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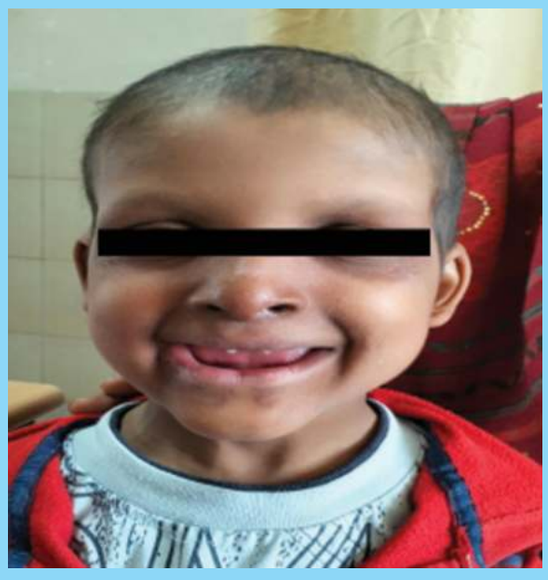

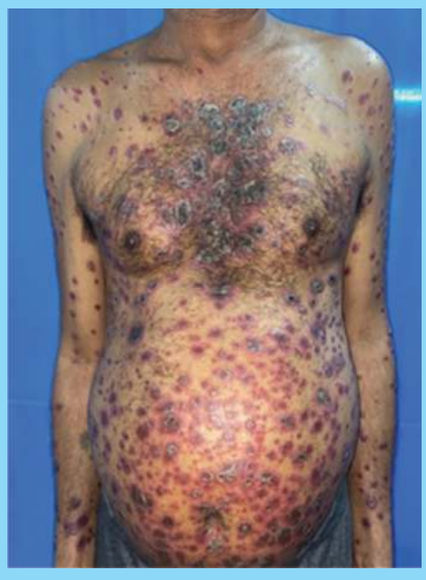

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EDITOR'S NOTE

Dear Friends,

Greetings!

The big news is that we have started online submission of manuscripts from our website page. Just visit *www.jicam*.in and click on the tab "Submit Article". It is a very simple electronic submission process. We have received more than 50 submissions till date on our electronic submission portal. Paper copies are no longer accepted now.

I would especially invite you to submit interesting images and videos in clinical medicine via the submission portal of *JIACM*.

The current issue has two very important and useful reviews on dry eye disease and pitfalls in interpreting peripheral blood smears. Both have great day-to-day implications for practice.

There are 3 interesting articles, emphasizing the importance of a thorough skin examination in clinical medicine. Health economics is taking center-stage these days and a study on out-of-pocket-expenditure highlights this often-forgotten aspect of treatment in resource-limited settings like India.

The section on *"Images in Clinical Medicine"* showcases a rare genetic syndrome of Hereditary Ectodermal Dysplasia.

A plethora of rare and unusual cases are presented to add to your knowledge. I encourage you to visit the website *www.jiacm*.in and enjoy all the above offerings and relish the flavours in an electronic format, along with past issues.

Lastly, I again request you *to inform, invite and involve your students, colleagues, seniors and friends from India and abroad to read and contribute to JIACM*.

Long live *JIACM*. long live *IACM* and long live Clinical Medicine.

Jai Hind

– Dr Sumeet Singla

CONTENTS

Journal, Indian Academy of Clinical Medicine • Vol. 26, Number 1-2, January-June, 2025

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

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Dr. Sumeet Singla

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Headquarters :

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

Editorial/Mailing Address

108 SFS Flats, Ashok Vihar, Phase-4, New Delhi - 110 052
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ORIGINAL ARTICLE

JIACM 2025; 26 (1-2): 7-12

Clinico-Pathological Profile of Anaemia in Adult Males at a Hospital in Uttar Pradesh

Shweta Sharma, Abha Gupta*, Remesh Rajappan**, Chhaya Mittal***, Anshu Singh*****

Abstract

Introduction: Every fourth person in the world (27%) has anaemia, with developing countries alone accounting for more than 89% of the burden. Population-based studies on anaemia in India have mostly focused on women and children, with men anaemia receiving much less attention despite anaemia having adverse effect on their health, wellbeing, and economic productivity.

Aims and objectives: To study the various determinants and co-morbid conditions associated with anemia in males aged 18 - 49 years.

Methods: A cross-sectional study on anaemic male patients aged 18 - 49 years attending SVBP Hospital, Meerut, Uttar Pradesh.

Results: Majority of participants belonged to the 46 - 49 years age group. Nutritional issues were the most prevalent condition, affecting 43.08% of patients. Chronic liver disease (CLD) followed, with a prevalence of 20.0%. Our study revealed a notable association between co-morbid conditions and the severity of anaemia.

Conclusion: Anaemia in adult males is intricate and multifaceted, necessitating personalised interventions.

Key words: Anaemia in males, anaemia severity, co-morbidities in anaemia.

Introduction

Anaemia is a condition in which the number of red blood cells or the haemoglobin concentration within them is lower than normal. The optimal haemoglobin concentration needed to meet physiologic needs varies by age, sex, altitude of residence, smoking habits and pregnancy status. WHO defines anaemia in children aged under 5 years and pregnant women as a haemoglobin concentration <11 g/dL at sea level, and anaemia in non-pregnant women as a haemoglobin concentration <12 g/dL and in males as <13g/dL. Anaemia is further classified depending upon the level of Hb into mild (Hb 11 - 12.9 g/dL), moderate (Hb 8 - 10.9 g/dL) and severe (Hb <8 g/dL)[1]. Every fourth person in the world (27%) has anaemia, with the developing countries alone accounting for more than 89% of the burden[2].

According to NFHS-5 survey, fifty-seven per cent of women and 25 per cent of men age 15 - 49 years have anaemia in India[3]. Anaemia is an important global health problem affecting men and women of reproductive age group. Various factors contribute to the prevalence of anaemia in males, encompassing socio-economic conditions, health status, behavioural factors and more (Fig. 1). These determinants collectively influence the likelihood of an individual developing anaemia and underscore the multifaceted nature of this health condition. Population-based studies on anaemia in India have mostly focused on women and children, with men with anaemia receiving much less attention despite anaemia having adverse effect on their health, wellbeing, and economic productivity[4].

Aim and Objectives

1. To study various aetiologies of anaemia in males aged 18 - 49 years attending a tertiary care hospital in Western Uttar Pradesh.
2. To study co-morbid conditions associated with anaemia in these adult males.

Material and Methods

This was a cross-sectional study of anaemic male patients attending SVBP Hospital, Meerut. During the study period of 3 months from 2023 May to 2023 July, in whiçh all eligible patients who visited Medicine OPD were included in this study. So a sample size of of 65 patients was selected for study . Clinically, biochemically, and pathologically, all patients were evaluated. All male anaemic patients aged 18 - 49 years attending SVBP Hospital were interviewed using a pre-designed and pre-tested questionnaire. Relevant

**Professor, **Junior Resident,Department of Medicine, ***Associate Professor, Department of Community Medicine, ***Assistant Professor, Department of Pathology, LLRM Medical College, Meerut - 252 002, Uttar Pradesh.*
Corresponding Author: Dr Remesh Rajappan, Junior Resident, Department of Medicine, LLRM Medical College, Meerut - 252 002, Uttar Pradesh. Tel: 6238365719, E-mail: remeshrajappan123@gmail.com

investigations were conducted and clinical data along with laboratory parameters were collected from patients' medical records. The collected information was analysed.

Eligiblity Criteria

Inclusion Criteria

1. Male patients attending SVBP Hospital, Meerut, aged 18 - 49 years.
2. Hb less than 13 g/dL.

Exclusion Criteria

1. Patients aged less than 18 years and more than 49 years.
2. Patients denying consent.
3. Patients at advanced stages of chronic illness.

Observations

The study evaluated a total of 65 anaemic male patients. Table I shows age distribution in which majority of participants were in the 46 - 49 years age group, accounting for 21.53% of the total. Following closely was the 26 - 30 years age group, comprising 18.46% of the participants. The 18 - 25 years and 36 - 40 years age groups had the lowest representation, with each group accounting for 13.84% of the total number of patients evaluated.

Table I: Age distribution of study participants.

Age Group (in years)	No. of Patients (%)
18 - 25	9 (13.84%)
26 - 30	12 (18.46%)
31 - 35	10 (15.38)
36 - 40	9 (13.84%)
41 - 45	11 (16.92%)
46 - 49	14 (21.53%)

Table II shows the occupational distribution of anaemic males, revealing that out of 65 participants, the largest group consisted of semi-skilled workers (30.77%), including farmers. Skilled workers made up 24.61% of the sample, while 18.46% were either unemployed or students, with 8 individuals specifically noted as unemployed. Unskilled workers, such as those in construction, accounted for 16.92% of the participants. Both semi-professional and professional workers each represented 4.61% of the sample. This distribution indicates that the majority of anaemic males are engaged in semi-skilled and skilled work, with a significant portion also being unemployed or students.

The Table II also illustrates the educational status of male anaemic participants, with individuals who completed only primary education being the majority of anaemic study population (36.46%), contrasting sharply with those educated beyond secondary level, who demonstrated the lowest prevalence (6.15%). Approximately 32.31% of participants attained a secondary education level. Furthermore, men lacking any formal education accounted for a significant portion, comprising approximately a quarter (24.61%) of the study cohort.

Table II: Occupational and educational status of study participants.

Occupation	Number of participants (%)
Unskilled	11 (16.92%)
Semi skilled	20 (30.77%)
Skilled	16 (24.61%)
Semi Professional	3 (4.61%)
Professional	3 (4.61%)
Unemployed and Students	12 (18.46%)
Educational Status	
Illiterate	16 (24.61%)
Primary	25 (38.46%)
Secondary	20 (30.77%)
Higher	4 (6.15%)

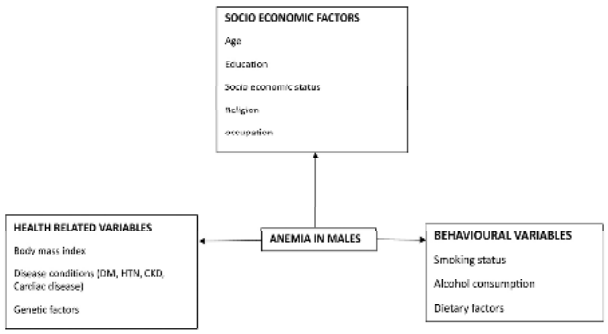

Fig. 1: *Factors affecting anaemia among men.*

Fig. 2 illustrates the distribution of socio-economic status among male anaemic participants, as assessed by the modified Kuppuswamy scale[5]. The highest percentage, 57.62%, falls under the lower-middle class category, indicating a significant portion of participants with moderate economic means. The upper-middle class accounted for 23.08% of patients, while the upper-lower class had 13.55%. A smaller percentage, 3.07%, was classified as upper class, while there were no participants classified

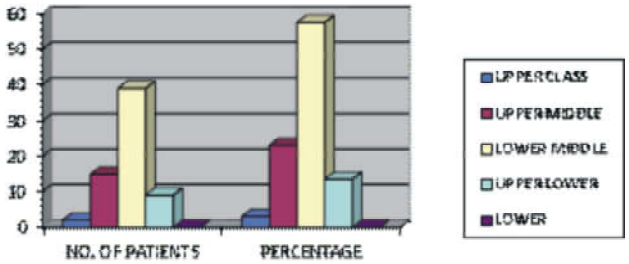

Fig. 2: *Socio-economic status of study participants.*

under the lower class. This data provides insights into the socio-economic backgrounds of male anaemic participants in the study, highlighting diversity within the sample.

Table III presents the severity of anaemia among adult male patients in our study, classified according to the World Health Organisation (WHO) criteria[6]. It shows that 9.23% of patients (6 individuals) had mild anaemia with haemoglobin levels between 11 - 12.9 g/dL. Moderate anaemia, with haemoglobin levels ranging from 8 - 10.9 g/dL, affected 36.92% of the patients (24 individuals). The majority, 53.85% (35 individuals), had severe anaemia with haemoglobin levels below 8 g/dL. Notably, the majority of participants exhibited microcytic hypochromic anaemia (53.84%), followed by normocytic anaemia (43.07%), and a smaller proportion had macrocytic anaemia (3.07%).

Table III: Haemoglobin concentration of study participants.

Severity of Anaemia (g/dL)	No of patients (Percentage)
Mild (Hb 11 - 12.9)	6 (9.23%)
Moderate (Hb - 8 - 10.9)	24 (36.92%)
Severe (Hb <8)	35 (53.85%)

Table IV shows symptoms in 65 individuals with mild-to-moderate and severe anaemia. Generalised weakness was the most common symptom, affecting 60% of participants (21 mild-to-moderate, 18 severe). Dyspnoea on exertion (DOE) affected 32.03 % (8 mild-to-moderate, 13 severe), and gastrointestinal (GI) symptoms, including nausea, vomiting, or diarrhoea, affected 27.69% (8 mild-to-moderate, 10 severe). Bleeding history was noted in 26.15% (10 mild-to-moderate, 7 severe), and fever in 10.77% (1 mild-to-moderate, 6 severe). The chi-square statistic was 5.4101 with a p-value of 0.24, indicating no significant difference in symptom distribution between the two groups ($p < 0.05$). Regarding symptom duration, a considerable number experienced symptoms for 7 days to 1 month (59.32%), hinting at potentially acute conditions. Interestingly, a minority reported symptoms lasting less than 7 days (3.38%), possibly indicating transient issues.

Table IV: Symptoms reported by participants.

	Mild-to-moderate anaemia group n (%)	Severe anaemia group n (%)	Total n (%)	p value
Generalised weakness	21 (18.35)	18 (20.65)	39 (60%)	
Dyspnoea on exertion	8 (9.88)	13 (11.12)	21 (32.03%)	0.2477
Gastrointestinal symptoms	8 (8.47)	10 (9.53)	18 (27.69%)	
Bleeding history	10 (8.00)	7 (9.00)	17 (26.15%)	
Fever	1 (3.29)	6 (3.71)	7 (10.77%)	

Chi square value = 5.4101

In our study, the majority of participants followed a mixed diet (42.05%), while only 16.95% adhered to a vegetarian regimen. Anaemia prevalence appeared higher among tobacco and alcohol consumers, with over half engaging in alcohol consumption (52.54%) and smoking (50.85%). Additionally, BMI distribution revealed a predominantly normal BMI (70.76%), but 18.46% fell below the healthy range, signaling potential nutritional deficiencies. A small fraction were overweight (7.69%) or obese (1.53%), highlighting varied metabolic health. These findings underscore the complex relationship between dietary habits, lifestyle factors, and anaemia, necessitating multifaceted interventions in clinical care and public health. Furthermore, hepatomegaly was observed in approximately 28.81% of participants, while splenomegaly was present in 18.64% of participants. These findings shed light on the diverse hematological profiles and associated clinical manifestations among our study cohort.

Table V: Causes of anaemia and associated conditions of study participants.

	Patients with Mild-to-moderate anaemia (n)	Patients with Severe anaemia (n)	Total n (%)
Nutritional Anaemia	17	11	28 (43.02%)
Chronic liver disease	6	7	13 (20%)
Renal dysfunction	5	6	11 (16.92%)
Hypertension	2	5	7 (10.77%)
Diabetes Mellitus	3	5	8 (12.31%)
Infections including TB	4	4	8 (12.31%)
Malignancy	2	0	2 (3.07%)
Congestive hart failure	1	0	2 (3.07%)
Thalassaemia	1	0	1(1.54%)
Hypothyroidism	1	1	2 (3.07%)
Haemorrhoids	4	0	4 (6.15%)

Table V outlines the causes of anaemia in 65 adult males, divided by severity (mild-to-moderate versus severe). Nutritional anaemia was the most prevalent, affecting 28 patients (43.02%), with 17 having mild-to-moderate anaemia and 11 having severe anaemia. Chronic liver disease (CLD) was the second most common cause, accounting for 13 patients (20%), split between 6 mild-to-moderate and 7 severe cases. Renal dysfunction affected 11 patients (16.92%), with a near-even distribution between mild-to-moderate (5) and severe (6) anaemia. Hypertension (HTN) and diabetes mellitus (DM) each accounted for 8 cases (12.31%), with HTN predominantly severe (5 severe versus 2 mild-to-moderate) and DM evenly split. Infections, including tuberculosis (TB), also affected 8 patients (12.31%), evenly distributed between both severities. Malignancy, hypothyroidism, and congestive heart failure (CHF) each caused anaemia in 2 patients (3.07%), with malignancy and CHF cases being mild-to-moderate and hypothyroidism cases split equally. Thalassaemia was the least comman cause, affecting only 1 patient (1.54%) with mild-to-moderate anaemia. Haemorrhoids caused anaemia in 4 patients (6.15%), all mild-to-moderate. This data highlights nutritional anaemia as the leading cause, followed by chronic liver disease and renal dysfunction.

Table VI: Association of co-morbid conditions with severity of anaemia.

	Mild-to-moderate anaemia group n (%)	Severe anaemia group n (%)	Total n (%)	p value
Patients with co-morbidity	13 (17.08)	24 (19.92)	37 (56.92%)	**0.04**
Patients without any co-morbid condition	17 (12.92)	11 (15.08)	28 (43.07%)	
Marginal Column Totals	30	35	65	

Chi-square value = 4.1962

Table VI examines anaemia severity in 65 patients, comparing those with and without co-morbid conditions. Among patients with co-morbidities, 13 had mild-to-moderate anaemia and 24 had severe anaemia. For patients without co-morbidities, 17 had mild-to-moderate anaemia and 11 had severe aneamia. The chi-square statistic was 4.1962 with a p-value of 0.04, indicating a significant association ($p < 0.05$) between co-morbid conditions and the severity of anaemia. Patients with co-morbidities were more likely to have severe anaemia than those without.

Discussion

Age distribution findings in our study highlight the prevalence of anaemia among males, with substantial representation in the 41 - 49 years age group. Conversely, the notable presence of participants in the 26 - 30 years age group suggests possible influencey by distinct physiological, lifestyle, or socio-economic factors. The lower representation in the 18 - 25 years and 36 - 40 years age groups underscores the need for further exploration of anaemia prevalence across different age cohorts. Older men above 40 years are more vulnerable to anaemia, possibly due to chronic co-morbid conditions such as diabetes, renal dysfunction, and uncontrolled blood pressure. A survey conducted by Adithya Singh *et al* on prevalance and determinants of anaemia in rural India also yielded similar results[7]. These findings emphasize the importance of tailored approaches to management and prevention that consider age-specific factors.

The data indicates that anaemia was prevalent across various occupational groups among males. The highest proportion of anaemic males were in semi-skilled and skilled occupations, which might suggest occupational factors contributing to anaemia, such as physical demands or limited access to healthcare. Physically demanding occupations may increase the risk of anaemia due to heightened nutrient requirements and dietary challenges. Conversely, the limited representation of professionals suggests better access to healthcare and a healthier diet, potentially lowering anaemia prevalence within this group. The significant percentage of unemployed participants underscores the potential impact of socio-economic factors on anaemia prevalence. This distribution highlights the need for targeted interventions addressing both occupational and socio-economic determinants of anaemia among males.

The study highlights significant impact of education on anaemia prevalence among men, with lower education levels correlating with higher vulnerability. Those completing only primary education had the highest prevalence (36.46%), while those educated beyond secondary level had the lowest (6.15%). This underscores education's pivotal role in disease awareness and advocating for essential health practices. Approximately 32.31% attained secondary education, while 24.61% lacked formal education, highlighting the need for interventions to improve educational opportunities and health literacy among vulnerable populations to combat anaemia effectively.

In our study, the majority of participants belonged to the lower middle class (57.62%), followed by the upper middle class (23.08%), and upper lower class (13.55%). A mere 3.07% were categorised as belonging to the upper class, while none fell into the lower socio-economic status category (Fig. 2). Previous research on anaemia consistently demonstrates a correlation between lower socio-economic

status and a heightened prevalence of the condition. This association is often attributed to restricted access to nutritious diets, which can lead to malnutrition and subsequent anaemia, compounded by limited access to healthcare services. Additionally, factors such as substandard living conditions, heightened exposure to diseases, and unhealthy lifestyle habits further exacerbate the development of anaemia within lower socio-economic strata.

The study revealed a higher prevalence of anaemia among individuals who consumed tobacco and alcohol, with over half of the participants engaging in alcohol consumption (52.54%) and smoking (50.85%). Lifestyle interventions are crucial for this group due to the adverse hematopoietic effects of chronic alcohol intake[8]. Additionally, while most participants had a normal BMI (70.76%), a notable percentage fell below the healthy range (18.46%), indicating potential nutritional deficiencies contributing to anaemia. These findings underscore the complex interplay between dietary habits, lifestyle factors, and physiological parameters in anemia development.

Anaemia in males presents with a spectrum of clinical features, often reflecting underlying causes[9]. Generalised weakness emerged as the most prevalent symptom, affecting 60% of participants, followed by dyspnoea on exertion (32.03%) and gastrointestinal symptoms (27.69%). Bleeding history was noted in 26.15% of cases, while fever affected 10.77% of individuals. Importantly, the chi-square statistic of 5.4101 with a p-value of 0.24 indicated no significant difference in symptom distribution between mild-to-moderate and severe anaemia cases ($p < 0.05$). The relatively high proportion of severe anaemia (29.23%) in our study is attributable to the tertiary care setup. Conducted in such a facility, our study inherently biases the participant pool towards more severe cases. As the facility primarily caters to patients with complex and critical conditions, including severe anaemia cases, it underscores the gravity of the findings.

Nutritional deficiency emerged as the primary cause behind anaemia in 43.08% of our study participants, underscoring the importance of addressing dietary inadequacies in combating this condition. Moreover, the high prevalence of co-morbidities (56.92%) highlights the complex interplay between anaemia and various underlying health conditions. Chronic liver disease, affecting 20.0%, deranged renal function in 16.92%, and infections in 12.31%, represent significant contributors to the anaemia burden, necessitating comprehensive management approaches. The identification of malignancy in a subset of participants (2 cases, 3.07%) underscores the importance of thorough evaluation in diagnosing underlying causes of anaemia. Furthermore, the co-existence of diabetes (12.31%) and hypertension (10.77%) emphasizes the interconnected nature of chronic diseases and their impact on haematological health[10,11].

Our study demonstrates a significant association between co-morbid conditions and the severity of anaemia. Patients with co-morbidities were more likely to have severe anaemia, as evidenced by 24 cases compared to 11 cases among those without co-morbidities. The chi-square statistic of 4.1962 with a p-value of 0.04 confirms this association, signifying that the difference in anaemia severity between the two groups is statistically significant ($p < 0.05$). This highlights the potential impact of co-morbidities on exacerbating the severity of anaemia in patients.

In a study conducted in a rural area of Haryana by Shashi Kant *et al* approximately 27.2% of participants reported the presence of a co-morbidities and among them, 6.5% has renal disorders, liver disorders, malignancies, or external bleeding[12]. The relatively higher occurrence of co-morbidities in the study group may be attributed to the tertiary care settings where severe cases were admitted and thoroughly evaluated.These findings underscore the multifactorial nature of anaemia and emphasize the need for a holistic approach to its management, addressing both nutritional deficiencies and underlying health conditions to effectively mitigate its impact on patient health.

Conclusion

In conclusion, our study provides a comprehensive understanding of anaemia in adult males, emphasizing its multifactorial nature and significant health impact. Lifestyle factors such as diet, alcohol consumption, and smoking habits are closely linked to anaemia prevalence. In this study nutritional deficiency was a predominant cause, along with co-morbidities like chronic liver disease, deranged renal function and infections. Additionally, clinical factors like haemorrhoids, diabetes, hypertension, malignancy, hypothyroidism, and cardiac failure underscore the complexity of anaemia management and the need for tailored interventions. The findings of our study reveal a notable association between co-morbid conditions and the severity of anaemia among patients. Our findings emphasize the critical importance of comprehensive evaluation and management strategies, addressing both nutritional deficiencies and underlying health conditions, to effectively mitigate the impact of anaemia on the health and well-being of adult males. These insights underscore the need for multidisciplinary collaboration and targeted interventions to address the diverse range of factors contributing to anaemia in this specific population.

Limitations of study

The study's limitations include the inclusion of more severe cases due to the tertiary care center setting and a relatively small sample size thus limiting the generalisability of the study findings. Additionally, the cross-sectional design limits causal relationships, and reliance on self-reported data may introduce bias. Despite these constraints, the study provides insights into anaemia among adult males, highlighting the need for further research to address these limitations.

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- Uma Kumar (New Delhi)
- Vaishali Bharwaj (New Delhi)
- Vineet Talwar (New Delhi)
- Vishal Sharma (Chandigarh)
- Vishakha Mittal (New Delhi)

ORIGINAL ARTICLE

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Evaluation of Fracture Risk by Fracture Risk Assessment (FRAX) Algorithm in Patients with Rheumatoid Arthritis

Rajnish Singh, Jainesh Jain**, Ishita Singh***, Anil Taneja*****

Abstract

***Objective:** An increased incidence of osteoporosis has been reported in patients of Rheumatoid Arthritis (RA). However, studies evaluating fracture risk and its predictors in such patients are limited. This study aimed to assess the fracture risk, using the FRAX algorithm, and its predictors in patients of RA.*

***Material and Methods:** This cross-sectional observational study, conducted in a tertiary care hospital at New Delhi, enrolled 40 cases of RA. Demographic characteristics and anthropometric measurements were recorded along with Lab investigations including Rheumatoid factor (RF), Anti-citrullinated protein antibody (ACPA), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Disease severity was calculated using DAS28-ESR score. Bone Mineral Density (BMD) was measured using Dual-energy X-ray Absorptiometry (DEXA) and FRAX score was calculated using India specific FRAX calculator. Regression analyses were done to find predictors of increased fracture risk in these patients.*

***Results:** The overall prevalence of osteoporosis in study population was 55%. The BMD at femur neck was found to be the lowest. The mean FRAX score for major osteoporotic fracture was 4.5 ± 5.18% and for hip fracture was 2.11 ± 2.95%. 9 patients (22.50%) were having FRAX score above the cut-off for initiating anti-osteoporotic treatment according to National Osteoporosis Foundation (NOF) guidelines. Age, disease duration, swollen joint count, ESR, CRP, DAS28-ESR, and FRAX scores for major osteoporotic fracture and hip fracture were significantly higher in patients with osteoporosis. The independent predictors for higher FRAX scores were age, history of previous fracture, current smoking, history of glucocorticoid intake and T-score at femur neck.*

***Conclusion:** There is a high prevalence of osteoporosis in patients with RA. An increased 10-year risk of major osteoporotic and hip fracture was observed in patients with RA as assessed by FRAX algorithm. We suggest that patients with RA should be assessed for fracture risk early in the course of the disease.*

***Key words:** Rheumatoid arthritis, FRAX, osteoporosis, bone mineral density, major osteoporotic fracture, hip fracture.*

Introduction

Rheumatoid arthritis (RA) is an autoimmune chronic inflammatory disease leading to symmetrical, progressive and erosive polyarthritis leading to joint deformities and functional disability[1].

RA patients have reduced bone density due to chronic inflammation; corticosteroids use and limited mobility further add to increased risk of osteoporosis[2,3,4]. Incidence of osteoporosis in RA patients has been reported twice as high as that seen in the general population[5]. As a result, patients with RA have a higher fracture risk, affecting their quality of life and causing increased morbidity and possibly mortality[6,7]. Considering the younger age group of RA patients, fracture risk assessment and intervention in the stage of early disease can reduce long-term morbidity.

Bone Mineral Density (BMD) is measured for diagnosing and assessing severity of osteoporosis. Currently, BMD measurement by dual energy X-ray absorptiometry (DEXA) is considered as the gold standard for assessing osteoporosis. However, it fails to incorporate osteoporotic risk factors when considering the probability of fractures in this subset of patients[8]. Also, there is limited availability of the DEXA scan in countries like India. Hence, there is a need for development of an inexpensive and an easily available tool to assess the fracture risk.

The FRAX tool is an online algorithm, that calculates the 10-year probability of hip fracture and major osteoporotic fracture (hip, vertebral column, humerus and forearm) based on readily identifiable risk factors. FRAX incorporates demographic data and risk factors such as age, gender, body mass index (BMI), history of fragility fracture or parental hip fracture, current smoking and consumption of alcohol, use of corticosteroids, conditions of secondary osteoporosis,

**Professor, **Senior Resident, Department of Medicine, ****Consultant and Professor, Department of Radiodiagnosis, ABVIMS and Ram Manohar Lohia Hospital, Baba Kharak Singh Marg, New Delhi - 110 001.*
****Post-Graduate Student, Department of Internal Medicine, Max Smart SS Hospital, Saket, New Delhi - 110 017.*
Corresponding Author: Dr Jainesh Jain, Senior Resident, Department of Medicine, ABVIMS and Ram Manohar Lohia Hospital, Baba Kharak Singh Marg, New Delhi - 110 001. Tel: 7045959397, E-mail: drjainesh031095@gmail.com

rheumatoid arthritis, and BMD at femur neck, to calculate the probability of major osteoporotic and hip fracture over 10 years[9-12]. Femoral neck BMD is an optional parameter while calculating FRAX score.

FRAX score is a well accepted tool to assess the fracture risk in post-menopausal women. Recently, some studies have used FRAX tool to calculate the probability of osteoporotic fractures in patients with Ankylosing spondylitis and RA. However, there is paucity of studies in Indian population[13].

The present study was undertaken to assess the fracture risk in Indian patients with RA, using country (India) specific FRAX algorithm, and to determine the predictors of increased fracture risk in these patients.

Material and Methods

Study Population and Design

The study was approved by the ethics committee and institutional review board. A written informed consent was taken from all participants.

Patient Assessment

Detailed history including joints involved, duration of disease, early morning stiffness, any extra-articular symptoms, smoking, alcohol consumption, prior history of any fracture, treatment received for osteoporosis or glucocorticoid use was obtained. History of fracture in parents was enquired. Anthropometric measurements were taken and patients were examined clinically with particular attention to musculoskeletal system. Tender Joint Count (TJC), Swollen Joint Count (SJC) and disease activity by DAS28-ESR score were recorded. Patients were investigated for laboratory tests including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Rheumatoid factor (RF), Anti-citrullinated protein antibody (ACPA) and X-rays of joints.

Patients were evaluated for BMD by DEXA using densitometer- HOLOGIC, INC. 35 CROSBY DRIVES BEDFORD, MA01730, USA (Model ASY- 00409). It was measured at 3 sites: femur neck, lumbar spine (L1-L4) and non-dominant forearm; values were obtained as T-score which was standard deviation from reference value. India-specific FRAX tool was used to calculate10-year risk for hip fracture and major osteoporotic fracture. (https://www.sheffield.ac.uk/FRAX/tool.aspx?country=51).

Statistical Analysis

Categorical variables were presented as numbers and percentage (%) and quantitative data were presented as mean ± standard deviation (SD). The Kolmogorov-Smirnov test was applied to check the data normality. The associations of quantitative variables, not normally distributed were analysed using Kruskal-Wallis test and those which were normally distributed were analysed using Analysis of Variance (ANOVA). The associations of the qualitative variables were analysed using Fisher's exact test. Univariate and multivariate linear regression was used to find out factors affecting FRAX score for major osteoporotic fracture and hip fracture. p-value less than 0.05 was considered statistically significant. Data entry and analysis was done in Microsoft EXCEL using Statistical Package for Social Sciences (SPSS) software, Chicago, USA, ver. 21.0.

Results

A total of 40 patients of RA were recruited in the study. Mean age of the study population was 43.92 ± 8.8 years and majority patients were females. The mean disease duration was 9.4 ± 4.4 years with a maximum of 20 years and minimum of 3 years.

12 patients (30%) had history of glucocorticoid intake, amongst which 4 had osteopenia and 8 had osteoporosis according to T-score at femur neck. This underlines the fact that glucocorticoid use is a major cause for reduced BMD in RA patients.

Mean DAS-28 ESR score in our patients was 3.94 ± 1.17, maximum being 6.4 and minimum 1.6. Twenty-six patients out of 40 (70%) had moderate to high disease activity.

The mean BMD at femur neck was -2.3 ± 0.72 gm/cm^2. Eighteen patients (45%) each had osteopenia and osteoporosis, while 4 (10%) had normal BMD. The mean BMD of lumbar spine and forearm was -2.19 ± 0.82 gm/cm^2 and -1.81 ± 0.91 gm/cm^2, respectively. Out of these,16 patients (40%) had osteoporosis, 21 (52.5%) had osteopenia and 3 (7.5%) had normal BMD at lumbar spine while 11 patients (27.5%) had osteoporosis, 21 (52.5%) had osteopenia and 8 (20 %) had normal BMD at forearm.

Overall prevalence of osteoporosis was 55%. The prevalence of osteoporosis in pre-menopausal females was 34.61%.

Patients were divided, on the basis of the T-score at femur neck, into 3 groups and baseline characteristics were compared. It was found that age, duration of the disease, swollen joint count, ESR, CRP, DAS28-ESR and FRAX score for hip fracture and major osteoporotic fracture were significantly higher in patients with osteoporosis (Table I).

Table I: Baseline characteristics of patients according to T-score at Femur neck.

Patient Characteristics	Normal (n = 4) T-score > -1	Osteopenia (n = 18) T-score -1 to -2.5	Osteoporosis (n = 18) T-score < -2.5	Total	p value
Age (years)	34.75 ± 4.27	40.11 ± 3.66	49.78 ± 9.55	43.92 ± 8.84	**<0.001**
Gender (Female)	4 (100%)	17 (94.44%)	12 (66.67%)	33 (82.50%)	0.101
BMI (kg/m^2)	25.8 ± 3.43	26.11 ± 1.67	26.3 ± 2.21	26.17 ± 2.07	0.904
Weight (kg)	58 ± 9.52	58.94 ± 2.6	61.94 ± 5.71	60.2 ± 5.17	0.148
Height (cm)	149.75 ± 5.44	150.39 ± 4.94	153.61 ± 8.13	151.78 ± 6.68	0.293
Duration (years)	4 ± 0.82	7.5 ± 2.26	12.5 ± 4.45	9.4 ± 4.47	**<0.001**
Current Smoker	0 (0%)	1 (5.56%)	2 (11.11%)	3 (7.50%)	1
Alcohol Intake	0 (0%)	1 (5.56%)	1 (5.56%)	2 (5%)	1
Previous Fracture	0 (0%)	0 (0%)	3 (16.67%)	3 (7.50%)	0.311
Parent with Hip Fracture	1 (25%)	0 (0%)	0 (0%)	1 (2.50%)	0.1
Glucocorticoid use	0 (0%)	4 (22.22%)	8 (44.44%)	12 (30%)	0.166
Tender Joint Count	2.75 ± 1.5	3.22 ± 2.39	5.22 ± 3.52	4.08 ± 3.03	0.111
Swollen Joint Count	0 ± 0	0.67 ± 0.97	1.33 ± 1.33	0.9 ± 1.17	**0.043**
ESR (mm/hr)	14 ± 4.32	20.44 ± 8.58	31 ± 14.52	24.55 ± 12.8	**0.007**
CRP (mg/L)	2.62 ± 2.5	6.58 ± 4.11	9.47 ± 4.99	7.49 ± 4.83	**0.019**
Rheumatoid Factor (IU/mL)	24.12 ± 12.22	17.5 ± 6.03	23.53 ± 9.56	20.88 ± 8.76	0.085
Anti CCP Antibody (IU/mL)	58.75 ± 42.53	99.53 ± 110.97	147.94 ± 221.98	117.24 ± 167.08	0.384
DAS28-ESR	3.08 ± 0.51	3.58 ± 1.05	4.49 ± 1.16	3.94 ± 1.17	**0.015**
FRAX Score for Major Osteoporotic Fracture	1.27 ± 0.49	2.27 ± 1.47	7.45 ± 6.52	4.5 ± 5.18	**<0.001**
FRAX Score for Hip Fracture	0.05 ± 0.06	0.74 ± 0.93	3.93 ± 3.54	2.11 ± 2.95	**<0.001**

The mean FRAX score for major osteoporotic fracture was 4.5 ± 5.18% with minimum of 1% and maximum of 23% whereas for hip fracture 2.11 ± 2.95% with minimum of 0 and maximum of 12%. There were 9 patients having FRAX score >= 3% for hip fracture while 2 patients had FRAX score >= 20% for major osteoporotic fracture. Overall, 9 (22.50%) patients were having FRAX score above the cut-off for initiating anti-osteoporotic treatment according to NOF and FRAX guidelines.

Univariate linear regression analysis was done to find out correlation between FRAX scores and factors affecting it. It was found that age, disease duration, tender joint count, ESR, DAS28-ESR score, glucocorticoid intake and history of previous fracture had a significant positive correlation, while T-score at femur neck, lumbar spine and forearm had a significant negative correlation with FRAX scores. Current smoking showed positive correlation with FRAX score for hip fracture (Tables IIA and IIB).

On further analysis by multivariate regression, it was found that age, history of previous fracture, glucocorticoid intake and T-score at femoral neck were independent predictors of FRAX score for major osteoporotic fracture and similarly age, history of previous fracture, smoking and T-score at femoral neck were independent predictors of FRAX score for hip fracture (Table III).

Discussion

This study is amongst the few Indian studies which evaluated fracture risk in patients with RA using FRAX calculator.

The present study showed a prevalence of osteoporosis as 55% in patients with RA, which was significantly higher compared to that seen in general population in community studies[14,15]. In a cross-sectional study by Gandhi AB *et al*, evaluation of femur neck and lumbar spine BMD in healthy females above 40 years of age showed a prevalence of osteoporosis as 8 %[14]. Another cross-sectional study by Nidhi S Kadam *et al*, done in healthy adults aged 40 years and above, found 5.7% of males and 12.7% of females having osteoporosis at the hip[15]. In our study, in spite of

Table IIA: Univariate regression analysis for association of FRAX score (for hip fracture) with various factors.

FRAX Score for Hip Fracture	Beta Co-efficient	Standard Error	p value	Lower Bound (95%)	Upper Bound (95%)
Age (years)	0.278	0.030	**<0.0001**	0.217	0.338
Duration (years)	0.538	0.062	**<0.0001**	0.413	0.663
Tender Joint Count	0.379	0.145	**0.013**	0.085	0.673
Swollen Joint Count	0.545	0.398	0.179	-0.261	1.351
ESR (mm/hr)	0.077	0.035	**0.034**	0.006	0.148
CRP(mg/L)	0.150	0.096	0.126	-0.044	0.344
Rheumatoid Factor	0.045	0.054	0.414	-0.065	0.154
Anti-CCP	0.004	0.003	0.134	-0.001	0.010
Gender-Male	2.259	1.187	0.065	-0.144	4.663
BMI (kg/m^2)	-0.192	0.229	0.408	-0.656	0.272
DAS28-ESR	1.072	0.370	**0.006**	0.324	1.821
Current Smoker	3.523	1.699	0.045	0.084	6.962
Alcohol Intake	3.466	2.092	0.106	-0.769	7.701
Previous Fracture	6.911	1.398	**<0.0001**	4.080	9.742
Parent with Hip Fracture	-2.059	3.005	0.497	-8.143	4.025
Glucocorticoids	3.358	0.874	**0.0005**	1.588	5.128
Femur T-Score	-2.381	0.537	**<0.0001**	-3.468	-1.294
Lumbar Spine T-Score	-1.908	0.495	**0.0004**	-2.910	-0.906
Forearm T-Score	-1.603	0.457	**0.001**	-2.529	-0.678

Table IIB: Univariate regression analysis for association of FRAX score (for Major osteoporotic fracture) with various factors.

FRAX Score for Major Osteoporotic Fracture	Beta Co-efficient	Standard Error	p value	Lower Bound (95%)	Upper Bound (95%)
Age (years)	0.487	0.053	**<0.0001**	0.379	0.594
Duration (years)	0.957	0.106	**<0.0001**	0.742	1.172
Tender Joint Count	0.680	0.254	**0.011**	0.165	1.195
Swollen Joint Count	1.067	0.696	0.134	-0.342	2.477
ESR (mm/hr)	0.136	0.062	0.034	0.011	0.261
CRP (mg/L)	0.273	0.168	0.113	-0.068	0.614
Rheumatoid Factor	0.097	0.095	0.314	-0.095	0.288
Anti-CCP	0.009	0.005	0.078	-0.001	0.019
Gender Male	2.147	2.158	0.326	-2.221	6.515
BMI (kg/m^2)	-0.323	0.403	0.428	-1.140	0.493
DAS28 ESR	1.934	0.647	**0.005**	0.625	3.243
Current Smoker	3.099	3.113	0.326	-3.202	9.401
Alcohol Intake	3.158	3.776	0.408	-4.486	10.802
Previous Fracture	12.793	2.374	**<0.0001**	7.987	17.599
Parent with Hip Fracture	-2.564	5.303	0.632	-13.300	8.172
Glucocorticoids	5.702	1.558	**0.001**	2.547	8.857
Femur T-Score	-4.004	0.966	**0.0002**	-5.959	-2.049
Lumbar spine T-Score	-3.248	0.882	**0.001**	-5.033	-1.463
Forearm T-Score	-2.673	0.817	**0.002**	-4.327	-1.018

Table III: Multivariate regression analysis for independent predictors of FRAX score

FRAX score for Hip Fracture	Beta Co-efficient	Standard Error	p value	Lower Bound (95%)	Upper Bound (95%)
Age (years)	0.155	0.052	**0.006**	0.049	0.261
Duration (years)	0.126	0.133	0.348	-0.145	0.398
Tender Joint Count	0.118	0.092	0.206	-0.069	0.306
ESR (mm/hr)	-0.016	0.025	0.525	-0.066	0.034
Femur T-Score	-1.627	0.696	**0.0001**	-5.057	-1.326
Lumbar spine T-Score	-0.102	0.697	0.885	-1.528	1.324
Forearm T-Score	-0.116	0.448	0.798	-1.032	0.800
Current Smoker	2.653	0.866	**0.005**	0.881	4.425

younger population, a higher prevalence of osteoporosis was observed in patients with RA. Due to ethical considerations, healthy controls could not be subjected to DEXA scan and hence were not included in our study; thus data from studies in general population was used as control.

In our study, 34.61% females in pre-menopausal group had osteoporosis at any one site. In the study by Zahraa Nour in Egyptian cohort of 100 RA patients, prevalence of osteoporosis in pre-menopausal females was found as 45.8%[16], while in a study done in 394 RA patients in Norway, the prevalence was 6%[5]. These differences may be attributed to poor intake of vitamin D and calcium along with racial predilection, leading to earlier loss of BMD[17].

A significant negative correlation between disease activity measured by DAS28-ESR and T-score at femoral neck (r =-0.38, p = 0.015) was found in our study. 16 out of 18 patients with osteoporosis had DAS28-ESR suggestive of moderate or high disease activity. In a study done in Asian cohort by Katherine D. Wysham *et al*, low disease activity was associated with higher mean BMD at femoral neck (β 0.071, P = 0.020) similar to our findings[18].

Our study showed that BMD was lowest at Femur amongst the three sites in our patients. In a similar study in patients with RA, Sugiguchi S *et al* also found BMD of the femoral neck lower than lumbar spine[19].

In our study, the mean FRAX scores were 4.5 ± 5.18% for major osteoporotic fracture and 2.11 ± 2.95% for hip fracture with 22.50% of patients having FRAX scores above NOF cut-off to initiate anti osteoporotic treatment. In a similar observational cross-sectional study in North India, which included 185 cases of RA and 185 controls, it was observed that patients with RA were at a higher risk of developing major osteoporotic fracture (4.77 ± 5.04 *versus* 2.05 ± 1.84) and hip fracture (1.71 ± 2.81 *versus* 0.5 ± 0.95). They found that 15% of the RA patients and 5% of the control population had FRAX scores above cut-off for initiation of anti-osteoporotic treatment. Similar findings were reported by Meng *et al* in their study, which were comparable to our results[20,21].

Our study showed that age, disease duration, tender joint count, ESR, DAS28-ESR score, glucocorticoid intake and history of previous fracture had a significant positive correlation, while T-score at femur neck, lumbar spine and forearm had a significant negative correlation with FRAX scores. Current smoking showed a significant association with FRAX score for hip fracture. RF and ACPA levels did not show any correlation with fracture risk. However, multivariate analysis found only age, history of previous fracture, glucocorticoid intake, T-score at femoral neck and smoking as the independent predictors of FRAX score for major osteoporotic fractureor hip fracture.

In similar studies by Phuan-udom R *et al* and Meng *et al*, age, disease duration, glucocorticoid use and DAS28-ESR score were significantly associated with FRAX scores[21,22]. They also did not find correlation of RF and ACPA with fracture risk. Mukesh Sharma *et al* showed a significant association between history of previous fracture and parental history of hip fracture with higher FRAX scores, although it did not show any correlation between glucocorticoid use and fracture risk[20].

Many studies have shown an association between inflammatory markers like ESR and fracture risk[23-25]. It is possibly due to raised ESR causing accelerated loss of BMD and hence increased fracture risk.

A meta-analysis of 14 prospective cohort studies done by Zhen-Jie Wu *et al* in 2016 showed that the pooled relative risk for hip fracture in smoker vs non-smoker was 1.47 [95% CI (1.28 - 1.66), p = 0.05] which is compatible with our findings[26].

Our study had many limitations such as control population was not included due to ethical consideration regarding exposure of normal population to radiation during DEXA scan. The sample size was small and it was a single centre cross-sectional study. Patients were not followed-up, and it

was not known whether actual fracture did happen according to the calculated risk. Repeated FRAX scores are required to monitor the change in fracture risk since patients are on treatment and fracture risk may vary temporally.

Conclusions

The study concludes that patients with RA have increased prevalence of osteoporosis and are at higher risk of fracture. The 10 year risk of major osteoporotic and hip fracture calculated by FRAX score was high in these patients. Age, history of previous fracture, glucocorticoid intake and T-score at femoral neck were independent predictors of FRAX score for major osteoporotic fracture while age, history of previous fracture, current smoker and T-score at femoral neck were independent predictors of FRAX score for hip fracture. It is prudent to assess for fracture risk in patients with RA and initiate anti-osteoporotic measures.

Future long-term large prospective interventional studies are recommended to validate the FRAX score in RA patients.

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ORIGINAL ARTICLE

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Vascular Endothelial Growth Factor in Tuberculous Meningitis with Stroke

Cho Mangsoson Aimol, AK Nigam**, Kamna Singh***, Niteesh Singh*, Ashish Kumar**

Abstract

***Introduction:** Tuberculosis (TB) remains a global health challenge, with severe forms like central nervous system TB posing significant risks. Tuberculous meningitis (TBM) is particularly dangerous, leading to high mortality and neurological complications. This study investigates the role of Vascular Endothelial Growth Factor (VEGF) in TBM-related strokes, hypothesizing that VEGF-induced blood-brain barrier (BBB) breakdown may be a key factor.*

***Objectives:** To compare serum VEGF levels in patients of TBM with stroke and TBM without stroke, to determine the association of serum VEGF level and occurrence of stroke in TBM and its association with various clinical, biochemical and radiological features of TBM.*

***Methods:** A hospital-based case-control study was conducted among 90 TBM patients, admitted to SN Medical College and Hospital, Agra, from January 2023 to June 2024. Patients were categorised into those with clinically and radiologically confirmed TBM with stroke (cases) and TBM without stroke (controls). Data was analyzed using SPSS software version 25.0, with statistical significance set at $p < 0.05$.*

***Results:** The cerebrospinal fluid analysis showed significantly higher CSF protein and ADA levels in cases whereas CSF glucose was significantly lower in cases than controls. Serum VEGF levels were significantly higher in cases (722.9 ± 228 pg/mL) compared to controls (451.3 ± 453 pg/mL) ($p = 0.001$). Hydrocephalus was more common in cases (64.4%) than controls (33.3%). GCS <10 was considerably higher in cases (33.3%) than in controls (13.3%). The mean duration of illness was longer in cases (28.82 ± 16 days) than controls (23.0 ± 13 days).*

***Conclusion:** Elevated serum VEGF levels, hydrocephalus, poor GCS scores, and prolonged illness are associated with and may predict stroke in TBM patients. Early initiation of antiplatelet therapy could potentially reduce stroke incidence in TBM. Further prospective studies are required to confirm these findings and develop predictive markers.*

***Key words:** Tuberculous meningitis, stroke, VEGF, hydrocephalus, Glasgow Coma Scale score.*

Introduction

According to the Global Tuberculosis Report 2021[1], the most widespread infectious illnesses worldwide and a key contributor to poor health is tuberculosis (TB). According to the report, there were 188 cases of tuberculosis per one lakh people in India in 2020. Globally, one of the leading causes of mortality in 2020 was tuberculosis, accounting for up to 1.3 million fatalities among HIV-negative individuals (up from 1.2 million in 2019). Although TB typically impacts the lungs, it infects other areas of the body and result in extra-pulmonary tuberculosis (EPTB). EPTB comprises 15 - 20 per cent of all TB cases among HIV non-infected individuals and comprises around 40 - 50 per cent of new cases among HIV-infected individuals in India[22].

In impoverished nations, TBM presents a serious risk to public health because of its high fatality rate and lingering neurological effects. In India, the estimated death rate from TBM is 1.5 per 100,000 people. TBM accounts for around 5% of all EPTB cases[3]. The exact percentage of TB complicated by TBM is not exactly known. Different studies give different rates of occurrence according to the local prevalence. In high TB burden areas, large proportions (about 10%) are proposed, whereas in low TB prevalence settings, low proportions (around 1%)[4]. TBM is further complicated by the occurrence of stroke. About 25% of patients with TBM have been documented to have had a stroke in recent studies; however, earlier research has indicated that the incidence may as high as 57%[5,6]. Stroke occurs more often in TBM patients, increasing their mortality rate[7,8]. Many theories have been advocated in an effort to clarify why stroke occurs in TBM, including the role of several chemokines and cytokines, such as vascular endothelial growth factor (VEGF)[9,10]. One powerful modulator of endothelial permeability is VEGF. Acute ischaemic stroke, bacterial meningitis, brain tumours, and cerebral oedema have all been linked to VEGF-induced

**Junior Resident, **Professor, Department of Medicine, ***Associoate Professor, Department of Biochemistry, Sarojini Naidu Medical College, Agra - 282 003, Uttar Pradesh.*

***Corresponding Author:** Dr Cho Mangsoson, Junior Resident, Department of Medicine, Sarojini Naidu Medical College, Agra - 282003, Uttar Pradesh. Tel: 9910572677, E-mail: mangso2009@gmail.com*

disintegration of the BBB[11,12]. Regarding the blood level of VEGF and risk of occurring stroke in TBM patients, there is contradictory evidence.

VEGF is a glycoprotein that regulates permeability of vascular endothelium. VEGF does play a role in damaging BBB in bacterial meningitis, central nervous system (CNS) neoplasms, and brain infarctions[10]. However, only a handful of studies[13,14] have evaluated the role of VEGF in TBM. Without definitive information from well-executed prospective research, the impact of VEGF in the pathogenesis of TBM is yet not clear. Future treatment protocols based on anti-VEGF therapies may help in improving outcomes in TBM. Our goal was to study the role of serum VEGF in TBM cases who also had stroke and compare with cases of TBM who did not have stroke.

Material and Methods

A case-control Study was conducted on 90 patients (45 cases and 45 controls) who were admitted in the Department of Medicine, Sarojini Naidu Medical College Agra, Uttar Pradesh, India from December 2022 to June 2024. This study was approved by the Institutional Ethics Committee of Sarojini Naidu Medical College. All patients fulfilling inclusion criteria were included in this study. Inclusion Criteria were age 14 - 70 years, meningitis due to tuberculosis – definitive, probable and possible Tuberculous Meningitis (TBM) cases. Patients who had meningitis clinically and fulfilled the diagnostic criteria for definite, probable and possible tuberculous meningitis with radiologically proven stroke were taken as cases. Patients aged 14 - 70 years who had meningitis clinically and fulfilled the criteria for definite, probable and possible tuberculous meningitis but without any evidence of stroke served as controls. Exclusion criteria were meningitis other than TB; patients who had chronic systemic illnesses such as diabetes mellitus, hypertension, chronic inflammatory Illnesses, autoimmune disorders, immunodeficiency disorders or any malignant disease; and suspected patients of meningitis who did not fulfill the criteria for definite, probable and possible TBM. Also those who had taken anti-tubercular treatment once or more in the past were excluded. Clinical examination was carried out for all patients. All patients were subjected to a series of tests including CSF analysis, serum VEGF, CT scan and/or MRI brain. Under all aseptic precautions blood and CSF was collected for study patients. For serum VEGF level, 2 mL of venous blood sample of each patient from both cases and control group were centrifuged at 3500 revolution per minutes for five minutes. Serum was aliquoted and stored at minus twenty degree Celsius for batch analysis by ELISA Method in the research laboratory of Biochemistry Department. The two groups (cases and controls) were compared for various parameters including duration of illness, blood haematological and biochemical parameters, clinical features, CSF parameters, serum VEGF levels and neuroimaging abnormalities.

Statistical analysis

Data was entered into Microsoft Excel and analysis was done with SPSS software v 25.0. The result was analysed using descriptive statistics and making comparisons among the two groups. Distributed variables were summarised as in proportion and percentage (%) while discrete variables were summarised as mean and Standard Deviation. Applying the chi-square/fisher-exact test for qualitative variables and the unpaired Student's t-test for quantitative variables, the two groups with normal distribution curves were compared. The results were classified as significant if $p < 0.05$.

Result

In this study, the majority participants were of age between 14 and 30 (55.5%) years in cases and 21 to 30 years in controls (51.1%) with mean age 32.8 ± 15.0 and 29.7 ± 14.2 years, respectively for cases and controls ($p > 0.05$).

Out of 90 studied patients (45 cases and 45 controls), the majority were males (64.4%) in cases whereas in controls majority were females (64.4%). We also compared hematological and biochemical variables between cases and controls and it was found that there were no significant differences in the parameters between the two groups ($p > 0.05$). The LFT variables were comparable between cases and controls with no difference between the two ($p > 0.05$). We compared the cerebrospinal fluid between cases and controls and it was found that CSF-TLC, protein and ADA levels were higher among cases than controls ($p < 0.05$). However, CSF glucose was considerably lower in cases than controls ($p < 0.05$). There was lymphocyte predominance in both cases and controls with no significant differences ($p > 0.05$) (Table I).

The comparison of serum VEGF levels in both groups was done. It was observed that the mean serum VEGF was significantly higher in cases (722.9 ± 228 pg/mL) than in controls (451.3 ± 453 pg/mL) ($p < 0.001$) (Table III). The distribution of patients based on hydrocephalus in both groups was studied and found that hydrocephalus was significantly higher numbers among cases (64.4%) than controls (33.3%) with p value <0.006 (Table IV). The presence of tuberculomas was comparable between cases (33.3%) and controls (28.9%) ($p > 0.05$) (Table V). Regarding the distribution of GCS score in both groups, it was found that among cases, GCS <10 was in a much higher proportion (33.3%) than controls (13.3%) but it was not significant ($p > 0.05$). Based on duration of their illness both groups were studied. The mean duration of illness among cases was

28.82 ± 16 days which was higher than controls (23.0 ± 13 days) but the difference was insignificant (p >0.05) (Fig. 2). Different locations of infarctions in the stroke groups were also studied and it was found that the majority of the cases had basal ganglia infarct (44.44%) followed by cortical infarct (37.77%), multifocal infarcts (31.11%), thalamic infarct (8.88%), and least had brain stem infarct (4.44%) and cerebellar infarct (4.44%) (Fig. 3).

Table I: Cerebro-Spinal Fluid (CSF) in both groups.

CSF	Cases (n = 45) (Mean ± SD)	Controls (n = 45) (Mean ± SD)	p-value
TLC (per cumm)	134.0 ± 25.8	121.5 ± 22.6	**0.016**
DLC- Polymorphs (%)	9.62 ± 8.21	8.8 ± 6.92	0.609
DLC- Lymphocytes (%)	90.48 ± 8.30	89.53 ± 13.89	0.693
Protein (mg/dL)	414.9 ± 121.5	233.4 ± 116.6	**0.004**
Glucose (mg/dL)	39.3 ± 11.8	44.98 ± 12.3	**0.030**
ADA (IU/L)	26.7 ± 21.0	19.5 ± 14.8	**0.005**

Table II: Clinical features in both groups.

Clinical features		Cases (n = 45)	Controls (n = 45)	p-value
Fever		40 (88.9)	41 (91.1)	1.00
Headache		37 (82.2)	33 (73.3)	0.447
Vomiting		30 (66.7)	30 (66.7)	1.00
Seizure		8 (17.8)	7 (15.6)	1.00
Weight Loss		24 (53.3)	24 (53.3)	1.00
Neck Rigidity/Kernig Sign		39 (86.7)	37 (82.2)	0.772
Altered Sensorium		39 (86.7)	40 (88.9)	1.00
Hemiparesis		35 (77.7)	0 (0.0)	0.001
Cranial Nerve Palsy	6th Cranial Nerve	3 (6.7)	2 (4.4)	0.510
	7th cranial nerve	2 (4.4)	0 (0.0)	
	3rd cranial nerve	1 (2.2)	1 (2.2)	
Ataxia		2 (4.4)	0 (0.0)	0.152
Hemianesthesia		4 (8.8)	0 (0.0)	0.040

Table III: Comparison of serum VEGF levels in both groups.

VEGF	Cases (n = 45)	Controls (n = 45)	p-value
Mean ± SD (pg/mL)	722.9 ± 228	451.3 ± 453	**0.001**

Table IV: Hydrocephalus in both groups.

Hydrocephalus	Cases (n = 45) (%)	Control (n = 45) (%)	p-value
Yes	29 (64.4)	15 (33.3)	**0.006**
No	16 (35.6)	30 (66.7)	

Table V: Tuberculoma in both groups.

Tuberculoma	Cases (n = 45) (%)	Control (n = 45) (%)	p-value
Yes	15 (33.3)	13 (28.9)	**0.820**
No	30 (66.7)	32 (71.1)	

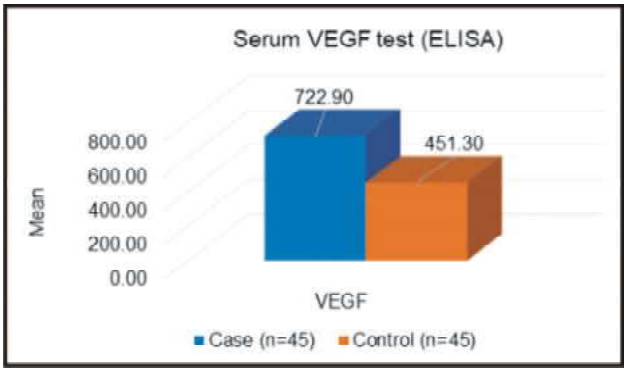

Fig. 1: *Comparison of serum VEGF levels in both studied groups.*

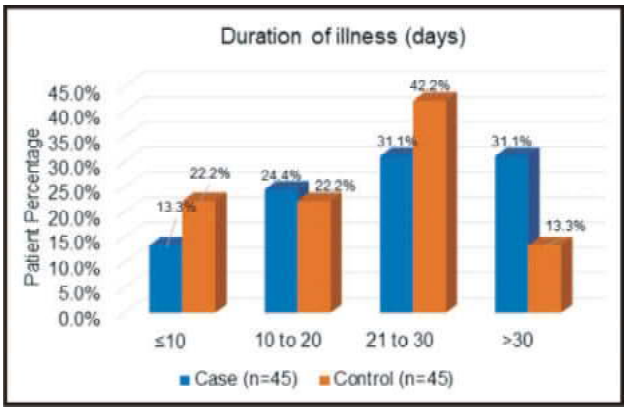

Fig. 2: *Duration of illness (days).*

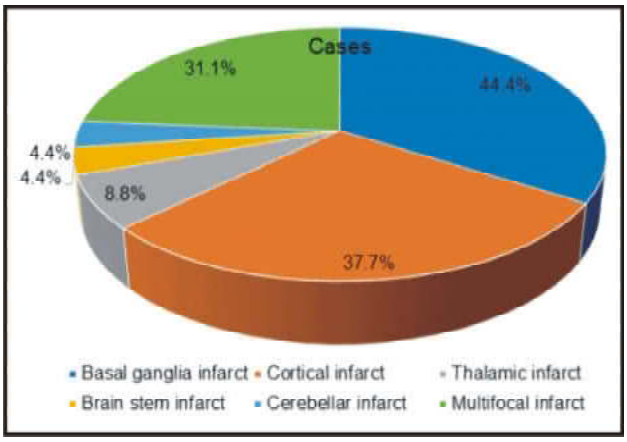

Fig. 3: *Locations of infarction in the stroke group.*

Discussion

Our results were similar to those of Jhamb *et al*[15] who

examined blood VEGF values in TBM patients with and without stroke. We compared 40 patients with suspected or confirmed tuberculous meningitis who have stroke with those who did not have stroke. The 2 groups were comparable regarding age and gender (p value greater than 0.05). Likewise, Tang *et al*[16] reported that the mean age of cases with TBM with stroke was 59.50 ± 18 years, and TBM without stroke was 54.00 ± 13. years with male predominance. Similarly, Kumar *et al*[17] reported that the mean age of TBM patients (29.9 ± 13.1 years) was significantly less (p <0.05) than the population of controls (41.82 ± 9.5 years). There were 33 (40.2%) men and 49 (59.8%) women in the TBM group and 22 (44.9%) men and 27 women (55.1%) among control group.

The current research revealed that the mean VEGF was significantly higher in cases (722.9 ± 228 pg/mL) than in controls (451.3 ± 453 pg/mL) (p <0.05). There were significantly greater numbers of hydrocephalus in the cases group (64.4%) than control group (33.3%). Tuberculoma was comparable between cases (33.3%) and controls (28.9%) (p >0.05). Our findings were supported by Jhamb *et al*[15] who reported that the mean serum levels of VEGF in TBM without stroke was 499.33 ± 230.32 pg/mL, but those with TBM plus stroke, the mean levels were 1218.37 ± 570.11 pg/mL. MRI results revealed that cases of hydrocephalus were notably more common than controls (p = 0.018). Tuberculomas on MRI have shown negligible difference between the patients and controls (p = 0.644). Comparable blood level of VEGF has been documented by Husain *et al*[1,18] whereby they measured the levels of VEGF in serum as well as CSF in twenty cases of intraparenchymal tuberculoma and twenty-two cases of TBM using an enzyme-linked immunoassay (ELISA). The mean blood levels of VEGF were 694.9 ± 820.6 pg/mL for active TBM, 499.62 ± 238.34 pg/mL for inactive TBM, and 541.02 ± 389.06 pg/mL for tuberculoma. In CSF, active TBM cases had significantly higher VEGF levels (106.02 ± 50.04 pg/mL) than inactive TBM (14.72 ± 10.08 pg/mL, p <0.05). VEGF expression was shown to be highly expressed in excised tuberculoma when stained with immuno-histochemistry. An increasing length of therapy for tuberculoma was associated with a serial decline in serum VEGF values. They concluded that elevated CSF and serum VEGF levels reflect disease activity in neuro-tuberculosis, and that a slow decline in these levels over time likely indicates a favourable therapy outcome.

Matsuyama *et al*[19] found a significant increase in VEGF (in blood and CSF) in TBM (n = 28) than other CNS infections (n = 31). Follow-up VEGF levels decreased in patients who showed clinical improvement (n = 12). They stressed the importance of VEGF in TBM. In another study conducted on the paediatric population, CSF VEGF was significantly higher in TBM (n = 26) than healthy children (n = 20). VEGF levels and the number of CSF mononuclear cells correlated positively. Thus, inflammatory cells in CSF secrete VEGF which, in turn, damages BBB. The authors suggested that steroids may exert their benefit in TBM by antagonizing the effects of VEGF.

Jhamb *et al*[15] reported that blood VEGF levels and stroke was associated with a low GCS score in patients suffering from TBM, according to a multivariate logistic regression study comparing TBM patients with and without stroke. Studies comparing the blood VEGF levels of TBM patients who have experienced a stroke to those who have not are extremely rare in the literature. In research done by Van Der flier *et al*[13,20], twenty children with fever whose lumbar puncture ruled-out meningitis were compared to a sample of blood as well as CSF samples of twenty-six children with TBM. There was elevated VEGF in the CSF of fifteen out of twenty-six (58.10%) patients with TBM (98 ± 32 pg/mL), while not a single control patient (all less than 25 pg/mL; p = 0.0393) had any detectable levels. Additionally, in contrast to controls (69 ± 13 pg/mL), the plasma VEGF concentrations in TBM patients (182 ± 52 pg/mL) were considerably greater (p = 0.045). The computed VEGF index was 486 ± 976, indicating intrathecal VEGF production. In their study, periventricular oedema, tuberculoma, and cerebral infarction were all seen on cranial CT scans in 66% of patients, 17%, and 38% patients, respectively. However, there was no correlation between the presence of these pathologic abnormalities with CSF VEGF concentrations[1,24].

Also, among cases lower GCS <10 (33.3%) were much higher in number than that of the controls (13.3%) but in those patients who have higher GCS score between 10 - 14 and GCS score ≥15 the p value was insignificant (p = 0.058) between the two studied groups. Our results aligned with those of Jhamb *et al*[15] that there were no significant variations between the two groups of participants with respect to the presenting signs and symptoms (cranial nerve palsy, fever, headache, vomiting, weight loss, and seizures) or duration of illness at presentation, except hemiparesis. Patients with stroke who had advanced TBM (stage 3 BMRC) were more prone to have low GCS, hemiparesis, and other symptoms at presentation (p = 0.05). This was corroborated by a similar observation made in another study by Kalita *et al*[21], where the incidence of stroke in TBM was associated with the presence of a localised neurological impairment at presentation.

In this study, the average length of illness for the cases was 28.82 ± 16 days which was higher than controls (23.0 ± 13 days) but the difference was insignificant (p >0.05). The majority of cases had basal ganglia infarct (44.4%) followed by cortical infarct (37.7%), multifocal infarct (31.1%), thalamic infarct (8.8%), least had brain stem infarct (4.4%)

and had cerebellar infarct (4.4%). Jhamb *et al*[15] reported that, at the time of presentation, the mean illness duration in cases was considerably longer (33.1 ± 9.34 days) than in controls (24.6 ± 6.92 days) ($p < 0.01$). Anuradha *et al*[22] state that among the locations where an infarct was looked for were the thalamus, internal capsule, cerebellum and brainstem. They also concluded that the regions of the main cerebral arteries namely the posterior cerebral arteries, anterior cerebral arteries, and middle cerebral arteries can also be affected.

The results of this study suggest a rise in VEGF levels during hyper-acute as well as acute phases of haemorrhagic or ischaemic stroke implying a shift of tissue and circulation abnormalities that are common in early stroke. Early subacute phases of ischaemic and haemorrhagic strokes are marked by elevated VEGF levels, which point to continued regeneration, including neo-angiogenesis.

Conclusion

We can conclude that characteristics like high serum VEGF levels, hydrocephalus, hemiparesis, poor GCS at presentation, and prolonged illness duration at presentation are associated with stroke in TBM and could be predictive markers for stroke in TBM. Early TBM diagnosis and treatment with anti-platelet medications (dipyridamole and aspirin) may reduce and even prevent stroke in TBM patients. If any metric or disease marker can be created that can preduct stroke in the initial phase of TBM, more prospective studies are essential to clarify the significance of the aforementioned factors in stroke prediction.

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ORIGINAL ARTICLE

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Out-Of-Pocket Expenditure by Patients in Pre-treatment Evaluation of Gynaecologic Cancer

Nazia Parveen, Sandhya Jain**, Vishakha Singla***, Pooja Sharma****, Rachna Agarwal***

Abstract

Objective: Out-Of-Pocket Expenditure (OOPE) is a substantial economic burden to gynaecologic cancer patients and their families. The purpose of this study was to calculate the Out-Of-Pocket Expenditure and incidence of Catastrophic Health Expenditure (If OOPE exceeds 40% of non-food expenditure of family) during the gynaecologic cancer diagnosis.

Methods: 89 patients of various gynaecological cancers were enrolled from the Out-Patient Department and data was collected regarding cost incurred by patients and caregivers under heading of direct medical, direct non-medical, and indirect cost.

Results: The average OOPE for diagnostic evaluation of a patient receiving care for gynecological cancers in this institute was found to be INR 27587.16 with a standard deviation (SD) of INR 27334.4. The average direct medical cost, direct non-medical cost, and indirect costs were INR 8106.8 (SD 8368.2), INR 3113.4 (SD 3346.99), and INR 16366.8 (SD 21507.14) respectively. The patients with ovarian cancers (INR 37356.80) spent the highest OOPE which was statistically significant ($p < 0.05$). The direct non-medical and indirect costs, were highest for ovarian cancer patients at INR 4115.29 (3921.62) and INR 22774.29 (25768.9) respectively. It was observed that 30.33% of the individuals were found to have catastrophic health expenditures.

Conclusion: The high cost paid by patients in terms of OOPE in gynaecologic cancers diagnosis has a direct impact on delayed cancer diagnosis and related morbidity.

Key words: Gynaecologic cancers, Out-Of-Pocket Expenditure, direct medical cost, direct non-medical cost, indirect cost, catastrophic health expenditure.

Introduction

The incidence of cancer is rising worldwide and is expected to increase further in the coming decades[1, 2]. According to the Global Cancer Observatory (GLOBOCAN) 2020, the total incident cancer cases were 19.3 million worldwide. India comes in third place after China and the United States of America[2]. The diagnosis and treatment of cancer are not only associated with physical and emotional burdens but also with a huge financial burden on the affected households. In developed countries, the state shares a large part of the financial burden of cancer treatment because of comprehensive health insurance policies. The greatest sources of economic burden among cancer patients include health services expenditures and lost income of patient and caretaker[3,4]. The situation is worse in developing countries like India with little assistance from the government. Only 25% of the Indian population is covered by some kind of health insurance scheme.

Like any other cancer, gynaecologic cancers are associated with a high economic burden of diagnosis and treatment on both families and society. The cost incurred by patients and families not only includes the cost of diagnostic investigations, medicines, and consultation charges but also the money spent on travel, food, accommodation, and daily wage losses. Out-of-pocket expenditure (OOPE) is defined as the total amount of money spent by the patient or family during diagnosis/treatment, which includes direct medical and non-medical costs as well as indirect costs. Direct medical expenditure includes costs of investigations, medicines, consultation charges, etc. Direct non-medical expenditures include costs on travel, food, and accommodation expenses[5]. Indirect cost is defined as loss of income due to absence from work of a patient/caretaker while being investigated/treated. Catastrophic health expenditure (CHE) is said to be present if the health expenditure of the family for the present cancer (total OOPE) is more than or equal to 40% of the annual Capacity To Pay (CTP). CTP can be defined as the total non-food expense of the family (household expenses-food expenses per month). The monthly CTP is multiplied by 12 to get the annual CTP[6].

According to the National Sample Survey Organisation (2015), around 60% of the healthcare expenditure is paid

**Associate Professor, **Director Professor, ****Senior Resident, Department of Obstetrics and Gynaecology, University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi - 110 095; ***Student, Department of Economics, St. Stephens College, Delhi University, Delhi - 110 007.*

Corresponding Author: Dr Sandhya Jain, Director Professor, Department of Obstetrics & Gynecology, University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi - 110 095. Tel: 9958811946, E-mail: drsandy2015@gmail.com

out-of-pocket by patients in India[7]. This causes an extra strain on household finances. Even before reporting to tertiary care hospitals, patients spend money going to small or private health facilities. To our knowledge, there have been very limited studies conducted in India which estimated the OOPE borne by cancer patients[8-11]. Therefore, we conducted this study to estimate the OOPE from the onset of symptoms till the diagnosis for various types of gynaecological cancers at a tertiary care hospital in Delhi. The various gynaecologic cancers were cervical, ovarian, uterine, vulval, and vaginal cancers. The primary objective was to calculate the OOPE (direct and indirect) by patients in the pre-treatment evaluation of gynaecologic cancer and the secondary objective was to calculate the CHE rate in the pre-treatment evaluation of gynaecologic cancers. The CHE rate is the proportion of patients who experience catastrophic expenditure out of total patients included in the study.

Methodology

This cross-sectional study was conducted at a tertiary care government hospital in Delhi from July 2023 to Oct 2024. We receive referrals from other smaller government hospitals and private clinicians from Delhi and other states. This was a pilot study, approved by the ethics committee of the hospital (GTBHEC 2024/P-201), and the study was registered under ClinicalTrials.gov (Reg. No.-CTRI/2024/07/070008). The patients who had been diagnosed/suspected gynaecological cancers referred from smaller health sectors, both government and private, were included in the study. The exclusion criteria were any other non-gynaecologic cancers. Patients were enrolled from the Out-Patient Department and data was analysed for 89 participants. Written consent was taken from all participants. Pre-designed performa was used to collect data from patients and/or family members. In the study, a bottom-up micro-costing method was used to estimate the OOPE (direct and indirect costs) associated with diagnosing gynaecologic cancer. Micro-costing or bottom-up costing is defined as a method of cost calculation in which each component of resource use (e.g., laboratory tests, drugs, travel, food expenses) is estimated and a unit cost is derived for each. This is used for precise calculation of the economic costs of health interventions. Here, the cost was calculated for each element of an intervention.

The data was collected by the principal investigator along with the co-investigator. The details were collected regarding demographics. The details of the money spent under various headings, e.g., laboratory investigations, imaging, drugs, blood transfusion and medical materials, transportation to the hospital, food expenses during hospital visits, and accommodation expenses for both the patients and the caretaker were collected based on the recall of patient and relatives. Details of the patient's total family income from all sources were collected. The total family expenditure pattern was obtained from the patient or the caregiver to calculate the capacity to pay. The CHE rate, i.e., the proportion of patients who experienced catastrophic expenditure out of the total patients included in the study, was also calculated. All costs are reported in Indian National Rupees (INR). We only took the details of the cost incurred during the diagnostic workup of gynecologic cancers, i.e., from the onset of first symptoms till the final diagnosis of cancers. The histopathological reports of gynaecological cancers were also collected and recorded to confirm the final diagnosis. Complete confidentiality of the information collected was ensured.

Statistical and sensitivity analysis

Data were managed by MS Excel and then statistically analysed using SPSS statistical software, version 22 (SPSS Inc., Chicago, IL). Descriptive statistics were used to describe basic characteristics. Age as a quantitative variable was presented as the mean, while qualitative variables including residence, education status, occupation, level of income per month, and payment scheme were presented as frequency and percentage. All costs were reported as INR in terms of mean and Standard Deviation (SD).

Results

A total of 89 cases of gynaecological cancers were recruited. The basic demographic characteristics are shown in Table I. The mean age of study participants was 49 years. Around 74.15% of participants were from urban backgrounds. Almost half (59.55%) of the participants received no formal education.

The disease characteristics of all participants are shown in Table II. Cancer patients comprised of ovarian (35), cervix (33), endometrial (19), choriocarcinoma (1), and vulval (1) cancer. The majority of patients (72.9%) presented in stage II and onward. Usually the cancer patients first approach nearby private practitioners or smaller government hospitals before being referred to tertiary care hospitals. Therefore, patients have to spend money and time before the final diagnosis and initiation of treatment. The mean duration from onset of symptoms till reporting to this tertiary care hospital was 10.56 months across all cancers. This could be a causative factor for presentation of cancers in the advanced stage. It was observed that almost 60% of participants showed up in other smaller government hospitals before coming to our hospital and the rest were

showing in private clinics, quacks, or ayurvedic doctors.

Table I: Socio-Demographic Characteristics of the Study Group.

Characteristics	N (%)	
Mean Age (years)	**49**	
Marital status	Unmarried	4 (4.49)
	Married	74 (83.14)
	Widow/ Divorced	11 (12.3)
Religion	Hindu	63 (70.7)
	Muslim	25 (28.0)
	Other	1 (1.1)
Education	Illiterate	53 (59.55)
	Senior Secondary	30 (33.7)
	Graduate	6 (6.7)
Occupation	Unskilled	65 (73)
	Semiskilled/Skilled	24 (26.96)
Type of family	Nuclear	50 (56.17)
	Joint	39 (43.82)
Locality	Urban	66 (74.15)
	Rural	23 (25.84)

Table II: Disease characteristics of cancer patients.

Stage	Ovarian	Cervix	Endometrial	Others
I (25.84%)	5	8	10	1 (Choriocarcinoma)
II (35.95%)	8	16	7	1 (vulval)
III (33.7%)	20	9	1	
IV (3.3%)	2	-	1	
Mean duration from onset of symptoms till hospital visit (months)	11.8	9.7	11.38	8.5
Type of Previous consultation				
Private (41.57%)	16	12	8	1
Government (59.55%)	19	22	11	1

Table III shows socio-economic characteristics of the study participants. Among the 89 participants, 77.52% had above the poverty line ration card. The awareness regarding various government health schemes was very limited and only 34.83% of participants were aware of the Ayushman Bharat Scheme. Only one of the participant reported utilisation of any health insurance scheme.

Out-Of-Pocket Expenditure

The average OOPE for diagnostic evaluation of a gynaecological cancers patients borne by was found to be INR 27587.16 with a SD of INR 27334.4 as mentioned in Table IV. The average direct medical, direct non-medical, and indirect costs were INR 8106.8 (SD 8368.2), INR 3113.4 (SD 3346.99), and INR 16366.8(SD 21507.14) respectively. The patients with ovarian cancers (INR 37356.80) spent the highest OOPE which was statistically significant ($p < 0.05$). The average money spent by other type of cancers (choriocarcinoma and vulval cancer) patients on direct medical costs was INR 14150.0 (20011.12) followed by ovarian cancer patients as INR 10467.23 (7850.17). Although the other group comprised only two patients. The Direct non-medical and indirect costs were highest for ovarian cancer patients at INR 4115.29 (3921.62) and INR 22774.29 (25768.9) respectively as shown in Table IV. The difference in direct non-medical and indirect costs among the various sites of cancer was found to be statistically significant (p value <0.005).

Table III: Socio-economic characteristics of the participants.

Characteristics	n (%)	
Type of Ration Card	Above Poverty Line	69 (77.52)
	Below Poverty Line	3 (3.37)
	No Ration Card	17 (19.10)
Awareness of Ayushman Bharat Scheme	Yes	31 (34.83)
	No	58 (65.16)
Recipient of any Health Benefit	Yes	0
	No	89 (100)
Recipient of any Health Insurance	Yes	1 (1.12)
	No	88 (98.87)

Table IV: Out of Pocket Expenditure (OOPE) of different cancer types.

Type of cancer	Ovarian	Cervical	Endometrial	Others (GTN, Vulval)	p-value
Direct Medical Mean (SD)	10467.23 (7850.17)	5431.21 (8325.32)	7770.00 (7235.38)	14150.0 (20011.12)	**0.005**
Direct Non-Medical Mean (SD)	4115.29 (3921.62)	2129.09 (2745.0)	3118.42 (2887.33)	1775.0 (1025.31)	**0.003**
Indirect Mean (SD)	22774.29 (25768.9)	9725.76 (14362.91)	17084.2 (21664.36)	7000 (707.11)	**0.001**
Total OOPE Mean (SD)	37356.80 (30457.36)	17286.06 (20249.09)	27972.63 (27676.83)	22925.0 (20329.32)	**<0.05**

**OOPE – Out of Pocket Expenditure, GTN – Gestational Trophoblastic Neoplasia*

**Direct (medical) cost includes costs of investigations, medicines, consultation charges, etc.*

**Direct (non-medical) cost include costs on travel, food, and accommodation expenses.*

**Indirect cost is defined as loss of income due to the absence from work of a patient/caretaker while being investigated/treated.*

**All costs are in INR.*

Table V: Direct (medical and non-medical) and indirect costs incurred by gynecological cancers (n = 89).

	Direct (Medical) Mean (SD)	p-value	Direct (Non-medical) Mean (SD)	p-value	Indirect Mean (SD)	p-value	Total OOPE Mean (SD)	p-value
Age (years)								
<30	11829.29 (8884.11)	0.41	3288.57 (1812.81)	0.72	9142.86 (5421.51)	0.41	24260.71 (11961.12)	0.42
31 - 60	8645.33 (8340.55)		3608.00 (3885.76)		17593.33 (16556.92)		29846.67 (23634.53)	
>60	7840.56 (6810.03)		3827.22 (5476.91)		21386.11 (29378.63)		33053.89 (36796.43)	
Occupation								
Unskilled	7209.74 (7767.76)	0.11	3068.85 (3705.42)	0.09	14776.92 (19812.5)	0.104	25055.51 (25482.22)	0.08
Skilled	10536.67 (9570.68)		3234.17 (2152.88)		20672.92 (25515.85)		34443.75 (31379.91)	
Locality								
Rural	9238.26 (9075.26)	0.36	3710.00 (3499.59)	0.25	15263.04 (14331.05)	0.41	28211.30 (20203.72)	0.31
Urban	7712.62 (8143.69)		2905.53 (3294.13)		16751.52 (23582.56)		27369.67 (29550.14)	
Education								
Illiterate	7763.36 (8934.21)	**0.03**	2793.49 (3008.09)	**0.01**	15576.42 (24493.76)	0.08	26133.26 (30595.37)	0.07
Senior secondary	7321.83 (7099.81)		2807.33 (2063.37)		18203.33 (17357.56)		28332.50 (22548.17)	
Graduate	15066.67 (6849.42)		7470.00 (7344.38)		14166.67 (11021.19)		36703.33 (18458.01)	
Socio-economic status								
Lower	9300	0.58	2200	**0.03**	24100	0.56	35600.00 (NR)	0.53
Lower-middle	7854.40 (8748.22)		2923.58 (2847.91)		15691.51 (21741.6)		26469.49 (28083.07)	
Upper-lower	7551.50 (8389.61)		2346.25 (2396.09)		17605.0 (26097.9)		27502.75 (29750.28)	
Upper-middle	9323.08 (7996.78)		3386.15 (2374.95)		16061.54 (14695.66)		28770.77 (21900.33)	
Upper	11850.0 (4454.77)		14500.0 (10606.61)		20000 (21213.21)		46350.0 (36274.57)	
Ration card								
Above poverty line (70)	7831.83 (8157.37)	0.28	3204.64 (3620.91)	0.57	16997.86 (22705.29)	0.52	28034.33 (29469.19)	0.37
Below poverty line (2)	20250.00 (15485.63)		4150.00 (2757.71)		15050.0 (12798.63)		39450.00 (5444.72)	
No card (17)	7810.88 (8021.31)		2615.88 (494.86)		13923.53 (17386.82)		24350.29 (18244.67)	
Health insurance utilisation								
Yes (1)	8700.0	–	7000	—	5000	—	207000.0 (NR)	NR
No (88)	8100.15 (8415.94)		3069.26 (3339.99)		16496.02 (21595.65)		27665.43 (27481.03)	
Awareness about Ayushman Bharat Scheme								
Yes	10857.03 (8691.01)	**0.01**	4445.16 (4302.88)	**0.01**	21801.61 (24192.21)	**0.003**	37103.81 (29534.64)	**0.002**
No	6636.98 (7876.92)		2401.64 (2463.78)		13462.07 (19530.51)		22500.69 (24876.53)	

Table V shows the section-wise direct (medical and non-medical) and indirect costs experienced by patients. Direct medical, direct non-medical, and total OOPE costs for each of the independent variable categories is given as mean with standard deviation (SD). Direct medical cost was higher in the <30 years age group (INR 11829.2) whereas direct non-medical cost and indirect cost were higher in the >60 year age group with INR 3827.2 and INR 21386.1 respectively. The OOP expenditure for the age group >60 years was highest at INR 33053.89 than younger age groups, although it was not statistically significant. As per the different occupational categories, there was no statistically significant difference in the total OOPE. Based on residence, we found no statistically significant difference in OOPE between urban and rural patients (INR 28211.30 vs INR 27369.67, p value 0.046).

As per the literacy status of the study group, graduates

spent the highest average OOPE of INR 36703.33, direct medical of INR 15066.67, and non-medical costs of INR and 7470.00 (p value 0.07, 0.03 and 0.01 respectively).

The OOP expenditure by upper class as per Modified Kuppuswamy Classification was higher. This could be due to the high direct non-medical cost spent by upper class patients (INR 14500.0). The upper-class patients had the highest average OOPE of INR 46350.0, although not statistically significant. The OOPE was slightly more in the patients having below poverty line ration card (INR 39450.00), although not statistically significant. In the present study, only one patient utilised health insurance, while rest 88 patients did not utilise health insurance, hence comparison was not done.

Patients who were aware about the Ayushman Bharat Scheme spent highest direct medical, non-medical (INR 10857.03, INR 4445.16) and indirect medical cost (INR 21801.61) when compared to those who unaware about this scheme (p value <0.005).

Catastrophic health expenditure calculation

The details of household expenditure patterns of families and the OOPE were analysed to explore the proportion of households suffering catastrophic health expenditure due to gynaecological cancer evaluation and diagnosis. The findings revealed that 30.33% of the patients' families had experienced catastrophic health expenditures (OOPE payments are greater than 40% of non-food expense of the family per year). According to type of gynaecological cancer, it was observed that 50% of other types of cancers (vulval and choriocarcinoma) and 45% of ovarian cancer patients had suffered CHE as mentioned in Table VI.

Table VI: Proportion of study population with Catastrophic health expenditure (CHE) present due to gynaecologic cancers (n = 89).

Variable	CHE Present n (%)
Pveralll	27(30.33%)
Site of cancer	
Ovarian	16 (45%)
Cervix	7 (21.2%)
Endometrial	3 (15.7%)
Other	1 (50%)

Discussion

The mean age of patients was ~ 49 years; the age distribution of the study participants of the present study was more towards the younger population as compared to previous studies conducted among head and neck cancer (HNC) patients in north india[12]. The same was seen in a study of 957 ovarian neoplasms, where malignant tumours presented between 41 and 50 years of age[13].

Most of the study population (74.15%) belonged to urban areas and from the lower middle class. The utilisation of health insurance was almost negligible (only one patient among 89), which is much less than reported in the study of Chauhan *et al*[12]. In the present study, awareness regarding Ayushman Bharat Scheme was also checked. Only 34.8% of patients were aware of Ayushman Bharat Scheme.

The results of the present study show that direct medical and direct non-medical costs for diagnostic workup of gynaecological cancers at a public facility in north India is INR 8106.8 and INR 3113.4, respectively. The indirect cost was highest at INR 16366.8. The addition of all, i.e., OOPE was INR 27587.16 which was less than the OOPE reported for various solid cancers treatment by KM Pradeep *et al*[14] from South India (INR 35,8169). The reported OOPE was INR 36,812 for Head and Neck Cancers from New Delhi in 2006. while a center from Chandigarh reported OOPE of INR 37,845 for Head and Neck Cancers (Chauhan *et al* 2017)[12]. The lower OOPE in the present study can be explained by the fact that we calculated the OOPE spent by patients from the onset of symptoms till the diagnosis was made, while other studies looked at the entire treatment of the cancers. To the best of our knowledge, no such study is reported in literature.

The present study focuses on the expenses of diagnostic evaluation during outpatient and in-patient care received by gynaecological cancer patients including the indirect cost. The indirect cost has not been studied in previous studies. The major part of the OOPE (59.32%) was in the indirect domain followed by direct medical cost (29.38%). This can be explained by the fact that although the diagnostic modalities are free of cost, the patients or the caregivers need to leave their daily jobs during their hospital visits. This loss of income due to the absentism from work of a patient/caretaker is directly proportional to the number of hospital visits and time spent in OPD and hospital. Sometimes the patients have to take loans or sell their land or jewelry also. This is observed by the significantly highest direct (medical and non-medical) and indirect costs among individuals who showed earlier to private practitioners before reporting to this hospital. Before reporting to tertiary care hospitals, patients spent money in small or private health facilities for the evaluation of symptoms. Older people (>60 yrs) were spending more money when compared to the younger people, although this was not statistically significant. This could again be attributed to the extra expense of traveling to the health facility. The richer households belonging to the upper socio-economic class were spending more on the management of cancer, which

was also observed in other studies by Chauhan *et al*[12] and Rajpal *et al*[8]. The OOPE was not significantly different between urban and rural patients, whereas other studies reported that individuals from urban settings were spending more than those from rural areas. Patients with ovarian malignancy spent more than any other type of cancer.

Catastrophic health expenditure

The 40% cut-off on the CTP was used to calculate the incidence of CHE in the present study. The calculated value of CTP was 30.33%, which was not higher, when compared to other studies[12]. Infact, lower CHE in the present study could be again explained by fact that our study took the account of OOPE in the diagnostic part of gynaecologic cancers. The incidence of CHE was found to be almost the same in all sites of cancer (50% for vulval cancer, and 45% of ovarian cancer).

The overall OOPE was contributed mainly by the indirect costs. In a tertiary care hospital setting, unnecessary OPD visits by both patients and caretakers can be avoided by utilizing telemedicine. Further research should focus on developing protocols for follow-up visits, along with establishing specialised cancer clinics in tertiary care hospitals.

Strengths and Limitations

Strengths

There are few studies in literature, regarding the cost analysis of gynaecological cancers. Moreover, the present study is the only study to look into cost by the gynaecological cancer type. The indirect costs under various headings (loss of income due to the absence from work of a patient/caretaker while been investigated/treated) was collected, which has not been done in most of previous studies. This would reflect the expenditure pattern and in calculating the OOPE. An important finding was that cancer patients paid substantial out-of-pocket costs under the category of indirect cost. Patients with higher socio-economic class and higher education (graduates) had the highest direct medical and direct non-medical expenditure. More then half of patients (65.16%) were aware about government scheme like Ayshman Bharat Scheme; however, almost all patients (98.87%) were not covered by any health insurance scheme.

Limitations

We collected information related to economic burden, based on the recall method. It was the patient's perspective for capturing the cost incurred during diagnoses of gynaecological cancers. The calculation of OOPE was dependent on self-reported costs by the patients, but lacked verification (e.g., bills or receipts). Information was not collected about coping strategies used by patients and families to overcome catstrophic health expenditure. It was a cross-sectional study to quantify OOPE among selected cancer patients attending the OPD of a tertiary care center. Therefore, the results of the study may not be representative of all cancers in the general population. The sample size was small, so further studies with large sample size may give more insight into the health related economic burden on patients.

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ORIGINAL ARTICLE

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Prevalence and Risk Factors of Skin Disorders among Diabetic Patients

Ashok Kumar, Shubha Laxmi Margekar**, Jay Patel***, Rajshree Singh*****

Abstract

Introduction: *Diabetes mellitus is a chronic metabolic disorder characterised by hyperglycaemia and is associated with various complications, including skin disorders. Diabetic patients often present with a range of skin manifestations, which can serve as indicators of underlying metabolic imbalances and disease severity. This study aims to evaluate the prevalence and risk factors of skin disorders among diabetic patients at a tertiary care center.*

Methods: *A cross-sectional study was conducted among 338 patients of type 2 diabetes mellitus at Santosh Hospital, Ghaziabad, India. Participants underwent detailed medical history assessments, physical examinations, and laboratory investigations. Dermatological evaluations, including culture and biopsy, were performed when indicated. Data were analysed using the Statistical Package for Social Sciences (SPSS).*

Results: *The results revealed that cutaneous infections were the most common skin manifestation, observed in 42% of patients, followed by skin disorders related to microangiopathy (10.4%) and neuropathy (15.1%). Poor glycaemic control, as indicated by high HbA1c levels, was significantly associated with an increased risk of skin disorders. Additionally, the duration of diabetes was positively correlated with the severity of skin manifestations.*

Conclusion: *Skin disorders are prevalent among diabetic patients, with infections being the most common manifestation. These findings underscore the importance of regular dermatological screening in diabetic patients, particularly those with poor glycaemic control, to enable early diagnosis and management of skin complications, potentially preventing further systemic complications.*

Key words: *Diabetes mellitus, skin disorders, acanthosis nigricans, cutaneous infections.*

Introduction:

Diabetes mellitus (DM), the most common endocrine disorder, poses a significant burden on the health care system as well as on society[1]. The rising incidence of diabetes mellitus and it's varied local and systemic manifestations make it one of the main health issues facing the world today. Approximately 500 million people worldwide suffer from diabetes, accounting for almost 10.5% of the adult population. In 2021, 536.6 million individuals (10.5%) globally were anticipated to have diabetes among those aged 20 to 79 years. This number is projected to rise to over 780 million people (12.2%) by 2045, according to the latest estimates. In comparison to rural areas (8.3%) and low-income countries, a higher prevalence has been noted in metropolitan areas (12.1%) and high-income nations. The dermatologist can play a crucial role in identifying such patients because diabetes can present with a wide range of symptoms, the most common of which are cutaneous in nature[2,3,4].

It has been proposed that oxidative stress, inflammation, and advanced glycation end products may cause early aeging of the skin, the development of diabetic dermopathy, and scleroderma diabeticorum[5]. In a comparable manner hormonal effects, insulin resistance, imbalances in growth factors and cytokines, and acrochordons and inflammatory dermatitis can cause skin lesions such as acanthosis nigricans and inflammatory dermatitis[5,6].

Prolonged diabetes can cause the body to irreversibly modify how it functions, which can lead to a number of problems. For individuals with diabetes mellitus, abnormal glucose, amino acid, and lipid metabolism directly results in physical symptoms[7]. During the long course of their illness, at least 30% of DM patients experience various cutaneous problems. These problems offer insight into the patient's past and present metabolic state[8]. Numerous studies have shown that during the long course of their condition, 30 - 82% of DM patients develop various cutaneous disorders. Maintaining the body's metabolic balance can help with treatment and possibly avoid some of these symptoms. However, a lot

**Professor and Head, ***Resident, ****Professor, Department of Medicine, Santosh Medical College, Ghaziabad - 201 001, Uttar Pradesh. **Professor, Department of Medicine, Lady Hardinge Medical College, New Delhi - 110 001.*
Corresponding Author: Dr Ashok Kumar, Professor and Head, Department of Medicine, Santosh Medical College, Ghaziabad - 201 001, Uttar Pradesh. Tel: 9990387457, E-mail: dr_ashk2006@yahoo.co.in

of glycaemic control drugs also cause adverse skin reactions . Even those without a history of DM who exhibit cutaneous symptoms linked to the disease should have their condition looked into[9]. There is a significant prevalence of diabetic morbidity; nevertheless, there is a paucity of specific information on cutaneous complications associated with DM.

The aim of this study was to assess the prevalence and pattern of skin disorders among diabetic patients at Santosh Hospital, Ghaziabad.

Material and Methods

This was a cross-sectional study conducted in the Departments of Medicine and Dermatology at Santosh Hospital, Uttar Pradesh. Approval was obtained from the ethics committee. 338 subjects diagnosed with type 2 diabetes mellitus showing dermatological manifestations were included in the study.

Inclusion criteria

- All patients/cases of diabetes mellitus with significant dermatological manifestations.
- All age groups and both sexes

Exclusion criteria

- Patients with gestational diabetes mellitus.
- Patients with Type 1 diabetes mellitus
- Critically ill patients.
- Any drug reactions
- Patients unable to give an informed consent

After obtaining informed consent from the subjects, they were evaluated and selected after detailed medical history, physical examination, systemic examination. Basic anthropometric measurements such as weight, height and waist circumference were calculated. Routine investigations including fasting and post-prandial blood sugar, lipid profile, complete blood count, renal function tests, liver function tests to rule-out any underlying diseases were done.

Results

Data collected was entered into Microsoft Excel and analysed through Statistical Package for Social Sciences, version 23 (SPSS Inc., Chicago, IL). Results for continuous variables are presented as mean ± standard deviation, whereas results for categorical variables are presented as number (percentage). Any possible association was calculated using chi square test or student's-t test. $p < 0.05$ was considered as the cut-off value of significance. The data was analysed and is summarised in Table II-VII, with explanations thereafter.

Table I: Distribution of cases by age, duration of diabetes, and blood sugar levels

A. Distribution of cases based on age category			
Age (Years)	**No. of Cases (n = 338)**	**Percentage**	**Mean ± SD**
21 - 30	32	9.5	46.28 ± 12.58
31 - 40	86	25.4	
41 - 50	88	26.0	
51 - 60	90	26.6	
61 - 70	21	6.2	
71 - 80	14	4.1	
>80	7	2.1	
B. Distribution of cases based on duration of diabetes mellitus			
<1 year	76	22.4	6.23 ± 3.82
1 - 5 years	124	36.6	
5 - 10 years	103	30.5	
>10 years	35	10.5	
C. Distribution of the cases based on fasting blood sugar			
<120 mg/dL	76	22.5	134.64 ± 25.32
121 - 160 mg/dL	208	61.5	
>160 mg/dL	54	16	
D. Distribution of the cases based on post-prandial blood sugar			
70 - 140 mg/dL	19	5.6	188.92 ± 33.50
141 - 200 mg/dL	213	63	
>200 mg/dL	106	31.4	

Table II: Distribution of cases based on systemic illnesses

Associated illness	**Cases**
Hypertension	140
Heart disease	28
Bronchial asthma	5
Hypothyroidism	5
Dyslipidemia	14
Total	199

Table III: Distribution of cases based on types of cutaneous manifestations

Skin Manifestation	Cases	Percentage
Cutaneous Infections	142	42
Skin Manifestation Associated with Microangiopathy	35	10.4
Neuropathic and ischaemic diabetic skin disease	51	15.1
Skin Manifestation more commonly associated with diabetes mellitus*	214	63.3
Non-specific manifestations	137	40.5

**See Table IV*

Table IV: Distribution based on skin manifestations commonly associated with diabetes mellitus

Skin Manifestation	Cases
Pruritus	29
Acrochordons	55
Psoriasis	14
Vitiligo	8
Acanthosis nigricans	80
Progressive pigmented purpura	5
Perforating folliculitis	6
Lichen planus	5
Cherry angiomas	6
Macular amyloidosis	4
Alopecia universalis	2
Total	214

Table V: Distribution of cases based on non-specific manifestations

Dermatoses	Cases
Eczema	57
Seborrheic keratoses	17
Dermatosis papulosa nigra	11
Melasma	16
Contact dermatitis	5
Drug reactions	4
Scabies	7
Sebaceous cyst	1
Polymorphous light eruption	2
Keloid	5
Parapsoriasis	1
Seborrheic dermatitis	1
Pemphigus	2
Senile comedones	4
Lichen simplex chronicus	4
Total	137

Fig. 1: *Showing logistic regression coefficients.*

Table VI: Distribution and comparison of cutaneous manifestations in controlled and uncontrolled diabetes

Dermatoses	Number of Patient (N)	HbA1c (<7%) (75)	HbA1c (>7%) (263)	p-value
Cutaneous infections	142	30	112	0.689
Skin manifestation associated with microangiopathy	35	12	23	**0.001**
Neuropathic and ischaemic diabetic skin disease	51	16	35	0.087
Skin manifestations more commonly associated with diabetes	214	50	164	0.495
Non-specific manifestations	137	33	104	0.488

Table VII: Logistic regression coefficients

Predictor	Coefficient
Age (years)	0.062413921
Sex, M = 1, F = 2	-0.250683044
Duration (Years)	0.2723622576078667
Family History Yes = 1, No = 2	-0.093979814
RBS (mg/dL)	0.4262537542514903
FBS (mg/dL)	0.079301319
PP (mg/dL)	-0.401034697
HbA1c (%)	-0.021041913

The majority of diabetic patients with skin manifestations were in the age groups of 21 - 30 years (9.5%), 31 - 40

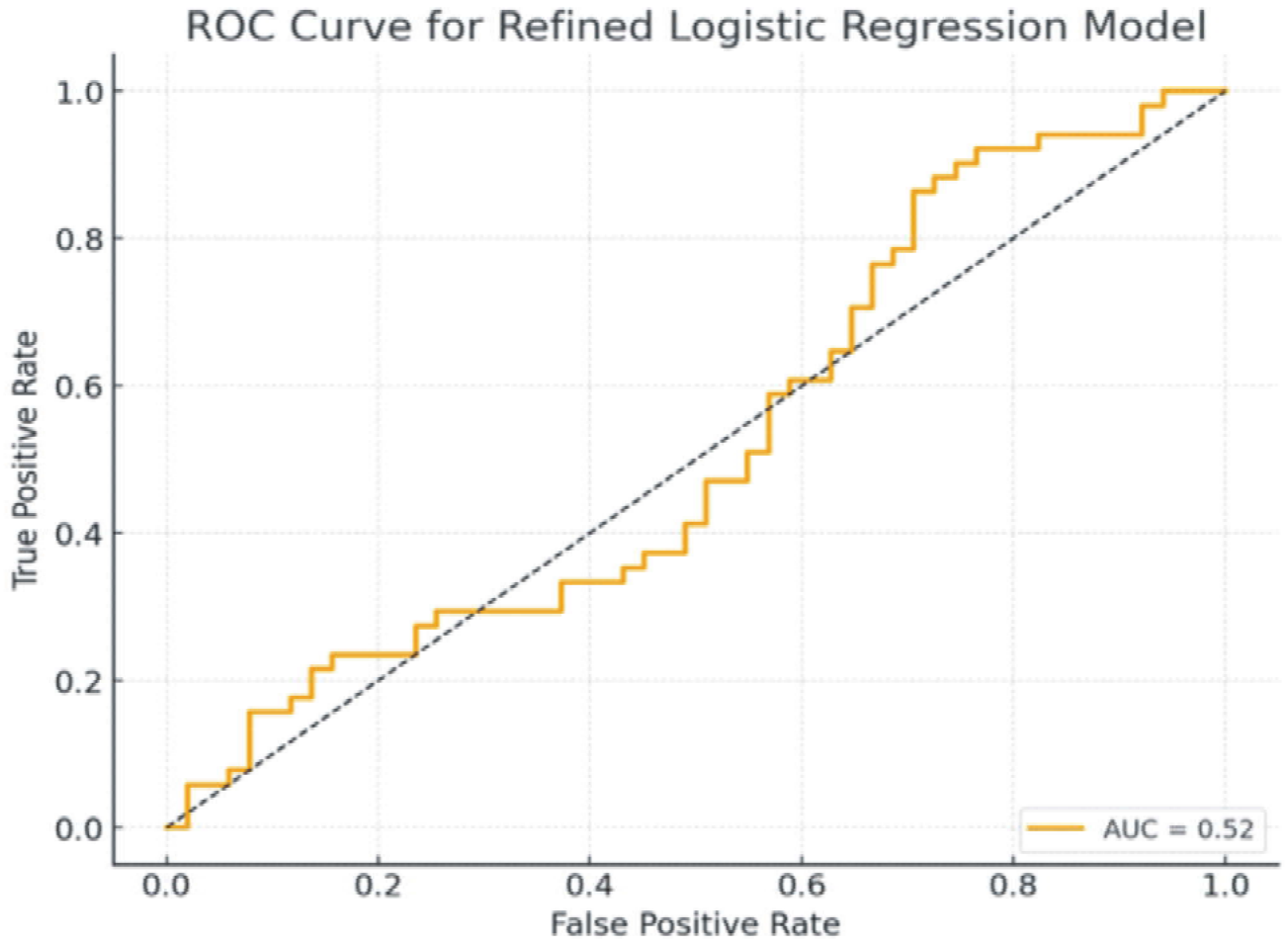

Fig. 2: *ROC curve for refined logistic regression model.*

years (25.4%), 41 - 50 years (26%), and 51 - 60 years (26.6%) (Table I). The mean age was 46.28 ± 12.58 years, indicating that middle-aged individuals are more prone to skin disorders. Regarding the duration of diabetes, 36.6% of patients had diabetes for 1 - 5 years, while 30.5% had diabetes for 5 - 10 years, suggesting that cutaneous manifestations tend to appear relatively early in the disease course. Most patients (61.5%) had fasting blood sugar levels in the range of 121 - 160 mg/dL, and 63% had post-prandial blood sugar levels between 141 - 200 mg/dL, with a mean post-prandial blood sugar level of 188.92 ± 33.50 mg/dL. This highlights the prevalence of inadequate glycaemic control among the study population.

Among the diabetic patients with skin disorders, a significant proportion (60%) also had associated systemic illnesses (Table II). Hypertension was the most common co-morbidity, present in 140 patients. Other notable associated conditions included heart disease (28 cases), chronic renal failure (10 cases-excluded in biostatistics), and dyslipidaemia (14 cases). These findings underscore the multifactorial nature of diabetes-related complications, where co-morbid conditions may exacerbate skin manifestations.

Cutaneous infections were the most prevalent skin disorder, affecting 42 % of patients (Table III). Skin manifestations commonly associated with diabetes, such as acanthosis nigricans and acrochordons, were present in 63.3% of cases. Non-specific skin manifestations, like eczema and melasma, accounted for 40.5% of cases. The prevalence of neuropathic and ischaemic diabetic skin diseases was 15.1%, while skin manifestations linked to microangiopathy, such as diabetic dermopathy, were seen in 10.4% of patients. This distribution highlights the broad spectrum of skin disorders that can arise in diabetic patients, often reflecting underlying pathophysiological changes related to diabetes.

Acanthosis nigricans was the most common specific skin disorder (Table IV), observed in 80 patients, followed by acrochordons (55 cases) and pruritus (29 cases). Other less common conditions included psoriasis (14 cases), vitiligo (8 cases), and cherry angiomas (6 cases). These findings indicate that hyperinsulinaemia and insulin resistance, common in type 2 diabetes, may be important contributors to these dermatological conditions. The variety of manifestations also emphasizes the need for dermatological screening in diabetic care.

Among the non-specific manifestations, eczema was the most frequently reported condition (Table V), affecting 57 patients. Other common conditions included seborrheic keratoses (17 cases), melasma (16 cases), and scabies (7 cases). The occurrence of these conditions suggests that diabetic patients may be more susceptible to general skin disorders, possibly due to altered immune responses or poor skin barrier function.

The comparison between controlled (HbA1c <7%) and uncontrolled diabetes (HbA1c >7%) revealed that uncontrolled diabetes was significantly associated with a higher incidence of skin manifestations (Table VI). Specifically, patients with poor glycaemic control had a significantly higher prevalence of microangiopathy-related skin conditions ($p = 0.001$) and neuropathic and ischaemic diabetic skin disease ($p = 0.087$). Cutaneous infections and non-specific skin manifestations were also more common in the uncontrolled group, though not statistically significant. This reinforces the importance of maintaining good glycaemic control to reduce the risk of cutaneous complications in diabetic patients.

Older age groups were more likely to experience infections, likely due to age-related changes in immunity and skin integrity. Poor glycaemic control, indicated by elevated FBS, PP, RBS, and HbA1c, was strongly associated with increased infection risk. Longer diabetes duration also raised risk, possibly due to complications like neuropathy. Sex may influence risk through hormonal and behavioural factors (Table VII). Positive co-efficients for predictors like age and glycaemic markers suggest that an increase in these factors raises the likelihood of infections (Fig. 1). The coefficients highlight how tightly controlled sugar levels may mitigate risk (Fig. 2) ROC analysis for a Refined Logistic Regression Model Showed limited predictive ability of models, indicating either additional factors need exploration, or that skin infections are influenced by a mix of multiple, complex factors.

Discussion

Cutaneous diseases in individuals with diabetes mellitus may occur prior to or coincide with the diagnosis of diabetes. A number of these lesions, such as diabetic dermopathy, diabetic bullae, and necrobiosis lipoidica, have a strong correlation with diabetes mellitus. Conversely, certain additional skin abnormalities linked to infection have been seen in diabetics[2,7]. Skin alterations might even be noticed before diabetes manifests. Long-term diabetic patients experience more severe skin diseases. The multiple metabolic problems associated with diabetes, such as persistent hyperglycaemia that causes glycosylation of diverse skin tissue components, are ultimately responsible for the alterations in skin[7].

In the present study, majority of the subjects belonged to the 4th and 5th decade with 26% and 26.6% respectively with mean age was 46.28 ± 12.58 years (Table I). Similar results were obtained in a study of Ramesh *et al*[10] and Sani *et al*[5] with 46% and 47% of their subjects, respectively belonging to the age group of 41 - 60 years. A mean age of

55.85 ± 13.04 years was seen in a study by Azizian *et al*[9].

Chronicity of diabetes plays an important role in cutaneous manifestations. In the present study, 36.6% of patients were presented with diabetes for a period of 1 - 5 years and 30.5% patients for 6 - 10 years (Table I). In a study by Sani *et al*[5], it was observed that 72% individuals had diabetes for <10 years while 24% had diabetes for 11 - 20 years. Azizian *et al*[9] observed a mean duration of diabetes to be 8.06 ± 7.16 years in their study.

In the current study, most patients had fasting blood sugar levels in the range of 121 - 160 mg/dL (62%) with a mean of 134.64 ± 25.32 mg/dL while mean PPBS was observed to be 188.92 ± 33.50 mg/dL. In a study by Azizian *et al*[9], the mean FBS was found to be 155.64 ± 53.16 mg/dL. 60% of subjects presented with associated systemic co-morbidity, out of which hypertension was observed in 40% cases. Ischaemic heart disease was seen in 8% and dyslipidaemia in 4% of subjects (Table II). In a study by Azizian *et al*[9], hypothyroidism was seen in majority (12.4%) cases.

Cutaneous infections were seen in 42% of cases (Table III). Although there is little evidence to support the widespread belief, people with diabetes are thought to be more susceptible to infections. Patients with poor metabolic control appear to be at higher risk for this; however, it is frequently unclear if these infections are the result of or a cause of the poor metabolic control. 20 - 50% of patients get cutaneous infections, which frequently co-exist with modest blood glucose control. Peripheral vascular diseases, peripheral neuropathy, immune response suppression, and problems with microvascular circulation; all increase the risk of infection[9].

The four types of cutaneous manifestations seen in diabetes are: infections (bacterial, fungal), manifestations of diabetic complications (microangiopathy, macroangiopathy, neuropathy), reactions to diabetic treatment (sulphonylureas or insulin), and lesions with strong-to-weak association with diabetes (necrobiosis lipiodica, diabetic dermopathy, diabetic bullae, yellow skin, eruptive xanthomas, perforating disorders, acanthosis nigricans, oral leucoplakia, lichen planus)[9]. Among the various dermatoses studied, acanthosis nigricans was most commonly seen in 37.3% subjects, followed by acrochordons (25.7%), infections (8.6%), psoriasis (6.5%) and vitiligo (3.7%) (Table IV).

Acanthosis nigricans is an important prognostic indicator for the development of type 2 diabetes. Additionally, certain ethnic groups may have a hereditary tendency or enhanced skin sensitivity to hyperinsulinaemia[2]. Acrochordons, also known as skin tags, fibroepithelial polyps, and soft fibromas, are pedunculated protuberances of healthy skin on a slender stalk that are typically found on the groin, neck, axillae, and eyelids. About 25% of individuals have them, and as people age, their numbers and prevalence increase. Acrochordons have been linked to acanthosis nigricans, obesity, and family history; the link between hyperinsulinaemia and skin tags is well-established[2]. In a 2014 study by Furqan *et al*[11] on 100 diabetic patients with DM types 1 and 2, the most prevalent cutaneous findings were cutaneous infections and diabetic dermopathy.

In the present study, among the 137 patients who presented with non-specific manifestations (Table V), the majority had eczema (41.6%) followed by seborrheic keratosis (12.40%), melasma (11.67%), diabetic peripheral neuropathy (8.02%) and scabies (5.10%). According to Sani *et al*. Idiopathic guttate hypomelanosis was the most predominant finding in 61% cases[5].

Among the 338 diabetic patients with cutaneous manifestations, 75 patients had HbA1c <7% (good to moderate control) while 263 patients had poor control of diabetes (HbA1c >7%) (Table VI). When cutaneous manifestation patterns of the controlled and uncontrolled groups were compared, it was found that the uncontrolled group had a significantly greater incidence of cutaneous infections, metabolic disorders, and cutaneous reactions to diabetic treatment. There was a statistically significant ($p < 0.05$) increase in the incidence of non-specific symptoms in the controlled group. There was no statistically significant correlation found between the incidence of cutaneous diseases and metabolic glucose control in a study by Chatterjee *et al* that examined the prevalence and pattern of skin problems in 680 diabetic patients[12]. Long-term uncontrolled diabetes mellitus seems to increase the risk of infections and other cutaneous illnesses in addition to involvement of other target organs[9].

There are many different types of skin manifestations, and they frequently act as a diagnostic indication for underlying diabetes. When a patient exhibits several skin symptoms, it is important to determine whether they are diabetic. The first step in both prevention and treatment is identifying these skin abnormalities. Diabetes-related skin symptoms will grow more frequent as diabetes prevalences rises. As a result, physicians must become acquainted with the spectrum of cutaneous diseases seen in diabetes patients.

The analysis reveals that age, glycaemic control, diabetes duration, and sex are key predictors of cutaneous infections. Older age, poor glycaemic control (evidenced by elevated FBS, PP, and HbA1c), and longer diabetes duration significantly increase the risk of infection. Despite these insights, the predictive models showed limited accuracy (~53%) and AUC (~0.52), indicating that other factors might influence infection risk. The refined logistic regression co-efficients suggest that tighter blood sugar control can help mitigate risks. The findings point to a need for further

exploration of additional factors influencing skin infection susceptibility (Fig. 2). The study found that skin infections, particularly fungal (22%), were the most common cutaneous manifestation in diabetic patients, followed by bacterial infections (16%). Diabetic dermopathy, vitiligo, and insulin-related skin reactions were also prevalent. Skin manifestations were more common in type 2 diabetes and with longer disease duration[13].

Conclusion

The goal of this study was to understand the spectrum of cutaneous symptoms associated with diabetes mellitus. The most prevalent skin finding among diabetics was infections. Cutaneous signs may raise a clinician's suspicions for diabetes mellitus, which in turn helps to prevent systemic derangements by allowing for early start of treatment. A long-term blood glucose control program and proper skin care can lower the chance of developing some diabetic skin lesions. If treatment is not received, problems, such as open sores (ulcers) and, in extreme circumstances, gangrene or a potentially fatal infection may develop. In individuals who are generally healthy, some skin anomalies may suggest the need for an assessment. Skin manifestations in a diabetic may indicate the need for more aggressive diabetes control. Therefore, it is critical that the primary care physician be empowered to identify these, suggest a course of treatment, and, when necessary, refer the patient to a dermatologist for additional assessment.

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International Normalised Ratio-to-Albumin Ratio as a Prognostic Tool among Patients of Liver Cirrhosis and Sepsis

Manan Agarwal, Anita Arya**, Shailendra Jain***, Simmi Dube****, Vivek Bajaj**

Abstract

***Background:** Liver cirrhosis is a chronic condition characterised by progressive liver dysfunction and is a significant cause of morbidity and mortality, globally. Sepsis is a common and severe complication in cirrhotic patients. The Prothrombin time-international normalised ratio (PT-INR) and serum albumin levels are critical indicators of liver function and nutritional status, respectively. This study aims to evaluate the prognostic value of INR to Albumin Ratio (PTAR) in patients of cirrhosis with sepsis.*

***Methods:** This prospective hospital-based observational study included 90 patients aged 18 - 65 years with cirrhosis and sepsis (qSOFA $\geq$2). Patients were excluded if they had bleeding disorders, were on anticoagulants, pregnant, malignancy, or other chronic illnesses. INR to Albumin Ratio was calculated at admission. Patients were categorised into low, intermediate, and high-risk groups based on the score and were followed up to record outcomes.*

***Results:** The study revealed that in low-risk patients (PTAR<0.55), 84% patients survived whereas 16% died. In intermediate risk patients (PTAR 0.55-1), 56.7% survived whereas 43.3% died. In high-risk patients (PTAR >1), 20% survived whereas 80% died. The p value was <0.001.*

***Conclusion:** The PTAR score can be easily calculated at the bedside and correlates significantly with prognosis, with higher scores assosciated with increased mortality. This underscores its utility in clinical settings and supports its use as a valuable marker for assessing prognosis in cirrhotics with sepsis.*

***Key words:** Cirrhosis, sepsis, INR, albumin.*

Introduction

Liver cirrhosis is a chronic and insidious condition marked by the progressive degeneration of liver function caused by tissue fibrosis and conversion of normal liver architecture into structurally abnormal nodules[1]. This complicated ailment, often caused by factors like chronic alcoholism or viral hepatitis, intricately disrupts the liver's structural integrity and undermines its vital functions[2]. A patient with liver cirrhosis is initially asymptomatic or in a phase of "compensated" cirrhosis. With further disease progression, patient develops complications of portal hypertension and liver dysfunction and develops a phase of "decompensated" cirrhosis which is defined by the presence of ascites, variceal bleeding, hepatic encephalopathy, and/or jaundice[3]. Cirrhosis is one of the leading causes of mortality and morbidity all over the world[4]. Around 2 million deaths worldwide per year are due to liver disease, with 1 million deaths due to the complications of cirrhosis and 1 million deaths due to viral hepatitis and hepatocellular carcinoma[5].

The International Normalised Ratio (INR) is a standardised measure of blood coagulation, primarily used to monitor the effectiveness of anticoagulant medications. In cirrhosis, compromised liver function results in decreased synthesis of clotting factors, leading to an elevated INR. As a standardised measure of blood clotting time, INR provides clinicians with profound insights into the liver's synthetic function, acting as a sentinel for the subtle changes and disruptions that characterise the relentless progression of cirrhosis[6].

Albumin, a protein synthesized by the liver, serves as a key component of the body's oncotic pressure, and contributes to maintaining vascular integrity. In cirrhosis, reduced liver function results in decreased albumin production, leading to hypoalbuminaemia. Beyond its role in maintaining osmotic pressure, albumin plays a crucial role in modulating immune response and inflammation.

Cirrhosis, in advanced stages predisposes an individual to various complications, with sepsis being a critical and life-threatening event, the occurrence of which is estimated to be around 30% to 50% of all hospital admissions[7]. The Third International Consensus Definition Task Force defines sepsis as life-threatening organ dysfunction due to a dysregulated host response to infection[8]. Physiologically, sepsis is viewed as a pro-inflammatory and pro-coagulant response to

**Post-Graduate Resident, **Professor, ****Professor and Head, Department of Medicine, ***Associate Professor, Department of Gastroenterology, Gandhi Medical College, Bhopal - 462 002, Madhya Pradesh.*
Corresponding Author: Dr Anita Arya, Professor, Department of Medicine, Gandhi Medical College, Bhopal - 462 002, Madhya Pradesh. Tel: 9425025799, E-mail: anita5799@gmail.com

invading pathogens with a progressively increased risk of end-organ failure and death[9]. Sepsis in cirrhotic patients leads to further worsening of liver function and development of organ or system failure and hence, emerges as a formidable adversary especially in cirrhotics. In patients with suspected infections, a bedside clinical score-quick Sequential Organ Failure Assessment Score (q SOFA) can predict poor outcomes typical of sepsis[8].

Prothrombin time-international normalised ratio (PT-INR) to Albumin Ratio (PTAR) is a novel, objective score developed by Haruki *et al* to assess liver functional reserves in patients with hepatocellular cancer following hepatic resection[10]. They showed that in a retrospective analysis involving 199 patients, the PTAR score was effective in forecasting both the short- and long-term results. Patients with cirrhosis experience abnormalities in liver function and decreased reserves, just like those who have undergone hepatocellular carcinoma resection.

The promise held within the integration of these two metrics lies in their collective ability to function as a prognostic tool. The PTAR score could be a reliable metric for evaluating patients of liver cirrhosis with sepsis. Consequently, we decided to conduct a study on patients suffering from cirrhosis of the liver with sepsis to evaluate the PTAR score and its prognostic value.

Aim

The study was conducted with the aim to study the combined prognostic value of INR to albumin ratio amongst patients of liver cirrhosis who have sepsis.

Material and Methods

The study was conducted in the Department of Medicine at Gandhi Medical College, Bhopal after approval from Institutional Ethics Committee. This was a prospective hospital based observational study. The inclusion criteria consisted of:

1. Age 18 - 65 years
2. Patients of cirrhosis of liver with sepsis (with history/ clinical examination/investigations supportive of infection)
3. qSOFA score ≥ 2

The exclusion criteria consisted of patients aged <18 years and >65 years, qSOFA score <2, individuals with other known bleeding disorders, those on anticoagulant or drugs affecting PT/INR (Table I), pregnancy, patients with malignancy, and, patients with any other chronic systemic illness.

Table I: Drugs affecting PT/INR.

Vitamin K antagonists	Warfarin, Acenocoumarin
Direct Factor Xa Inhibitors	Apixaban, Rivaroxaban, Edoxaban
Direct Thrombin Inhibitors	Argatroban, Dabigatran
Antibiotics	Cotrimoxazole, Macrolides, Fluoroquinolones
Antifungals	Azoles (Fluconazole)

After a detailed clinical history, examination and investigations, the data was collected in a proforma which was pre-designed and included lab parameters such as CBC, LFT, RFT, PT-INR, blood and urine cultures, serology (HBsAg, anti-HCV and HIV), and ultrasound of abdomen. Even though biopsy is the gold standard for diagnosing cirrhosis, patients of cirrhosis were identified using clinical, laboratory and radiology as biopsy is not always required[11]. The qSOFA score was calculated for all patients at the time of admission. The score consists of three components with 1 point to each component - respiratory rate >22/min, Change in mental status (GCS <15) and systolic blood pressure <100 mm of Hg. A score of two or more points in patients with presumed infection defines sepsis. Patients of cirrhosis of liver with presumed infection based on history and clinical examination along with qSOFA score ≥2 were recruited for the study on fulfillment of inclusion and exclusion criteria. The PTAR score on the day of admission was calculated by using a simple formula, INR divided by albumin (g/dL). Based on this score, patients were classified as low-risk (PTAR score <0.55), intermediate-risk (PTAR score 0.55 - 1.00), or high-risk (PTAR score >1.00). These patients were then followed up and the outcome was recorded (discharged/expired) at the end of the hospital stay.

Results

The study revealed a predominant middle-aged demographic (Fig. 1) with most participants, 44.4% in the age group 41 - 50 years, followed by 25.6% in the 51 - 60 years group, 24.4% in the 31 - 40 years group, 5.6% in 61 - 65 years group and none in 18 - 30 years group. Additionally, 88.9% of participants were males.

Aetiological work-up (Fig. 2) of the participants revealed that the probable cause of cirrhosis was alcohol in 75.6%, viral (Hepatitis B and C) in 22.2% and 2.2% could be attributed to other causes like NAFLD.

The study revealed that the possible source of sepsis (Fig. 3) was pneumonia in 28.9%, urinary tract infection in 26.7%, spontaneous bacterial peritonitis in 13.3%, skin and soft tissue infections in another 13.3% and gastrointestinal tract infections in 6.7%. A positive blood culture indicating septicaemia was found in 5.6% cases. No cause could be

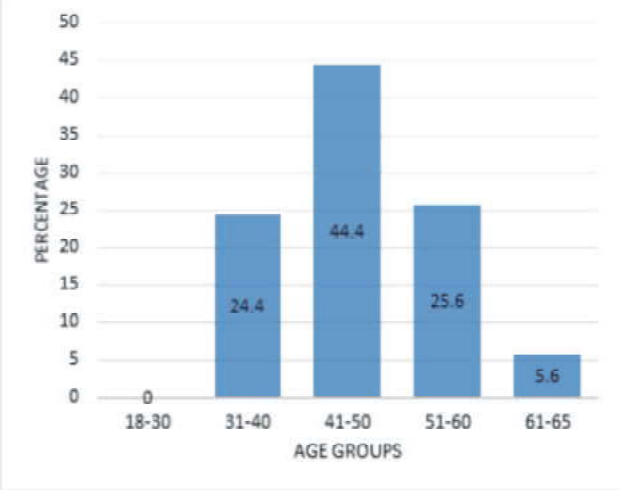

Fig. 1: *Age-wise distribution of cases*

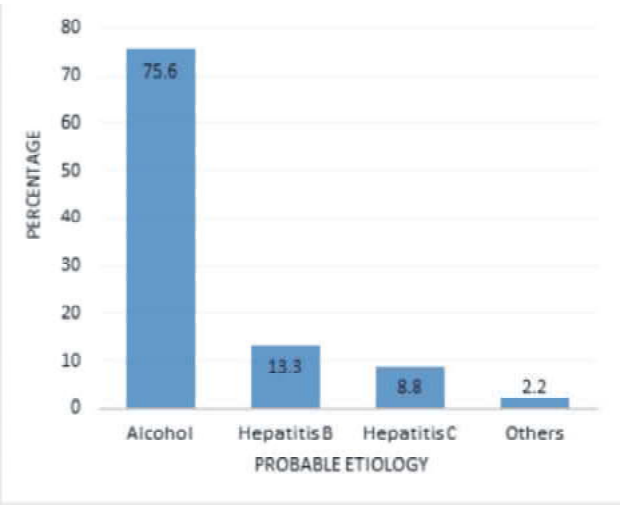

Fig. 2: *Probable aetiology of cirrhosis*

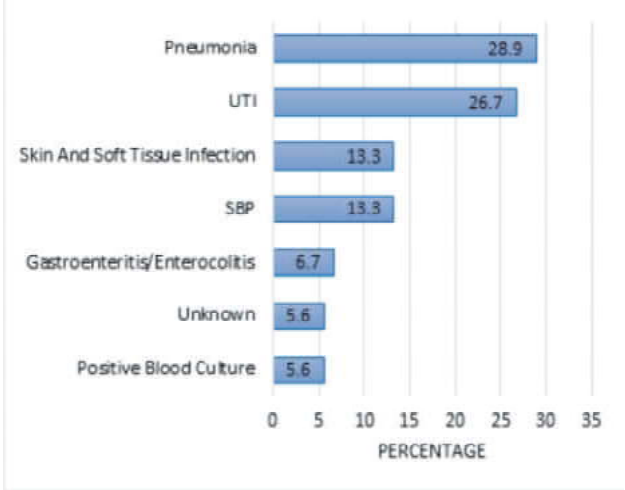

Fig. 3: *Possible source of sepsis in cases*

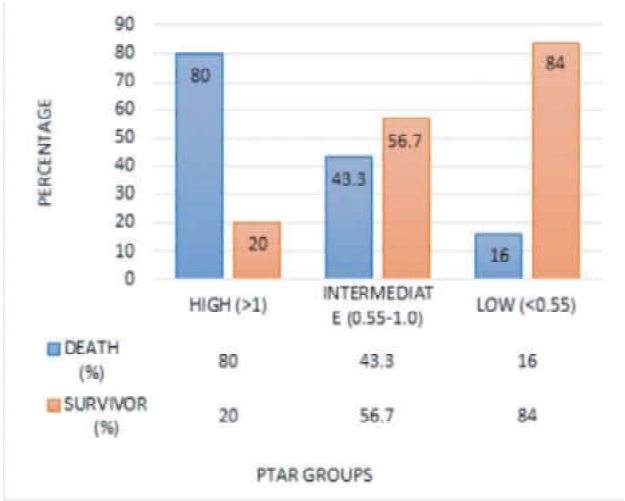

Fig. 4: *Outcome of cases according to PTAR scores (in percentage)*

identified in another 5.6% patients.

Blood cultures yielded a growth in 57.8% of cases, the most common organism being *Enterococcus*. Additionally, 42.2% of cases were negative for any growth. Urine cultures revealed a growth in 26.7% of cases and the most common organism isolated was *Escherichia coli*. Additionally, 73.3% of urine cultures were negative. The percentage distribution of the sample with cirrhosis of the liver with sepsis in various PTAR scores shows that 38.9% had a high score (>1), 33.3% had an intermediate score (0.55 - 1.00), and 27.8% had a low score (<0.55). The association between PTAR score and outcome (Fig. 4) revealed that:

- Out of 25 (27.7%) low risk patients, 21 (84%) patients survived (discharged) whereas 4 (16%) died.
- Out of 30 (33.3%) intermediate risk patients, 17 (56.7%) survived (discharged) whereas 13 (43.3%) died.
- Out of 35 (38.8%) high-risk patients, 7 (20%) survived (discharged) whereas 28 (80%) died.

The p value was <0.001, indicating a significant association between PTAR score and outcome.

Discussion

Our study revealed male predominant demographics with majority of participants in the age group of 41 - 50 years of age. Comparatively, Bhattacharya *et al*[12] study reported a higher mean age of 58.87 years with a male preponderance of 69.8%. A study by Karvellas *et al*[13] found a mean age of 55 years and a male percentage of 60%. However, in other studies carried out by Acharya *et al*[96] and Wang *et al*[14], 83.62% and 83.16% of study participants were males. Lucidi *et al*[15] included patients with a mean age of 49.7 years and 75.7% of participants were males. Thulstrup *et al*[16]

population-based study reported a mean age of 58.1 years and a male percentage of 59%. Our younger age group and higher male percentage highlight potential regional variations in alcohol consumptions, lifestyle, healthcare access and epidemiology of cirrhosis.

Worldwide, hepatotropic viruses are the most common causes of cirrhosis of liver. However, our study shows that 75.6% of cirrhosis cases were due to alcohol, 22.2% were viral, and 2.2% were attributed to other causes. This is consistent with findings from several other studies on the aetiology of cirrhosis carried out in India. Alcohol could be attributed as the aetiology of cirrhosis of liver in 72.2% in the study by Bhattacharyya *et al*[17], 62.9% by Sharma *et al*[18], 63.3% by Mishra *et al*[19] and 69% by Ahmed *et al*[20]. The increasing prevalence of alcohol consumption in the country is increasing the burden of alcohol-induced liver cirrhosis and mortality, particularly in the productive age group. Alcohol in itself is an independent risk factor for sepsis and mortality.

The possible sources of sepsis among participants in our study showed that 28.9% were due to pneumonia, 26.7% from UTIs, 13.3% from skin and soft tissue infections and 13.3% from SBP. Bhattacharya *et al*[12] found that sepsis was a significant predictor of mortality, present in 47.31% of survivors and 100% of non-survivors. Their study highlighted the prevalence of healthcare-associated infections, which aligns with our finding of pneumonia and urinary tract infections as major sources of sepsis. Karvellas *et al*[13] specifically focused on SBP, identifying it as the most frequent infection in cirrhotic patients. They demonstrated that delays and inappropriate antimicrobial therapy were associated with adverse outcomes in SBP cases. In a study by Fernandez *et al*[21], out of 572 patients with cirrhosis of liver with sepsis, the most common infection was SBP (25%), followed by urinary tract infection (20%), pneumonia (15%) and cellulitis (6%). In another study carried by Borzio *et al*[22], out of 150 (34%) bacterial infections (89 community- and 61 hospital-acquired) involving urinary tract (41%), ascites (23%), blood (21%) and respiratory tract (17%) were diagnosed. The prevalence of bacterial peritonitis was 12%. Our study's 13.3% incidence of SBP as a source of sepsis corroborates their findings and underscores the importance of prompt diagnosis and effective antimicrobial treatment. Cholongitas *et al*[23] and Haruki *et al*[10] noted the prevalence of severe infections, including SBP and other bacterial infections, in cirrhotic patients, reinforcing the importance of managing these infection sources to improve outcomes.

In the study by Haruki *et al*[10], the prothrombin time-international normalised ratio to albumin ratio (PTAR) was found to be a predictor of cancer recurrence and poor overall survival in hepatocellular carcinoma patients. The prognostic value of the INR-to-albumin ratio in cirrhotic patients is strongly supported by existing literature. Gao *et al*[24] validated the PTAR score as an effective tool for predicting 90-day mortality in critically-ill cirrhotic patients, demonstrating a significant association with increased mortality rates and good discrimination ability (AUC of 0.72). Their research validates our focus on the INR-to-albumin ratio as a critical metric in liver disease prognosis.

The percentage distribution of our sample with cirrhosis of the liver and sepsis according to PTAR scores shows that 38.9% had a high score (>1), 33.3% had an intermediate score (0.55 - 1.00), and 27.8% had a low score (<0.55). This distribution highlights the varying degrees of risk and severity among the study participants. Our study revealed that among low-risk patients (PTAR <0.55), 84% patients survived whereas 16% died. Among intermediate risk patients (PTAR 0.55 - 1), 56.7% survived whereas 43.3% died. Among high-risk patients (PTAR >1), 20% survived whereas 80% died. The association between PTAR score and outcomes shows a significant correlation, with higher PTAR scores (>1) associated with increased mortality ($p < 0.001$). These findings align with the study by Gao *et al*[24] who validated the prognostic value of the PTAR score in predicting 90-day mortality among critically-ill cirrhotic patients and found out that higher PTAR scores were significantly associated with increased mortality rates (13%, 30% and 58.5% among low risk, intermediate risk and high-risk patients respectively.) Haruki *et al*[10] also found that a higher PTAR score predicted poor overall survival and increased recurrence rates among hepatocellular carcinoma patients, further supporting the utility of PTAR in predicting adverse outcomes. The significant association between PTAR score and outcomes in our study underlines the importance of this ratio as a prognostic tool in clinical practice, helping to identify patients at higher risk and guiding appropriate treatment strategies.

The relatively small sample size may affect the generalisability of the findings. Additionally, the study was conducted at a single centre, potentially introducing selection bias. The observational nature of the study also limits the ability to establish causal relationships. Furthermore, variations in the management and treatment protocols for cirrhosis and sepsis across different institutions could impact the applicability of our results.

Conclusion

Our study highlights the prognostic value of the INR-to-albumin ratio in predicting outcomes during hospital stays for patients with cirrhosis of the liver and sepsis. Our study demonstrated that patients with sepsis and cirrhosis of the liver experienced high mortality rates. Both INR and serum albumin levels are widely available, even in a low resource

setting and inexpensive. The PTAR score can be easily calculated at the bedside and correlates significantly with the prognosis of the patient, with higher scores correlating significantly with increased mortality. This underscores its utility in clinical settings and supports the use of the INR-to-albumin ratio as a valuable marker for assessing prognosis and guiding treatment strategies in cirrhotic patients with sepsis.

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ORIGINAL ARTICLE

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Artefacts in Haematology: Lessons to be Learnt

Pooja Saini, Sarika Singh**, Zoya Hasan*, Bembem Khuraijam***, Garima Rakheja*****

Introduction

Peripheral blood smear (PBS) examination provides invaluable information about morphology of cells, as many diseases manifest with changes in peripheral blood cells. It is an inexpensive method for diagnosis of both haematological and non-haematological disorders. A systematic and thorough examination of PBS is adjuvant to clinical data and, most of the times, sufficient to make a diagnosis like haemoparasite and leukaemia. Recent advancements in the technology of automated cell counters have reduced the work load in laboratories; however, microscopic examination of PBS is still important for the evaluation of cytopaenias or for flagging a report of the automated haematology analyser. The art of PBS preparation and staining is gradually losing its shine. A good PBS needs ideal pre-analytical, analytical and post-analytical variables as important ingredients to work on; if PBS is not made according to standard laboratory practices, it can lead to various artefacts. Artefacts need to be correctly identified as they can be misinterpreted as pathological abnormality.

The present study highlights the importance of various artefacts on PBS to avoid misinterpretation of the smears.

Material and Methods

This study was conducted over a period of one month February to March 2023 at the Department of Pathology, Maulana Azad Medical College, New Delhi, including routine and emergency cases with control slides for assessing the staining characteristics using standard laboratory practices. A total of 500 cases were included in this study out of which 50 cases had artefacts.

Anticoagulants used for blood collection included EDTA, Trisodium Citrate and Heparin. EDTA and sodium citrate remove calcium from blood, hence prevent coagulation. EDTA is the most commonly used anticoagulant.

Excess amounts of EDTA affect both red cells and WBCs, produce shrinkage and degenerative changes. Platelets are also affected. Due to excess EDTA, they swell and then disintegrate leading to pseudo-high platelets count. So, proper blood to anticoagulant ratio is must for PBS. It is used for coagulation studies. This is because anti-EDTA antibodies induce pseudo-thrombocytopaenia. Lithium or sodium salt of heparin at a concentration of 10 - 20 IU/mL is commonly used for chemistry, arterial blood gas analysis and emergency tests. It is not good for blood counts and making PBS because it induces platelets and leucocytes clumping and gives a faint blue colour to the background when films are stained by Romanowsky dyes[1].

Procedure: Staining of slides

The peripheral blood sample is received in a Dipotassium Ethylene Diamine Tetraacetic acid (EDTA) vial. The blood samples are kept at room temperature until the smear making and staining, and for next 24 hours in the refrigerator for delta check. The glass slides are cleaned to ensure they are grease and dirt free. To make a blood film, a small drop of blood is put on the centre line of the slide and about 1 cm from one end. A spreader slide with smooth end is placed at an angle of about 30 degrees to the base of the slide, then moved backwards to touch the drop of blood. The drop should spread quickly along line of contact. Ideally it should cover two-third of slide with oval feathered end. The faster and steeper the smear, the thicker it is. Ideally blood films should be made as soon as blood has been collected. However, in routine practice samples come to laboratories after a variable delay. Smears should be made soon after arrival of samples to prevent changes in morphology of blood films.

Smears should be properly air dried and fixed within 4 hours, ideally within one hour. Smears are fixed with absolute methanol and stained with Romanowsky stain.

Romanowsky stain contains both acidic and basic dyes that gives a differential staining to the different cellular components. Commonly used stains are Leishman stain, MGG (May- Grunwald- Giemsa), and Giemsa stain. We used MGG stain to stain the peripheral blood films.

Fixed films are put into a staining jar containing MGG stain, freshly diluted with equal volume of buffered water. The films are allowed to stain for 15 minutes. Then they are transferred without washing into a jar containing Giemsa stain freshly diluted with 9 volumes of buffered water, pH

**Senior Resident, **Professor, ***Associate Professor, ****Assistant Professor, Department of Pathology, Maulana Azad Medical College, New Delhi - 110 002.*

Corresponding Author: Dr Sarika Singh, Room No. 72, Department of Pathology, Pathology Block, Maulana Azad Medical College, Bahadur Saha Zafar Marg, New Delhi - 110 002. Tel: 9911182326, E-mail: sarikasingh97b@gmail.com

6.8. After 10 - 15 minutes, slides are transferred to a jar containing buffered water, pH 6.8; rapid washing is done 3 - 4 times and then allowed to stand undisturbed for a short time for differentiation to take place. When differentiation is complete, slides are placed upright to become dry[2,3]. The control peripheral smear for comparison and to assess the various artefacts is shown in Fig. 1-A.

Causes of artefacts including *in-vivo* and *ex-vivo* factors with their effects on PBS have been compiled in Table I.

Various artefacts on PBS

Fixation artefact: Fixation artefacts are formed when there is presence of water in methanol used for fixation of the blood film. This is manifested as refractile rings in red cells, interfering in assessment of morphology of red blood cells. To remove this, methanol must be stored in a bottle with tight fitting lid to prevent its exposure to atmosphere. This is very important in humid climates. Even the presence of 1% water in methanol affects the morphology of films. Methylated spirits should not be used for fixation because they contain water (Fig. 1-B)[2,3].

Also, the duration of fixation and dryness of the smear before staining affect the morphology of cells as inadequately fixed and dried smear can lead to poor staining and altered morphology (Fig. 1-C).

Tailing artefacts: Tailing artefacts are produced when excessive pressure is applied while preparing the smear. Due to tailing, there is poor distribution of leucocytes. One should be careful in proper smearing of the smear (Fig. 1-D).

Table I: Causes of artefacts on PBS

***In-vivo* factors**	**Effects on PBS**
Antibodies to blood cells	Agglutination of platelets, erythrocytes and leucocytes
Increased plasma volume	Pseudo-anaemia
Decreased plasma volume	Pseudo-polycythaemia
Treatment-related	Platelets agglutination and Pseudo-Pelger-Huet anomaly
Monoclonal immunoglobulins	Pseudo-thrombocytosis and Pseudo-leucocytosis
***Ex vivo* factors**	**Effects on PBS**
Anticoagulants: EDTACitrate, Oxalate and Heparin	➢ Agglutination of leucocytes; agglutination, satellitism and degranulation of platelets ➢ Agglutination of leucocytes and platelets
Overfilling of tubes	Pseudo-polycythaemia, Pseudo-thrombocytopaenia and Pseudo-leucopaenia
Prolonged storage of specimen	Pseudotoxic changes, pseudo-echinocytosis and platelet degranulation
Temperature of specimen	Agglutination of erythrocytes, leucocytes and platelets

Tailing artefacts: Tailing artefacts are produced when excessive pressure is applied while preparing the smear. Due to tailing, there is poor distribution of leucocytes. One should

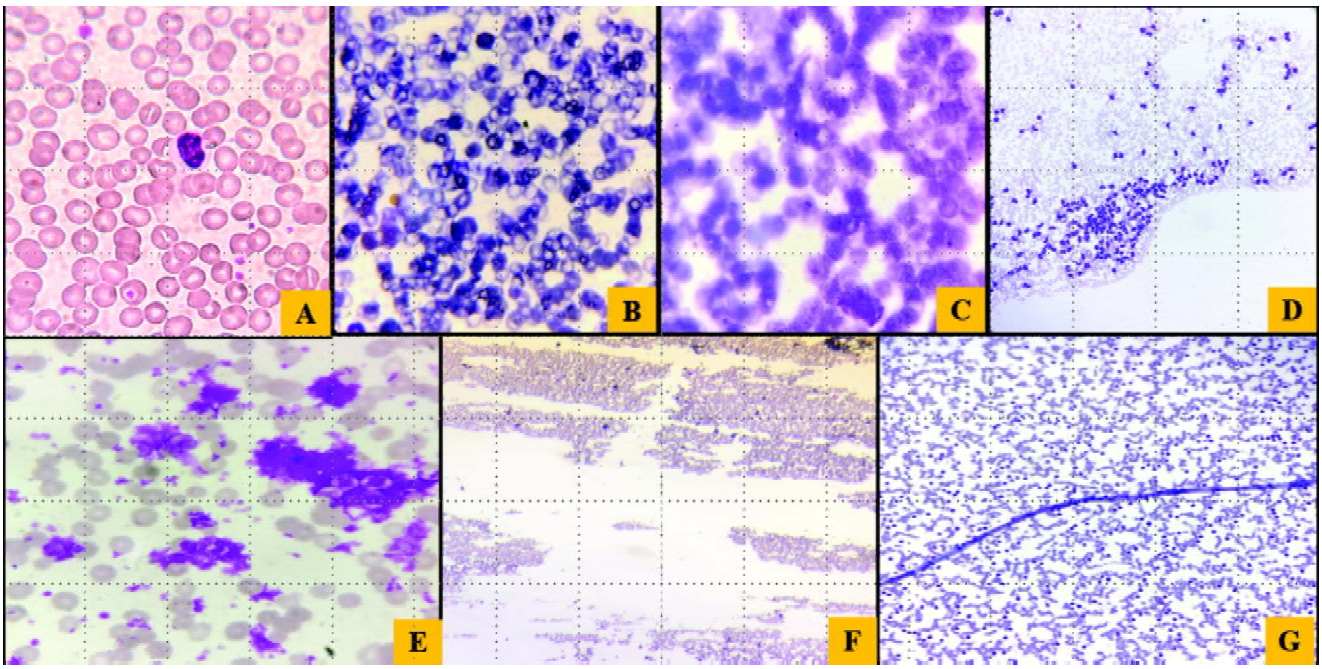

Fig. 1: A) *Control peripheral smear,* ***B)*** *Water artefact,* ***C)*** *Poor Staining,* ***D)*** *Poor spreading leading to Tailing artefact,* ***E)*** *Stain deposits,* ***F)*** *Grease artefact,* ***G)*** *Cotton artefact.*

be careful in proper smearing of the smear (Fig. 1-D).

Stain precipitates: Stain precipitates are formed as a result of evaporation of methanol. They are formed when slides are over-stained and inadequately washed under running water. Washing of slides at proper time, filtration of stain and using fresh working solution are remedies to remove stain deposits (Fig. 1-E).

Grease: Due to presence of grease on slide, there is presence of holes and streaks on smear. Also, RBCs will not take the stain and remain unstained. Properly cleaned slides should be used for making smear (Fig. 1-F).

Cotton: Cleaning of slides with cotton can lead to presence of cotton fibre on the slide. They can mimic microfilariae in stained smears. They can also mimic fungal hyphae. To rectify this, slides should be cleaned with lint cloth (Fig. 1-G)[4].

Storage artefacts: Smears made from stored blood show marked degenerative changes in all cell lines. RBCs show crenation. Cytoplasmic changes observed in WBCs are formation of cytoplasmic vacuoles, blebs and rupture and psuedotoxic changes. Nuclear changes observed are nuclear lobes fusion followed by fragmentation, karyolysis and rupture (Fig. 2). These degenerative changes can be mistaken as toxic changes as a result of infection or inflammatory condition. Absence of dark staining granules help in correct interpretation of these cases.

Platelets can become swollen (Fig. 3-A). If these swollen platelets burst into fragments, it can result in psuedo-thrombocytosis[1].

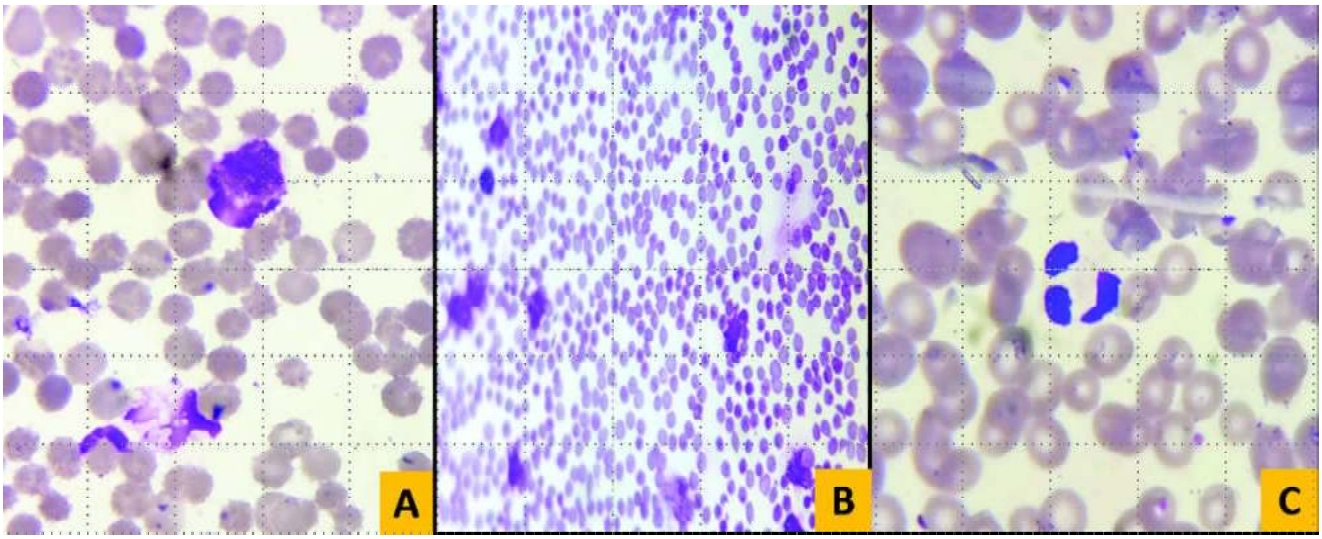

Fig. 2: A) *Cytoplasmic blebs and rupture,* ***B)*** *Cytoplasmic fragments,* ***C)*** *Nuclear lobes fragmentation.*

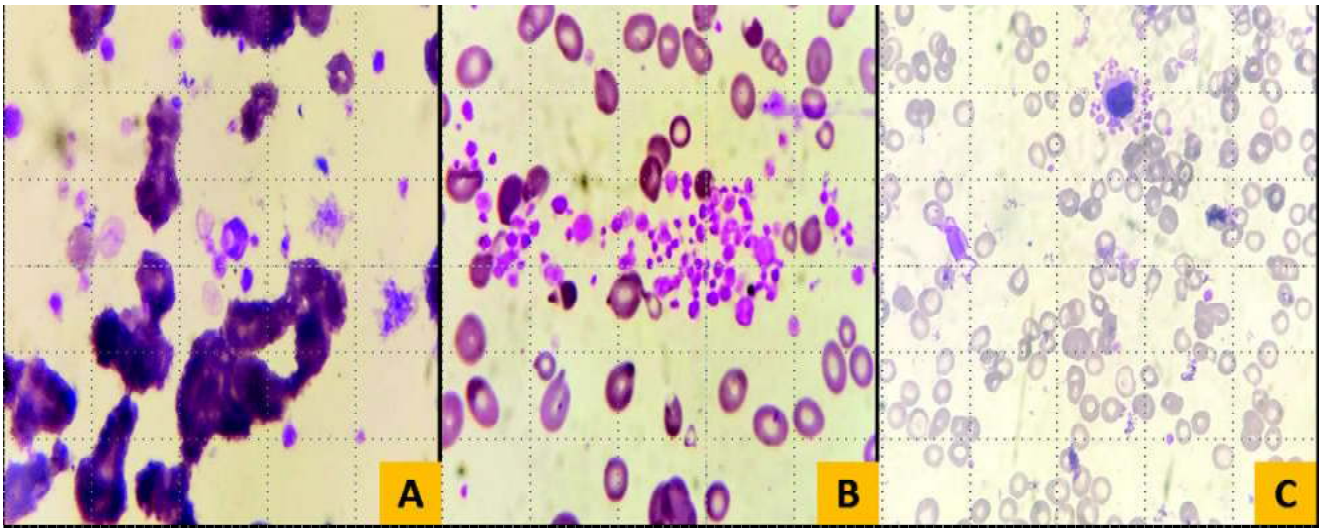

Fig. 3: A) *Platelet swelling,* ***B)*** *Platelet clumps,* ***C)*** *Platelet satellitism.*

Psuedo-thrombocytopaenia and platelets agglutination: It is the commonest quantitative abnormality noted secondary to platelets agglutination. This phenomenon is noted more commonly in severely ill patients, e.g., malignancy, chronic liver disease, autoimmune diseases, infection and cardiovascular diseases. However, it can be seen in patients with no underlying disease. It is caused by an autoantibody against glycoprotein IIb/IIIa present on the cell membrane of platelets. In the presence of EDTA, the epitope of glycoprotein IIb is revealed which normally remains hidden in the glycoprotein IIb/IIIa. Binding of the autoantibody to this epitope, results in aggregation[5] (Fig. 3-B).

Pseudo-thrombocytosis: Falsely elevated platelet count can be seen when the blood contains particulate matter with similar size and scatter properties as platelets; e.g., bacteria, cryoproteins, cytoplasmic fragments. Neutrophilic cytoplasmic debris ranging in size from 2 to 5 µm in diameter is noted in peripheral blood samples from patients with hairy cell leukaemia/ acute myeloid leukaemia or lymphoma or in patients with severe infections. These fragments may also get counted as platelets by automated analysers. As platelet transfusions are frequently required in leukaemic patients with low platelet counts, this masked thrombocytopaenia can delay appropriate transfusion. Therefore, all leukaemic patients should be reviewed with low platelets counts. Cryoglobulins, microcytic red cells, bacteria, red cell inclusions like Pappenheimer bodies, red cell fragments or microspherocytes can also result in falsely elevated platelet count[5].

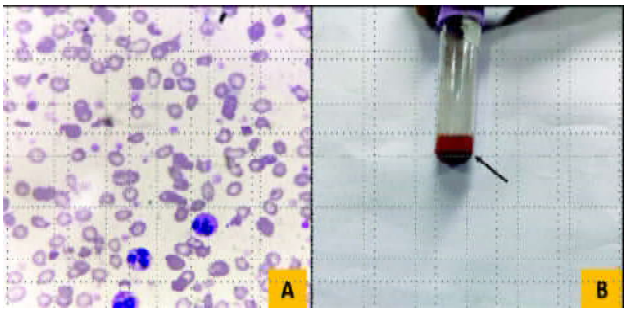

Fig. 4: *Pseudoechinocytes due to low quantity of sample.*

Platelet satellitism

Platelet satellitism is a rare cause of pseudo-thrombocytopaenia due to the adhesion of platelets to the surfaces of circulating leukocytes. It occurs when circulating auto-antibodies bind to cryptic antigens exposed because of the calcium-chelating activity of EDTA. The antibody platelet antigen (antiglycoprotein IIb/IIIa) binds to the Fca receptor (CD16) on the cell surface (Fig. 3-C)[6].

Pseudo-echinocytes

Echinocytes are RBCs with numerous fine, uniform spicules along the periphery. These are formed due to exposure of red cells to high pH while exposure to an acidic pH produce stomatocytes. Exposure of blood to glass (tubes or slides) may cause change in pH because of the release of alkali

Table II: Types of artefacts and their remedial measures.

Types of artefacts	Cases (n = 50) (%)	Causes	Remedial measures
Fixation artefact	6 (12%)	Presence of water in methanol	Usage of tight-fitting lid bottle/ Quality control of Methanol
Tailing	12 (24%)	Excessive pressure during smearing Roughened edges of spreader Dust-ridden slides	Spreader slide with smooth end should be used with appropriate pressure
Stain deposits	10 (20%)	Overstaining and inadequate washing	Usage of fresh working solution, filtration of stain and proper washing
Grease artefact	4 (8%)	Due to grease on slide and improper cleaning	Properly cleaned slides should be used
Cotton	2 (4%)	Cleaning of slides with cotton	Lint cloth should be used for cleaning
Storage artefact: Cytoplasmic blebs and rupture Cytoplasmic fragments Nuclear lobes fragmentation Platelet swelling and fragmentation	12 (24%) 2 (4%) 2 (4%) 5 (10%) 3 (6%)	Prolonged storage	Avoid prolonged storage Smear should be made within 4 hours (ideally 1 hour) of collection of blood
Platelet clumps	5 (10%)	EDTA induced agglutination Certain *in-vivo* factors	Collection in Citrate vial Fresh Finger-prick smears
Platelet satellitism	2 (4%)	Ca-chelating activity of EDTA Infections	Repeat sample in Citrate vial Treat the cause
Pseudo-echinocytes	6 (12%)	Low quantity of sample taken	Optimum blood sample should be taken in EDTA vial as per the insert
Increased hematocrit	3 (6%)	Overfilling of tube	Adequate quantity of blood sample should be taken

from the glass. It is reversible by correction of the pH. Pseudo-echinocytosis can also sometimes be seen on blood films, possibly as a result of flattening of red cells on the glass slide depending on the type of glass used. Other common cause of pseudo-echinocytes is low quantity of blood samples in vials (Fig. 4)[5].

Pseudo-polycythaemia

Pseudo-polycythaemia is due to an increased haematocrit caused by reduction in plasma volume rather than a true increase in red blood cells. Causes are physical stress, severe burns, excess alcohol consumption, diarrhoea or vomiting, insufficient water intake, fluid loss or diuretic therapy. Gaisbock's disease is also a cause of Pseudo-polycythaemia. It is associated with obesity, a history of smoking, hypertension, elevated erythrocyte count, elevated haemoglobin with reduced plasma volume. Overfilling of vacutainers may result in artifactually high hematocrit[5].

In the present study, 50 out of 500 cases showed artefacts. The most commonly encountered artefacts were storage artefacts and tailing artefact, each seen in 24% of cases followed by stain deposits in 20% of cases. Also, in 12 cases (24%), there was overlapping of different artefacts noted. The list of various measures helpful in prevention of these artefacts has been compiled in Table II.

Discussion

The word artefact is derived from a latin word *"arsfactum"* means art (*"ars"*) plus made (*"factum"*). Artefacts are artificially produced feature, introduced in the specimen under study. PBS examination is most useful and crucial for evaluation of anaemia, thrombocytopaenia, morphological assessment of cells such as blasts in leukaemia, and malarial parasites, etc. Poor staining of films hamper the morphology of blood cells. Each laboratory needs to follow standard operating procedure for blood film staining so that artefacts are kept to a minimum. Suboptimal staining leads to loss of RBC morphology and polychromasia.

Artefacts on EDTA are extensively studied as it is the anticoagulant of choice and cellular components and morphology of cells are preserved with EDTA if smears are made within an hour of collection of blood. After 6 hours, marked EDTA changes were noted on PBS, comparable with the study done by Narsimha *et al*[1]. These can range from crenation of RBCs, platelets swelling and nuclear fragmentation, cytoplasmic rupture of WBCs. In the present study as well, the most common artefacts noted were due to prolonged storage of blood due to delay in transport and processing of the blood sample (Table II).

Stain deposits are formed due to inadequate washing and improper staining. Due to stain deposits, it is difficult to diagnose malarial parasite and can even lead to misinterpretation. Cotton fibres can mimic fungal or filarial parasite to an untrained laboratory personnel.

Conclusion

Artefacts can be a serious handicap in day-to-day laboratory practices, and if not identified and rectified, can lead to misinterpretation and wastage of resources.

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ORIGINAL ARTICLE

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Topical Steroid Dependent Face: A Cross-Sectional Study From a Tertiary Care Hospital in Northern India

Shefali Mahlawat, Shitij Goel**, Kalindi Sud*, Kritika Bansal****

Abstract

Background: Topical corticosteroids (TCS) are commonly used in dermatology for inflammatory skin conditions. However, it's misuse may cause side-effects like pruritus, burning, and acneiform eruptions. This study aims to evaluate the side-effects of TCS misuse over the face and a detailed analysis of various steroids with their resultant side-effect among patients.

Method: This cross-sectional study was conducted in the Department of Dermatology of a tertiary care teaching hospital in Western Uttar Pradesh. It enrolled 150 patients who met the inclusion criteria, with a history of topical steroid misuse on the face. Data was collected through a detailed history, questionnaire, and physical examination, documenting patient demographics, steroid use history, duration, adverse effects, and steroid potency.

Results: In this study, out of 150 patients, the age ranged from 4 to 56 years, among which 114 (76%) were females. The primary reasons for using TCS were acne (30.7%) and hyperpigmentation (28.0%), with betamethasone valerate 0.1% being the most commonly misused steroid (58.7%). Most participants (47.3%) used TCS based on advice from friends or relatives, followed by pharmacists dispensing creams without a prescription. The duration of use varied, with 44% using TCS for less than six months, 10.7% for 6 months to 1 year, 29.3% for 1 to 3 years and 16% for over 3 years. A significant proportion (90%) were unaware of the side-effects and most common side-effects observed were pruritus (63.3%), erythema (58%), burning (52%), and acneiform eruptions (52%).

Conclusion: This study highlights the widespread misuse of topical corticosteroids, often without medical supervision, and a significant lack of awareness about their side-effects among users.

Key words: Topical corticosteroids (TCS), misuse, topical steroid damaged face.

Introduction

The term "Topical Steroid Dependent/Damaged Face" (TSDF), coined in 2008, refers to the skin damage caused by prolonged or excessive use of topical corticosteroids (TCS) on the face, often resulting in semi-permanent or permanent side-effects on the skin. Common components of TSDF include erythema, itching, burning, monomorphic acne, atrophy, rosacea, telangiectasia, perioral dermatitis, striae, hypertrichosis, and pigmentation. The misuse of TCS, particularly on the face, is a significant factor contributing to TSDF, especially in India, where these medications are easily accessible and often used without proper medical guidance. This misuse is frequently exacerbated by unlicensed practitioners and the societal obsession with fairness, leading many to apply corticosteroids for cosmetic purposes. The consequences include not only physical damage but also psychological dependence on the medication due to worsening symptoms upon discontinuation. While TCS are highly effective for treating inflammatory skin conditions, their improper use can lead to severe cutaneous side-effects, particularly in sensitive areas like the face.

Material and Methods

The study was conducted in the Department of Dermatology at a tertiary care teaching hospital in western Uttar Pradesh, between August 2022 and February 2024. The sample size of 150 patients was calculated using Cochran's formula. Following approval from the Institutional Ethics Committee, patients meeting the inclusion criteria were enrolled. Comprehensive histories – including demographics, steroid use, and adverse effects – were recorded. General physical examinations and photographs were taken when indicated.

The study included patients diagnosed with TSDF who had applied topical corticosteroids (TCS) on their face and reported experiencing one or more side-effects related to these agents. Patients who had overused TCS for various conditions for at least one month of continuous application or more than three months of intermittent application on the face were enrolled. Exclusion criteria involved patients diagnosed with TSDF but unable to provide adequate documentation or a reliable history of TCS usage. Also patients with co-morbidities that could cause skin changes

Junior Resident, **Professor and Head, ***Senior Resident, Department of Dermatology, School of Medical Sciences and Research, Sharda University, Greater Noida - 201 306, Uttar Pradesh.

Corresponding Author: Dr Shitij Goel, Professor and Head, Department of Dermatology. School of Medical Sciences and Research, Sharda University, Greater Noida - 201 306, Uttar Pradesh, Tel: 9560825292, E-mail: drgoelderma@gmail.com

similar to TCS side-effects, such as polycystic ovary syndrome, Cushing's syndrome, or thyroid disorders were excluded.

Statistical analysis

All data was collected in the case record forms and entered in MS excel sheet and analysed using SPSS 26 operating on windows 10. The demographic data were summarised as frequency, percentage, mean and standard deviation and represented using Tables, Figures, and Pie charts. The association between categorical variables was analysed using Chi-square test. A p-value <0.05 was considered statistically significant.

Results

This study encompassed 150 participants who met the inclusion criteria. The mean age of the study population was 30.15 years (SD = 10.061). Sixty-one participants (40.7%), were in the 21 to 30 years age group, followed by 42 (28.0%) in the 31 to 40 years age group. The youngest participant was 4-years-old and the oldest was 56-years-old. Among them, 114 (76.0%) were females while 36 (24.0%) were males.

Forty-three (28.7%) patients had education up to the 10th grade, followed by 37 (24.7%) who completed graduation. Uneducated individuals and those with education up to the 8th and 12th grades made up 21 (14%), 18 (12%), and 22 (14.7%) of the sample, respectively.

The most common reason for TCS application was acne, observed in 46 patients (30.7%), followed by hyperpigmentation in 42 (28.0%). Twenty-five participants (16.7%) used it for itching, 18 (12.0%) as a general face cream, 16 (10.7%) for fungal infections, and 3 (2.0%) for hypopigmentation, as shown in Fig. 1.

In our study, 123 (82%) participants used creams containing single steroid while 27 (18.0%) participants used multiple steroids over time. Betamethasone valerate 0.1% was the most commonly used steroid, used by 88 patients (58.7%), followed by clobetasol propionate 0.05% in 49 patients (32.7%) and mometasone furoate 0.1% in 38 patients (25.3%). Hydrocortisone and fluticasone were used by 2 (1.3%) and 1 (0.7%) patients, respectively (Fig. 2).

The source of information for TCS misuse were friends or relatives, reported by 71 participants (47.3%), followed by pharmacists in 33 (22.0%) and quacks in 32 (21.3%). Only 7 individuals (4.7%) received recommendations from doctors other than dermatologists, 6 (4.0%) from dermatologists, and 1 (0.7%) obtained the information

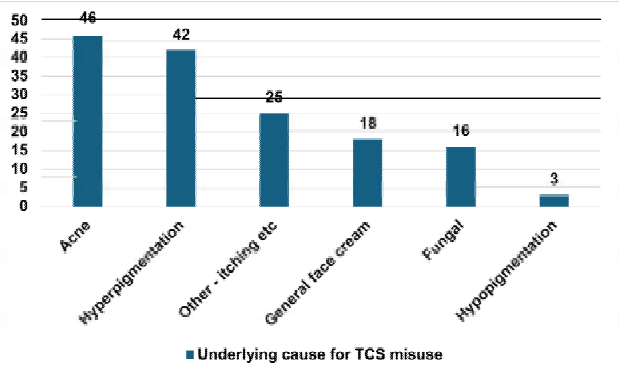

Fig. 1: *Bar graph showing distribution of the underlying cause for TCS misuse.*

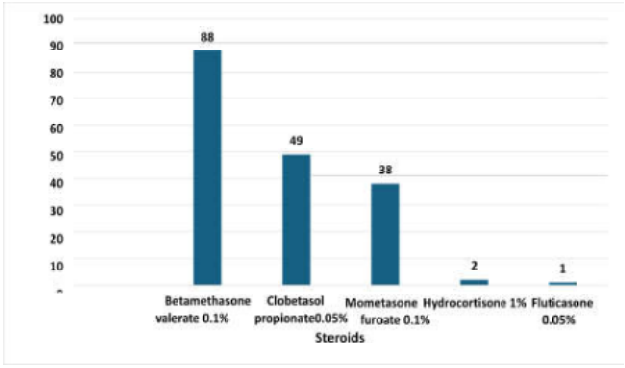

Fig. 2: *Bar graph showing distribution of type of steroids used among the participants.*

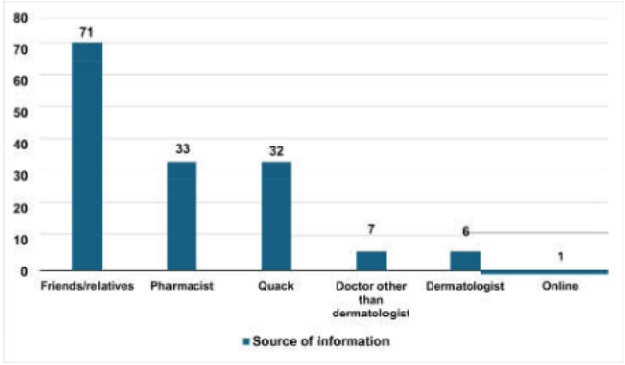

Fig. 3: *Bar graph showing distribution of source of information for TCS.*

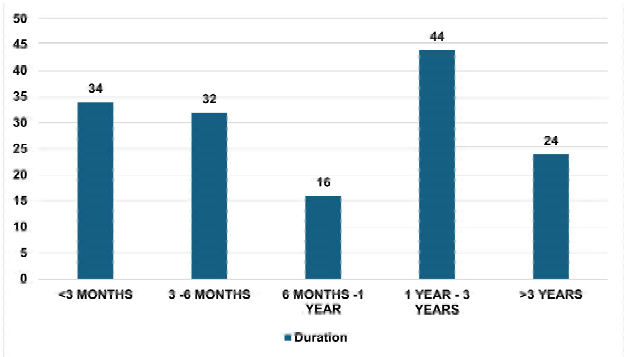

Fig. 4: *Bar graph showing duration of steroids application among participants.*

online as shown in Fig. 3.

Sixty-six (44%) participants used TCS for less than 6 months, 16 (10.7%) for 6 months to 1 year, 44 (29.3%) for 1 to 3 years and 24 (16%) for over 3 years (Fig. 4).

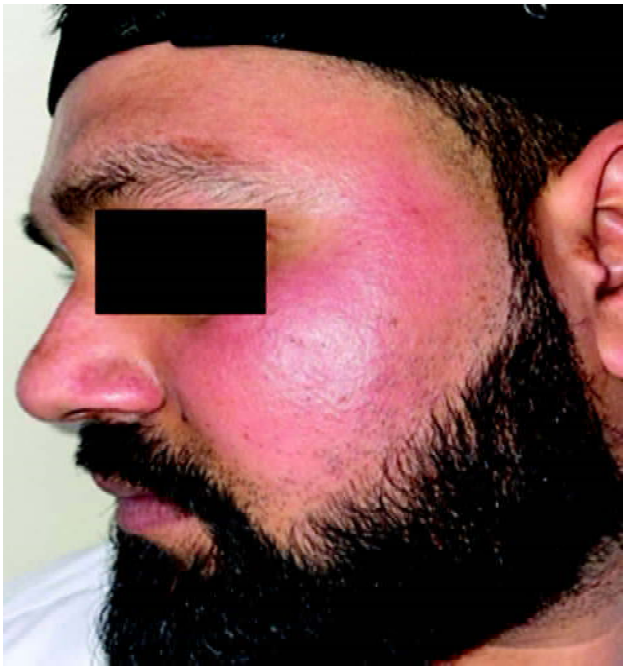

Fig. 5: *Erythema seen over the cheek due to overuse of betamethasone cream for 6 months.*

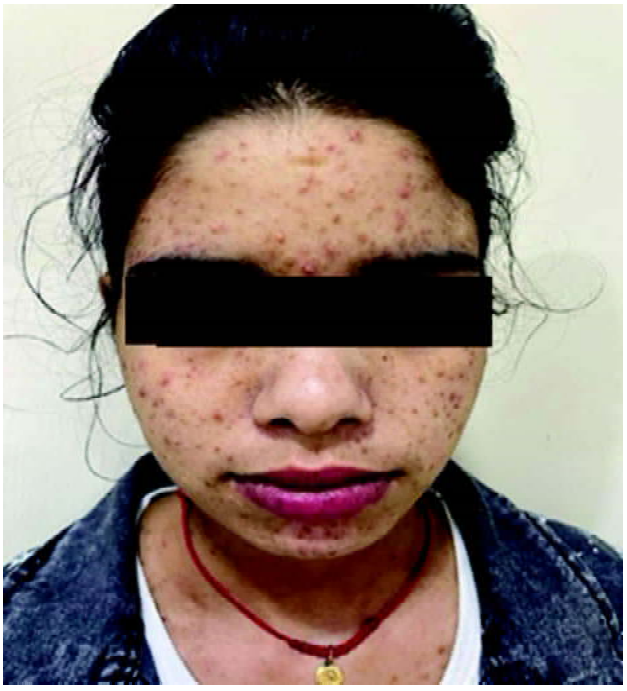

Fig. 6: *Multiple monomorphic papules present over whole face on using mometasone cream for 2 years.*

The majority of participants, 119 (79.3%), applied topical corticosteroids once daily, followed by 21 (14.0%) who applied it twice daily. Less frequent usage included 3 (2.0%) twice a week, 5 (3.3%) three times a week, and 2 (1.3%) four times a week.

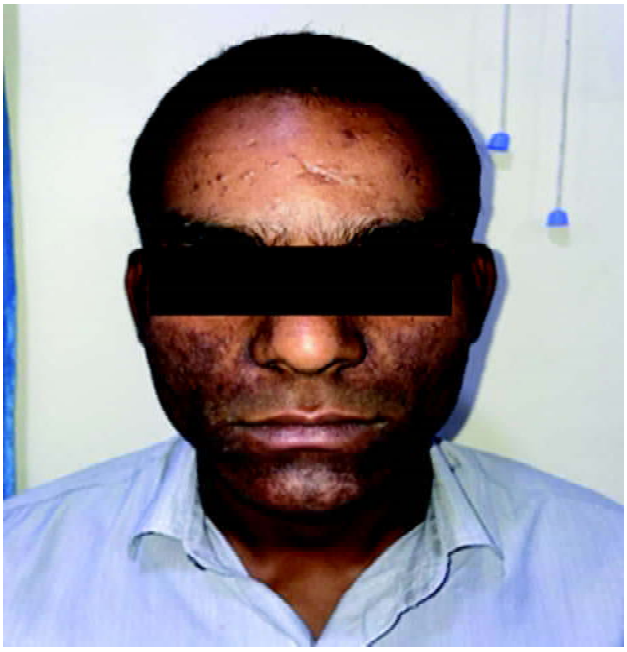

Fig. 7: *Hyperpigmentation present over bilateral cheeks and chin after using multiple TCS.*

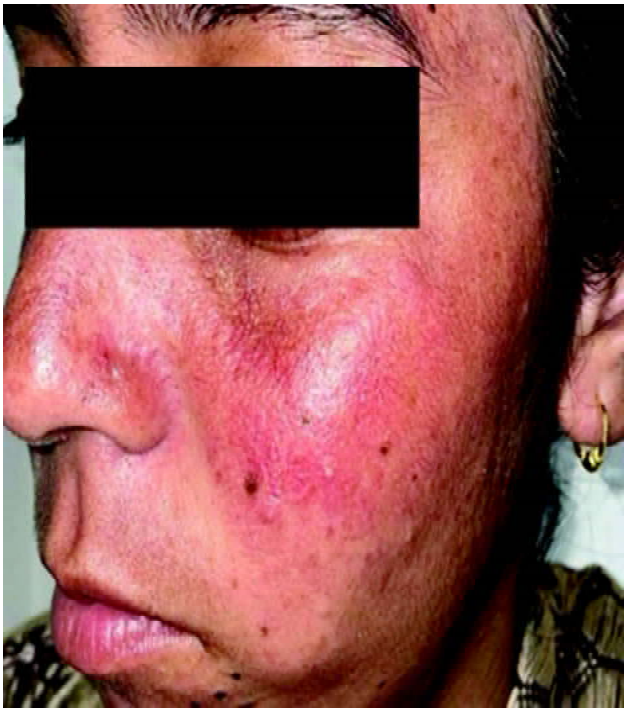

Fig. 8: *Prominent telangiectasia present over cheek and nose after using betamethasone for 3 years*

Thirth-four (22.7%) participants applied TCS only on the lesions while 116 (77.3%) participants applied TCS over whole face.

Out of 150 participants, one hundred and thity-five (90%) were not aware of the side-effects of TCS abuse, while 15 (10%) participants were aware.

The most common side-effect observed was pruritus in 95 participants (63.3%), followed by erythema in 87 (58%), burning sensation and acneiform eruptions in 78 each (52%). Photosensitivity was seen in 71 (47.3%), hyperpigmentation in 46 (30.7%), hypertrichosis in 37 (24.7%), and telangiectasia in 33 (22.0%). Less common effects included hypopigmentation in 5 (3.3%) and atrophy in 3 (2%) (Table I, Figs. 5-9).

Table I: Distribution of side-effects of steroids among the participants.

Side-effect	No. of cases	Percentage (%)
Pruritus	95	63.3
Erythema	87	58
Burning sensation	78	52
Acneiform eruptions	78	52
Photosensitivity	71	47.3
Hyperpigmentation	46	30.7
Hypertrichosis	37	24.7
Telangiectasia	33	22.0
Hypo-pigmentation	5	3.3
Atrophy	3	2

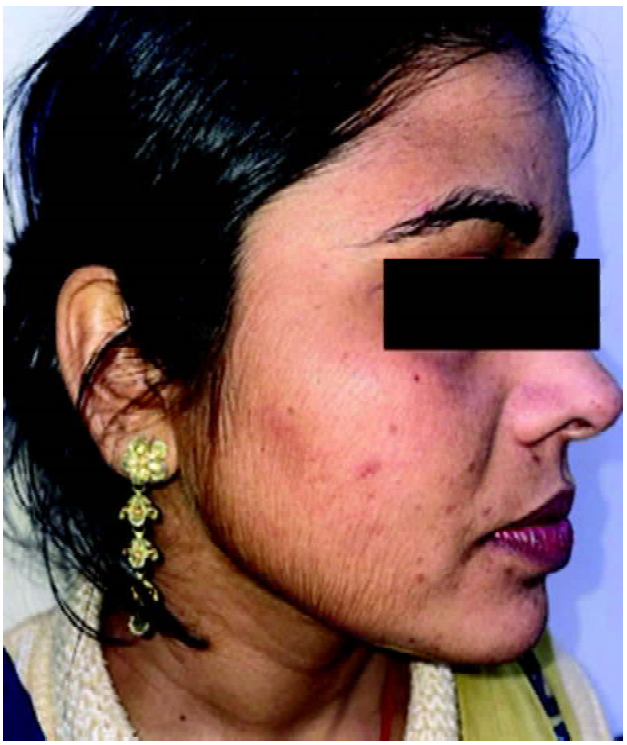

Fig. 9: *Hypertrichosis over the cheeks after application of clobetasol for more than 2 years.*

In this study, we analysed the side-effects reported as per the duration and potency of TCS usage. The participants were divided into two groups based on the duration of their treatment: those who received treatment for less than 6 months and those who received treatment for more than 6 months (Table II, III, IV).

Table II: Distribution of side-effects of betamethasone valerate among participants.

		<6 months	>6 months
	Total	**23**	**21**
Erythema	N (%)	13 (56.50%)	10 (47.62%)
Burning sensation	N (%)	9 (39.10%)	13 (61.90%)
Pruritis	N (%)	14 (60.90%)	13 (61.90%)
Acneiform eruptions	N (%)	15 (65.20%)	8 (38.10%)
Telangiectasia	N (%)	5 (21.70%)	3 (14.29%)
Atrophy	N (%)	2 (8.70%)	0 (0.00%)
Hyperpigmentation	N (%)	7 (30.40%)	5 (23.81%)
Hypopigmentation	N (%)	0 (0.00%)	1 (4.76%)
Photosensitivity	N (%)	7 (30.40%)	9 (42.86%)
Hypertrichosis	N (%)	2 (8.70%)	6 (28.57%).

Table III: Distribution of side-effects of clobetasol propionate among participants

		<6 months	> 6 months
	Total	**13**	**15**
Erythema	N (%)	9 (69.20%)	8 (53.33%)
Burning sensation	N (%)	6 (46.20%)	10 (66.67%)
Pruritis	N (%)	8 (61.50%)	11 (73.33%)
Acneiform eruptions	N (%)	5 (38.50%)	10 (66.67%)
Telangiectasia	N (%)	1 (7.70%)	4 (26.67%)
Hyperpigmentation	N (%)	3 (23.10%)	6 (40.00%)
Hypopigmentation	N (%)	1 (7.70%)	0 (0.00%)
Photosensitivity	N (%)	5 (38.50%)	8 (53.33%)
Hypertrichosis	N (%)	4 (30.80%)	4 (26.67%)

Table IV: Distribution of side-effects of mometasone furoate among participants

		<6 months	> 6 months
	Total	**6**	**14**
Erythema	N (%)	4 (66.70%)	10 (71.43%)
Burning sensation	N (%)	2 (33.30%)	7 (50.00%)
Pruritis	N (%)	4 (66.70%)	4 (28.57%)
Acneiform eruptions	N (%)	2 (33.30%)	4 (28.57%)

Telangiectasia	N (%)	0 (0.00%)	5 (35.71%)
Atrophy	N (%)	1 (16.70%)	0 (0.00%)
Hyperpigmentation	N (%)	0 (0.00%)	5 (35.71%)
Photosensitivity	N (%)	3 (50.00%)	6 (42.86%)
Hypertrichosis	N (%)	1 (16.70%)	5 (35.71%)

Discussion

Topical steroid-dependent face is a significant concern warranting thorough discussion and investigation. Our study reveals widespread misuse of topical corticosteroids, evident from the significant number of patients experiencing related side-effects.

We enrolled 150 patients aged 4 to 56 years, with a mean age of 30.15 years. The 21 - 30 years age group was most common, comprising 40.7% of the participants. Bains *et al*[1] also reported the most common age group was 21 - 30 years with 49% patients. This suggests that the younger population is more attentive to their appearance, leading them to be more vulnerable to misusing topical steroids in pursuit of aesthetic enhancement.

Majority of patients were educated, with most having completed up to the 10th grade or graduation. This highlights that misuse of topical corticosteroids (TCS) was prevalent even among the educated population, indicating a lack of awareness despite higher educational status.

The most common reasons for topical steroid use in the study were acne (30.7%), hyperpigmentation (28%), and itching (16.7%). Similar studies by Manchanda *et al*[2] and Swaroop *et al*[3] also found acne to be the leading cause.

One hundred and twenty four participants had used a single topical steroid while 26 participants used multiple steroids of different potencies. Betamethasone valerate 0.1% was the most commonly used steroid (58.7%), followed by clobetasol propionate 0.05% (32.7%) and mometasone furoate 0.1%(25.3%). Similar studies by Bains *et al*[1], Jain *et al*[4], and Kakroo *et al*[5] also found betamethasone valerate 0.1% and clobetasol propionate 0.05% to be the most frequently misused. In contrast, in a study conducted in Saudi Arabia, noted mometasone furoate 0.1% as the most commonly used steroid[6].

47.3% of patients used TCS based on advice from their friends and relatives. Other sources included pharmacists (22%), unqualified medical practitioners/quacks (21.3%) and non-dermatology doctors (4.7%) (Fig. 3). Similar findings in studies by Mahar *et al*[7], Saraswat *et al*[8], and Kakroo *et al*[5] confirmed that friends, family, and pharmacists were the primary sources of misuse.

The most common duration of TCS usage was 1 - 3 months (22.7%), with 21.3% using it for 3 - 6 months. This is consistent with Bains *et al*[1] findings, but differs from Ambika *et al*, where the average duration ranged from 6 months to 1 year, with some cases lasting up to 8 years.

90% of the participants were unaware of the side-effects while 10% of participants were aware about the potential side-effects of topical corticosteroids (TCS) but proceeded with their usage, suggesting that their persistence in seeking a desirable appearance might have overshadowed their awareness of associated risks.

The most common adverse effects were pruritus (63.3%), erythema (58%), and burning sensations (52%), followed by acneiform eruptions (52%) and photosensitivity (47.3%). Similar studies by Manchanda *et al*[2] and Nyati *et al*[10] reported acneiform eruptions, erythema, and photosensitivity as common side-effects. Other studies, like those by Kakroo *et al*[5] and Mahar *et al*[7], found tinea incognito and acne to be predominant adverse reactions.

In our study, we analysed the side-effects of frequently abused TCS which were – betamethasone, clobetasol propionate 0.05%, and mometasone furoate 0.1% – with respect to their potency, duration of use, and occurrence of cutaneous side-effects. Hydrocortisone and fluticasone were excluded from this analysis due to their lower usage and insufficient sample size. Patients who applied a single TCS once daily were included in the analysis.

For simplification, we classified side-effects as early and late. Side-effects resulting from steroid misuse within a period of less than six months were considered as early side-effects, whereas those arising after a period exceeding 6 months were considered as late side-effects.

In our study, among patients utilising betamethasone valerate 0.1%, the most significant early side-effect seen was acneiform eruptions. While the most significant late side effects observed were hypertrichosis and burning sensation. Among patients using clobetasol propionate 0.05%, the most common late side-effects observed were acneiform eruption, burning sensation, telangiectasia. Among patients using mometasone furoate 0.1%, the predominant early side-effect seen was pruritus while late side-effects observed were hypertrichosis, telangiectasia, and hyperpigmentation.

This detailed analysis and its findings are unique features of our study as we could not find a similar analysis in any other Indian studies on TSDF. In our study, there was no significant correlation found between potencies of the steroid used and resultant cutaneous side-effects. All potencies resulted in pruritus, erythema, telangiectasias, acneiform eruptions and others. However, some correlation between the duration of steroids usage and appearance of side-effects

was observed with respect to the different potencies of TCS.

Conclusion

The study highlights the widespread misuse of topical corticosteroids, particularly among individuals aged 21 - 30 years, with a higher prevalence in females. Acne was the most common reason for steroid use, with betamethasone valerate 0.1% being the most commonly misused steroid. Many patients obtained TCS without proper medical guidance, relying on friends and family for advice. Awareness of potential side-effects was low, and adverse reactions such as pruritus and erythema were common, with side-effect profiles varying based on the steroid type. The study calls for increased public awareness, health care provider education, and stricter regulation of TCS availability, along with further research on mitigating adverse effects and promoting safe usage.

Limitations

While this study provides valuable insights into the misuse of topical corticosteroids and their associated side-effects, it has a few limitations. Recall bias may have influenced the accuracy of self-reported data, as participants might not accurately remember or report their steroid usage history. Additionally, grading of the severity of side-effects was not performed, which could have offered more nuanced insight into the clinical impact. Correlation with dermoscopic findings was also not done, which might have strengthened the clinical observations with objective evidence.

Declaration of patient consent

The authors confirm that all necessary patient consent forms have been obtained. In these forms, the patient(s) have granted permission for their images and other clinical information to be included in the journal. The patients are aware that their names and initials will not be disclosed, and every effort will be made to protect their identity, although complete anonymity cannot be assured.

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REVIEW ARTICLE

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Dry Eye Disease: What Should a Non-Ophthalmologic Clinician Know?

Parul Jain, Chitra Ogia**, Aparna Soman***

Dry Eye Disease (DED) is a prevalent and often debilitating condition that affects millions of people worldwide. Although its primary management falls under the purview of ophthalmologist but non-ophthalmologic clinicians- such as primary care physicians, rheumatologists and dermatologists-play a crucial role in identifying, diagnosing, and managing this condition. Understanding dry eye disease, its symptoms, risk factors, and treatment options can enhance patient care and improve outcomes.

The prevalence of DED ranges from 5 to 50% among various populations around the world[1-3]. The prevalence of DED in North India is 32%, with the age group of 21 - 40 years affected most commonly[2]. Computer vision syndrome, smoking, diabetes and contact lens wear have been associated with an increased risk of developing DED.

It has been reported that rheumatoid arthritis (RA) tends to cause keratoconjunctivitis sicca (KCS), scleritis, episcleritis and peripheral corneal ulcers, and Sjögren's syndrome (SS) develops as a complication in 11% to 31% of RA patients[4].

Dry eye was found positive in 16.6% of patients with ocular rosacea. Meibomian glands play an important role in structuring the lipid layer of the tear film. Meibomian gland disorder (MGD), which is present in up to of 92% of patients with rosacea, consequently causes dry eye, mainly of the evaporative type[5]. One of the most common ocular features of systemic sclerosis (SSc) is DED, which has been identified to occur in 37 - 79% of patients. It is due to fibrosis of the conjunctiva and lacrimal gland that leads to a tear deficiency[6].

The prevalence of DED symptoms in patients suffering from depression and anxiety was estimated between 21% to 52% (Ulusoy *et al* 2019)[7]. Apart from the disease process itself, antidepressant, antipsychotic and antianxiety medication use are considered as risk factors for DED due to the potential side-effects on the tear film status.

DED can substantially affect vision and quality-of-life, as symptoms often interfere with daily activities, such as reading, writing, or working on video display monitors. Prevalence rates range from 5% to 50%, but can be as high as 75% among adults over 40 years of age, with women most often affected. Among younger adults ages 18 to 45 years, only 2.7% experience DED[3].

Definition

According to Tear Film and Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II)

"Dry eye is a multifactorial disease of the ocular surface characterised by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play aetiological roles"[8].

Pathophysiology

The ocular surface (cornea, conjunctiva, accessory lacrimal glands), meibomian glands (specific sebaceous glands of the eyelid margin, which produce the outer lipid film of the tear film), the main lacrimal gland, and the innervation between them form a functional unit. Any or all of these structures may be affected in dry eye disease. Many recent studies have stated that dry eye is an inflammatory disease that has many features in common with autoimmune disease. Any stress to the ocular surface (environmental factors, infection, endogenous stress, antigens, genetic factors) is considered as the pathogenetic triggering mechanism. Pro-inflammatory cytokines, chemokines, and matrix metalloproteinases lead to the expansion of autoreactive T helper cells which infiltrate the ocular surface and lacrimal gland .The result is a vicious circle of damage to the ocular surface and inflammation. The pathophysiology has been summarised in Fig. 1 and the immunomodulatory pathways depicted in Fig. 2.

Risk Factors and Aetiology

DED is influenced by a variety of risk factors and underlying causes. Age plays a significant role, as older adults are more prone to DED due to natural declines in tear production. Gender is another critical factor; women, particularly during menopause, experience hormonal changes that can increase their likelihood of developing dry eye symptoms.

**Associate Professor, **Post-Graduate Resident, Department of Ophthalmology, Maulana Azad Medical College and Guru Nanak Eye Centre, New Delhi - 110 002.*

Corresponding Author: Dr Parul Jain, Associate Professor, Department of Ophthalmology, Maulana Azad Medical College and Guru Nanak Eye Centre, New Delhi - 110 002. Tel: 9971927902, E-mail: pjain811@gmail.com

Infrequent blinking, often linked to extended computer use or conditions like Parkinson's disease, reduces tear distribution and leads to dryness. Neurologic conditions such as stroke, Bell's palsy, or trigeminal nerve dysfunction can lead to DED. Inflammatory eye conditions, including uveitis and iritis, as well as infectious keratitis caused by herpes simplex or herpes zoster, can also contribute to dry eye (Table I).

Table I: Ocular and non- ocular causes of dry eye

Systemic Diseases:	Lids:
– Sjögren's disease	– Blepharitis
– Rheumatoid arthritis	– Meibomian gland dysfunction
– Systemic lupus erythematosus	– Ectropion
– Diabetes mellitus	– Entropion
Hormonal Changes:	**Meibomian Gland Dysfunction**
– Menopause	**Tear Film Abnormalities**
– Androgen deficiency	
Medications:	**Ocular Surgeries**
– Antihistamines	– LASIK
– Antidepressants	– Cataract surgery
– Diuretics	
– Beta-blockers	
– Isotretinoin	
Vitamin A deficiency	**Contact Lens Use**
Environmental Factors:	**Ocular Surface Disorders**
– Low humidity	**Infections**
– Air conditioning	
– Wind exposure	
– Prolonged screen time	
Neurological Disorders:	
– Parkinson's disease	
– Bell's palsy	
– Stroke	

Nutritional factors and systemic diseases like rheumatoid arthritis, lupus, Sjögren's disease, rosacea, thyroid disorders, and diabetes are associated with an increased risk of developing DED[8]. Various systemic disorders causing dry eye have been summarised in Table II.

As medication is a known risk factor for ocular surface diseases, the Dry Eye Workshop II report on iatrogenic dry eye focused on conventional medications such as antihypertensive, antidepressants, antihistamines, corticosteroids, or nonsteroidal anti-inflammatory drugs.

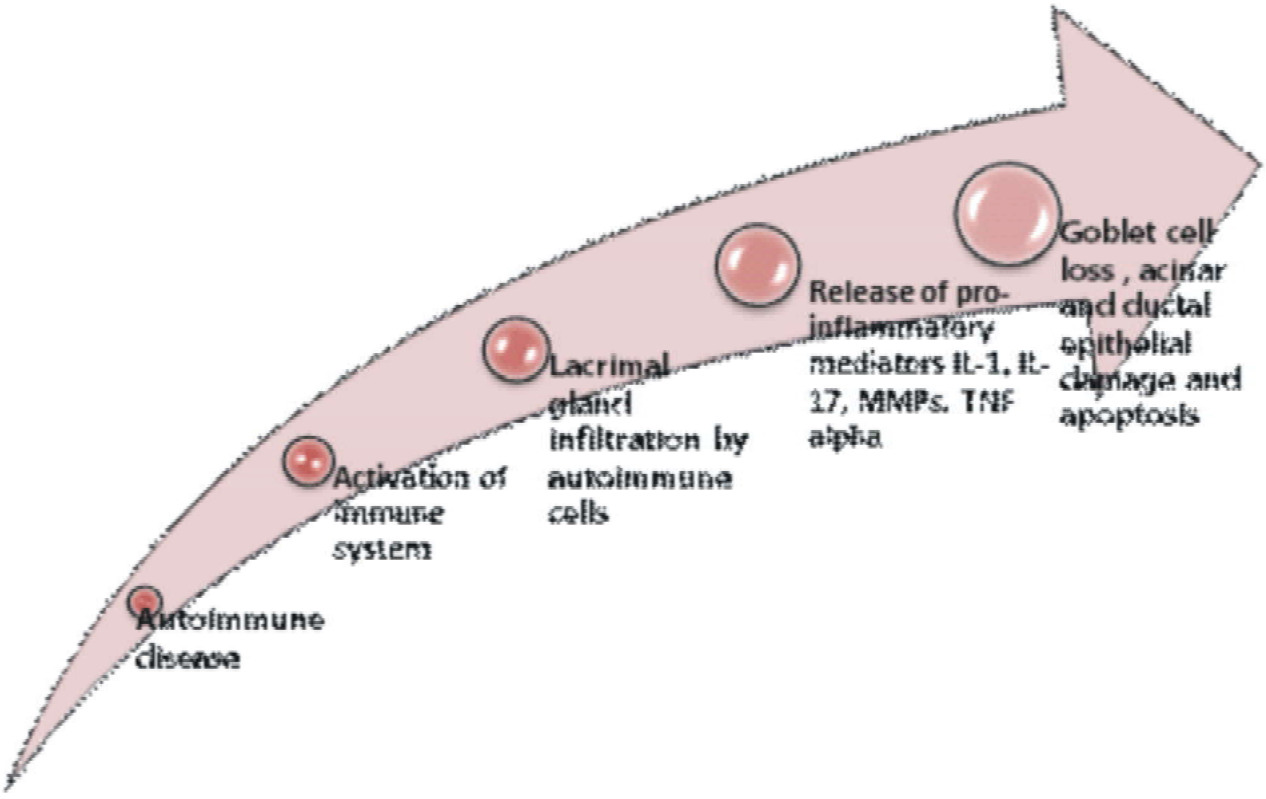


Fig. 1: *Pathophysiology of DED*

Immuno-inflammatory pathway:

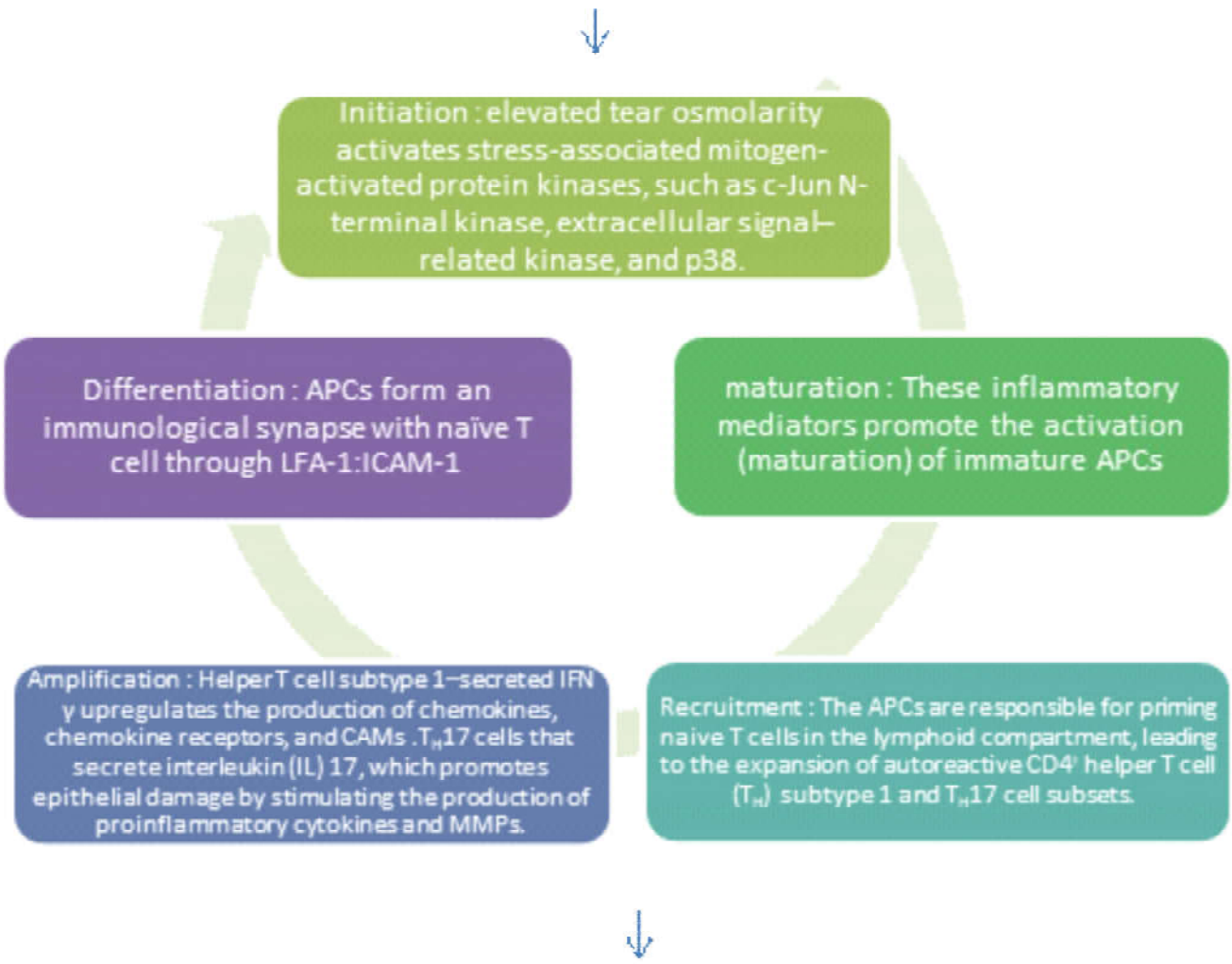


Fig. 2: *Immunoinflammatory pathway. IL: (interleukin), CAMs: (cell adhesion molecules), LFA-1: (lymphocyte function-associated antigen-1), ICAM-1: (intercellular adhesion molecule-1), interferon: (IFN), antigen-presenting cells, MMP: (Matrix metalloproteinase), MPTP: (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine).*

Table II: Systemic diseases associated with DED.

Rheumatologic Disorder	Metabolic Disease	Dermatologic Disease	Psychiatric Disease	Others
Rheumatoid arthritis	Diabetes	Rosacea	Depression	Asthma
Sjögren's disease	Thyroid disorder	Psoriasis	Insomnia	Vitamin A deficiency
Osteoporosis		Skin allergy	Use of antidepressant TCA>SSRI/SNRI	Stevens-Johnson Syndrome
Systemic Sclerosis		Eczema	Parkinson Disease	Migraine
Sarcoidosis	Hypercholesterolemia	Use of isoretinoin		Graft-versus-host disease (GVHD)
	Irritable Bowel Syndrome			

TCA = Tricyclic antidepressant, SSRI = Selective serotonin reuptake inhibitor, SNRI = Serotonin nor-adrenalin reuptake inhibitor.

Some common medications causing dry eye have been summarised in Fig. 3.

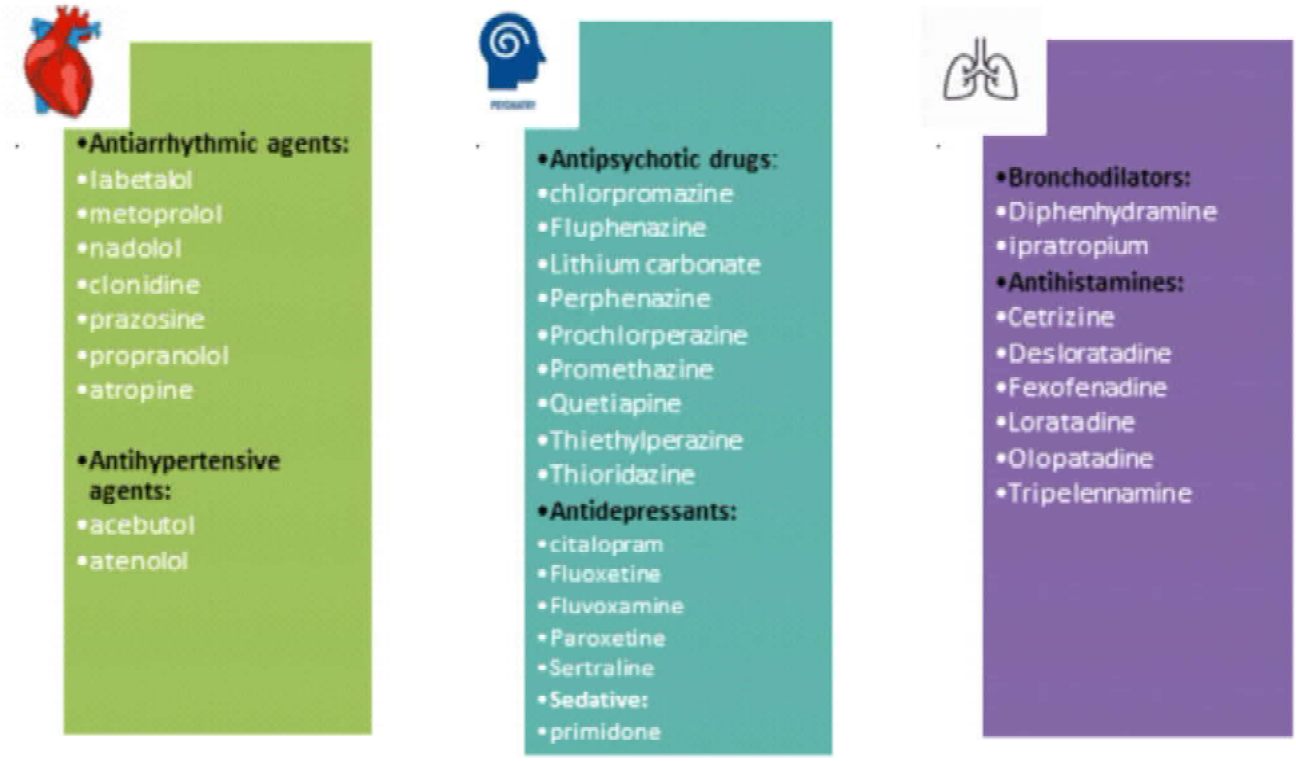


Fig 3: *Some common medications which causes DED*

Classification of DED

National eye institute (NEI)/Industry Workshop classification was useful and durable scheme for over a decade, but it did not reflect newer knowledge on pathophysiological mechanisms, effects on vision, and the utility of an assessment of severity of disease (Fig. 4). So, a classification scheme was presented by the TFOS DEWS based on aetiopathogenesis (Fig. 5).

Due to potential overlap between aqueous deficient and evaporative categories and issues regarding accuracy of placement of some conditions within the DEWS sub-classification zone, a new dry eye classification scheme was made which incorporates triaging elements to provide clarity in diagnosing DED (Fig. 6).

Symptoms

Dry eye disease presents with a range of symptoms (Fig. 7). Individuals often experience persistent dryness and a gritty sensation in their eyes, accompanied by burning or stinging feelings. Redness may also be noticeable. Excessive paradoxical tearing can occur as a reaction to the irritation, leading to watery eyes. This is because the unhealthy tear film and the irritation that comes from it stimulate the brain to produce reflex of tears. It helps in counteracting the irritation. Additionally, blurred vision is common, particularly during prolonged activities like reading or using screens. Some may also notice stringy mucus in or around the eyes. These symptoms can vary in severity and may worsen throughout the day[8].

Diagnosis

Persons with DED symptoms should be referred for a complete ophthalmologic examination. There is no single gold standard sign or symptom for diagnosing DED. Evaluation of symptoms and signs of DED is recommended, as signs may be present without symptoms and *vice-versa*. Understanding the work-up can help non-ophthalmic clinicians identify patients at higher risk and consider appropriate preventive measures or referrals.

Patient's history: A comprehensive history is very essential including risk factors, systemic disease and medication use. Some questionnaires are available for history taking in DED (Table III). Ocular surface disease index (OSDI) or dry eye questionnaire-5 (DEQ-5) are well suited questionnaires for non-ophthalmologists because of ease of use and reliability.

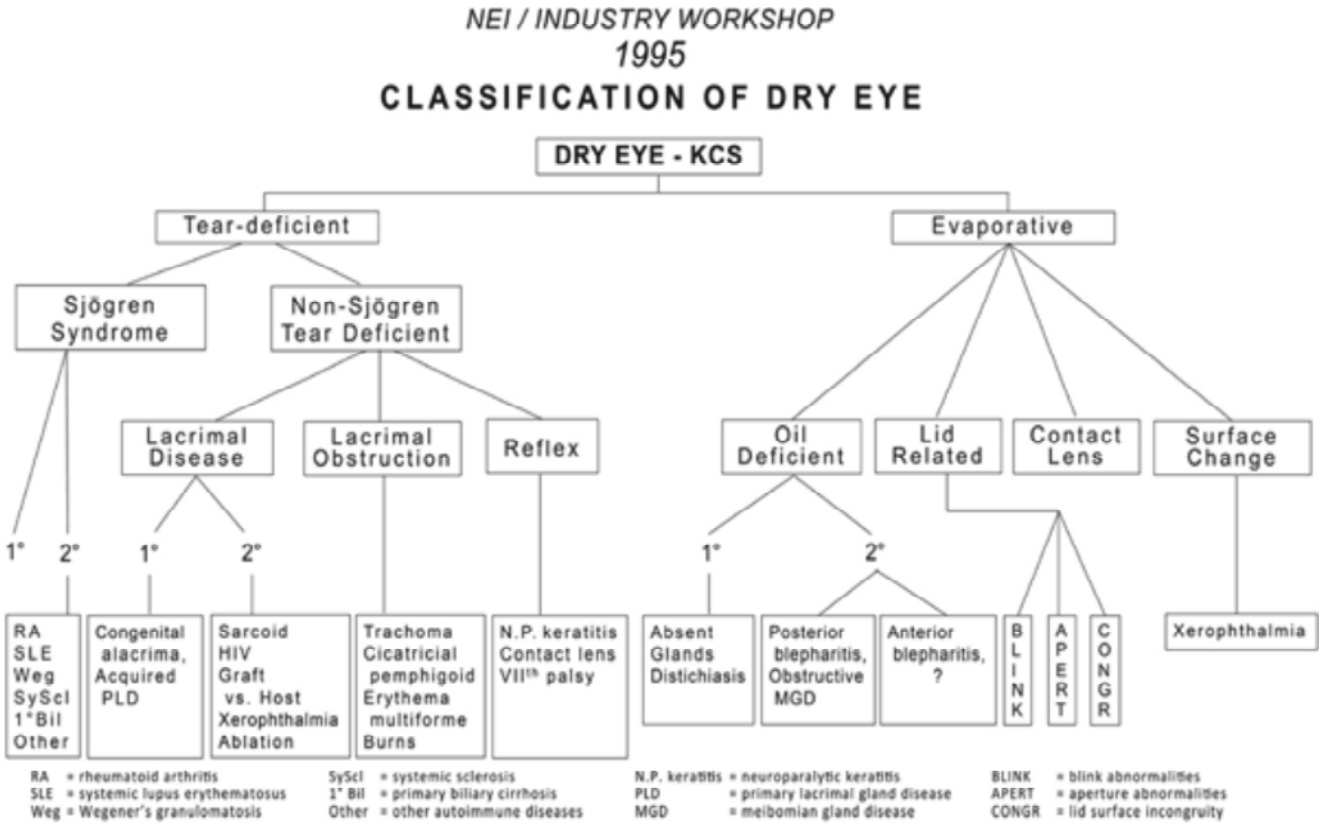


Fig 4: *NEI/Industry Workshop classification[8].*

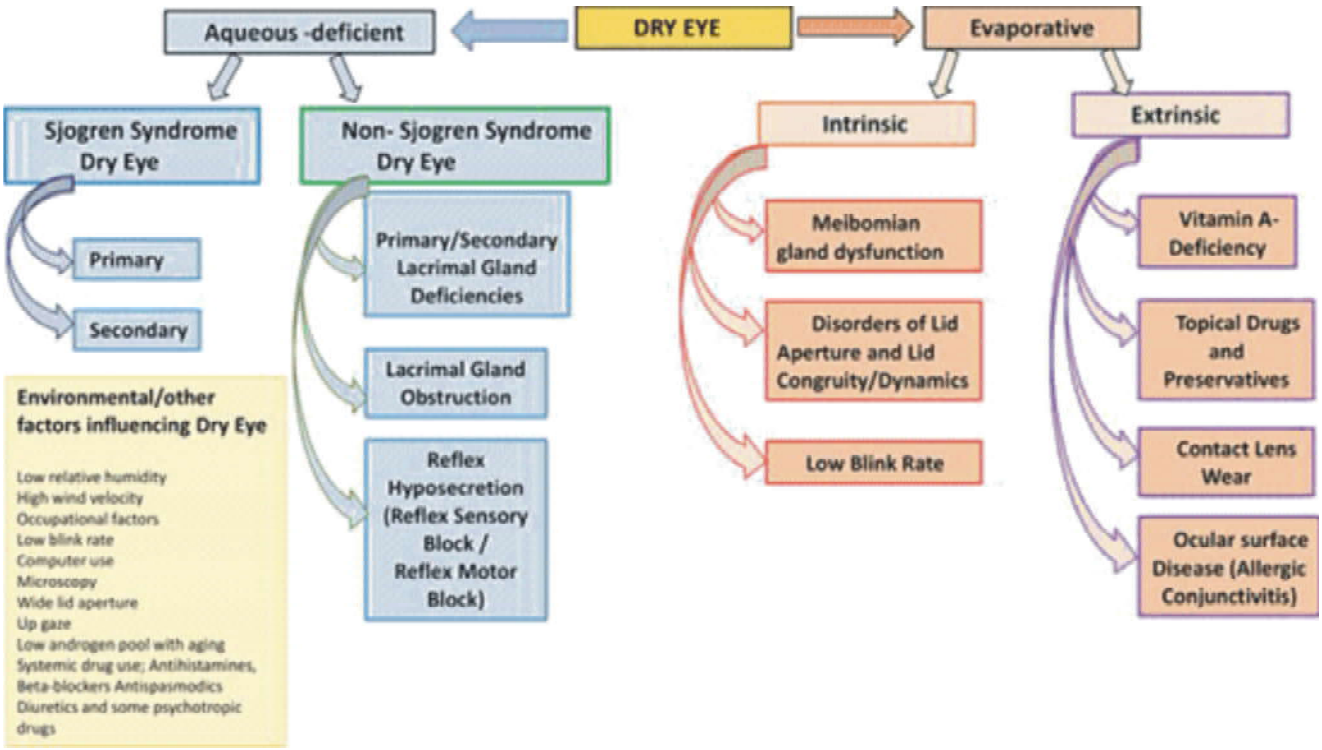


Fig. 5*: The 1995 Classification of dry eye[9].*

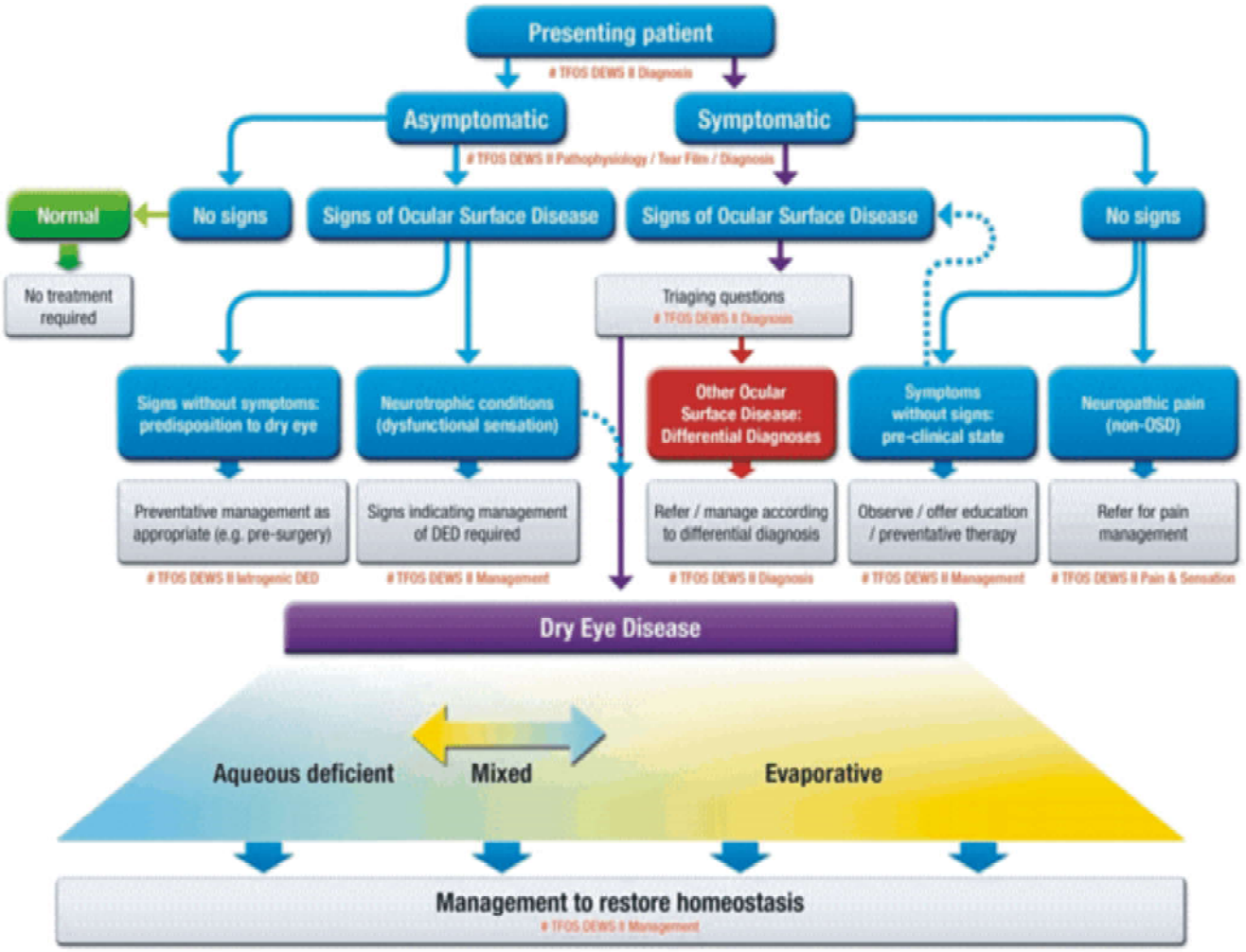


Fig. 6: *Classification of DED which incorporates a clinical decision algorithm[8].*

External examination

Patients can present with a variety of signs and symptoms, especially when DED is associated with autoimmune diseases. Examination of cranial nerves, particularly the trigeminal and facial nerves should be done. The eyelids must also be carefully examined for incomplete closure or malposition, as these can lead to complications like exposure keratopathy. Additionally, erythema of the eyelid margins, abnormal deposits or secretions should be noted, as they can signify conditions such as blepharitis. Furthermore, assessing for trichiasis, ectropion and entropion should be checked properly. Finally, the adnexa should be inspected for enlargement of lacrimal glands, which can suggest lacrimal system disorders. This thorough examination provides critical insights into the health of the ocular surface.

Slit-lamp examination

During a slit lamp examination for DED, several key findings may be observed. These findings have been summarised in Table V.

Diagnostic tests

Diagnostic tests are necessary in order to distinguish

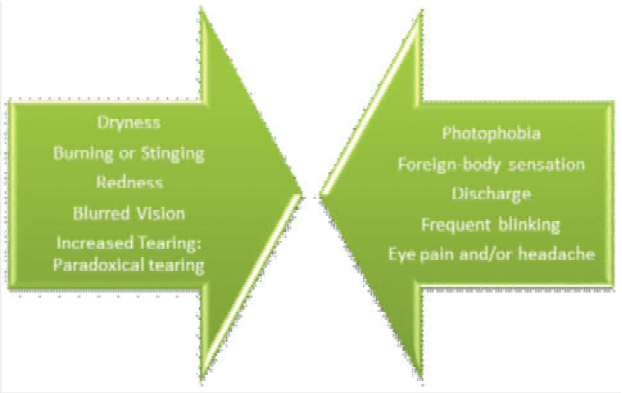


Fig. 7: *Symptoms of DED.*

between dry eye, infections and allergies as patients can present with a similar clinical presentation, but require different treatments. On the other hand, antiallergic or epitheliotoxic antibiotics can worsen the DED. A series of diagnostic modalities are available for the diagnosis of DED and the same have been summarised in Tables VI and VII.

Tear film stability can be assessed by corneal topography, interferometer, and aberrometry.

Table III: Commonly available questionnaires for dry eye assessment.

	OSDI	SPEED	DEQ-5	IDEEL	SANDE	DEEP	NEI-VFQ-25	McMonnies	CLDEQ-8
Items	12 (3 subscales)	8	5	57	2	19	25	14	8
Score Scale	0 - 100	0 - 28	0 - 22	0 - 100	Visual analog scale	0 - 114	0 - 100	0 - 45	0 - 37
Year of development	1997	2005	2009	2003	2007	1998	2001	1986	2009
Description	Symptoms, vision related function, Environment triggers, Quality of life	Frequency and severity of symptoms, assessment of diurnal and 3- month interval changes	Frequency and intensity of symptom within previous month	Symptoms, quality-of-life, treatment satisfaction	Frequency and intensity of symptoms/ discomfort	Frequency of symptoms	Effect of visual impairment on health related quality-of-life	Risk factors, frequency of symptoms, Environment trigger sensitivity	Frequency and intensity of symptoms among contact lens users
Access	Open	Open	Paid	Paid	Paid	Open	Open	Paid	Paid
Validity	Good	Good	Good	Fair	Good	Epidemiologic studies, High specificity	Fair-Good	Weak	Good
Designated Diagnostic cut-off value	Present (Mild 13-22 Moderate 23-32 Severe 33-100)	Absent	Present (>6- suspected dry eye >12- suspected Sjogrens)	Absent	Absent	Absent	Absent	Present (14.5)	Present (12)
Assessment of Quality-of-Life	Present	Absent	Absent	Present	Absent	Absent	Present	Absent	Moderate
Validated Languages	English, Spanish, Portuguese, Chinese, Farsi, Bahasa, Japanese, Filipino	English Italian	English, Spanish	English, Chinese	English	English	Over 50 languages	English, Chinese	English, Japanese

OSDI: Ocular Surface Disease Index, SPEED: Standard Patient Evaluation of Eye Dryness, DEQ-5: Dry Eye Questionnaire-5, IDEEL: Impact of Dry Eye on Everyday Life, SANDE: Symptom Assessment in Dry Eye, DEEP: Dry eye screening for dry eye epidemiology projects, NEI-VFQ-25: National Eye Institute Visual Function Questionnaire-25, CLDEQ-8: Contact Lens Dry Eye Questionnaire-8.

Table IV: Signs and symptoms of autoimmune diseases associated with DED.

Rheumatoid Arthritis	Sjögren's Disease	Psoriasis	Rosacea	SLE	SSc	SJS
Swollen joints	Dry mouth	Scaly silver plaque with clear border	Facial flushing	Skin rashes	Thick and immobile skin	Fever
Morning stiffness	Dry skin	Nail pitting, thick nails	Facial bumps and pimples	Joint pains	Raynauds phenomenon	Lymphadeno-pathy
Joint pains	Difficulty in opening mouth	Dry skin	Phymatous changes	Headache	Sclerodactyly	Erythematous, Purpuric macule of irregular size and shape
Rheumatoid nodules	Difficulty in swallowing	Joint pains		Muscle pain, etc.	Calcinosis	
Joint deformity of metacarbo-phalangeal joints in late stage					Telangiectasia	

SLE = Systemic lupus erythematous; SJS = Stevens-Johnson syndrome; SSc = Systemic sclerosis.

Table V: Slit lamp examination in DED.

Adnexa:	Conjunctiva	Cornea:
Eyelashes: trichiasis, distichiasis, deposits on eyelashes **Anterior and posterior eyelid margins:** abnormalities of meibomian glands, (e.g., orifice metaplasia, reduced expressibility, atrophy), character of meibomian gland secretions, [e.g., turbid, thickened (tooth-paste sign), foamy, scarring, deficient], keratinisation, scarring **Puncta:** position, patency, position of plugs if present **Tear film:** height of the meniscus, debris, mucus strands, and foam	Inferior fornix and tarsal conjunctiva: e.g., mucous threads, gross scarring, stellate scar (in healed trachoma), erythema, papillary reaction, enlarged follicles, keratinisation, fornix shortening, symblepharon Bulbar conjunctiva: e.g., punctate staining with fluorescein, follicles, Herbert's pit , hyperaemia, localised drying, Bitot's spot, keratinisation Temporal lid parallel conjunctival folds (LIPCOFs): They are the result of increased friction between lid and conjunctiva.	localised inter-palpebral drying, punctate epithelial erosions, superficial punctate staining with Rose Bengal or fluorescein dyes, filamentary keratopathy, epithelial defects, mucous plaques, keratinisation, pannus formation, localised dellen, thinning, infiltrates, ulceration, scarring, neovascularisation, corneal or keratorefractive surgery

Table VI: Slit lamp examination in DED.

Test	Findings
Schirmer I test (without anaesthesia) basal and trigeminal reflex tear production	**Wetting of schirmer paper:** • 0 to 5 mm: extremely dry eyes • 5 to 10 mm: moderately dry eyes • 10 to 15 mm: possible dry eyes • Longer than 15 mm: normal tear function The Dry Eye Workshop proposes a Schirmer test I cut-off value of 10 mm for 5 minutes as one of the criteria for diagnosing DED[10].
Schirmer II (with anaesthesia) basal tear production	>10 mm = normal If <10 mm → irritate nasal mucosa: <1 mm = Sjögren's disease >1 mm = non-Sjögren dry eye
Schirmer III (without anaesthesia)	Schirmer test III assesses reflex-stimulated lacrimal secretion after looking at the sun for some time. It has less diagnostic value.
Phenol red impregnated thread test **Yellow to red colour after placing in cul-de-sac for 15 seconds**	<6 mm abnormal
Tear function index = Schirmer II/tear clearance	<96% = suggestive of dry eye <34% = diagnostic of dry eye
Tear Meniscus Assessment	<0.25 mm is suggestive of dry eye
Tear breakup time	Less than 10 seconds is abnormal Grade 1 = 10 sec Grade 2 = 5 - 10 sec Grade 3 = 3 - 5 sec Grade 4 = <3 sec

Tear film integrity

Fluorescein Staining

It stains areas of the corneal and conjunctival epithelia where there is disruption of intercellular junctions to allow the dye to permeate into the tissue. Saline-moistened fluorescein strips are used to stain the tear film. After instilling dye, the ocular surface is examined through a slit lamp microscope using a cobalt blue filter.

Table VIII: Some laboratory tests.

Tear film osmolarity	Matrix Metalloproteinases (MMP) and Lactoferrin	Biopsy
Elevated osmolarity and increased variability of osmolarity of the tears are characteristics of DED. Osmolarity values typically increase with disease severity. Various cutoff values have been reported: 308 mOsm/L = mild-to-moderate disease, whereas 316 mOsm/L is cut-off for more severe disease[6].	MMPs are found in the tears of individuals with dry eyes. Matrix metalloproteinase-9 (MMP-9) levels can be tested using a point-of-care test. MMP-9 levels can be elevated in other inflammatory conditions, such as graft-versus-host disease, Stevens-Johnson syndrome, and following corneal surgery. lactoferrin is secreted by lacrimal glands. So, abnormality in this test is an indicator of lacrimal gland dysfunction.	**Conjunctival biopsy:** Conjunctival sample is taken from lower fornix as maximum goblet cells are present there. Decrease in goblet cell is suggestive of mucin deficiency. **Lacrimal gland and minor salivary gland biopsy:** Lymphocyte and plasma cell infiltration in gland is diagnostic of Sjögren's disease. This is the most specific test for Sjögren's disease diagnosis

Table IX: DEWS dry eye severity grading scheme[9].

Dry eye severity level	1	2	3	4
Discomfort,severity and frequency	Mild and/or episodic; occur under environmental stress	Moderate episodic or chronic, stress or no stress	Severe frequent or constant without stress	Severe and/or disabling and constant
Visual symptoms	None or episodic mild fatigue	Annoying and/or activity limiting episodic	Annoying chronic and/or constant limiting activity	Constant and/or possibly disabling
Conjunctival injection	None to mild	None to mild	+/-	+/++
Conjunctival staining	None to mild	Variable	Moderate to marked	Marked
Corneal staining severity/location	None to mild	Variable	Marked central	Severe punctate erosion

Rose Bengal staining

It may be performed using a saline moistened strip. The saline drop used to moisten the strip should remain in contact with the strip for at least a minute to achieve an adequate concentration of Rose Bengal to stain the ocular surface. Patients should be informed that the drop might irritate the eye. Rose Bengal staining is more intense on the conjunctiva than the cornea. The dye stains ocular surface cells that lack a mucous coating as well as debris in the tear film.

Lissamine green dye

It has a staining profile similar to that of Rose Bengal and may cause less ocular irritation.

Laboratory tests

While the diagnosis of DED is primarily based on clinical evaluation and symptom assessment, certain laboratory tests can provide valuable information regarding tear production, ocular surface health, more accurate diagnosis and help in ruling out other potential conditions which lead to ocular discomfort. A series of relevant laboratory tests available for the diagnosis of DED as in Table VIII.

Some newer laboratory tests

Serum autoantibody measurement

Assessment of autoantibodies (ANA, RF, SS-A, and SS-B) is performed for diagnosis of Sjögren's disease. Of these, SS-A is probably the most sensitive and specific antibody for Sjögren's but alone is not diagnostic since it may be present in other autoimmune disorders. It may be absent in up to a third of Sjögren's disease cases[11].

Anti-centromere antibodies are predominantly observed in limited cutaneous systemic sclerosis, although they may occur in diffuse cutaneous systemic sclerosis. Anti-topoisomerase I antibodies and Anti-RNA polymerase III are predominantly observed in diffuse cutaneous systemic sclerosis. Anti-U3-RNP (fibrillarin) antibodies correlate with increased internal organ involvement, diffuse cutaneous manifestations, interstitial lung disease, pulmonary hypertension and poor prognosis[12].

Tear cytokines and chemokines

The levels of tear cytokines and chemokines are important and reflect the level of epithelial disease. Certain cytokines can highlight a specific disease process, for example, elevation of Th1 and Th17 subclasses of cytokines suggest involvement of particular T lymphocyte differentiation pathways in the disease[13].

Elevation of tear Th2 cytokines suggests a more allergic-based disease. Tear assay for tumour necrosis factor alpha, interferon gamma, IL-1 beta and IL-6 helps in assessing dry eye disease.

Management

The aims for treating DED are to reduce or alleviate signs and symptoms of dry eye, maintain and improve visual function and reduce or prevent structural damage. Patients with dry eye symptoms often have many contributory factors. Tear replacement is frequently unsuccessful when used as the sole treatment if additional causative factors are not concomitantly addressed.

Treatment for dry eye disease involves a step ladder approach, corresponding to disease severity and must take into account the assosciated local and systemic diseases. For patients with irreversible tear deficiency or evaporative disease associated with blephritis or any autoimmune disease – ophthalmologist should educate the patient about the natural history and chronic nature of dry eye disease. Patient education is an important aspect of successful management of DED. Treatment of mild eye disease has been summarised in Table X.

Table X: Management of mild DED.

Mild Dry Eye:	• Education • Environment modifications: Use humidifiers, avoid direct air (fans, cooler, heater, air conditioner), wear sunglasses outdoors • Elimination of offending topical and/or systemic medications • Avoid cigarette smoking • Stay hydrated • Artificial tear substitutes; gels, ointments • Eyelid warm compression and eyelid hygiene • Treatment for contributing ocular factors such as blepharitis or meibomitis – e.g., Systemic Tetracyclines.

Moderate Dry Eye

Preservative free tears are important. The frequency may be increased from 6 - 12 times depending upon the patient's need, occupation, and lifestyles.

In patients with moderate to severe dry eye disease, anti-inlammatory treatment is necessary to break the vicious cycle of surface damage and inflammation. 0.05% topical cyclosporine prevents activation and nuclear translocation of cytoplasmic transcription factors that are required for T-cell activation and inflammatory cytokine production. It also inhibits mitochondrial pathways of apoptosis of lacrimal gland and goblet cells. Topical corticosteroids have been reported to decrease the symptoms of ocular irritation, decrease corneal fluorescein staining, and improve filamentary keratitis. Low-dose topical corticosteroids therapy can be used at infrequent intervals for 2-week to suppress irritation secondary to inflammation. Patients prescribed corticosteroids for dry eye should be monitored closely for adverse effects such as increase in intraocular pressure, corneal melting, and cataract formation. Treatment of moderate DED has been summarised in Table XI.

Severe Dry Eye

In addition to the treatments for mild and moderate dry eye, the following treatments may be considered:

Oral cholinergic agonists like pilocarpine and cevimeline, have been used to treat the symptoms of dry mouth in patients with Sjögren disease. These medications bind to muscarinic receptors, which stimulate secretion of the salivary and sweat glands, and they appear to improve tear production. Oral pilocarpine (5 mg) 4 times daily-causes a significant overall improvement. The most common side effect is excessive sweating. Oral cevimeline (30 mg) 3 times daily, is another cholinergic agonist that has been found to improve ocular irritation symptoms and aqueous tear production. This agent may have fewer adverse systemic side-effects than oral pilocarpine.

Table XI: Management of moderate DED.

Moderate Dry Eye:	• In addition to the treatments for mild dry eye, the following treatments may be considered: • Artificial tears: Use preservative free artificial tears • Anti-inflammatory therapies: • 0.05% topical Cyclosporine (FDA approved) prevents activation and nuclear translocation of cytoplasmic transcription factors that are required for T-cell activation and inflammatory cytokine production. It also inhibits mitochondrial pathways of apoptosis of lacrimal gland and goblet cells. It is used 2 times a day usually for 2 - 4 weeks. • 0.03% Tacrolimus eyedrops • Topical Corticosteroids

Table XII: Management of severe DED.

Severe Dry Eye:	In addition to the treatments for mild and moderate dry eye, the following treatments may be considered: • Oral cholinergic agonists • Oral pilocarpine (5 mg) 4 times daily • Oral cevimeline (30 mg) 3 times daily • Systemic immunosuppressants • Autologous serum drops • Mucolytic agents Topical acetyl-cysteine (10%) • Correction of eyelid abnormalities • Punctal occlusion: It can be temporary and permanent. • Tarsorrhaphy

Systemic immunosuppressants are used for patients with systemic disease such as rheumatoid arthritis, progressive

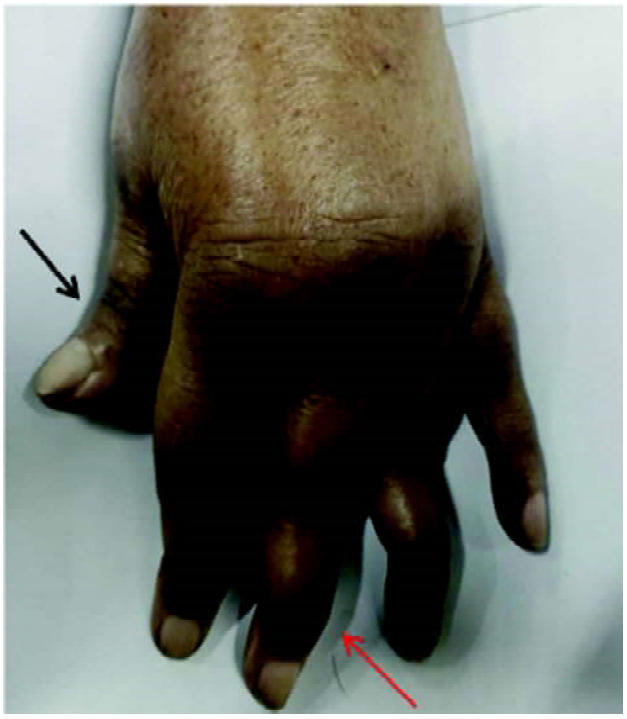


Fig. 8: *Hands in rheumatoid arthritis (red arrow shows swan neck deformity, black arrow shows boutonniere deformity).*

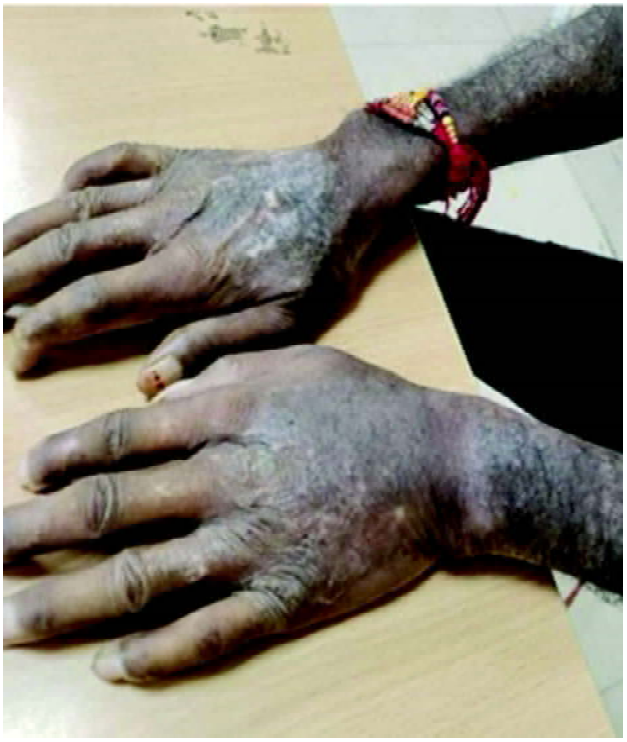


Fig. 9: *Cutaneous systemic sclerosis.*

systemic sclerosis or SLE.

Autologous serum drops have been reported to improve ocular irritation symptoms as well as conjunctival and corneal dye staining in patients.

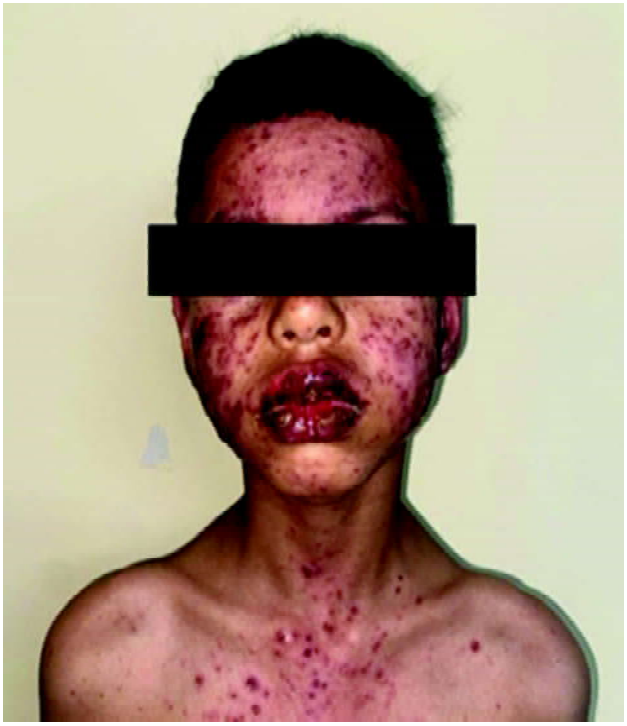


Fig. 10: *Stevens-Johnson syndrome.*

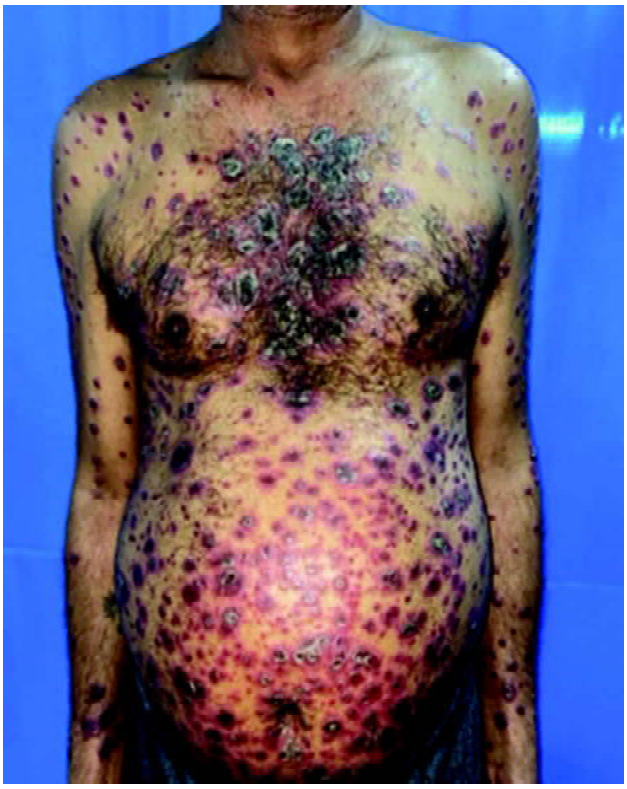


Fig. 11: *Psoriasis vulgaris.*

Table XIII: Some newer drug for traeatment of DED.

Topical Lifitegrast (Xiidra) 5%:
– Dosage :twice a day with artifical tears
– Mimics intercellular adhesion molecule-1 (ICAM-1), blocking interactions between ICAM-1 and lymphocyte functional associated antigen-1 (LFA-1), thus inhibiting T-cell activation and migration
Rebamipide (2%):
– Rebamipide increases the secretion of both membrane-associated and secreted-type mucins through mucin production in the conjunctival goblet cells and has a good effect on corneal healing
– It has anti-inflammatory action.
– It improves ocular surface epithelial health.
Lacritin:
– It is an ocular specific glycoprotein secreted primarily by acinar cells of lacrimal gland.
– Lacritin levels are significantly decreased in patients with Sjogren's disease as compared to healthy controls.
– Topical lacritin has been found to increase tear secretion, decrease lissamine green staining, and reduce signs of epithelial damage.
Lubricin:
– Mucin-like glycoprotein that is expressed by the normal ocular surface.
– It is an essential part of the ocular surface glycocalyx, preventing epithelial dysfunction and degradation.It decreases friction between cornea, conjunctiva and eyelid .
– It significantly outperformed sodium hyaluronate in ameliorating both signs and symptoms.

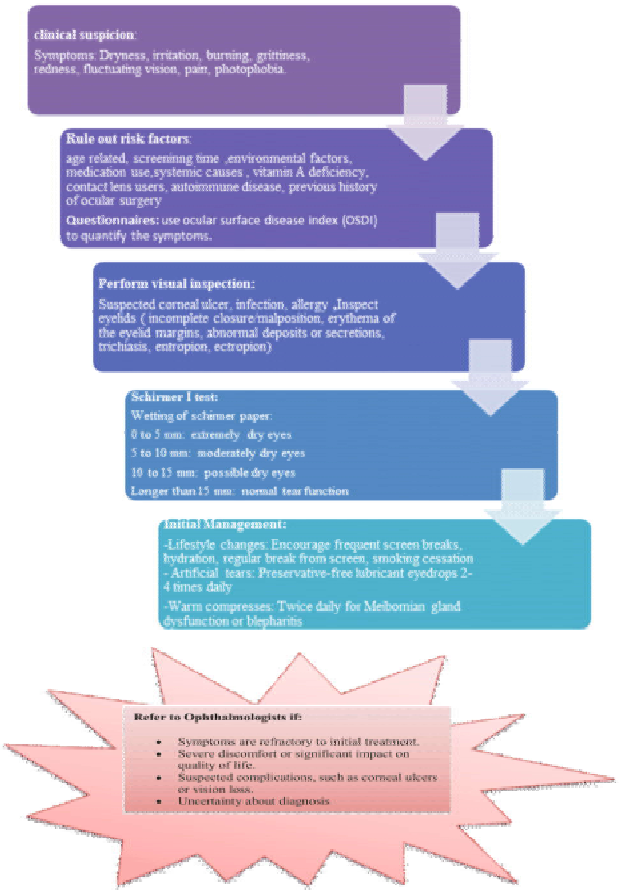
Topical acetylcysteine (10%), a mucolytic agent may be used four times a day to treat filamentary keratitis. Filaments can also be debrided with a cotton-tip applicator, dry cellulose sponge, or with a blunt forceps.

Correction of eyelid abnormalities resulting from blepharitis, trichiasis, or lid malposition, (e.g., lagophthalmos, entropion/ectropion) may be considered prior to permanent punctal occlusion.

Punctal occlusion is considered in dry eye when the medical means of tear substitutes are ineffective or impractical. It can be done surgically with silicone or thermo-labile polymer plugs that are lodged at the punctal orifice. Tarsorrhaphy may be required to decrease tear evaporation.

A collaborative approach to managing DED enhances adherence, addresses underlying causes. Multidisciplinary team involvement of following clinicians can help in createing a patient-centered care environment.

- Rheumatologists: Evaluate and manage autoimmune conditions like Sjögren's disease, SLE, and rheumatoid arthritis.



Flow chart 1: *Approach to the patient with suspected Dry eye disease.*

- Endocrinologists: Manage thyroid eye disease, diabetes or other hormonal conditions which can cause or exacerbate DED.
- Dermatologists: Address rosacea-related ocular surface inflammation and psoriasis.
- Psychiatrist: Many antipsychotic and antidepressant medications cause DED.
- General Physicians: Address systemic diseases like diabetes, rheumatoid arthritis, thyroid dysfunction or medication use contributing to DED.
- Pharmacists: Educate on medication side-effects, (e.g., antihistamines or diuretics) that may worsen dry eye.

Conclusion

Dry Eye Disease is a common and multifaceted condition that requires awareness and understanding from all healthcare providers, not just ophthalmologists. Non-ophthalmic clinicians, by recognising the symptoms, understanding the risk factors, and being knowledgeable about initial management strategies, can significantly

contribute to the effective treatment and management of dry eye disease. A collaborative approach, including timely referrals to specialists will ensure comprehensive care and improved quality-of-life for patients suffering from this condition.

Educating patients about dry eye disease is a critical and essential aspect of management. Non-ophthalmic clinicians should provide information on the chronic nature of the condition, the importance of adhering to treatment regimens, and lifestyle changes that can improve symptoms. Regular follow-up and monitoring of patient progress are essential to adjust treatment plans and ensure optimal outcomes.

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CASE REPORT

JIACM 2025; 26 (1-2): 66-68

Fahr's Syndrome – A Rare Manifestation of Hypoparathyroidism

Twinkle Khanna, Chavi Sharma*, Himanshu Khutan**, Ravinder Garg***, Swaranjeet Singh****, Lovish Batheja*****

Abstract

Background: Fahr's syndrome is a rare (prevalence <1/1,000,000) neurological disorder characterised by abnormal deposition of calcium in basal ganglia, dentate nuclei and cerebral cortex leading to various neurological manifestations. Distinguishing Fahr's syndrome from Fahr's disease is important because of differences in their aetiology, location of lesions, prognosis, and therapy.

Methods: A 36-year-old lady presented with generalised tonic clonic seizures and a past history of thyroidectomy. Her serum calcium and PTH levels were markedly decreased and her serum magnesium levels were just below normal. Her NCCT head and MRI brain revealed calcifications in white matter of bilateral fronto-parietal lobes, bilateral basal ganglia and bilateral cerebellar hemispheres (dentate nucleus).

Results: A diagnosis of secondary Fahr's syndrome post-thyroidectomy was made. The patient gradually responded to calcium infusions, anti-convulsants and supportive treatment. She was discharged in a satisfactory condition after 2 weeks on oral calcium supplementations, anti-convulsants and thyroxine sodium.

Conclusion: This case highlights the importance of measuring calcium levels and parathyroid hormone levels in patients who present with seizures, especially post-thyroidectomy, which can be life saving.

Key words: Hypoparathyroidism, hypocalcaemia, Fahr's syndrome.

Introduction

Fahr's syndrome is a rare neurological disease with a prevalence of <1/1,000,000 resulting from abnormal intracranial calcific deposits in the basal ganglia, dentate nucleus, and cerebral cortex. This rare condition was first described by German neurologist Karl Theodor Fahr in 1930. Fahr's disease arises from a primary hereditary condition while Fahr's syndrome results from on underlying secondary causes[1]. It is important to differentiate between them because Fahr's syndrome has a specific treatment related to the underlying cause with symptomatic therapy while effective treatment for Fahr's disease is currently unavailable. This case report presents Fahr's syndrome secondary to hypoparathyroidism (HP), which developed as a complication of thyroidectomy.

Case Report

A 36-year-old lady was admitted to the Medicine department with complaints of abnormal body movements for 9 days. There was a history of generalised convulsions with uprolling of eyeballs and urinary incontinence. There was no history of fever, cough, bowel problems or trauma. The patient had similar problems in the form of generalised tonic clonic seizures (GTCS), and muscle spasms for 8 years, for which she used to take medications, but was not relieved. There was a history of thyroidectomy (sub total thyroidectomy) 15 years ago and again 8 years back (total thyroidectomy). Following the surgery, after 1 year, she had the above complaints and was started on anti-convulsants. On examination, the patient was drowsy but oriented to time, place and person. The thyroidectomy scar mark was present on the neck (Fig. 1). The rest of the general physical examination was unremarkable. Chvostek' s sign was negative. Trousseau' sign was positive. Her systemic

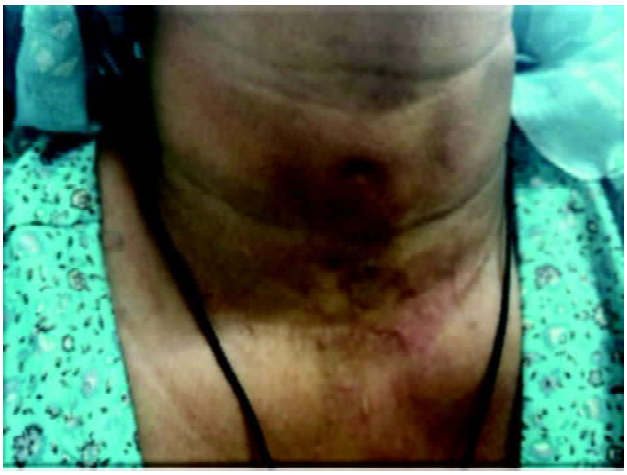

Fig. 1: *Thyroidectomy scar mark.*

****Senior Resident, **Associate Professor, ***Professor and Head, ****Junior Resident, Department of Medicine, Guru Gobind Singh Medical College, Fardikot - 151 203, Punjab.***

Corresponding Author: Dr Twinkle Khanna, Senior Resident, Department of Medicine, Guru Gobind Singh Medical College, Fardikot- 151 203, Punjab. Tel: 7889190564, E-mail: twinklekhanna600@gmail.com

examination was within normal limits. There was no focal neurological deficit and no sign of meningeal irritation.

Investigations

Her complete blood count, renal functions, electrolytes, blood glucose and urine examination were normal. Her serum calcium level was markedly decreased – 6 mg/dL, ionised calcium level was low – 0.89 mmol/L, serum magnesium level was just below the normal – 1.60 mg/dL and serum phosphorus level raised – 5.4 mg/dL. Her PTH level was decreased – 3.5 pg/mL. The ECG showed a prolonged QT interval, T-wave inversions. NCCT head and MRI brain showed calcifications in white matter of bilateral fronto-parietal lobes, bilateral basal ganglia and bilateral cerebellar hemispheres (dentate nucleus) (Figs. 2, 3). A diagnosis of secondary Fahr's syndrome post-thyroidectomy was made and patient was started on Intravenous calcium

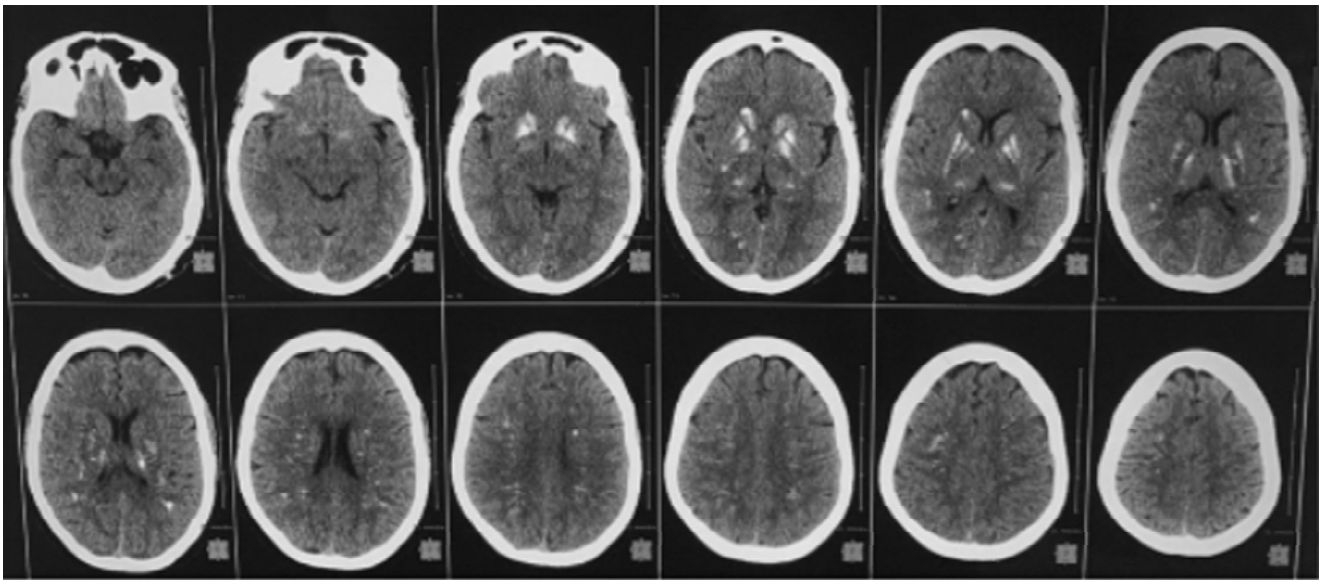

Fig. 2: *NCCT brain showing calcifications in white matter of bilateral fronto-parietal lobes, and bilateral basal ganglia.*

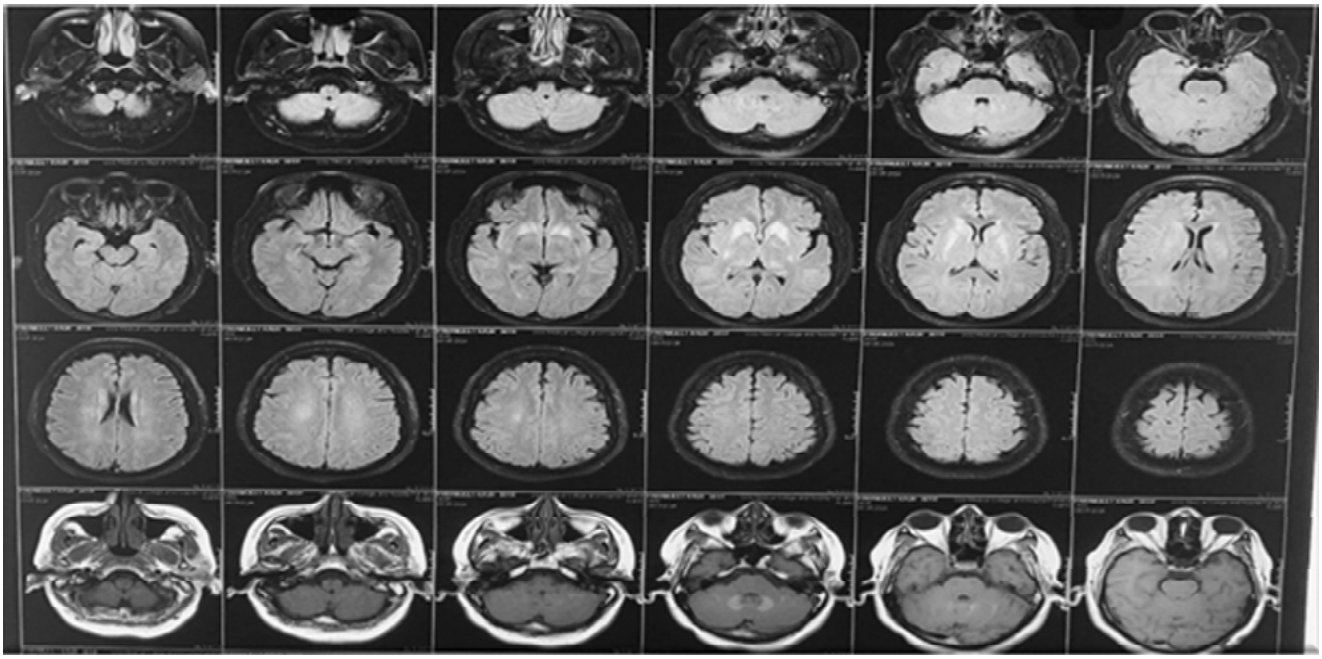

Fig. 3: *MRI brain showing hyperintensities in bilateral basal ganglia, and dentate nuclei.*

infusion, anticonvulsants, vitamin D and tablet thyroxine sodium 50 ug. Her general condition improved and GTCS were controlled with repeat calcium levels - 8.0 mg/dl. Finally, she was started on oral anticonvulsants, calcium supplements,thyroxin sodium 50 ug and was discharged in a satisfactory condition after 2 weeks.

Discussion

Fahr's syndrome is a rare neurological disorder characterised by abnormal deposition of calcium in basal ganglia, dentate nuclei and cerebral cortex leading to various neurological manifestations such as gait disorder, speech dysfunction, cognitive impairment, neuropsychiatric disorders, generalised or partial seizures[1]. The most common endocrine disorder related to Fahr's syndrome is hypoparathyroidism[2]. It is important to differentiate between Fahr's syndrome and Fahr's disease. Fahr's syndrome typically presents in individuals aged 30 - 40 years and is characterised by symmetric bilateral intracranial calcifications and an underlying disorder while Fahr's disease is more commonly observed in individuals aged 40 - 60 years, with progressive symmetric bilateral calcification in the basal ganglia and autosomal dominant or recessive inheritance. Fahr's syndrome has a specific treatment related to the underlying cause with symptomatic therapy while effective treatment for Fahr's disease is currently unavailable[3]. Secondary hypoparathyroidism is a comparatively frequent complication of total or subtotal thyroidectomy with an incidence ranging from 0.9% to 1.6% for permanent hypoparathyroidism[4]. There occurs metabolic dysfunction in hypoparathyroisdism which results in ectopic soft tissue calcifications[5]. A variety of organs can be affected by calcification, more frequently kidneys (as nephrolithiasis or nephrocalcinosis), but also joints, eyes, skin, vasculature and, although rarely seen, intracerebral calcifications[5]. According to Clarke *et al*, anterior neck surgery is the most common cause of acquired HP, and responsible for about 75% of cases; less than 1% - 5% experience permanent HP, even though as many as 50% may develop transient HP[6]. The diagnosis of HP occurs when the iPTH level is normal or inappropriately low in a patient with subnormal total or ionized calcium values, high serum phosphorus or at the high end of the normal range, and after hypomagnesaemia has been ruled-out[6,7]. CT and MRI of brain are the imaging of choice in patients with Fahr's syndrome[8]. Management of Fahr's syndrome involves symptomatic management and treatment of underlying cause. Benzodiazepines are prescribed for dystonia, atypical antipsychotics for neuropsychiatric manifestations, and seizures are managed with antiepileptics[9,10].

Conclusion

Fahr's syndrome is a poorly understood and rare condition. However, it should be kept in mind in all cases of patients with classical clinical manifestations of hypocalcaemia (Carpopedal spasm, Chvostek's sign and Trousseau sign and neuroimaging findings (Intracranial Calcification). Any suspected hypoparathyroidism should be treated immediately, especially in patients who have undergone thyroidectomy, to prevent the formation and progression of brain calcific lesions.

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CASE REPORT

JIACM 2025; 26 (1-2): 69-72

Skin: The Mirror of Internal Disease

Rahul Kumar Adhikary, Shafeek Ahamed*, Vivek Digambar Londhe*, Amit Kumar Adhikary***

Abstract

Systemic lupus erythematosus (SLE) is associated with diverse mucocutaneous manifestations. Bullous SLE (BSLE) is associated with sub-epidermal blisters with profuse neutrophilic infiltration. Other bullous lesions in SLE include bullous pemphigoid (BP), dermatitis herpetiformis (DH), and epidermolysis bullosa acquisita (EBA). Histopathology is essential to clinch the diagnosis, on the backdrop of SLE. We report a case of isolated BSLE, which was not associated with SLE flare, or with systemic involvement like lupus nephritis (LN).

Key words: Bullous SLE, SLE flare, lupus nephritis.

Introduction

Mucocutaneous manifestations of systemic lupus erythematosus (SLE) range from discrete oral ulcers, malar rash or discoid lupus erythematosus (DLE), to little-known variants like hypertrophic LE, chilblain LE and lupus panniculitis. Bullous skin lesions are relatively rare in SLE, with a reported prevalence of around 5% among SLE patients[1]. LE-nonspecific skin disease includes skin changes that are frequently associated with LE but are not specific to the disease itself. Among these, bullous SLE is associated with sub-epidermal blisters with profuse neutrophilic infiltration, in contrast to the lymphocytic predominance seen in classical cutaneous lesions of SLE[2].

Case report

A 30-year-old lady, was admitted under our care with multiple joints pain for six months and multiple, blistering, fluid filled lesions for last two months. The joint pain was insidious in onset, boring in character, migrating, symmetrical, was associated with morning stiffness, and involved wrists, proximal interphalangeal joints, elbows, and knees. The pain worsened with rest and improved with activity, was initially associated with surrounding soft tissue swelling, and was not associated with weakness or wasting of surrounding muscles. The joint pains were accompanied with a low grade fever, malaise and unintentional weight loss, without any history of cough, headache, bleeding manifestations, night sweats or photophobia.

The lady developed bullous lesions 2 months back, which were acute in onset, initially involving the trunk and spreading to the extensor surfaces of limbs, mildly itchy and not painful or tender. Individual lesions appeared as small vesicles, progressed to the size of bullae, and eventually ruptured, leaving an area of crusting, without any feature of pustule formation. She had associated hair loss and a single, painless oro-mucosal ulcer on the hard palate (Fig. 1). There was no history of muscle weakness, frothy urine, oliguria, facial rash, chest pain or heaviness, sensation of pins and needles, numbness or discoloration of fingertips, purpura, pain abdomen, seizure or decline in cognitive function. She had no pre-existing co-morbidities, no similar past history, no addictions, and an uneventful obstetric history with a single full term normal delivery. She was using intramuscular (IM) depot medroxyprogesterone acetate 150 mg every three months as contraception for the last five years.

The general examination was significant for severe pallor. Musculo-skeletal system examination revealed inflammatory arthritis predominantly involving the proximal interphalangeal, wrist and knee joints. Overall, the patient had a swollen joint count of 2 and a tender joint count of 10, without any joint deformity.

Skin examination was significant for multiple flaccid bullous vesicles on an erythematous base, with crust formation and negative Nikolsky sign. A single painless ulcer with erythematous base was noted on the hard palate. There were no genital ulcers, purpura, livedo reticularis or digital gangrene. Examination of chest, cardiovascular and neurological systems was unremarkable.

Investigations showed Hb 5.6 g/dL, MCV 77 fL, ESR 85 mm in 1st hour, normal fasting blood glucose, TSH, LFT and renal function tests. Rheumatoid factor, ASO titer, viral markers were all negative. ANA by IIF method was positive (2+) with nuclear speckled and cytoplasmic pattern, and

Junior Resident, **Assistant Professor, Department of Medicine, North Bengal Medical College, Darjeeling - 734 012, West Bengal.

Corresponding Author: Dr Shafeek Ahamed, Junior Resident, Department of Medicine, North Bengal Medical College, Darjeeling - 734 012, West Bengal. Tel: 9585806244, E-mail: shafeek66ahamed@gmail.com

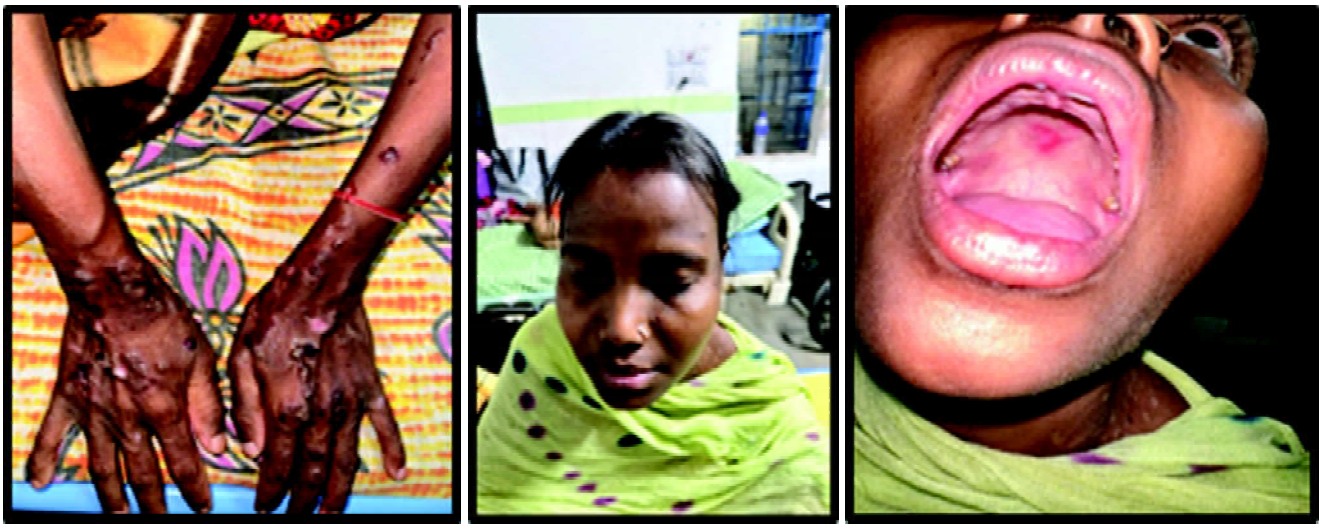

Fig. 1: *Mucocutaneous manifestations showing bullous lesions with crusting (1A), non-scarring alopecia (1B) and oral ulcer (1C).*

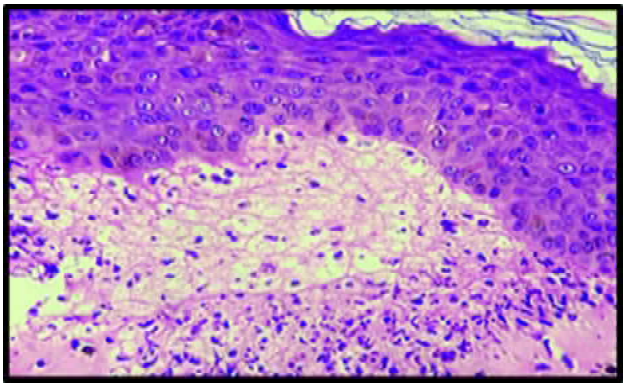

Fig. 2: *Histopathology of skin showing superficial vesiculobullous lesions with subepidermal neutrophilic infiltration.*

reduced C3 (49.50 mg/dL, normal 90 - 180 mg/dL), and C4 (6.80 mg/dL, normal 10 - 40 mg/dL) levels. Routine examination of urine and urinary ACR were non-contributory. The 24-hour urinary protein was 53 mg and quantitative anti-dsDNA was below the cut-off, essentially ruling out a disease flare. Skin histopathology revealed subepidermal vesiculobullous lesions harbouring predominantly neutrophils, along with dermal perivascular inflammation (Fig. 2). DIF showed linear deposits of immune complexes of IgA, IgG and C3 (Fig. 3).

The patient fulfilled the 2019 EULAR classification criteria of SLE[3]. In view of her clinical and laboratory findings, we entertained a diagnosis of BSLE and managed the patient with tablet Hydroxychloroquine 5 mg/kg daily, tablet Prednisolone 40 mg/day in tapering dose over 6 weeks, and tablet Dapsone 50 mg daily for 2 weeks followed by 100 mg daily to continue. We noticed significant clinical improvement with resolution of the bullous lesions with hypopigmentation but without residual scarring (Fig. 4). She is currently asymptomatic on follow-up over the past 4 months.

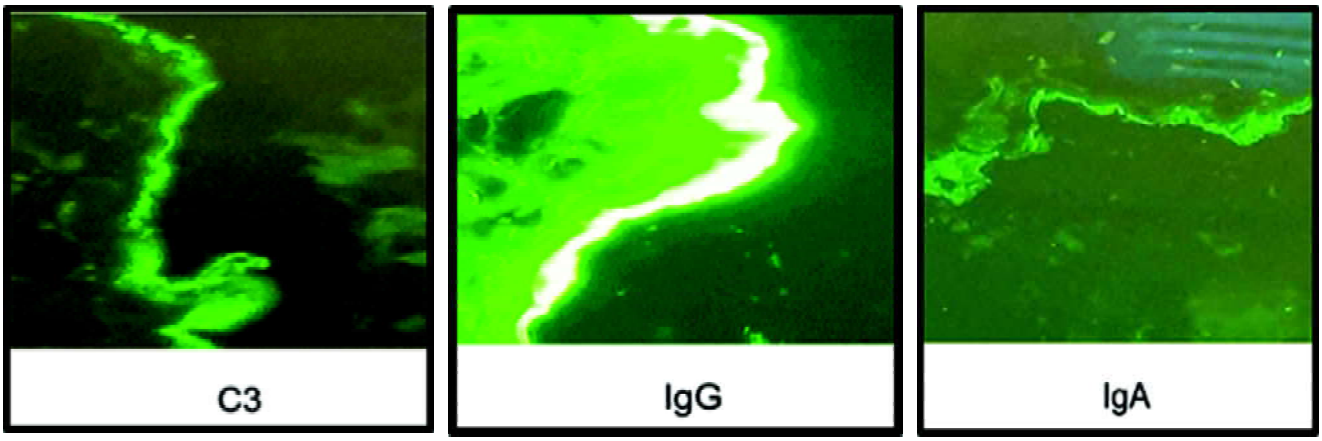

Fig. 3: *Direct immunofluorescence (DIF) of skin biopsy showing linear deposition along the basement membrane of C3 (3A), IgG (3B) and IgA (3C).*

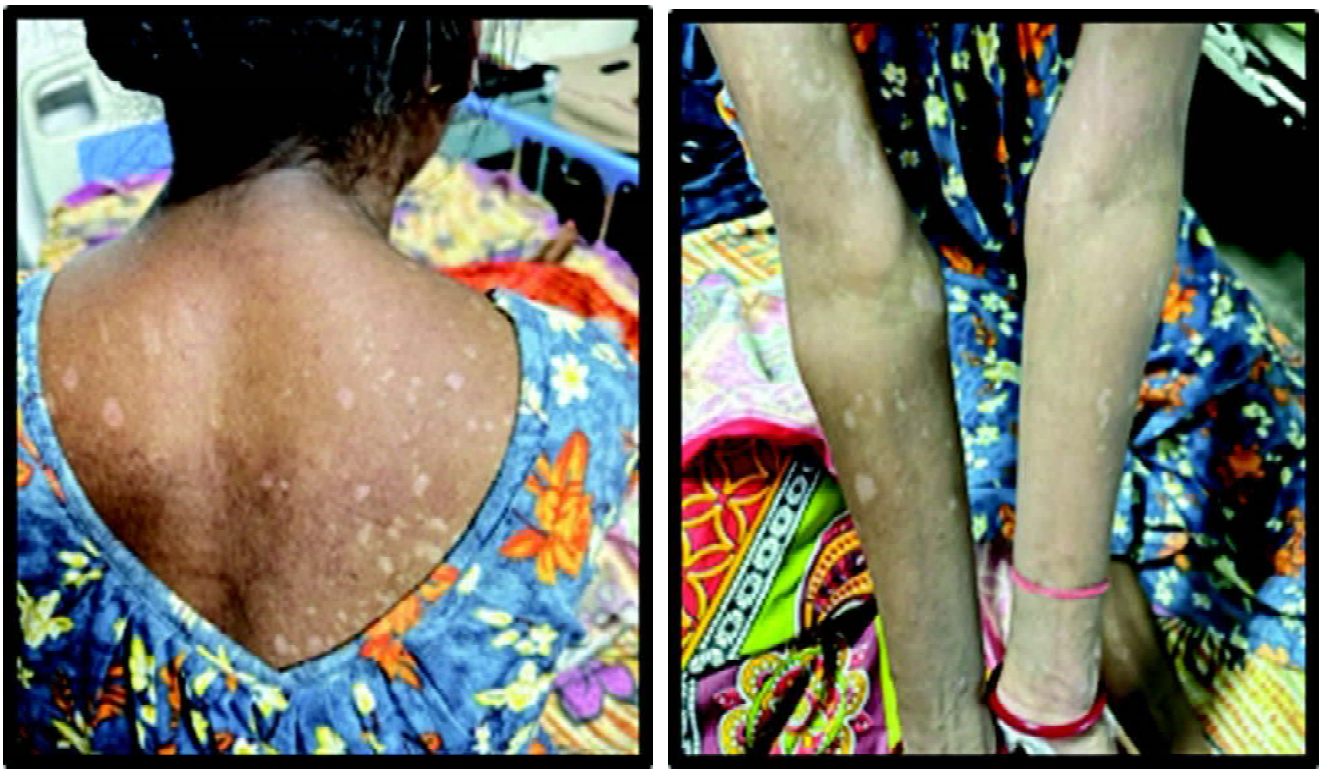

Fig. 4: *Patient after 24 weeks of Dapsone initiation showing no fresh vesiculobullous lesion and resolution of previous lesions with hypopigmentation.*

Discussion

Subepidermal blister formation in the course of severe SLE can occur due to extensive interface inflammation and basal cell vacuolation, presenting as polycyclic erosions with advancing blistering border, predominantly on sun-exposed areas[4]. However, BSLE is a distinctive bullous eruption occurring in patients with SLE, presenting with typical clinical and pathological findings including circulating antibodies primarily directed against type VII collagen {NC1 (noncollagenous domain 1) domain}, or sometimes against laminin 5, laminin 6, and BP230 (bullous pemphigoid antigen)[5].

Differentials to be considered for vesiculobullous lesions in lupus include bullous pemphigoid (BP), dermatitis herpetiformis (DH), and epidermolysis bullosa acquisita (EBA)[6]. BP is characterised by tense blisters, more intense pruritus and a densely eosinophilic infiltrate, in contrast to the neutrophilic predominance of BSLE lesions[7]. DH is a chronic, autoimmune, blistering disease that causes an extremely pruritic rash, sometimes associated with blister formation, and demonstrating granular IgA deposits within the dermal papilla[8]. Lastly, both inflammatory EBA and mechanobullous EBA emerge as differentials of BSLE[9]. However, EBA is associated with more severe scarring and poorer response to dapsone. Above all, a diagnosis of BSLE must satisfy the criteria of SLE.

Our case satisfied the 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus[3]. The following criteria for the diagnosis of bullous SLE have been proposed: (1) a diagnosis of SLE; (2) vesicles and bullae arising upon but not limited to sun-exposed skin; (3) histopathology compatible with DH; (4) negative indirect immunofluorescence for circulating basement membrane zone (BMZ) antibodies; (5) direct immunofluorescence positive for IgG and/or IgM and often IgA at the BMZ[10].

Blistering eruptions are rare cutaneous manifestations of SLE that can result from two distinct mechanisms: vesicles arising from a subepidermal blistering disease with an acute neutrophil-predominant infiltrate in the upper dermis, known as BSLE, or blisters developing from hydropic degeneration of the basal layer and severe oedema in the upper dermis, also referred to as SLE with blisters[11]. BSLE is a rare, transient autoimmune bullous disease which is closely associated with lupus nephritis (LN). In contrast, SLE with blisters has not been associated with systemic manifestations of SLE. Our case belongs to the former category, and remains unique in being a case of BSLE without associated LN, or any other organ – system involvement. The resolution of skin lesions in our case with hypopigmentation and no residual scarring is supported by the world literature[12].

Conclusion

SLE is associated with diverse mucocutaneous manifestations. Among these, BSLE is a rare entity, usually seen during SLE flares, in association with extra-cutaneous involvement like lupus nephritis (LN). Our case appears unique in neither presenting as an episode of SLE flare, nor being associated with other organ – system involvement. The fact that our patient remained undiagnosed for more than six months highlights the need to identify such uncommon dermatological manifestations in resource restricted settings, where both the diagnosis and the treatment of SLE are often delayed.

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CASE REPORT

JIACM 2025; 26 (1-2): 73-76

Cefoperazone induced Coagulopathy in a Patient with Community-Acquired Pneumonia

Ravi K, Nagaraja Kamath**, Rishika Das***, Aditya Chandrashekar****

Abstract

Cephalosporin antibiotics, such as Cefoperazone, are widely used to treat sepsis and other bacterial infections. Although generally considered safe, rare cases of drug-induced coagulopathy have been reported. We present the case of a 31-year-old man with no prior co-morbidities who developed coagulopathy following the initiation of cefoperazone.

The patient presented with fever, cough, shortness of breath, and severe hypoxaemia. Chest X-ray revealed homogenous opacity in the middle zone of right lung field. He was diagnosed with Community-acquired pneumonia (CAP) and Cefoperazone-sulbactam was initiated. Within four days of starting the antibiotic, the patient developed hematuria and ecchymoses with a progressive increase in PT/INR values, leading to a presumptive diagnosis of drug-induced coagulopathy. Cefoperazone was discontinued, and Vitamin K therapy was initiated, resulting in symptom resolution and PT/INR values normalisation within two days.

This case underscores the importance of closely monitoring coagulation parameters in patients receiving Cefoperazone, especially those with hepatic or renal dysfunction.

Key words: Coagulopathy, cefoperazone, pneumonia.

Introduction

Cefoperazone is a third-generation cephalosporin antibiotic used to treat various bacterial infections, including septicaemia. It is generally well tolerated; however, in rare instances, it may lead to drug-induced coagulopathy. Cefoperazone contains an N-methyl-thio-tetrazole (NMTT) side chain, which inhibits vitamin K epoxide reductase. This inhibition disrupts the gamma-carboxylation of glutamic acid, resulting in a deficiency of vitamin K-dependent clotting factors (II, VII, IX, and X)[1,2]. Consequently the risk of hypoprothrombinaemia and bleeding is raised. This report highlights a case of drug-induced coagulopathy associated with cefoperazone, emphasizing the importance of prompt identification and management of this adverse effect. Additionally, we aimed to explore the underlying mechanisms that contribute to this phenomenon.

Case presentation

A 31-year-old man presented to our hospital with a 10-day history of fever, productive cough, and progressively worsening shortness of breath. He had no history of abdominal pain, chest pain, or hematuria, was an occasional smoker, and had an unremarkable medical history without known co-morbidities.

On examination, the patient was alert and oriented but exhibited severe hypoxaemia (oxygen saturation at 70% on room air), fever of 101° F, tachycardia, and tachypnoea. Respiratory auscultation revealed bilateral crepitations and rhonchi. Arterial blood gas analysis indicated persistent hypoxaemia (pH 7.31, PaO_2 44 mmHg, $PaCO_2$ 28 mmHg). A chest X-ray demonstrated a well defined homogenous opacity in the middle zone of right lung field with multiple patchy nodular opacities in the right mid- and lower zones, leading to a provisional diagnosis of Community-acquired pneumonia (CAP) (Fig. 1). Laboratory investigations revealed leukocytosis (WBC 33,670 cells/cumm), markedly elevated erythrocyte sedimentation rate (ESR 65 mm/hr), and high procalcitonin levels (43.2 ng/mL). Hepatic function tests indicated elevated AST (139 IU/L) and ALT (134 IU/L), while renal function tests showed increased serum creatinine levels (1.61 mg/dL). Baseline coagulation studies were within normal limits (PT/INR: 12/1.1). High-resolution computed tomography (HRCT) of the thorax revealed centrilobular nodules and tree-in-bud opacities with patchy consolidation in the right middle lobe. The patient was subsequently diagnosed with Sepsis secondary to Community-acquired pneumonia and Type I Respiratory failure, necessitating admission to the intensive care unit

Professor and Unit Head, **Junior Resident, ***Medical Student, Department of General Medicine, Bangalore Medical College and Research Institute, Fort, Krishna Rajendra Road, City Market, Bengaluru - 560 002, Karnataka.

Corresponding Author: Dr Nagaraja Kamath, Junior Resident, Department of General Medicine, Bangalore Medical College and Research Institute, Fort, Krishna Rajendra Road, City Market, Bengaluru- 560002, Karnataka. Tel: 8762957560, E-mail: nagaraj.kamath1998@gmail.com.

(ICU) and mechanical ventilation. Blood and sputum cultures were collected, and empirical therapy with Cefoperazone-sulbactam (3 g twice daily, IV) and Clarithromycin (500 mg twice daily, IV) was initiated, per institutional antibiotic protocols.

The sputum culture revealed the growth of *Klebsiella pneumoniae*. The organism was found to be sensitive to Cefoperazone-sulbactam, Clarithromycin, Meropenem, Tigecycline, Gentamicin, and Amikacin but resistant to Amoxicillin, Trimethoprim/sulfamethoxazole, and Levofloxacin. Based on the antimicrobial susceptibility reports, the patient was continued on Cefoperazone-sulbactam and Clarithromycin. On day 4 of hospitalisation, the patient developed hematuria and ecchymotic patches on his extremities. Repeat coagulation studies revealed elevated Prothrombin time (PT) and International Normalised Ratio (INR) levels, with normal activated partial thromboplastin time (APTT), raising concerns regarding coagulopathy. We initially suspected Disseminated intravascular coagulation (DIC), prompting the continuation of Cefoperazone-sulbactam and Clarithromycin therapy. However, further evaluation revealed normal fibrinogen levels (322 mg/dL), fibrinogen degradation products (<10 mcg/mL), and D-dimer (260 ng/mL), effectively ruling out DIC. A declining trend in serum procalcitonin levels (Day 5: 32.4 ng/mL, Day 8: 24.8 ng/mL) and negative antinuclear antibody (ANA) testing excluded autoimmune aetiologies. Improvement in liver function tests was noted, suggesting preserved hepatic synthetic function. Vitamin K1 supplementation was administered to address the coagulation abnormalities. Given the patient's clinical deterioration and laboratory findings, and with DIC ruled out, we hypothesized that the observed coagulopathy was linked to drug therapy. A review of the side effect profile for the medications revealed a rare association between coagulopathy and Cefoperazone. A Naranjo Adverse Drug Reaction assessment yielded a score of 6, indicating a probable relationship between Cefoperazone and the observed coagulopathy. Consequently, on day 8, Cefoperazone-sulbactam was discontinued and replaced with Meropenem (1 g IV three times a day). Additionally, Clarithromycin was halted on day 7. Over the next four days following the discontinuation of Cefoperazone, the patient's prothrombin time (PT) and international normalised ratio (INR) levels normalised, further supporting the diagnosis of drug-induced coagulopathy (Fig. 2).

The patient was gradually weaned off the ventilator and extubated on day 12 of hospitalisation. By day 14, the patient's renal function had improved, white blood cell counts returned to normal, the coagulation profile stabilised, and the patient was transferred to the ward, ultimately leading to a full recovery.

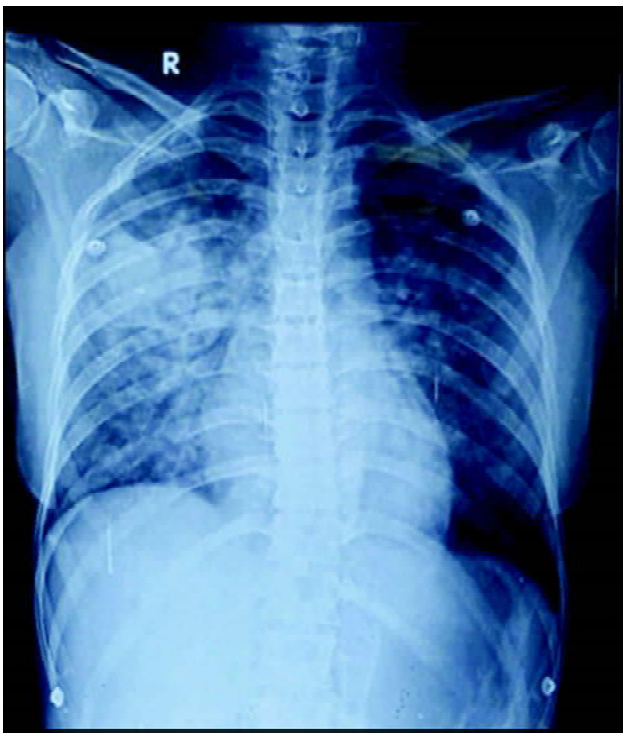

Fig. 1: *Chest X-ray demonstrating well defined homogenous radiopacity in the middle zone of right lung fields with multiple patchy nodular opacities in the right mid and lower zones.*

Discussion

Cefoperazone, a widely used third-generation Cephalosporin, is often combined with Sulbactam, a beta-lactamase inhibitor, for enhanced efficacy. Despite its safety, Cefoperazone has been associated with haemorrhagic complications, particularly in patients receiving prolonged high-dose therapy[3-6]. Several mechanisms have been

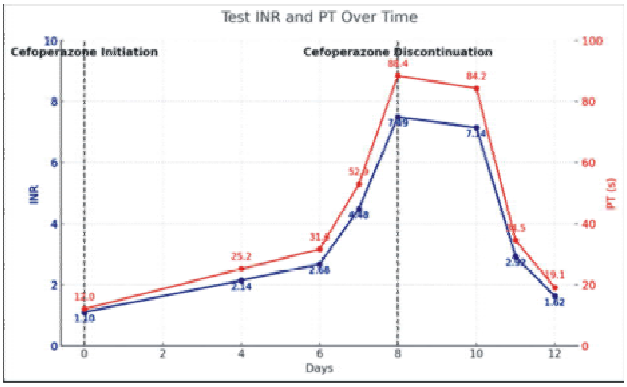

Fig. 2: *Temporal trends of prothrombin time (PT) and international normalised ratio (INR) levels. The INR values are represented on the primary y-axis (left, in blue), while the PT values are displayed on the secondary y-axis (right, in red). The figure shows an initial spike in PT levels on day 4, followed by a gradual decline, leading to normalisation by day 12.*

proposed for these complications (Fig. 3). The primary mechanisms include the inhibition of Vitamin K epoxide reductase by the NMTT side chain, which prevents the gamma-carboxylation of Vitamin K-dependent clotting factors and the suppression of Vitamin K-producing bacteria in the intestines[7].

Similar effects have been observed with other NMTT-containing cephalosporins, such as Cefamandole, Cefoperazone, Cefotetan, Cefmetazole, and Moxalactam[1,8,9]. Chen *et al,* reported that Cefoperazone and Cefmetazole, which contain NMTT-side chains, are associated with a 4.5-fold and 2.8-fold higher risk of bleeding events, respectively, with a dose-dependent response[7]. In a study by Shao *et al*, Cefoperazone/sulbactam-induced coagulation dysfunction occurred in 24.39% of 200 patients. The incidence typically occurred 2 - 19 days after starting 9.0 g/day of Cefoperazone[10].

Other contributing factors may include hepatic and renal impairment. Cochet *et al*, suggested that hypo-albuminaemia may reduce the extrarenal clearance of Cefoperazone[11]. This implies that patients with low albumin levels might be particularly susceptible to coagulation disturbances and hypoprothrombinaemia.Serum albumin levels and INR have been found to be inversely correlated in intensive care unit patients on Cefoperazone, which aligns with our case findings, where significant hepatic dysfunction and hypoalbuminaemia likely contributed to coagulopathy[12].

In patients with hepatic impairment and renal dysfunction, the dosage of Cefoperazone should not exceed 1 - 2 g/day without close monitoring of coagulation parameters[12]. Our case emphasizes the need for vigilance in high-risk patients, including those with hepatic dysfunction, hypoalbuminaemia, or high-dose Cefoperazone therapy.

This case highlights a young man with Sepsis-induced multiple organ dysfunction syndrome (MODS) due to severe pneumonia who developed coagulopathy after receiving Cefoperazone-sulbactam. Despite ongoing treatment, PT and INR abnormalities emerged, raising concerns of coagulopathy. Differentiating between DIC and drug-induced coagulopathy was crucial. Negative DIC markers, such as normal fibrinogen and FDP levels and

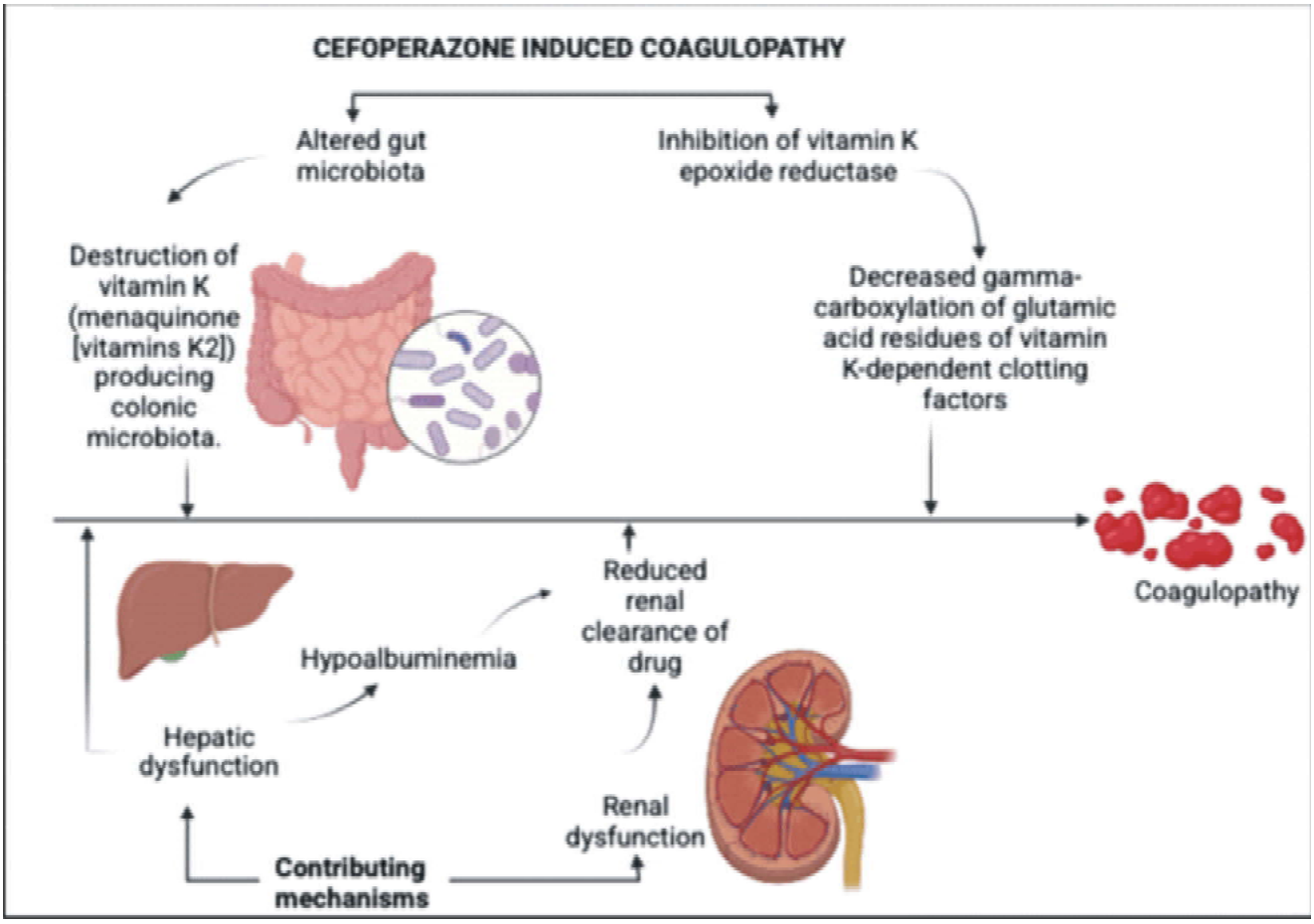

Fig. 3: *Diagram illustrating the possible mechanisms for Cefoperazone-induced coagulopathy.*

stable D-dimer levels, alongside negative autoimmune screening, helped rule-out DIC and autoimmune causes[13]. The coagulation profile was normal before antibiotic initiation, but it deteriorated after cefoperazone exposure and improved rapidly upon discontinuation. The patient's recovery after substituting Meropenem provided further evidence that drug-induced coagulopathy was the underlying cause of their condition.

Conclusion

Cefoperazone-induced coagulopathy is a rare but serious adverse effect, particularly in patients with hepatic dysfunction or hypoalbuminaemia. Early recognition, prompt cessation of the offending drug, and Vitamin K supplementation are essential for management[9,11]. Clinicians should maintain a high index of suspicion for drug-induced coagulopathy in critically ill patients receiving Cefoperazone and monitor coagulation parameters closely to prevent life-threatening bleeding complications. Early identification and discontinuation of the suspected drug can lead to a full recovery of coagulation function, as demonstrated in this case.

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Hereditary Ectodermal Dysplasia – A Rare Entity

Ragini Ram, K Rajeshwari***

A 5-year-old boy presented with complaints of sparse hair on the scalp. The parents gave a history of heat intolerance and inability to sweat noticed in the child. Child was born to a second gravida mother with uneventful antenatal and birth history. The developmental milestones were normal. On close questioning the younger male sibling 1-year-old also had sparse scalp hair and absent teeth. The maternal uncles also had absent scalp hair, premature loss of teeth, and inability to sweat. In addition, he had wrinkles on the face, loose skin folds and absent eyebrows. The picture of the child is shown in Figs. 1, 2, 3 and 4.

Intraoral examination revealed partial anodontia of the maxillary arch with the presence of four teeth suggestive of maxillary central incisors and canines on either side of the midline. The mandibular arch was completely edentulous with poorly developed alveolus. Moderate dryness of the mouth, with inflamed mucosa was evident. Skin below his eyes showed hyperpigmentation as seen with aging.

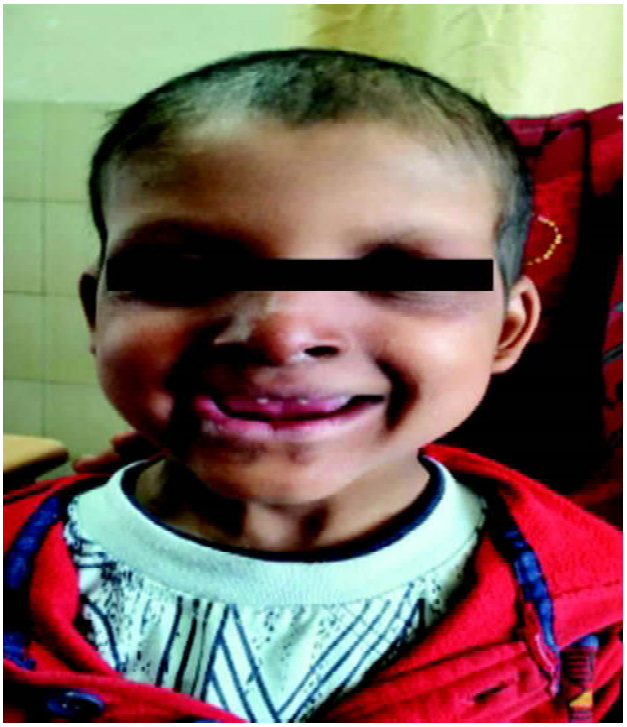

Fig. 1: *Full frontal face showing pigmantation, facial wrinkles, loss of eyebrows.*

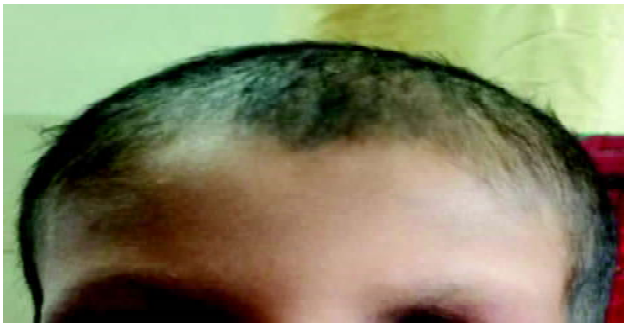

Fig. 2: *Scalp showing hypotrichosis.*

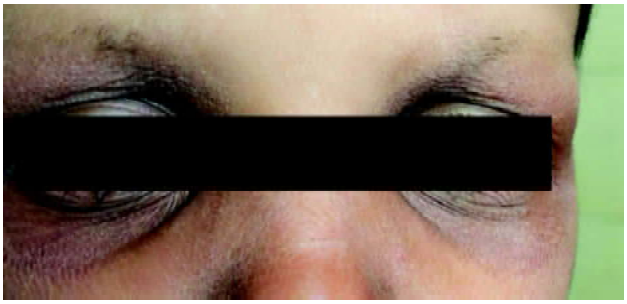

Fig. 3: *Face showing wrinkles and loss of eyebrows.*

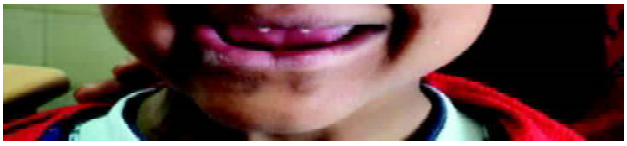

Fig. 4: *Teeth showing edentulous arches.*

Discussion

Hereditary ectodermal dysplasia (HED) is a rare genetic disorder chiefly affecting ectodermally derived structures including hair, nails, sweat glands, etc., with pathognomic manifestations such as hypotrichosis, hypohidrosis, and hypodontia. Hypohidrotic ectodermal dysplasia, is the most frequently encountered subtype and HED, being the rare subtype. HED is primarily transmitted through X-linked recessive trait in which the gene is carried by the female and manifested in male[1]. Although rare, this disorder may be seen affecting lot of members of the same family as seen in this case. In a publication by Gupta *et al*, a series of four cases

Medical Student, **Director-Professor, Department of Paediatrics, Maulana Azad Medical College, New Delhi - 110 002. Corresponding Author: Dr K Rajeshwari, Director-Professor, Department of Paediatrics, Maulana Azad Medical College, New Delhi - 110 002. Tel: 9968604312, E-mail: rajeshwari.dr@gmail.com

with common classical manifestations accompanied by spoon shaped nails, hyperpigmentation, oligodontia and hypotrichosis have been described. Indian literature on this rare entity is limited. In another publication by Puttaraju *et al* ectodermal dysplasia has been described in identical siblings[2]. These publications focussed on adult patients.

Three disease-causing genes have been hitherto identified, namely, (1) EDA1 accounting for X-linked forms, (2) EDAR, and (3) EDARADD, causing both autosomal dominant and recessive forms. Recently, WNT10A gene was identified as responsible for various autosomal recessive forms of ectodermal dysplasias, including onycho-odonto-dermal dysplasia (OODD) and Schöpf-Schulz-Passarge syndrome[3]. The EDA1 gene was the most common disease-causing gene (58% of cases), and WNT10A and EDAR were each responsible for 16% of cases. Moreover, a novel disease locus for dominant HED/EDA mapped to chromosome 14q12 - q13.1. Although no clinical differences between patients carrying EDA1, EDAR, or EDARADD mutations could be identified, patients harboring WNT10A mutations displayed distinctive clinical features (marked dental phenotype, no facial dysmorphism).

The youngest case report published is an eight-year-old with ectodermal dysplasia[4]. The current report on a 5-year-old is perhaps the youngest paediatric case report.

Early prosthetic treatment leads to significant improvements in appearance, speech and masticatory function. Young patients should be recalled periodically for the prosthetic modification that is required due to continuing growth and development. The transitional prosthesis should be replaced by more definitive prosthesis once the skeletal growth is completed. Other management include protection from heat, wearing clothes that keep body cool and prevention of hyperthermia.

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