silver methenamine stain. IF showed coarse granular deposits of IgG, C3, IgM, IgA, C1q, kappa, lambda in predominantly the mesangium and focally along the peripheral capillary walls. The extra glomerular immune deposits of IgG, C3, IgA, IgM , C1q, Kappa, Lambda are also seen along the blood vessels and peritubular capillaries. Findings s/o mesangial lupus nephritis class II.

On day 10 of illness, patient developed sudden onset shortness of breath without cough and expectoration. It was not associated with fever. On respiratory examination, bilateral normal vesicular breath sounds were present. ECG showed sinus tachycardia. D- dimer was raised (19,000 ng/mL). CXR showed bilateral lower lobe heterogeneous opacities. CECT chest with CTPA showed multiple thin linear concentric filling defects seen in bilateral lower lobe segmental arteries and their branches circumferentially surrounded by contrast. Pericardial effusion and bilateral pleural effusion with diffuse ground glass opacities and

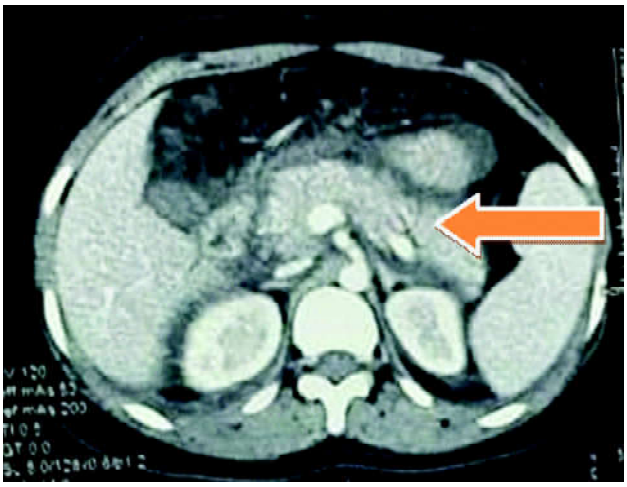


Fig. 1: The image shows CECT abdomen of the patient demonstrating bulky pancreas, predominantly the tail with peripancreatic fluid and fat stranding suggestive of acute pancreatitis.

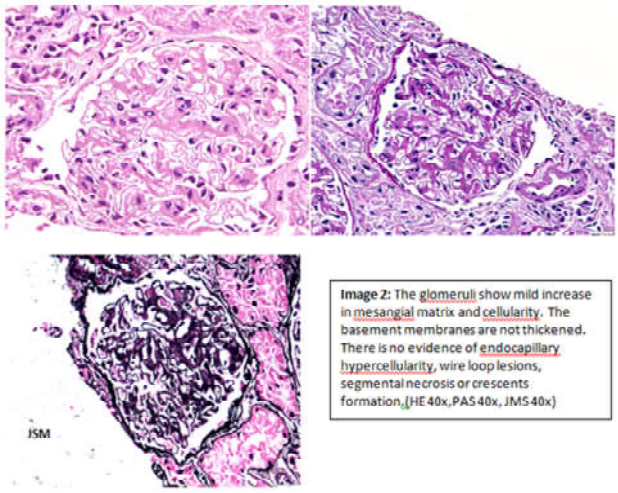


***Fig. 2:** The glomeruli show mild increase in mesangial matrix and cellularity. The basement membranes are not thickened. There is no evidence of endocapillary hypercellularity, wire loop lesions, segmental necrosis or crescents formation. (HE 40X, PAS40X, JMS 40X).*

wedge-shaped area of consolidation in bilateral lower lobe were also seen suggestive of acute pulmonary thromboembolism with pulmonary infarction. (Fig. 4 and Fig. 5) 2D echo showed mild TR/ moderate PAH (RVSP - 50+ RAP)/normal LVSF. Patient was started on LMWH (Enoxaparin) subcutaneous BD injection with T. warfarin with INR monitoring. T. aspirin 75 mg OD was started. Investigations during hospital stay are shown in Table V.

Antiphospholipid antibody profile showed normal beta 2 glycoprotein (4.97 SGU) and borderline raised cardiolipin antibody (18.90 GPL) and lupus anticoagulant (54.70 seconds, control - 38.20 seconds. CECT abdomen with angiography done on day 14 revealed bulky body of

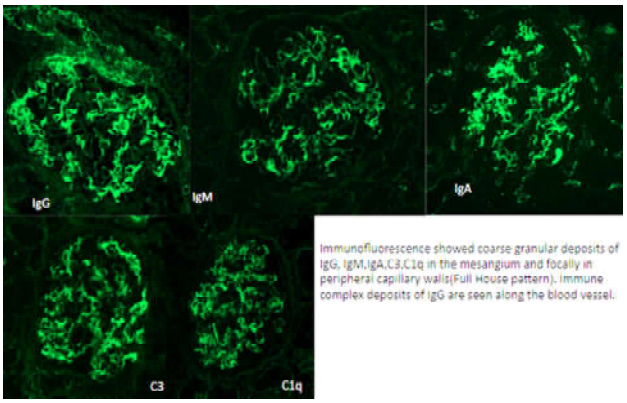


Fig. 3: *Kidney biopsy immunofluorescence. Immunofluorescence showed coarse granular deposits of IgG, IgM, IgA, C3, C1q in the mesangium and focally in peripheral capillary walls (full house pattern). Immune complex deposits of IgG are seen along the blood vessel.*

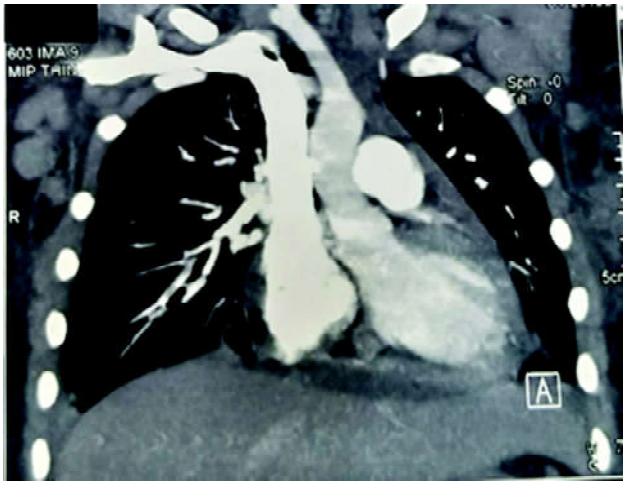


Fig. 4: *The image shows multiple thin linear concentric filling defects in bilateral lower lobe segmental arteries and their branches s/o thrombi circumferentially surrounded by contrast.*

pancreas with minimal ascites and normal angiography.

A diagnosis of antiphospholipid syndrome with APS with secondary ITP with class II lupus nephritis with acute pancreatitis (? SLE induced ?? secondary to pANCA vaculitis) with DLE with anal fissure with pulmonary thromboembolism was made.

In view of persistent thrombocytopenia despite Ivlg and suspecting vasculitis leading to pulmonary embolism, she was started on rituximab and mycophenolate mofetil after ruling-out infections (Mantoux, HBsAg, Anti HCV and HIV were negative) and premedication with anthelmintics, on day 14. Swelling started resolving on day 16, and completely resolved on day 20. The patient developed severe neutropenia during follow-up, hence MMF had to be stopped and patient was kept on maintenance with low dose steroids (tapered over 6 months to 5 mg/day) and rituximab 6 monthly

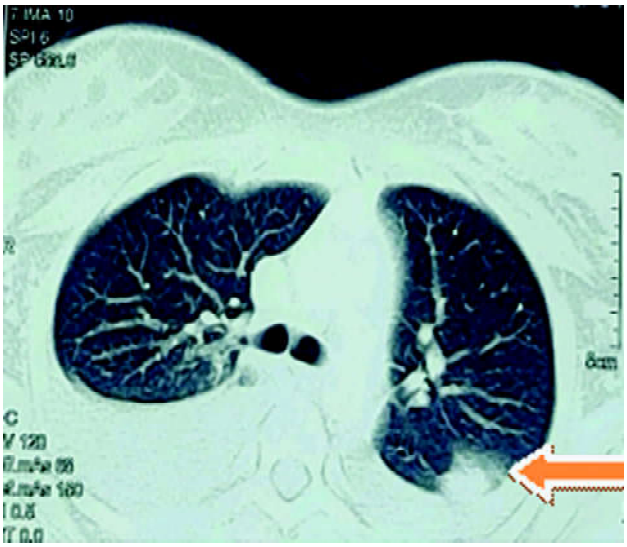


Fig. 5: *This image shows diffuse ground glass opacities in bilateral lung parenchyma with wedge-shaped areas of consolidaton in superior segment of left lower lobe and basal segments of bilateral lower lobes.*

dosing. She has since then been following up in OPD and is currently doing well with no disease activity (as monitored clinically, by anti-dsDNA levels and 24-hour urinary proteins).

Table V: Investigations during hospital stay.

Date	Day 5 of admission	Day 8 of admission	Day 10 of admission	Day 15 of admission	Day 20 of admission
Hb (g/dL)	9.3	10.3	9.2	9.8	9.2
TLC (cells/µL)	5,340	6,410	7,800	5,900	5,420
DLC (Polymorphs%/ lymphocytes%)	64/34	78/17	70/21	72/22	80/16
PLC (cells/µL)	51,000	10,000	18,000	22,000	82,000
TG (mg/dL)	323	780	337	288	156
Urea (mg/dL)	96	77	54	43	23
Creatinine (mg/dL)	1.3	0.9	0.8	0.9	0.6
TP/SA (g/dL)	6.1/2.5	6.7/2.8	7.0/3.1	7.0/3.0	7.2/3.1
Urine alb	2+	3+	2+	1+	Trace
Urine RBC	8/hpf	6 - 8/hpf	8 - 10/hpf	4 - 5/hpf	Nil
Amylase (U/L)	109	96	82	78	74
Lipase (U/L)	331	230	182	124	108
D-dimer (ng/dL)	892	2,084	19,000	10,337	2,731

Discussion

Acute Pancreatitis in SLE not only masquerades as gastroenteritis[3], but can also have a subclinical presentation in high proportion of cases[6]. So there are chances of misdiagnosis (as high as 88.6%), delay in diagnosis and improper treatment which may contribute to unfavorable

prognosis, even life threatening events[3,6]. In this case, the patient presented with pain abdomen, loose motion, and hypotension. Keeping a high index of suspicion, acute pancreatitis was suspected and investigated. It is also true that acute pancreatitis is more commonly seen with high SLEDAI score, more organ system involvement, high frequency of fever, liver involvement, haematological disorder, serositis, elevated CRP, positive anti-La[3]. Also, paediatric-onset acute pancreatitis is generally more severe than adult-onset[3]. Richer *et al*, found that pancreatitis in paediatric-onset lupus developed severe acute pancreatitis in 57% patients and mortality rate of 45%[7]. The index case was a case of SLE with high SLEDAI (SLE disease activity index) score of 26, multi-organ involvement in the form of lupus nephritis and pulmonary thromboembolism, haematological involvement, serositis.

After ruling-out other causes of acute pancreatitis – like trauma, obstruction, infection (sterile urine and blood culture, normal procalcitonin), hypertrigiceridaemia (only mildly raised at beginning), toxic exposure to alcohol, steroid, azathioprine, and considering high SLE disease activity index, underlying autoimmune condition was attributed as the cause of acute pancreatitis[3]. Although the patient had hypertriglyceridaemia, it could not be established as the cause of hypertriglyceridaemia as on presentation, the triglyceride levels were only mildly raised (< 500 mg/dL) when pancreatitis symptoms had started and it never reached >1,000 mg/dL, which is a strong risk factor for pancreatitis. According to a study by Scherer *et al*, the risk of pancreatitis was 5% in patients with triglyceride levels >1,000 mg/dL and 10 - 20% in levels >2,000 mg/dl[8].

Steroid treatment for autoimmune pancreatitis was considered controversial because of fear of steroid-induced pancreatitis, however, this concern is regarded as minimal and immunosuppressive effect of steroid can significantly improve prognosis and is recommended for autoimmune pancreatitis[9].

The index patient had incomplete improvement of disease including pancreatitis (CECT abdomen showed bulky pancreas) despite pulse steroids, so immunosuppressants were given for adequate response. Azathioprine itself can cause pancreatitis so it was not chosen. Cyclophosphamide has issues of infertility, teratogenesis and carcinogenesis. B cell depleter (Rituximab and Belimumab) were good choices in view of accompanying vasculitis (suspected because of associated pulmonary thromboembolism and pulmonary infarct and Raynaud's phenomenon) and positive pANCA. Rituximab (chimeric monoclonal antibody against CD - 20 cells) has been beneficial in RA and cANCA associated vasculitides[10]. Belimumab is approved for use in SLE with moderate disease activity but Rituximab use in SLE is restricted to off label as found to be beneficial only in particular subset of patient who are severe aggressive phenotype and greatly based on B cell driven pathogenesis[1] as shown in EXPLORER[11] and LUNAR trial[12]. Rituximab was preferred because of its in-hospital availability and better adverse event profile. The patient showed remarkable improvement when rituximab was given in combination with basal steroids.

This case helps conclude that autoimmune diseases – like SLE can affect almost every organ of the body and that wark-up for autoimmune diseases should be a routine in case of acute pancreatitis especially in a young girl where other non-autoimmune causes have been ruled-out.

A similar case was reported in Peru by Rodriguez in which a 21-year-old lady, a known case of SLE and lupus nephritis on steroids and pulse cyclophosphamide presented with acute pancreatitis. In this case also, SLE was attributed as the cause of pancreatitis after ruling-out other causes, and as the patient had received the last pulse dose of cyclophosphamide 6 months ago and she high anti-dsDNA values and low C3 and C4 suggesting disease activity of SLE. This patient also did not respond to conservative management – like our patient, but responded well to pulse methylprednisolone[13].

Jia *et al* reported a case in which a 23-year-old lady presented with acute pancreatitis which worsened despite conservative management and the patient was eventually diagnosed with SLE with class III lupus nephritis with mesenteric vasculitis with high anti-ds DNA levels and low C3 and C4 levels. This patient was treated with methylprednisolone, cyclophosphamide, levofloxacin, metronidazole, bactrim, and mesna; and the patient improved[14].

Conclusion

Acute pancreatitis in SLE is a marker of disease activity. Autoimmune causes should be ruled-out in a young girl with pancreatitis. Patients with high SLEDAI score not showing adequate response with conventional treatment may be given a trial of B cell depletor therapy – like rituximab – especially in those with pANCA positivity and vasculitis.

Patient Consent: Informed consent for the publication of this case report was obtained from the patient's father.

References

1. Wise LM, Stohl W. Belimumab and Rituximab in Systemic Lupus Erythematosus: A Tale of Two B Cell-Targeting Agents. *Front Med*

(Lausanne) 2020; 7: 303.

2. Jia Y, Ortiz A, Mccallum R *et al*. Acute pancreatitis as the initial presentation of systematic lupus erythematosus. *Case Rep Gastrointest Med* 2014; 2014: 571493.
3. Yang Y, Ye Y, Liang L *et al*. Systemic-lupus-erythematosus-related acute pancreatitis: a cohort from South China. *Clin Dev Immunol* 2012; 2012: 568564.
4. Xu D, Yang H, Lai CC *et al*. Clinical analysis of systemic lupus erythematosus with gastrointestinal manifestations. *Lupus* 2010; 19 (7): 866-9.
5. Wang CH, Yao TC, Huang YL *et al*. Acute pancreatitis in paediatric and adult-onset systemic lupus erythematosus: a comparison and review of the literature. *Lupus* 2011; 20 (5): 443-52.
6. Medeiros MM, Fernandes GH, Pinto NS. Clinical and subclinical pancreatitis in a cohort of patients diagnosed with systemic lupus erythematosus. *Clin Exp Rheumatol* 2011; 29 (5): 776-82.
7. Richer O, Ulinski T, Lemelle I *et al*. French Pediatric-Onset SLE Study Group. Abdominal manifestations in childhood-onset systemic lupus erythematosus. *Ann Rheum Dis* 2007; 66 (2): 174-8.
8. Scherer J, Singh VP, Pitchumoni CS. Issues in hyper-triglyceridaemic pancreatitis: an update. *J Clin Gastroenterol* 2014; 48 (3): 195-203.
9. Breuer GS, Baer A, Dahan D. Lupus-associated pancreatitis. *Autoimmun Rev* 2006; 5 (5): 314-8.
10. Stone JH, Merkel PA, Spiera R *et al*. RAVE-ITN Research Group. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 2010; 363 (3): 221-32.
11. Merrill JT, Neuwelt CM, Wallace DJ *et al*. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomised, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. *Arthritis Rheum* 2010; 62 (1): 222-33.
12. Rovin BH, Furie R, Latinis K *et al*. LUNAR Investigator Group. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. *Arthritis Rheum* 2012; 64 (4): 1215-26.
13. Rodriguez EA, Sussman DA, Rodriguez VR. Systemic lupus erythematosus pancreatitis: an uncommon presentation of a common disease. *Am J Case Rep* 2014; 15: 501-3.
14. Jia Y, Ortiz A, Mccallum R *et al*. Acute pancreatitis as the initial presentation of systematic lupus erythematosus. *Case Rep Gastrointest Med* 2014; 2014: 571493.

CASE REPORT

JIACM 2023; 24 (3-4): 234-38

Thymoma associated Myasthenia Gravis with Polycythaemia

Mukesh Kumar Sarna, Nipun Goel**, Ravi Godra**, Nasreen Bano**, Abhishek Sanadhya**, Rahul**, Manish Raj Pahadia***, Pallaavi Goel*****

Abstract

A persistent post-synaptic autoimmune condition of the neuromuscular junction is known as myasthenia gravis. The skeletal muscles become feeble as a result of the autoantibodies destroying nerve-muscle connection. The goal of this case report is to emphasize the value of meticulous history taking, examination, investigations, anticipating difficulties, and taking prompt corrective action.

We discuss the case of a 38-year-old man who complained of drooping eyelids and generalised fatigue. Myasthenia gravis was initially identified in this patient; afterwards, thymoma and polycythaemia were identified. He had a very long, uncertain course in the hospital, but a multidisciplinary strategy was used to successfully manage him.

Key words: Secondary polycythaemia, myasthenic crisis, myasthenia gravis, thymoma.

Introduction

A persistent post-synaptic autoimmune condition of the neuromuscular junction is known as myasthenia gravis. Skeletal muscles become feeble as a result of the autoantibodies' destruction of nerve-to-muscle transmission[1]. It affects the body's voluntary muscles, particularly those in-charge of the limbs, mouth, throat, and eyes. It can happen to anyone at any age, but young women (between 20 and 30) and older males are more likely to experience it. Although the disease is usually curable and has an unknown aetiology, it can cause considerable morbidity and even death. With prompt disease diagnosis and effective treatment, this may typically be avoided. Thymoma, a rare tumour of the thymus gland, is seen in 10 - 15% of instances with myasthenia, and 50% of these tumours are cortical in nature[2]. Red blood cell synthesis is very high in polycythaemia. Rarely are thymoma and myasthenia gravis linked to it.

Case report

A 38-year-old man, presented with complaints of generalised fatigue for 15 days, difficulty in holding his neck, nasal twang of voice, drooping of both eyelids, double vision, difficulty in swallowing and chewing since 4 - 5 days, and difficulty in breathing since 2 days. This fatigue used to gradually worsen as the day progressed, maximum during evening and night hours, relieved after rest and sleep, it mainly involved neck muscles, hands, and legs; he was unable to lift his head up on his own and would use his hands to hold his neck and had difficulty in walking and lifting his arms above his head. There was drooping of both his eyelids which was gradually progressive, it was also more in the evening hours and involved the right eye more than the left. He had double vision on and off, more apparent on gazing towards the left side, and used to resolve automatically on forward gaze or on gazing towards the right. It was so prominent that he needed to turn his neck to look to the left side. There was difficulty in swallowing and chewing for both solids and liquids, which worsened along the day, hence he was unable to consume dinner, but was relatively better in the morning at breakfast. Difficulty in breathing progressively increased and was evident in supine position, relieved on leaning forward.

There was no history of fever, trauma to the head, seizure-like activity, snake bite, or any similar complaints. On examination, he had raised blood pressure, plethora, and bilateral ptosis. He was conscious, and oriented to time, place, and person, with a mini-mental score of 30/30. There was no difficulty in speech; only a nasal twang was present. There was involvement of bilateral 3rd cranial nerves, bilateral 5th cranial nerves, left 6th cranial nerve, bilateral 9th cranial nerves, and bilateral 11th cranial nerves. Fundus was normal and the bilateral pupils were reactive to light. The patient had hypotonia and power was 4/5 at all joints in all movements in both limbs; power used to vary after repeated examination. No cerebellar signs or involuntary movements were noted. All deep tendon reflexes were slightly diminished on both sides, and superficial reflexes were normal. The sensory system was intact. Gait was unstable.

**Professor and Unit Head, **Resident, ***Professor, ****Senior Resident, Department of Medicine, Mahatma Gandhi Medical College and Hospital, (MGUMST), Jaipur - 302 022, Rajasthan.*

Corresponding Author: Dr Abhishek Sanadhya, Resident, Department of Medicine, Mahatma Gandhi Medical College and Hospital, (MGUMST), Jaipur - 302 022, Rajasthan. Phone: 9461189080, E-mail: abhishek.sanadhya27@gmail.com.

Differential diagnosis

The first differential was myasthenia gravis since this patient had a classical history of easy fatiguability and weakness which was relieved on rest and used to worsen as the day progressed. Guillain Barrë Syndrome (GBS) was the second differential but the patient had no ascending paralysis and no history of fever. Miller- Fischer Syndrome (MFS) is a variant of GBS, that has a classical triad of areflexia, ataxia, and ophthalmoplegia which was absent in this patient. Lambert-Eaton Myasthenic Syndrome (LEMS) is a presynaptic neuromuscular junction disorder in which the symptoms classically worsen on rest and are improved after repeated work – not present in this patient. Multiple Sclerosis can be another differential, but it usually has a relapsing and remitting pattern, not in this patient. Amyotrophic lateral sclerosis (ALS) usually does not have an acute presentation like this case. There was no sensory deficit and no involvement of the spine; this ruled-out acute myelopathy. No history of consumption of canned and preserved foods ruled-out botulism, and no history of any obvious snake bite ruled-out snake envenomation, and no history of any obvious insect bite ruled-out tick paralysis.

Management

Since our patient had myasthenia-like symptoms, to make a primary diagnosis we did a basic nerve conduction velocity (NCV) and repeated nerve stimulation (RNS) study. NCV was normal; this ruled-out MFS and GBS. Whereas RNS was suggestive of decremental response that pointed to myasthenia gravis and also ruled-out LEMS. To confirm this diagnosis, we got the acetylcholine receptor antibody (AchR) and muscle-specific tyrosine kinase antibody (MUSK) titres. Till the results were awaited, a neostigmine test was done. Atropine 0.6 mg was administered introvenously, followed by Neostigmine 1 gm given slow IV, and the patient's ptosis, muscle weakness, and single breath count were assessed before and after. An improvement in ptosis, muscle weakness, and single breath count would be considered a positive test, but in our patient, the test was negative. The edrophonium test is the classical test used, but due to its unavailability, this could not be done. Since the diagnosis was still not confirmed and reports were awaited, a pyridostigmine challenge was given, the patient improved after the first dose of pyridostigmine and it was continued in a dose of 60 mg thrice a day. AchR Antibody levels later reported were 6.83 nmol/L, (>0.5 nmol/L is considered a positive titre value). MUSK antibody levels were 0.13 U/mL, (>0.4 is considered a positive titre value). A routine chest X-ray (Fig. 1) was done which suggested a mass-like lesion with mediastinal widening.

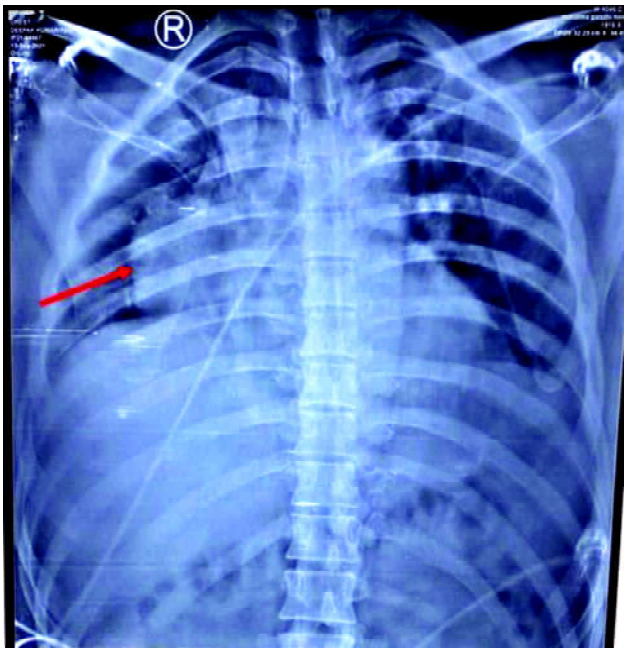


Fig. 1: *Mass lesion with mediastinal widening on chest X-ray.*

Contrast-enhanced chest computed tomography scan (CECT Chest) was done for further workup; it revealed a predominantly cystic mass lesion measuring approximately 7.5 cm x 10.6 cm x 13.7 cm in the anterior mediastinum on the right side at the level of the aortic arch, extending

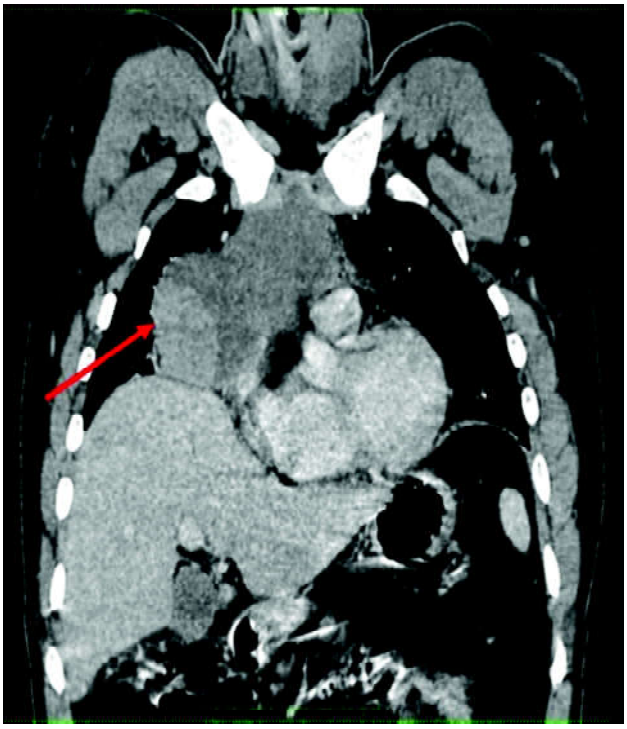


Fig. 2: *Thymoma on CECT chest coronal view.*

inferiorly to the level of the right ventricle, possibly of thymic origin (Fig. *2*, Fig. *3*). It was seen closely abutting the surrounding structures; however, no obvious infiltration or invasion was seen. According to MASAOKA staging, the diagnosis of stage 1 thymoma was made.

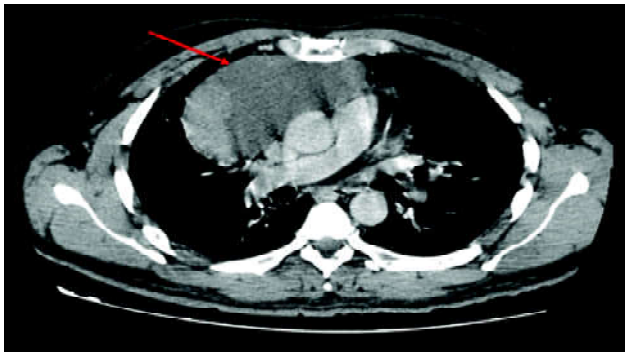


Fig. 3: *Thymoma on CECT chest axial view.*

CECT chest was also suggestive of a mass measuring 2 cm x 3 cm in the left adrenal gland; a possibility of Incidentaloma was kept. Triple phase CECT abdomen was done for further workup which suggested a well-defined hypodense cystic lesion with peripheral calcific foci in the left adrenal gland showing no significant enhancement – possibility of benign adrenal lesion – most likely adenoma (Fig. 4).

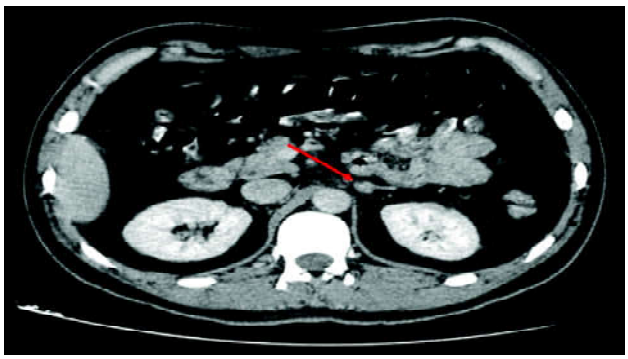


Fig. 4: *Adrenal incidentaloma on CECT abdomen axial view.*

Alfa-fetoprotein (AFP) and Beta-human chorionic gonadotrophin (beta-HCG) levels were done to rule-out a germ cell tumour; both were in the normal range. An ultrasound-guided biopsy was taken to know the nature of this mass. It was suggestive of a small round cell tumour, which was possibly lymphoproliferative or thymic in origin. Immunohistochemistry extended panel was done for further confirmation that was suggestive of a thymic neoplasm of WHO type B1, (which is a cortical thymoma) (Fig. 5), and ruled-out a lymphoproliferative disorder. Tumour, node, metastasis staging of this tumour was T1a N0 M0. A whole-body positron emission tomography scan was done to rule-out any other primary tumour in the body.

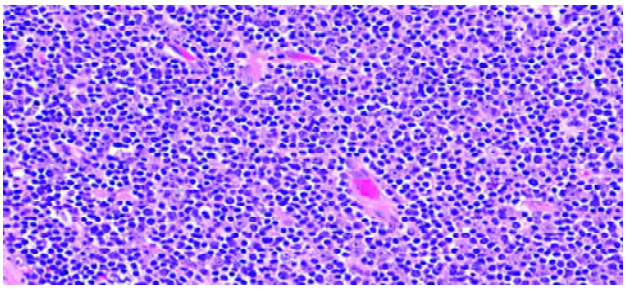


Fig. 5: *Type B1 thymoma on histopathology slide.*

Constant high levels of haemoglobin and haematocrit with a plethora was suggestive of polycythaemia. This is rarely seen to be associated with thymoma. 1-unit phlebotomy was done. Erythropoietin levels were very low, 1.03 mIU/mL. Janus Kinase 2 (JAK 2) mutation was negative. During this workup, the patient had complaints of difficulty breathing lying down flat. The patient was on antihypertensives, pyridostigmine, oxygen support and other supportive treatment. His difficulty in breathing gradually deteriorated and he had to be put on mechanical ventilatory support. This was diagnosed as a myasthenic crisis. Intravenous immunoglobulin (IVIG) therapy was started. A 2g/kg dose was given, and a total of 140 grams of IVIG was administered over 5 days. IVIG therapy did not show much improvement in the patient's condition. The patient was on continuous ventilator support and could not be weaned off the ventilator, hence tracheostomy was done. Thymectomy was planned and performed. After thymectomy too there was no significant improvement in the patient's breathing and he required ventilator support. Therefore, the decision for plasmapheresis was taken and 5 cycles of plasmapheresis were done every alternate day. Throughout this course, pyridostigmine was continued on a dose of 60 mg thrice daily, given up to a maximum dose of 300 mg/day.

Discussion

The most prevalent autoimmune condition that affects the neuromuscular junction is myasthenia gravis[1]. The symptoms might be simply ocular or quite severe, affecting the muscles of the limbs, bulbar region, and respiratory system. The age of onset ranges from childhood to maturity, with younger women and older men experiencing the highest incidence. Our patient a 38-year-old had an earlier onset. It is a common illustration of an antibody-mediated autoimmune illness. IgG autoantibodies react with intracellular or extracellular antigens in a class II hypersensitivity reaction that damages end-organs. As was the case with our patient, autoantibodies against acetylcholine receptors (AChRs) are present in the majority of myasthenia gravis patients[3]. Muscle-specific kinase

(MuSK)-directed antibodies are present in a small number of cases, although they were negative in this patient[4]. Thymus hyperplasia and thymoma are specifically associated with myasthenia gravis. An apparent thymoma-like growth on a chest X-ray in this patient raised the possibility of myasthenia gravis. Although our patient was a reasonably young man, myasthenic patients with thymomas often are usually much older. It is important to remember that having a thymoma does not always indicate a poor prognosis for remission from myasthenia gravis[5]. In patients with myasthenia gravis and thymomas, like in the case of our patient, there have been cases with satisfactory outcomes following thymectomy[6,7]. The abrupt onset of myasthenic weakness affecting the respiratory muscles is known as a myasthenic crisis, which necessitates ventilatory support to prevent death. Respiratory failure may result from upper airway obstruction brought on by respiratory muscle weakness or oropharyngeal muscular weakness[8]. In the intensive care unit (ICU), prompt respiratory assistance and management of the myasthenic crises results in favourable outcomes. The prognosis for myasthenic crisis may not be as good overall in underdeveloped countries, since many patients still receive treatment outside of the and immunomodulatory medication is prohibitively expensive[9]. Even though our patient was young and had early-onset myasthenia gravis, he nonetheless experienced a myasthenic crisis and was in a critical situation; for the same, plasmapheresis was performed and IVIG was given. He had a more serious illness than would be anticipated in a patient his age. According to studies, hospital IVIG use has grown dramatically in comparison to plasma exchange and thymectomy[10]. Pure red cell aplasia is typically linked to thymoma[11,12]. Although the JAK2 mutation was negative, this patient experienced polycythaemia that was possibly related to myasthenia gravis. Myasthenia gravis and thymoma instances connected to polycythaemia are extremely rare[13,14]. Myasthenia gravis and thymoma are known to be associated; however, it is uncommon for polycythaemia to also co-exist in this situation. Thymoma is just one of the underlying disorders that can cause polycythaemia. The condition is managed by treating the underlying cause and lowering the red cell mass. In addition, the patient had an adrenal tumour that was most likely an incidentaloma but was initially misdiagnosed as a phaeochromocytoma due to the patient's ongoing hypertension. A case report of subclinical hypercortisolism caused by an accidental adrenal tumour that later developed into myasthenia gravis exists[15]. Following thymectomy, plasmapheresis, and IVIG, the patient experienced complete remission[16,17]. Our patient too returned for follow-up visits while walking unassisted from home.

This patient's management needed a multidisciplinary strategy involving several teams. Thymectomy and immunosuppressive medication are used to treat myasthenia gravis. Thymoma is treated with surgical excision and ongoing monitoring for recurrence. Phlebotomy is used in the treatment of polycythaemia, along with addressing the underlying cause.

Conclusions

Myasthenia gravis is a chronic autoimmune disorder that can lead to significant morbidity and mortality if not diagnosed and treated in a timely manner. A thorough history and physical examination, along with appropriate investigations and a multidisciplinary approach, are essential for the successful management of this disease. The case report highlights the importance of considering myasthenia gravis as a differential diagnosis in patients presenting with weakness, easy fatiguability, and involvement of cranial nerves. The case also underscores the need for vigilant monitoring for potential complications associated with myasthenia gravis, such as thymoma and polycythaemia. Despite a prolonged hospital course, the patient, in this case, was managed successfully, emphasizing the importance of coordinated care in the treatment of myasthenia gravis. It outlines the complexity of managing patients with multiple comorbidities. Myasthenia gravis, thymoma, and polycythaemia are rare conditions that require a thorough evaluation and a unique approach to management. Early recognition and prompt treatment can lead to better outcomes for these patients.

References

1. Dresser L, Wlodarski R, Rezania K et al. Myasthenia Gravis: Epidemiology, Pathophysiology and Clinical Manifestations. *J Clin Med* 2021; 21: 2235.
2. Romi F. Thymoma in myasthenia gravis: from diagnosis to treatment. *Autoimmune Dis* 2011; 2011: 474512.
3. Patrick J, Lindstrom J. Autoimmune response to acetylcholine receptor. *Science* 1973; 25: 871-2.
4. Hoch W, McConville J, Helms S *et al*. Auto-Antibodies to the Receptor Tyrosine Kinase MuSK in Patients with Myasthenia Gravis without Acetylcholine Receptor Antibodies. *Nat Med* 2001; 7: 365-8.
5. de Perrot M, Liu J, Bril V *et al*. Prognostic significance of thymomas in patients with myasthenia gravis. *The Annals of Thoracic Surgery* 2002; 74: 1658-62.
6. Dahal S, Bhandari N, Dhakal P *et al*. A case of thymoma in myasthenia gravis: Successful outcome after thymectomy. *Int J Surg Case Rep* 2019; 65: 229-32.
7. Aydin Y, Ulas AB, Mutlu V *et al*. Thymectomy in Myasthenia Gravis. *Eurasian J Med* 2017; 49: 48-52.
8. Chaudhuri A. PO: Behan, Myasthenic crisis. *QJM: An Int J Med* Vol 102: 97-107.

9. Sharma S, Lal V, Prabhakar S *et al*. Clinical profile and outcome of myasthenic crisis in a tertiary carehospital: A prospective study. *Ann India Acad Neurol* 2013; 16: 203-7.
10. Alshekhlee A, Miles JD, Katirji B *et al*. Incidence and mortality rates of myasthenia gravis and myasthenic crisis in US hospitals. *Neurology* 2009; 72: 1548-54.
11. Rosu C, Cohen S, Meunier C *et al*. Pure red cell aplasia and associated thymoma. *Clin Pract* 2011; 1: 3981205.
12. Thompson CA, Steensma DP. Pure red cell aplasia associated with thymoma: clinical insights from a 50-year single-institution experience. *Br J Haematol* 2006; 135: 405-7.
13. Sasi S, Yassin MA, Kamran S. Association of polycythaemia vera with positive JAK2V617F mutation and myasthenia gravis: A report of two cases. *Clin Case Rep* 2020; 22: 531-4.
14. Voigt S. Polycythaemia vera associated with thymoma. Case report. *Acta Pathol Microbiol Immunol Scand A* 1986; 94: 351-2.
15. Petramala L, Marinelli C, Giallonardo AT *et al*. A case report of subclinical hypercortisolism due to adrenal incidentaloma complicated by myasthenia gravis after adrenalectomy. *Tumori* 2016; 11: 27103206.
16. AL-Bulushi A, Al Salmi I, Al Rahbi F *et al*. The role of thymectomy in myasthenia gravis: A programmatic approach to thymectomy and perioperative management of myasthenia gravis. *Asian J Surg* 2020; 44: 819-28.
17. Barth D, Nabavi Nouri M, Ng E *et al*. Comparison of IVIg and PLEX in patients with myasthenia gravis. *Neurology* 2011; 7: 2017-23.

CHECKLIST FOR SUBMISSION OF MANUSCRIPT TO THE JIACM

- Covering letter including copyright release.
- Undertaking by ALL Authors, as below.
- Three copies of typescript of the article on A-4 size paper.
- CD of the manuscript.
- Name and address of author responsible for correspondence about the manuscript, including highest degree and affiliations of each author.
- Abstract (upto 250 words) along with 3 - 6 key words.
- Three glossy prints for each illustration (10 cm x 8 cm), appropriately labelled and each illustration is cited in the text. Submit the legends on a separate sheet in the manuscript.
- Check all references for accuracy and completeness. Put references in Vancouver format in numerical order, making sure each is cited in the text.
- Individual ICMJE Conflict of Interest forms filled and signed by each author, separately. The form is available at the Journal website, www.jiacm.in, under the heading "Author Guidelines".
- Registration of ALL types of studies (especially clinical trials) in the Clinical Trials Register of India, CTRI – available from http://ctri.nic.in/Clinicaltrials/login.php

UNDERTAKING BY AUTHORS

We, the undersigned, give an undertaking to the following effect with regard to our article titled .....

.....

.....

submitted for publication in the *Journal, Indian Academy of Clinical Medicine*:-

1. The article mentioned above has not been published or submitted to or accepted for publication in any form, in any other Journal.
2. We also vouchsafe that the authorship of this article will not be contested by anyone whose name(s) is/are not listed by us here.
3. We also agree to the authorship of the article in the following sequence:-

	Authors' Names (in sequence)	E-mail ID	Contribution to the Paper	Signature
1.	.....			
2.	.....			
3.	.....			
4.	.....			
5.	.....			
6.	.....			

IMPORTANT

1. All the authors are required to sign this form independently in the sequence given above.
2. Each author should have generated at least a part of the intellectual content of the paper.
3. Each author should be able to defend publicly in the scientific community, that intellectual content of the paper for which he/she can take responsibility.
4. No addition/deletion/or any change in the sequence of the authorship will be permissible at a later stage, without valid reasons and permission of the Editor.
5. By signing this undertaking, each author also affirms to have read, understood, and agreed to the ICMJE and COPE guidelines for ethical publishing.

Annual Subscription
Journal, Indian Academy of Clinical Medicine

Now, subscribe to the *Journal, Indian Academy of Clinical Medicine* without being a Member or Fellow of the Indian Association of Clinical Medicine. Keep abreast with the latest in the field of clinical medicine with your personal copy of the *JIACM*. The *Journal* covers the entire gamut of internal medicine with an in-depth, yet well-balanced mix of theoretical and practical aspects relevant to the teaching and practice of medicine in the Indian subcontinent.

Offer open to all Medical Colleges/Institutions/Libraries/Academic Bodies.

No subscription needed for Members/Fellows.

SUBSCRIPTION SLIP

Yes, I/we would like to subscribe to the *Journal, Indian Academy of Clinical Medicine (JIACM)*, published quarterly.

One-Year subscription (4 Issues) : Inland – Rs. 3,000.00
: Overseas (Air Mail) – US$ 200.00

Name : Dr. .....

Postal Address : .....

.....

.....

City ..... State ..... PIN .....

Please find enclosed Cheque/DD No. ..... dated ..... for Rs./US$ ..... drawn on (Bank) .....

favouring "Journal, Indian Academy of Clinical Medicine" payable at New Delhi.

Date ..... *Signature .....*

Send your Cheque/Demand Draft to:
Dr Sumeet Singla, Editor, JIACM
108 SFS Flats, Ashok Vihar, Phase-4, Delhi - 110 052.

Follow Your Heart

with **the original & imported ARNI**[1,2]

Guideline recommended
ACC[3] / ESC[4]
Approved for ALL HF patients[#2]

Leave nothing to chance

Unique salt complex[2,5]

Positive 5+years of clinical experience[1,2]

78 lac patient years of exposure world-wide[1,2]

Initiate early with

Vymada®

sacubitril/valsartan

Live life, your way

Now at half the price!*

#Vymada is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal.
*Applicable for Vymada 50 mg.
ARNI, angiotensin receptor-neprilysin inhibitor; ACC, American College of Cardiology; ESC, European Society of Cardiology; HF, heart failure.

References: 1. Novartis. Data on file; **2.** Vymada. India BSS 10 Jun 2022 effective from 4 Jul 2022; **3.** Heidenreich PA, et al. J Am Coll Cardiol. 2022 May 3;79(17):e263-e421; **4.** McDonagh TA, et al. Eur Heart J. 2021 Sep 21;42(36):3599-3726; **5.** European Medicines Agency. Assessment report. Entresto. Available at URL [online]: https://www.ema.europa.eu/en/documents/assessment-report/entresto-epar-public-assessment-report_en.pdf. As accessed on 10th February 2023.

Basic Succinct Statement

Vymada® tablets

Presentation: Tablets: film-coated tablets containing 50 mg (24mg + 26mg), 100 mg (49mg + 51mg), or 200 mg (97mg + 103mg) LCZ696 (sacubitril/valsartan) as sodium salt complex. **Indications:** VYMADA TABLETS is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal. LVEF is a variable measure, so use clinical judgment in deciding whom to treat. **Dosage and administration: Adults: Heart Failure** • The recommended starting dose of VYMADA is 49/51 (100mg) mg orally twice-daily. • Double the dose of VYMADA after 2 to 4 weeks to the target maintenance dose of 97/103 (200mg) mg twice daily, as tolerated by the patient. • In patients not currently taking an ACE inhibitor or an angiotensin II receptor blocker (ARB) and for patients previously taking low doses of these agents, start VYMADA at half the usually recommended starting dose. • After initiation, increase the dose every 2 to 4 weeks in adults. • **Pediatric patients:** VYMADA has not been studied. Use of VYMADA is not recommended. • **Geriatric patients:** No dosage adjustment is required. • **Renal impairment:** No starting dose adjustment is required in patients with mild to moderate renal impairment; In adult patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2), start VYMADA at half the usually recommended starting dose. After initiation, increase the dose to follow the recommended dose escalation thereafter. • **Hepatic impairment:** No starting dose adjustment is required in patients with mild hepatic impairment. In adults patients with moderate hepatic impairment (Child-Pugh B classification), start VYMADA at half the usually recommended starting dose. After initiation, increase the dose to follow the recommended dose escalation thereafter. Use in patients with severe hepatic impairment is not recommended. • **Method of administration** For oral use. May be administered with or without food. **Contraindications:** • in patients with hypersensitivity to any component. • in patients with a history of angioedema related to previous ACE inhibitor or ARB therapy. • with concomitant use of ACE inhibitors. Do not administer within 36 hours of switching from or to an ACE inhibitor • with concomitant use of aliskiren in patients with diabetes. **Warnings and precautions:** • **Fetal Toxicity:** VYMADA TABLETS can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. When pregnancy is detected, consider alternative drug treatment and discontinue VYMADA TABLETS. However, if there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system, and if the drug is considered lifesaving for the mother, advise a pregnant woman of the potential risk to the fetus • **Angioedema:** VYMADA TABLETS may cause angioedema. If angioedema occurs, discontinue VYMADA TABLETS immediately, provide appropriate therapy, and monitor for airway compromise. VYMADA TABLETS must not be re-administered. In cases of confirmed angioedema where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, administer appropriate therapy, e.g., subcutaneous epinephrine/adrenaline solution 1:1000 (0.3 mL to 0.5 mL) and take measures necessary to ensure maintenance of a patent airway. VYMADA TABLETS has been associated with a higher rate of angioedema in Black than in non-Black patients. Patients with a prior history of angioedema may be at increased risk of angioedema with VYAMDA TABLETS. VYMADA TABLETS must not be used in patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy. VYMADA TABLETS should not be used in patients with hereditary angioedema. • **Hypotension:** VYMADA TABLETS lowers blood pressure and may cause symptomatic hypotension. Patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), are at greater risk. Correct volume or salt depletion prior to administration of VYMADA TABLETS or start at a lower dose. If hypotension occurs, consider dose adjustment of diuretics, concomitant antihypertensive drugs, and treatment of other causes of hypotension (e.g., hypovolemia). If hypotension persists despite such measures, reduce the dosage or temporarily discontinue VYMADA TABLETS. Permanent discontinuation of therapy is usually not required. • **Impaired renal function:** As a consequence of inhibiting the renin-angiotensin-aldosterone system (RAAS), decreases in renal function may be anticipated in susceptible individuals treated with VYMADA TABLETS. In patients whose renal function depends upon the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with ACE inhibitors and angiotensin receptor antagonists has been associated with oliguria, progressive azotemia and, rarely, acute renal failure and death. Closely monitor serum creatinine, and down-titrate or interrupt VYMADA TABLETS in patients who develop a clinically significant decrease in renal function. As with all drugs that affect the RAAS, VYMADA TABLETS may increase blood urea and serum creatin • **Hyperkalemia:** Through its actions on the RAAS, hyperkalemia may occur with VYMADA TABLETS. Monitor serum potassium periodically and treat appropriately, especially in patients with risk factors for hyperkalemia such as severe renal impairment, diabetes, hypoaldosteronism, or a high potassium diet. Dosage reduction or interruption of VYMADA TABLETS may be required **Pregnancy, lactation, females and males of reproductive potential. Pregnancy:** VYMADA must not be used during pregnancy. Patients should be advised to discontinue VYMADA as soon as pregnancies occur and to inform their physicians. **Lactation:** It is not known whether VYMADA is transferred into human milk. Because of the potential risk for adverse drug reactions in breastfed newborns/infants, VYMADA is not recommended during breast-feeding. **Females and males of reproductive potential:** Female patients of childbearing potential should be advised about the consequences of exposure to VYMADA during pregnancy and to use contraception during treatment and for 1 week after their last dose of VYMADA. **Adverse drug reactions: Clinical Trials Experience**

Adverse Reactions Reported in ≥ 5% of Patients Treated with VYMADA in the Double-Blind Period of PARADIGM-HF

	ENTRESTO (n = 4,203) %	Enalapril (n = 4,229) %
Hypotension	18	12
Hyperkalemia	12	14
Cough	9	13
Dizziness	6	5
Renal failure/acute renal failure	5	5

In PARAGON-HF, no new adverse reactions were identified.

The following additional adverse reactions have been reported in postmarketing experience. Hypersensitivity including rash, pruritus, and anaphylactic reaction. **Interactions:** • **Dual Blockade of the Renin-Angiotensin-Aldosterone System:** Concomitant use of VYMADA TABLETS with an ACE inhibitor is contraindicated because of the increased risk of angioedema. Avoid use of VYMADA TABLETS with an ARB, because VYMADA TABLETS contains the angiotensin II receptor blocker valsartan. The concomitant use of VYMADA TABLETS with aliskiren is contraindicated in patients with diabetes. Avoid use with aliskiren in patients with renal impairment (eGFR < 60 mL/min/1.73 m^2). • **Potassium-Sparing Diuretics:** As with other drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium. • **Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) Including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors):** In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, concomitant use of NSAIDs, including COX-2 inhibitors, with VYMADA TABLETS may result in worsening of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically. • **Lithium:** Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists. Monitor serum lithium levels during concomitant use with VYMADA TABLETS.

Packs: 50 mg: Pack of 28 tablets (blister strip of 2 x 14). 100 mg: Pack of 28 tablets (blister strip of 2 x 14). 200 mg: Pack of 28 tablets (blister strip of 4 x 7).

Before prescribing, please consult full prescribing information available from Novartis Healthcare Private Limited, Inspire BKC, Part of 601 & 701, Bandra Kurla Complex, Bandra (East), Mumbai – 400 051, Maharashtra, India. Tel +91 22 50243335/36, Fax +91 22 50243010.

WARNING: To be sold by retail on the prescription of a Registered Medical Practitioner only.

India BSS dtd 10 Jun 2022 based on international BSS dtd 24 Jun 2020 effective from 4 Jul 2022.

Disclaimer: Novartis does not recommend the use of its products in unapproved indications and recommends to refer to complete prescribing information prior to using any of the Novartis products.

NVS/Vymada/JAPI_Reprint/605484/24/02/2023
For the use of only registered medical practitioners or a hospital or a laboratory.

NOVARTIS

Novartis Healthcare Pvt. Ltd.,
Inspire BKC, Part of 601 and 701, Bandra - Kurla Complex, Bandra (East), Mumbai - 400 051, Maharashtra, India.
Tel: 91 22 50243335/36; Fax: 91 22 50243010. www.novartis.com

Registered with the Registrar of Newspapers for India under RNI No.: DELENG/2000/1686