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Nuzaira Nahid¹



Editorial Board

Cluster headache- An overlooked headache disorder

Wazib A¹

Cluster headache (CH), also known as Horton's disease or migranous neuralgia of Harris, is a less common primary headache disorder with a prevalence of 0.1% and an incidence of 21–98/100,000/year¹, much infrequent than more common causes of hemicranial headaches such as sinusitis, migraine, trigeminal neuralgia and giant cell arteritis. Males are more affected with a 2.5:1 ratio². The oldest description of CH is found in the literature by the Dutch physician Nicolas Tulp in 1641. Wilfred Harris, a British neurologist, provided the most complete description of the condition in 1926³.

The pathophysiology of CH is intricate, and the fundamental mechanisms remain inadequately understood. CH represents a complex interplay of genetic and environmental factors that disrupt the normal functioning of the trigemino-vascular system, the trigeminal autonomic reflex, and the hypothalamic networks. The hypothalamus

appears to play a fundamental role in the generation of a permissive state that allows the initiation of an episode, whereas the attacks are likely to require the involvement of the peripheral nervous system⁴.

CH is characterized by episodes of excruciating unilateral sharp retro-orbital, peri-orbital and/or temporal pain lasting 15 minutes to 3 hours occurring at a specific hour of the day. The majority of episodes are strictly unilateral, but can switch sides in 14-18% cases. The headache is accompanied by one or more of lacrimation, ptosis, red eye, rhinorrhoea, nasal stuffiness, aural fullness and flushing ipsilaterally. The patients are extremely agitated and restless, which differentiates CH from migraine patients who prefer to lie still in a calm and dark environment. The frequency varies among sufferers from 0.5 to 8 times a day. Common triggers of CH are alcohol, strong odour and nitrate-rich food³.

International Classification of Headache Disorders version 3 (ICHD-3) diagnostic criteria of cluster headache⁵:

- A. At least five attacks fulfilling criteria B-D.
- B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes (when untreated).
- C. Either or both of the following:
 - 1. At least one of the following symptoms or signs, ipsilateral to the headache:
 - Conjunctival injection and/or lacrimation
 - Nasal congestion and/or rhinorrhoea
 - Eyelid oedema
 - Forehead and facial sweating
 - Miosis and/or ptosis
 - 2. A sense of restlessness or agitation
- D. Occurring with a frequency between one every other day and 8 per day
- E. Not better accounted for by another ICHD-3 diagnosis.

A bout, defined as the time frame of CH episodes, is typically 6 to 12 weeks. CH with remission of ≥ 3 months between bouts is classified as episodic CH (ECH). Chronic cluster headache is diagnosed when the remission is < 3 months and/or the bouts last ≥ 1 year. ECH and CCH comprise 80% and 20% CH patients, respectively⁶.

Cluster headache is a clinical diagnosis. Other trigeminal autonomic cephalgias (Paroxysmal hemicrania, hemicrania continua, SUNCT and SUNA), migraine and trigeminal neuralgia are excluded from the frequency and duration of episodes, location and nature of pain and accompanying

symptoms. Complete blood count with ESR, C-reactive protein and x-ray of paranasal sinuses are done to exclude giant cell arteritis and sinusitis. Magnetic resonance imaging (MRI) with or without angiogram (MRA) and venogram (MRV) of the brain is recommended to rule out relatively uncommon CH mimics (often referred to as secondary CH) like pituitary tumour, carotid dissection and cavernous sinus thrombosis⁷.

Acute CH episodes are managed with 100% (12 L/min) oxygen and triptans. Recommended triptans are intranasal Sumatriptan 20 mg, intranasal Zolmitriptan 5 mg or

subcutaneous Sumatriptan 6 mg⁸. Intranasal, subcutaneous, intravenous or intramuscular preparations of Dihydroergotamine are alternatives to triptans⁹.

Transitional therapy is recommended with Prednisolone 80 mg daily initially, with subsequent gradual decrement by 20 mg every 3 days before discontinuation⁸.

Prophylactic therapy is indicated for CCH and also ECH with bouts exceeding 4 weeks. Treatment is continued for 4 weeks after the expected duration of the cluster bout (usually weeks to months), followed by slow tapering. Verapamil, a calcium channel blocker, is the drug of choice given 120-960 mg daily in 3 divided doses.⁸ An electrocardiograph is mandatory during the escalation of doses.⁷ Lithium is the second option when Verapamil is contraindicated, not tolerated or ineffective. The dose of Lithium is usually 900-2200 mg daily to maintain a trough serum lithium level of 0.8-1.0 mmol/L. Serum lithium, creatinine and thyroid profile should be monitored during Lithium therapy⁸.

Topiramate 100-150 mg daily, Gabapentin 1000-1800 mg daily and Melatonin 10 mg daily can also be tried despite weaker recommendations. Galcanezumab, an anti-CGRP monoclonal antibody, is approved for ECH at a 120 mg subcutaneous monthly dose⁸.

Neuromodulation with non-invasive vagus nerve stimulation (nVNS) is recommended for acute and prophylactic therapy. Occipital nerve block (ONB) is often used in acute CH. Percutaneous and surgical occipital nerve stimulations and deep brain stimulation are reserved for refractory CCH¹⁰. CH episodes during pregnancy and lactation are managed with oxygen, Prednisolone, nVNS and ONB¹⁰. CH patients are advised to abstain from alcohol and maintain a good sleep cycle¹⁰.

Transformation between CH subtypes is common. The ECH to CCH transformation was observed in 13%, and the opposite in 33%. With advancing age, individuals may experience a reduction in the frequency of cluster headaches, accompanied by longer durations of remission between episodes¹¹.

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Correlation of Abnormal Liver Function with Dengue Severity.

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Abstract

Background: Bangladesh has been experiencing a notable rise in dengue outbreaks in 2000, the 2023 outbreak is the biggest one till date. Hepatic involvement is common in dengue infection.

Objective: This study was conducted to assess the correlation between the severity of the disease with the extent of hepatic dysfunction.

Methods: This was a cross-sectional study on 100 serologically confirmed in-hospital dengue patients aged ≥ 18 years between May and October 2022, after securing written consents, excluding chronic liver disease, alcoholism, hepatotoxic drug use, viral hepatitis, suspected malaria, sepsis, leptospirosis and MAFLD. The patients were categorized into dengue without warning sign (DWWS), dengue with warning sign (DWS) and severe dengue (SDG). Clinical manifestations, liver function tests and platelet counts were compared across the three categories.

Results: The mean age of the participants was 35 ± 15 years, with a male-female ratio of 1.7. Frequencies of DWWS, DWS and SDG were 55%, 35% and 10%, respectively. SDG group had significantly lower platelet count (p-value < 0.001) and higher proportions of high SGOT (p-value < 0.001), SGPT (p-value 0.003) and bilirubin (p-value 0.003) than DWS and DWWS. SGOT-SGPT ratio > 1 in all participants. Participants with elevated liver enzymes had greater frequency of bleeding. SGPT and SGOT levels negatively correlated with platelet count.

Conclusion: Hepatic dysfunction is associated with severe categories of the dengue infection.

Keywords: Dengue, hepatic dysfunction, severe dengue.

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Introduction

Dengue is a mosquito-borne infection caused by the dengue virus (DENV). It is hyperendemic in tropical and subtropical climates worldwide, with increasing incidence over recent years placing nearly half of the world's population at risk¹. Approximately 5 million dengue cases and 3000 deaths were reported globally in 2025². Since 2000, Bangladesh has been experiencing a notable rise in the frequency and distribution of dengue outbreaks³. The 2023 outbreak is the biggest one till date with the highest number of reported cases and deaths⁴.

Clinical manifestations of dengue infection range from asymptomatic infection to dengue fever or severe dengue that includes dengue hemorrhagic fever, dengue shock syndrome and expanded dengue syndrome^{5,6}. Hepatic injury with dengue infection has been described since 1967⁷. Liver dysfunction varies from mild injury with elevation of transaminases to severe hepatocyte injury, resulting in jaundice. Direct hepatotoxicity as well as deranged host immune response against the virus is responsible for the hepatic dysfunction. Though there have been isolated cases of fulminant hepatic failure, the derangements in the transaminases are usually self-limiting and may serve as a predictor for assessing the disease severity^{8,9}. Limited studies are available in our geographic location to understand the pattern of liver involvement in dengue patients based on 2009 WHO categorization. Our aim of the study was to assess the correlation between the severity of the disease with the extent of hepatic dysfunction.

Methods

This was a cross-sectional study on 100 serologically confirmed dengue patients admitted in Department of Medicine between May and October 2022. The present study was conducted after obtaining written consent from the patients. Febrile patients aged ≥ 18 years with a positive Dengue NS1 antigen and/or anti-Dengue IgM were included as participants. Patients with chronic liver disease, alcoholism, hepatotoxic drug use, viral hepatitis, suspected malaria, sepsis, leptospirosis and MAFLD were excluded. The patients were categorized into dengue without warning sign (DWWS), dengue with warning sign (DWS) and severe dengue (SDG) as per 2009 WHO classification⁶. Demographics, category of dengue, symptoms, signs, complete blood count, SGPT, SGOT and serum total

bilirubin were documented. SGPT >45 IU/L, SGOT >35 IU/L and serum bilirubin 1.3 mg/dL were considered as elevated.

Data analysis was done using the Statistical Package for the Social Science (SPSS) Version 25. Continuous variables were summarized as mean $\pm$ standard deviation (SD) and categorical variables as frequencies (n) and percentages (%). Comparison of multiple means across disease severity was done using One Way-ANOVA with post hoc analysis using least significant difference. Pearson's correlation coefficient test was used to calculate the correlation between variables (transaminases and platelet count). P-value of <0.05 was accepted as the level of statistical significance.

Results

Out of 100 participants, frequencies of DWWS, DWS and SDG were 55(55%), 35 (35%) and 10 (10%), respectively. The mean $\pm$ SD age of the participants was 35 ± 15 years. More than 50% participants were within 18-30 years age range. Male to female ratio was 1.7. Majority (87%) participants were from urban areas. There was no statistically significant difference in age, gender and area of residence distribution across the three groups (**Table-I**).

Table-I: Demographic parametres among the three categories

Parametres	Dengue category			p-value
	DWWS (n=55)	DWS (n=35)	SDG (n=10)	
Age ¹	35.5 $\pm$ 15.6	39.1 $\pm$ 14.3	40.8 $\pm$ 10.5	0.39 ^a
Male ²	35(63.6)	21(60.0)	7(10.0)	0.83 ^b
Urban residence ²	50(90.9)	28 (80.0)	9(90.0)	0.49 ^c

1-mean $\pm$ SD, 2-n(%)

a-ANOVA, b-Chi square test, c-Chi square test with Yate's correction

Platelet counts were significantly lower in SDG than in DWS, that also had a lower platelet than DWWS. Elevated SGOT, SGPT and serum bilirubin were found in greater proportions in SDG than in DWS than in DWWS (**Table-II**).

Table-II: Platelet count and liver biochemistry among the three categories

Parametres	Dengue category			p-value
	DWWS (n=55)	DWS (n=35)	SDG (n=10)	
Platelet (10^3 /cumm) ¹	113.3 $\pm$ 60.4	85.5 $\pm$ 57.4	39.1 $\pm$ 32.9	<0.001 ^a
High SGOT ²	28(50.9%)	30(85.7%)	10(100%)	<0.001 ^b
High SGPT ²	23(41.8%)	18(51.4%)	10(100%)	0.003 ^b
High bilirubin ²	1(1.8%)	8(22.8%)	4(40%)	0.003 ^c

1-mean $\pm$ SD, 2-n(%)

a-ANOVA, b-Chi square test, c-Chi square test with Yate's correction

A unique feature found in all participants was a SGOT-SGPT ratio >1 . Elevated liver enzymes were seen in 48(70.5%) of patients with abdominal pain, 58(85.2%) of patients with persistent vomiting, 64(94.1%) of patients with multiple site bleeding and 68(100%) of patients with lethargy. Patients with elevated SGPT (85.1%) and SGOT (95.1%) had a higher incidence of bleeding manifestations. SGOT and SGPT showed negative correlation with platelet count (**Figure-1 and 2**).

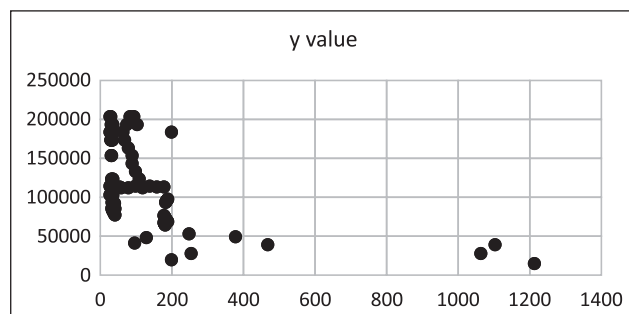


Figure 1: Correlation of SGPT and platelet count

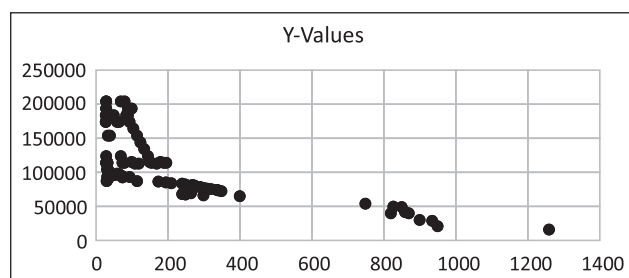


Figure 2: Correlation of SGOT and platelet count

Discussion

The study found a male predominance in the dengue patients, aligning with the gender distribution found in a few recent Asian studies¹⁰⁻¹². The mean age of the patients in our study was 38.4 ± 13.4 years, similar to a recent study in India reporting a mean age of 34.30 ± 15.0 years in dengue patients³.

Elevated SGOT, SGPT and serum bilirubin was observed in 68%, 51% and 13% participants of this study. Lee et al. and Souza et al. reported similar frequency of abnormal liver biochemistry^{14,15}. However, much higher percentages of abnormal liver function was observed in studies by Shukla et al., Kuo et al., Wong et al., Itha et al. and Prakash et al¹⁶⁻²⁰.

SGOT-SGPT ratio >1 was seen in all participants, opposite to that found in acute viral hepatitis. SGOT released from damaged RBC, skeletal muscle and cardiac muscle may explain this unique finding. SGOT/SGPT >1 with thrombocytopenia and persistence of fever even after jaundice appears may hint towards dengue infection when the presentation and laboratory parameters mimic acute viral hepatitis.

The highest SGOT and SGPT found in this study were, 1260 and 1214 IU/L in two different participants, both belonging to the severe dengue group but had early recoveries. The latter had severe epistaxis at presentation that supports the fact of SGPT being the more specific marker of hepatic dysfunction.

Greater proportion of abnormal LFTs in severe categories of dengue infection, their association with shock and bleeding,

and their negative correlations with platelet counts make these parameter strong candidates for biomarkers of severe dengue. Tinambunan *et al.* and Soni *et al.* made similar conclusions^{21,22}.

Karoli *et al.* found abdominal pain, vomiting and anorexia as most common symptoms dengue hepatitis²³. Participants with lethargy, abdominal pain, persistent vomiting and multiple site bleeding were also found to have high proportion of abnormal LFTs suggestive of their potential role as predictors of hepatic dysfunction in dengue.

Limitations

Small sample collected from single centre might affect the generalizability of the results of this study. The study also lacks a comprehensive assessment of liver function as prothrombin time and serum albumin were skipped.

Conclusion

Hepatic dysfunction is common in dengue and associated with severe categories of the infection. Multicentre prospective studies with larger sample are recommended for further exploration of hepatic dysfunction in dengue.

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Role of Prophylactic Magnesium Sulphate infusion on Post Spinal Shivering in Total Abdominal Hysterectomy

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Abstract

Introduction: Total Abdominal Hysterectomy (TAH) is a major surgery frequently performed under subarachnoid block (SAB), with perioperative shivering is a potential complication. This study aimed to evaluate the effect of prophylactic IV infusion of Magnesium Sulphate (MgSO₄) on post-spinal shivering following TAH under SAB.

Methods: This Quasi-experimental study was conducted on 60 patients undergoing TAH under SAB. The participants were randomly divided into two groups. Group-A received MgSO₄ 65mg /kg in 250 ml Normal Saline as infusion for 20 minutes before SAB. Group-B was given 250 ml Normal saline infusion for 20 minutes before SAB. The frequency & severity of shivering and adverse outcomes were recorded and compared between the two groups.

Result: The frequency of shivering in Group-A was significantly lower compared to Group-B (13.3% versus 61.3%, p-value <0.001).

Conclusion: Prophylactic MgSO₄ infusion reduces the frequency of post-spinal shivering without any significant adverse effects in TAH under SAB.

Key words: Prophylactic MgSO₄, post-spinal shivering, Total abdominal hysterectomy.

Introduction

Perioperative shivering is defined as involuntary muscle contractions triggered by rising body core temperature¹. It aims to boost metabolic heat production and maintain

temperature equilibrium². However, the increased oxygen consumption and carbon dioxide production by 600% leads to hypoxemia, myocardial ischemia, wound pain, delayed healing, and monitoring disruptions, particularly in patients with compromised cardiac and pulmonary reserves^{3,4}. Shivering is common in subarachnoid block (SAB) with reported incidences as high as 50–65%, primarily driven by vasodilation-induced rapid heat loss and core-to-peripheral heat redistribution⁵. To address this challenge, various pharmacological interventions with agents like Pethidine, Tramadol, Clonidine, Dexmedetomidine and Magnesium Sulfate have been employed⁶.

Magnesium Sulphate (MgSO₄), recognized for its antinociceptive effects through N-methyl-D-aspartate (NMDA) receptor antagonism and neuromuscular junction acetylcholine release inhibition not only lowers shivering threshold but also exhibits mild muscle relaxant properties⁶.

This study aimed to assess the effectiveness of intravenous (IV) MgSO₄ in preventing post-spinal shivering in patients undergoing Total Abdominal Hysterectomy (TAH) under SAB.

Methods

This study was conducted on 60 women aged ≥18 years undergoing TAH under SAB, with a ASA physical status I or II in Dhaka Medical College Hospital from October 2022 to March 2024. Individuals with previous hypersensitivity to MgSO₄, fever, obesity (BMI >30 kg/m²), concurrent use of calcium-channel blocker or vasodilator, pre-existing significant cardiovascular, respiratory, hepatic, neurological and psychiatric disorders were excluded from the study.

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All participants were kept fasted 8 hours and anxiolytic Midazolam 7.5 mg was advised orally at bed time to take on the day before surgery. On arrival at the operating room, after placement of standard monitors including continuous electrocardiogram, pulse oximetry, and noninvasive blood pressure measurements, two 18-gauge IV cannulas were placed. Before giving of anaesthesia, all patients received 500 mL of warm Hartman's solution and then 10mL/ kg/ hour of the same solution till the end of the operation.

The participants were randomly divided into two groups, each having 30 participants. Group-A received MgSO₄ 65mg /kg in 250 ml Normal Saline as infusion for 20 minutes before SAB. Group-B was given 250 ml Normal saline infusion for 20 minutes before SAB. In both groups, these 250ml infusions were infused through separate infusion set.

After completion of drug infusion, SAB was performed through L3-4 or L4-5 interspace in lateral decubitus position. After dural puncture with a 25G Quincke needle 3mL of hyperbaric bupivacaine 0.5% solution was injected into the subarachnoid space over 30 seconds. The patient was then turned supine before surgery starts. Appropriate draping with warm sheath was done. The level of sensory block was evaluated by the loss of pinprick sensation using 20-gauge hypodermic needle. Motor blockade was scored using a Modified Bromage Scale⁷. Readiness to surgery was defined as the presence of adequate motor block (Bromage score ≤ 2) and loss of pinprick sensation at T6 level. Core temperature of the patients was measured by standard thermometer in patient's tympanic membrane. Room temperature was maintained within 20 to 24°C.

Frequency of shivering was noted and graded according to Crossley and Mahajan shivering score⁸ (**Table-I**). IV Pethidine 25 mg along with IV Ondansetron 8 mg were used as rescue drugs for shivering.

Haemodynamic variables were measured at five minutes interval after spinal anaesthesia for first 30 minutes. After that recorded at 45 minutes, 1st hour, 2nd hour, 4th hour, 6th hour, 8th hour, 10th hour, 12th hour following SAB. Hypotension was managed accordingly.

Data was recorded by a separate investigator who was unaware of the group participant belonged. The frequency & severity of shivering, change in core body temperature, perioperative haemodynamic parameters and adverse outcomes were recorded and analyzed.

Results

The mean age of the participants was 45.2±7.2 years, comparable between the two groups (p-value 0.39). The two groups did not differ in respect of BMI, ASA physical status and duration of surgery (p-values 0.07, 0.71 and 0.57, respectively) (**Table-I**).

Table-I: Baseline characteristics of the two groups (n=60)

Characteristics	Group-A (n ₁ =30)	Group-B (n ₂ =30)	p-value
Age (Years) ¹	45.9 ± 7.7	44.5 ± 6.7	0.39 ^a
BMI (Kg/m ²) ¹	25.3±2.1	24.1±2.5	0.07 ^a
ASA			
ASA-I ²	26(86.7)	25(83.3)	0.72 ^b
ASA-II	4(13.3)	5(16.7)	
Duration of surgery (minutes) ¹	116.9 ± 28.5	113.4 ± 28.8	0.57 ^a

1-Mean±SD, 2-n(%)

a-Student's t-test, b-Chi-square test

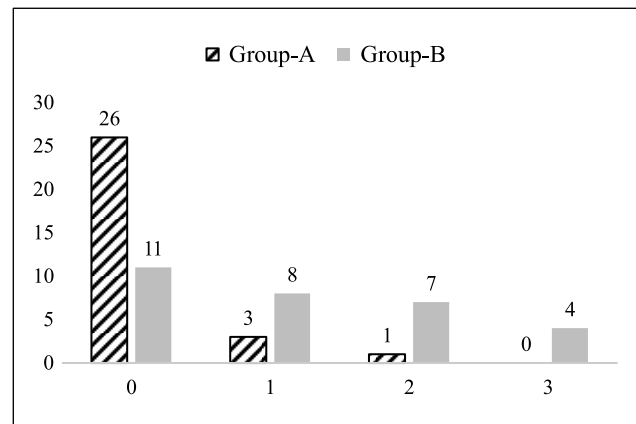


Figure-1: Shivering score in the two groups

The distribution of perioperative shivering score is illustrated in **Figure-1**. The shivering score ranged 0-3 among the participants. Group-A showed shivering score 0, 1 and 2 in 26(86.7%), 3(10.0%) and 1(3.3%), respectively. In group-B, 11(36.7%), 8(26.7%), 7(23.3%) and 4(13.3%) participants had shivering score 0, 1, 2 and 3, respectively. Shivering occurred in significantly lower frequency in Group-A (36.7% versus 86.7%, p-value <0.001) (**Table-II**).

Table-II: Frequency of shivering in the two groups (n=60)

Shivering	Group-A (n ₁ =30)	Group-B (n ₂ =30)	p-value
Present	4 (13.3)	19 (63.3)	
Absent	26 (86.7)	11 (36.7)	<0.001 ^a

a-Chi-square test

Percentages are given within the parentheses

Among the participants developed shivering, shivering score did not differ significantly between the two groups (p-value 0.86) (**Table-III**).

All participants were kept fasted 8 hours and anxiolytic Midazolam 7.5 mg was advised orally at bed time to take on the day before surgery. On arrival at the operating room, after placement of standard monitors including continuous electrocardiogram, pulse oximetry, and noninvasive blood pressure measurements, two 18-gauge IV cannulas were placed. Before giving of anaesthesia, all patients received 500 mL of warm Hartman's solution and then 10mL/ kg/ hour of the same solution till the end of the operation.

The participants were randomly divided into two groups, each having 30 participants. Group-A received MgSO₄ 65mg /kg in 250 ml Normal Saline as infusion for 20 minutes before SAB. Group-B was given 250 ml Normal saline infusion for 20 minutes before SAB. In both groups, these 250ml infusions were infused through separate infusion set.

After completion of drug infusion, SAB was performed through L3-4 or L4-5 interspace in lateral decubitus position. After dural puncture with a 25G Quincke needle 3mL of hyperbaric bupivacaine 0.5% solution was injected into the subarachnoid space over 30 seconds. The patient was then turned supine before surgery starts. Appropriate draping with warm sheath was done. The level of sensory block was evaluated by the loss of pinprick sensation using 20-gauge hypodermic needle. Motor blockade was scored using a Modified Bromage Scale⁷. Readiness to surgery was defined as the presence of adequate motor block (Bromage score ≤ 2) and loss of pinprick sensation at T6 level. Core temperature of the patients was measured by standard thermometer in patient's tympanic membrane. Room temperature was maintained within 20 to 24°C.

Frequency of shivering was noted and graded according to Crossley and Mahajan shivering score⁸ (**Table-I**). IV Pethidine 25 mg along with IV Ondansetron 8 mg were used as rescue drugs for shivering.

Haemodynamic variables were measured at five minutes interval after spinal anaesthesia for first 30 minutes. After that recorded at 45 minutes, 1st hour, 2nd hour, 4th hour, 6th hour, 8th hour, 10th hour, 12th hour following SAB. Hypotension was managed accordingly.

Data was recorded by a separate investigator who was unaware of the group participant belonged. The frequency & severity of shivering, change in core body temperature, perioperative haemodynamic parameters and adverse outcomes were recorded and analyzed.

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The mean age of the participants was 45.2±7.2 years, comparable between the two groups (p-value 0.39). The two groups did not differ in respect of BMI, ASA physical status and duration of surgery (p-values 0.07, 0.71 and 0.57, respectively) (**Table-I**).

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Duration of surgery (minutes) ¹	116.9 ± 28.5	113.4 ± 28.8	0.57 ^a

1-Mean±SD, 2-n(%)

a-Student's t-test, b-Chi-square test

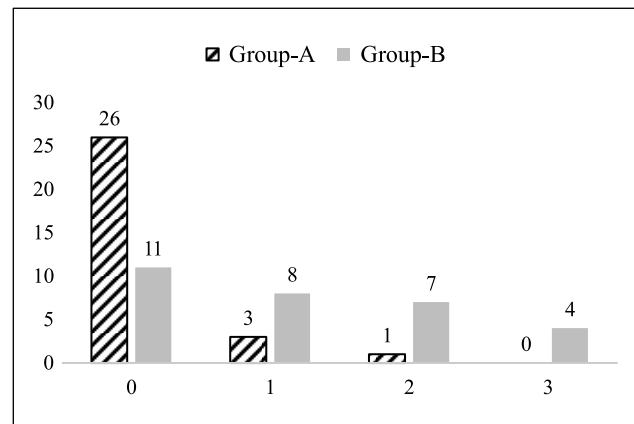


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Shivering	Group-A (n ₁ =30)	Group-B (n ₂ =30)	p-value
Present	4 (13.3)	19 (63.3)	
Absent	26 (86.7)	11 (36.7)	<0.001 ^a

a-Chi-square test

Percentages are given within the parentheses

Among the participants developed shivering, shivering score did not differ significantly between the two groups (p-value 0.86) (**Table-III**).

Table-III: Severity of shivering in the two groups (n=23)

Shivering score	Group-A (n ₁ =4)	Group-B (n ₂ =19)	p-value
1	3 (75.0)	8 (42.1)	0.86 ^a
2	1 (25.0)	7 (36.8)	
3	0(0.0)	4 (21.1)	

a-Chi-square test with yates' correction
Percentages are given within the parentheses

Table-IV: Adverse effects in the two groups (n=60)

Adverse effects	Group-A (n ₁ =30)	Group-B (n ₂ =30)	p-value
Hypotension	3 (10.0)	5 (16.7)	0.71 ¹
Bradycardia	0 (0.0)	3 (10.0)	0.24 ¹
Nausea/vomiting	1 (3.3)	2 (6.7)	1.0 ¹

1-Fisher's exact test
Percentages are given within the parentheses

Table-IV shows the intraoperative adverse effects observed among the participants, which included hypotension (8, 13.3%), bradycardia (3, 5.0%) and nausea/vomiting (3, 5.0%). Frequency of hypotension was lower in Group-A than Group-B (16.7% versus 10.0%). All the bradycardia events occurred in group-B. Nausea/vomiting was also less frequent in group-A than group-B (3.3% versus 6.7%). None of these adverse effects showed significant difference between the two groups (p-value 0.71, 0.24 and 1.0 for hypotension, bradycardia and nausea/vomiting, respectively).

Discussion

MgSO₄ is an effective treatment for post-spinal shivering through its central effect and mild muscle relaxant actions⁹. Participants in this study getting MgSO₄ had significantly higher proportion of absence of shivering. Gozdemir et al. demonstrated a significant reduction in post-spinal anaesthesia shivering in patients who underwent transurethral prostatectomy¹⁰. The frequency of shivering was smaller than that observed in this study, possibly due to the higher dose (80mg/kg) used. In a study by Ibrahim et al. showed that the use of prophylactic IV bolus of MgSO₄ 50 mg/kg followed by 2 mg/kg per hour of infusion versus Normal Saline in post-spinal anaesthesia also showed a lower incidence of severe grade shivering in the prophylactic group⁹.

No significant difference in the incidence of adverse effects like hypotension, bradycardia and nausea/vomiting was observed between the two groups in this study. This aligns with the observations of Agrawal et al. and Shah et al. No incidence of bradycardia was found in the MgSO₄-treated group in this study that aligns with the findings of Benevides et al¹¹.

Limitation

This was a single-center study on a small sample which may affect the generalizability of its findings.

Conclusion

Prophylactic administration of IV MgSO₄ infusion reduces post-spinal shivering in total abdominal hysterectomy without significant adverse effects.

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A Comparative study on Phacotrabeculectomy and Phacoemulsification in Primary Angle Closure Glaucoma with Cataract

Rahman MM¹, Bin Maruf SN², Ferdous Z³

Abstract

Objective: The purpose of this study was to compare clinical outcomes of phacoemulsification and phacotrabeculectomy in primary angle closure glaucoma (PACG) eyes with cataract.

Methods: This was a retrospective study and analysed the 1-year follow-up data of 40 cases of 30 patients with PACG refractory to conservative treatment and cataract who underwent either phacotrabeculectomy (20 cases) or phacoemulsification (20 cases). The best corrected visual acuity (BCVA), IOP, anterior chamber depth (ACD), glaucoma medications, and complications were compared between the two groups.

Results: At one year after surgery, the mean IOP was decreased by 20.7% and 29.5% after phacoemulsification and phacotrabeculectomy, respectively (p-value <0.001 for both groups). Phacotrabeculectomy was significantly more effective than phacoemulsification in reducing IOP up to 1 years after surgery (p-value <0.001) but was associated with more postoperative complications (p-value <0.001).

Conclusions: Phacotrabeculectomy was more effective in reducing IOP than phacoemulsification alone but was associated with more postoperative complications.

Keywords: primary angle-closure glaucoma, cataract, phacoemulsification, phacotrabeculectomy.

Introduction

Primary angle-closure glaucoma (PACG) is a major cause of blindness worldwide, especially in Asians and Chinese^{1,2}. Its prevalence increases with age; therefore, it frequently coexists with cataract. In such patients, combined cataract extraction and trabeculectomy (phacotrabeculectomy) treat both diseases at the same time³.

Recent evidence suggested that cataract extraction alone could result in a significant lowering of intraocular pressure (IOP) in PACG eyes^{4,7}. Cataract extraction alone may, therefore, suffice as the primary surgical treatment for PACG eyes with coexisting cataract. It avoids the complications associated with trabeculectomy, such as

hypotony, shallowing of the anterior chamber, malignant glaucoma, and blebitis⁸⁻¹⁰.

The previous studies compared the IOP control after phacoemulsification alone versus combined phacotrabeculectomy with adjunctive mitomycin C chemotherapy in both medically controlled and uncontrolled PACG eyes with cataract during a 24-month follow-up period¹⁰⁻¹¹. It was shown that phacoemulsification alone could effectively lower IOP in PACG eyes, at least in the initial 24 months. Although phacotrabeculectomy was more effective in IOP control, it was associated with more complications. This study compares the long-term clinical outcomes after phacoemulsification and phacotrabeculectomy in PACG eyes with cataract.

Methods

This was a retrospective study conducted in the Department of Ophthalmology, Bangladesh Medical college and Hospital, Dhanmondi, Dhaka. The informed consent was signed by all patients. 40 cases with PACG and coexisting cataract received phacotrabeculectomy (phacotrab) or phacoemulsification (Phaco) between January 2019 and December 2023. The clinical diagnostic criteria for cataract were as follows: presence of nucleus sclerosis, cortical cataract, or subcapsular cataract which confirmed by slit-lamp examination; visual acuity of 6/12 or worse. The diagnostic criteria for PACG were as follows: presence of typical symptoms including ocular pain, blurry or halo vision; presenting IOP of more than 21 mmHg and the presence of typical signs including conjunctival injection,

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corneal epithelial edema, mid-dilated unreactive pupil, over 180° of iridotrabecular contact or peripheral anterior synechiae (PAS), and shallow anterior chamber. Patients with glaucomatous optic neuropathy, secondary ocular hypertension, surgery history, and any other ocular or system diseases were excluded. A-scan biomicroscopy was performed to measure the axial length and to calculate IOL power. The value of visual acuity was converted into that in the logarithm of the minimum angle of resolution (LogMAR).

The surgical procedure, all conducted by the same surgeon, in brief was as follows: after local anesthesia and sterile procedure, all patients underwent a standard phacoemulsification was performed through a 2.8-mm clear corneal incision. After an IOL implantation and removal of viscoelastic material, for phacotrab group, a fornix based conjunctival flap (width: 5 mm) was used for trabeculectomy. A partial-thickness (approximately 50 % depth) triangular scleral flap was prepared, measuring approximately 3 mm at the limbus. Mitomycin C (0.4 mg/mL) was placed under the sclera flap for 2 to 3 min before irrigation with balanced salt solution. A sclerostomy was created using a Kelly Descemet's punch, followed by a surgical peripheral iridectomy. The sclera flap was closed with 1 interrupted 10-0 nylon suture on the top and 2

releasable sutures on the waist. The fornix-based conjunctival flap was closed with continuous suture. Postoperative medications included moxifloxacin eye drops and prednisolone acetate ophthalmic suspension were administered six times a day and reduced within 4 to 6 weeks depending on the degree of postoperative inflammation. Timolol 0.5% (with brinzolamide in persistent raised IOP) was used to achieve the target IOP.

Postoperative data regarding BCVA and IOP (primary outcome measures), ACD, glaucoma medications and complications (secondary outcome measures) were obtained on week 1 and month 1, 3, 6, 9 and 12. Surgical success was defined as IOP $\leq$ 21 mmHg without glaucoma medications. Sutures removal and bleb needling to improve bleb function were not considered failure of the procedure. Statistical analysis was performed using SPSS software version 21 (SPSS Inc, Chicago, Illinois, USA). Continuous variables were expressed as mean $\pm$ standard deviation (SD), and categorical data were represented by number (n) and percentage (%). Parametric variables were analyzed using analysis of variance (ANOVA). Variables were compared using a paired t test. P value of <0.01 was considered statistically significant.

Results

Among the 40 cases, 20 underwent phacotrab and 20 underwent phaco. The demographics and ocular characteristics did not differ significantly between the two groups (**Table-I**).

Table-I: Pre operative ocular characteristics

Traits	Phacotrab (n ₁ =20)	Phaco (n ₂ =20)	p-value
Age ¹	47.38 $\pm$ 9.45	49.32 $\pm$ 8.48	0.98 ^a
Male : Female	20:45	18:37	0.94 ^b
Axial length(mm) ¹	21.54 $\pm$ 0.90	22.77 $\pm$ 1.06	0.41 ^a
Lens thickness(mm) ¹	4.24 $\pm$ 0.45	4.48 $\pm$ 0.48	0.78 ^a
Preoperative IOP (mm Hg)	21.8 $\pm$ 6.1	23.3 $\pm$ 5.1	0.61 ^a
Number of preoperative glaucoma drugs	2.7 $\pm$ 1.0	2.8 $\pm$ 0.9	0.56 ^a
Preoperative BCVA (logMAR)	0.74 $\pm$ 0.51	0.75 $\pm$ 0.34	0.41 ^a
Vertical cup to disc ratio	0.73 $\pm$ 0.16	0.74 $\pm$ 0.88	0.81 ^a

1-Mean $\pm$ SD, a-Student's t-test, b-Chi square test

The pre- and post-operative best corrected visual acuity (BCVA) (converted into Log-MAR) of the two treatment groups comparable. Post-operative improvement of VA occurred in 70 % in phacotrab group and 75 % in phaco group. In phacotrab group 8 patients retained the same initial VA, and 1 patient had light perception (LP) before and after surgery. In phaco group 5 patients retained the same initial VA, and 2 patients had LP before and after surgery.

The pre-operative, post-operative and follow-up IOP of the participants are illustrated in **Table-II**. The mean IOP in phacotrab group and phaco group at the time of acute PACG attack were 37.38 $\pm$ 8.52 and 32.60 $\pm$ 8.15 mmHg respectively. The mean postoperative IOP levels at all follow up time points were significantly lower than the mean preoperative IOP in both groups (p-value <0.001). Statistically significant difference in mean IOP between the two groups only at 12 months postoperatively (p-value 0.006).

Table-II: Pre- and Post-Operative and follow-up IOP of the two treatment groups

Recording time	Phacotrab (n ₁ =20)	Phaco (n ₂ =20)	p-value
Pre-operative ¹	37.38 ± 8.52	32.60 ± 8.15	0.61 ^a
Post-operative ¹	13.58 ± 3.74	14.60 ± 3.63	0.34 ^a
1 month ¹	12.38 ± 3.02	13.64 ± 3.21	0.16 ^a
3 months ¹	13.08 ± 3.15	14.36 ± 2.61	0.13 ^a
6 months ¹	13.04 ± 3.18	14.40 ± 3.01	0.13 ^a
9 months ¹	13.96 ± 2.88	15.44 ± 2.83	0.08 ^a
12 months ¹	12.71 ± 3.99	15.64 ± 3.08	0.006 ^a

Mean±SD mmHg, a-Student's t-test

In phacotrab group the success rate was 85.33 % (20 eyes) (without medications) and 90 % (with medications). In phaco group the success rate was 79 % (18 eyes) (without medications) and 85 % (with medications) respectively.

The mean anterior chamber depth (ACD) of the two treatment groups increased post-operative, without significant intergroup difference at 6 months. In phacotrab group, bleb needling procedure with 5-fluorouracil (5 mg) was performed in 2 eyes at 3 months. All eyes had diffuse blebs or elevated blebs with microcystic changes in the conjunctiva between 3 months to 12 months. There were no serious intra- or post-operative complications in the two treatment groups.

Discussion

The previous studies demonstrated that cataract extraction alone resulted in significant IOP lowering in PACG eyes, at least in the initial postoperative period^{4,14}. Lens extraction significantly deepens the anterior chamber and widens the drainage angle and thus at least partially reverses the anatomical predisposition to angle closure in the long term¹⁵⁻²³. Our study showed that combined phacotrabeculectomy with adjunctive mitomycin C was more effective than phacoemulsification alone in controlling IOP in PACG with coexisting cataract, up to 24 months after surgery^{10,11}.

However, phacotrabeculectomy resulted in significantly more surgical complications than phacoemulsification alone during the first 24 months after surgery²¹. It was not known whether the IOP-lowering effect of cataract extraction alone would be maintained in the longer term.

With time, a proportion of the filtration surgery would also likely lose their IOP-lowering effect, and so it was not known whether the advantage in IOP lowering of phacotrabeculectomy over phacoemulsification alone could be maintained in the longer term. It would also be interesting to know what proportion of PACG eyes receiving phacoemulsification alone might need secondary trabeculectomy in the longer term, and also whether there is a significant difference in the rate of surgical complications between the 2 treatments in the longer term.

Our study demonstrated that, the phacotrabeculectomy group maintained a clear advantage in IOP lowering over the phacoemulsification group up to at least 1 years after initial surgery. In terms of decreasing the dependence on glaucoma drugs, our study demonstrated that, with either treatment, drug reduction remained statistically significant up to at least 2 years after surgery. With either treatment, the required number of glaucoma drugs did seem to increase

gradually over time, up to 2 years.

The advantage of phacotrabeculectomy in reducing drug dependence over phacoemulsification alone remained statistically significant throughout the follow-up period up to 1 years. By one year after surgery, the mean IOP in the phacotrabeculectomy group was 2.1mmHg lower than the phacoemulsification group (P=0.001). The difference was small but statistically significant. Our finding is partially in line with previous studies comparing phacoemulsification alone versus combined phacotrabeculectomy^{17,18}, which showed no significant IOP-lowering advantage of combined surgery over phacoemulsification alone in PACG eyes. One of the reasons might be because, by simply opening up the angles or lysing the peripheral anterior synechiae during phacoemulsification, the mechanical restriction to aqueous outflow is already largely eliminated, such that trabeculectomy might not offer much additional benefit. It remains uncertain, however, whether such a difference in mean IOP level would make a difference to long-term glaucomatous progression, which was not demonstrable in this study.

However, the retrospective nature of the data collection carried all the limitations of any retrospective study, such as the lack of predetermined follow-up regularity and investigation protocols. Fortunately, all PACG patients in our glaucoma subspecialty clinics were managed quite uniformly, with standard Goldmann applanation techniques for IOP measurement, and regular VF testing following standard operating procedures.

Conclusions

Phacoemulsification alone can reduce IOP and the requirement for glaucoma drugs in PACG eyes with coexisting cataract, and these effects persisted for at least 1 years after surgery. Combined phacotrabeculectomy with

adjunctive mitomycin C achieves more IOP reduction than phacoemulsification alone, and the requirement for glaucoma drugs, in only medically controlled PACG eyes for up to at least 1 years after surgery. Combined surgery may provide additional benefits in patients with advanced glaucoma or in those suffering from side effects of glaucoma medications, in whom maximum IOP reduction or drug reduction could be of value.

Conflict of interest

The authors do not have any conflict of interest to reveal.

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Antihypertensive efficacy of Perindopril and Ramipril in grade-1 hypertension- A double-blind head-to-head randomized trial

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Abstract

Introduction: A substantial reduction in cardiovascular mortality can be accomplished through the effective control of hypertension. ACE inhibitors are the recommended first-line group of antihypertensive agents. Perindopril and Ramipril have the advantage of once daily dosing among ACE inhibitors available in Bangladesh. This study was conducted to compare the antihypertensive efficacy of Perindopril and Ramipril.

Methods: This double-blind head-to-head randomized trial was conducted in the Medicine outpatient of Shaheed Monsur Ali Medical College Hospital, Dhaka, Bangladesh, on seventy patients with grade-1 hypertension. The study participants were randomly divided into two groups to be treated with either Perindopril or Ramipril, setting a target blood pressure (BP) of <130/80 mmHg. The proportion of target BP achievement and the mean reduction of BP were compared between the two groups.

Results: Perindopril at higher dose demonstrated a greater proportion of target BP achievement (71.9% vs 42.4%, p-value 0.02) and a more significant reduction of both systolic BP (26.4±8.3 vs 21.8±6.4 mmHg, p-value 0.02) and diastolic BP (17.1±7.0 vs 10.5±6.6, p-value <0.001), with comparable frequency of troublesome dry cough (8.6% vs 5.7%, p-value 1.0).

Conclusion: Both Perindopril and Ramipril are effective antihypertensive drugs for grade-1 hypertension. Perindopril exhibited a superior efficacy with comparable side effects.

Key words: Perindopril, Ramipril, grade-1 hypertension.

Introduction

Hypertension is the key modifiable risk factor for

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cardiovascular disease, the leading cause of death globally¹. Two-thirds of the 1.3 billion people having hypertension worldwide live in low- and middle-income countries². The pooled prevalence of hypertension in Bangladesh is 20% overall, 17% in males and 21% in females³. Lowering blood pressure (BP) by 20 mmHg of systolic blood pressure (SBP) or 10 mmHg of diastolic blood pressure (DBP) is associated with a 50% reduction of the risk of a fatal cardiovascular event⁴. Only 54% of hypertension are diagnosed, 42% receive treatment, and 21% get their BP controlled⁵.

ACE inhibitors (ACEI) are the recommended first-line antihypertensive drugs, especially with co-existing diabetes mellitus, chronic kidney disease, heart failure and post-myocardial infarction⁶⁻⁸. Among the ACE inhibitors available in Bangladesh, Perindopril and Ramipril have the advantage of better treatment adherence due to their once daily dosage⁹⁻¹¹.

Objectives

This study aimed to compare the anti-hypertensive efficacy of Perindopril and Ramipril.

Methods

This was a double-blind head-to-head randomized trial conducted on 70 non-pregnant patients with grade-1 hypertension (SBP 130-159 mmHg and/or DBP 90-99 mmHg)¹², not on any antihypertensive drug, who attended the Medicine outpatient of Shaheed Monsur Ali Medical College Hospital, Dhaka, Bangladesh, from January to June 2025. Age, gender and co-morbidities were documented in all participants. The study participants were randomly divided

into two groups – group A and group B, each comprising 35 participants, to be treated with Perindopril and Ramipril, respectively. The starting doses of Perindopril and Ramipril were 2 mg and 2.5 mg at bedtime, respectively. All participants were advised to follow a salt-restricted diet and lifestyle modifications. The target BP was set $<130/80$ mmHg¹². A follow-up visit was made after four weeks. The dose of Perindopril and Ramipril was increased to 4 mg and 5 mg at bedtime, respectively, among the participants who did not achieve the target BP, with a second follow-up at eight weeks.

BP was recorded, maintaining a standard protocol at baseline and follow-ups. Any adverse effect experienced was also documented at the follow-ups. The data collectors were kept blind about the treatment group the participants belonged. The reduction of BP and the proportion of participants achieving the target BP were compared between the two groups. Student's t-test and Chi-square test were employed for quantitative and qualitative variables, respectively. A p-value of <0.05 was considered statistically significant. Statistical software SPSS version 25 and Microsoft Excel were used for data analysis.

Ethical consideration

The study received formal approval from the Institutional Ethical Review Board (IERB) of Shaheed Monsur Ali Medical College Hospital [Ref: SMAMC/IERB/24/10(7) dated 15/10/2024]. Written informed consent was taken from all participants. The nature & aim of the study were explained to every study participant in simple understandable language before requesting their consent. The identity of the study participants were kept confidential. Every participant had the right to withdraw from the study at any time.

Results

The study participants had an age range of 25-77 years, with mean $\pm$ standard deviation (SD) of 51.8 ± 11.7 years. The mean age of group A was comparable to group B (54.6 ± 11.4 years versus 49.1 ± 11.5 years, p-value 0.05) (Table-I). Both groups had 20 males and 15 females.

Diabetes mellitus (DM), coronary artery disease (CAD), chronic kidney disease (CKD) and heart failure were the common co-morbidities found in the two groups at comparable (p-value ≥ 0.05 for all variables).

Table-I: Age and co-morbidities in the study participants

Co-morbidity	Total (n=65)	Group A (n1=32)	Group B (n2=33)	p-value
Age	51.8 ± 11.7	54.6 ± 11.4	49.1 ± 11.5	0.05 ¹
DM	24(36.9)	13(40.6)	11(33.3)	0.5 ²
CAD	11(16.9)	7(21.9)	4(12.1)	0.4 ³
CKD	6(9.2)	2(6.3)	4(12.1)	0.7 ³
Heart failure	3(4.6)	1(3.1)	2(6.1)	1.0 ³

1-Student's t-test, 2-Chi-square test, 3-Fisher's exact test

Five participants withdrew from the study due to troublesome dry cough (3 in group A and 2 in group B). The frequency of dry cough was comparable between group-A (8.6%) and group-B (5.7%) (p-value 1.0 by Fisher's exact test).

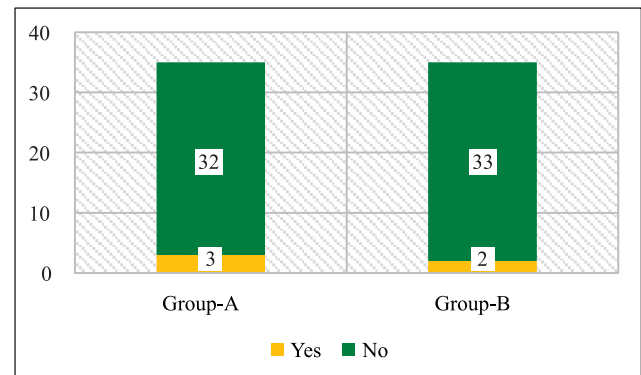


Figure-1: Frequency of dry cough in the participants

The antihypertensive effect could be assessed in the remaining 65 participants (32 in group A and 33 in group B).

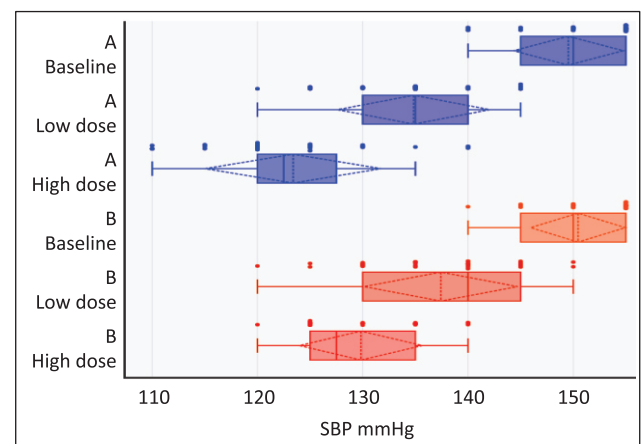


Figure-2: Systolic BP in the participants

Figure-2 shows the mean $\pm$ SD (range) of SBP at baseline and with low and high-dose antihypertensives in both groups. In group A, SBP at baseline, with low dose and with high dose were 150.0 ± 4.9 (140–155), 134.8 ± 7.3 (120–145) and 123.4 ± 8.5 (110–135) mmHg, respectively. In group B, these values were 150.5 ± 4.6 (140–155), 139.3 ± 7.4 (120–150) and 130.0 ± 6.1 (120–140) mmHg, respectively.

Mean $\pm$ SD (range) of DBP was exhibited in **Figure-3**. DBP at baseline, with low dose and with high dose in group A were 85.2 ± 10.9 (65–95), 75.9 ± 9.3 (55–95) and 68.6 ± 10.3 (45–90) mmHg. In group B, these values were 89.9 ± 7.0 (70–95), 83.6 ± 9.2 (60–95) and 80.1 ± 7.0 (65–95) mmHg. There was no significant difference in baseline SBP and DBP between the two groups (p-value 0.46 and 0.1, respectively) (Table-II).

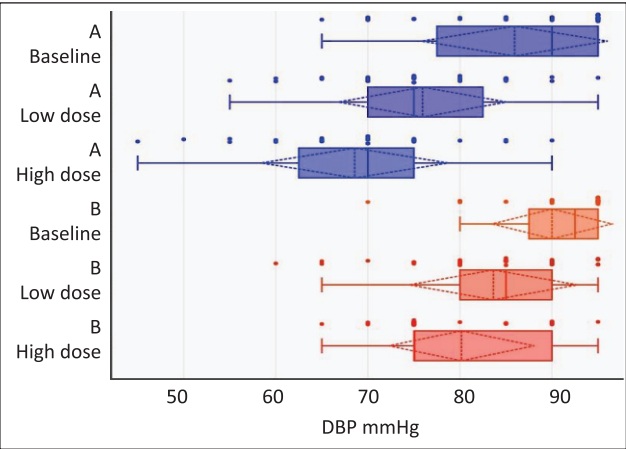


Figure-3: Diastolic BP in the participants

Target BP was achieved in 7(10.8%) participants at low dose, 4(12.5%) in group A and 3(9.1%) in group B, without any statistically significant inter-group difference (p-value 0.71) (Table-II).

Table-II: Blood pressure of the study participants

Parameter	Total (n=65)	Group A (n1=32)	Group B (n2=33)	p-value
Baseline BP ¹				
SBP	150.0±4.9	149.5±5.3	150.5±4.6	0.46 ^a
DBP	87.8±8.9	85.9±10.3	89.6±7.0	0.1 ^a
Target BP achieved ²				
Low dose	7 (10.8)	4 (12.5)	3 (9.1)	0.71 ^b
High dose	37 (56.9)	23 (71.9)	14 (42.4)	0.02 ^c
BP reduction at low dose ¹				
SBP	14.2±5.7	15.5±6.0	12.9±5.2	0.07 ^a
DBP	7.8±5.1	9.7±4.7	6.1±4.8	0.003 ^a
BP reduction at high dose ¹				
SBP	24.0±7.6	26.4±8.3	21.8±6.4	0.02 ^a
DBP	13.6±7.5	17.1±7.0	10.5±6.6	<0.001 ^a

1-mmHg, mean±SD; 2-n(%)
a-Student’s t-test, b-Fisher’s exact test, c-Chi-square test

The remaining participants (28 and 30 in group A and B, respectively) were prescribed the high dose. The cumulative number of participants achieving the target BP after the second follow-up was 37(56.9%). A significantly greater proportion of Group A participants achieved the target BP, 23(71.9%), than group B, 14(42.4%) (p-value 0.02) (Table-II).

The mean reduction of BP was also compared between the two groups. There was no significant difference in SBP reduction at low dose (p-value 0.07) (Figure-4 and Table-II).

Group A had a significantly greater reduction of SBP at high dose (p-value 0.02) (Figure-4 and Table-II).

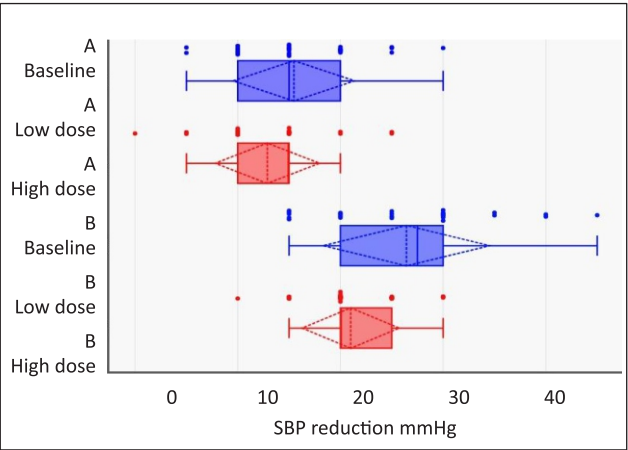


Figure-4: Systolic BP reduction in the participants

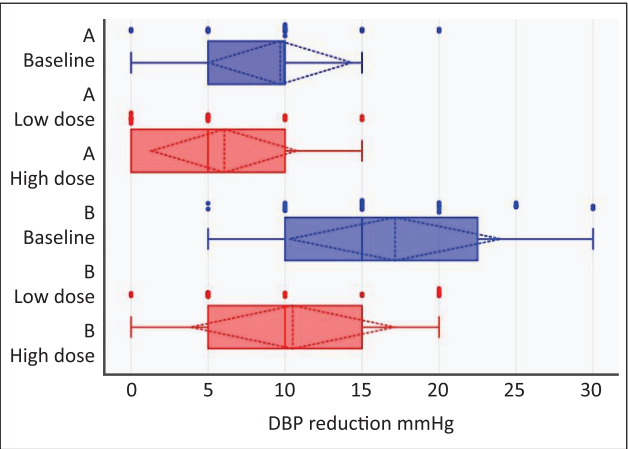


Figure-5: Diastolic BP reduction in the participants

Group A exhibited a more significant reduction in DBP at both low and high dosages (p-value 0.003 and <0.001, respectively) (Figure-5 and Table-II).

Discussion

With a mean age of 51.8 years, the participants' demographics were consistent with those observed in contemporary studies on hypertension in Bangladesh¹³⁻¹⁴. Diabetes mellitus, coronary artery disease, heart failure, and chronic kidney disease were prevalent comorbidities, aligning with findings from recent studies¹⁵⁻¹⁷.

Perindopril and Ramipril are long-acting ACE inhibitors that offer the benefit of once-daily administration. Both are the preferred anti-hypertensive agents following ischaemic stroke due to their established effectiveness in secondary prevention¹⁸⁻¹⁹. Perindopril and Ramipril exhibit comparable effectiveness in reducing all-cause mortality post-myocardial infarction²⁰.

The pleiotropic effects of perindopril are distinct from those of other ACE inhibitors, featuring bradykinin site selectivity that promotes nitric oxide enhancement and prevents apoptosis in endothelial cells. It is the preferred ACE inhibitor for heart failure with preserved ejection fraction²¹. Besides, Perindopril tops the list of ACE inhibitors in terms of cardiovascular protection²².

This study revealed that Perindopril had a more pronounced effect on lowering blood pressure than Ramipril, both in qualitative and quantitative terms. These results corroborate the findings of the CONFIDENCE trial, which concluded that Perindopril showed greater efficacy in controlling blood pressure than its ACE inhibitor counterparts²³. Troublesome dry cough was experienced in a small proportion of participants that aligns with the findings of Sankar et al and Nazir et al^{24,25}.

Limitations and recommendations

This single-centre study was conducted on a small sample. Besides, the frequency of potential adverse effects like renal impairment and hyperkalaemia was not assessed. Multi-centre placebo-controlled studies with larger samples are recommended to compare the efficacy and adverse effect profile of Perindopril and Ramipril.

Conclusion

Both Perindopril and Ramipril were effective antihypertensive agents in grade-1 hypertension. Perindopril showed more pronounced blood pressure lowering effect than Ramipril, with a comparable frequency of dry cough.

Author contribution

Amit Wazib- Conceptualization, study design, protocol development. **Shaila Rahman, Farah Naz Kamal and Safwanul Aman**- Data collection, **Hiya Bhatta**- Data analysis, **Arman Ibne Haq and Mehnaz Kamal**- Critical review.

Conflict of interest

The authors do not have any conflicts of interest.

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Data availability

Available upon request to corresponding author.

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Comparison between Footprint and Foot Outline of Bangladeshi males

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Abstract

Background: Foot dimension has great use in anatomy, physiology, ergonomics, forensic science, plastic surgery, radiology, podiatry, archaeology, anthropology, nutrition science and diagnostic knowledge between patient and normal population. The data of foot dimensions of Bangladeshi male is essential for the anatomist for normative reference, to the radiologist and podiatrist for diagnosis of diseases in their respective fields. Stature can be correlated from foot dimensions using different foot segments from footprints.

Objective: This cross-sectional analytical study was planned to determine the different dimensions of the footprint of the Bangladeshi males and to find out the correlation of stature with foot dimensions from footprint of male Bangladeshi medical students.

Methods: Two hundred (200) male medical college students of 18-25 years of age were selected from different medical colleges of Dhaka city and their age was determined by their national ID cards. Both feet of the same individual were painted with ink with the help of the brush. After ensuring that toes and sole were inked properly, footprints were taken at the same time for both feet while the ink was still wet. After ensuring that toes and sole were inked properly, foot outlines were drawn using a sharp 2B pencil while both feet were still placed on the paper. Length of different toes were then measured in centimetre from the footprints and foot outlines using a Vernier digital spreading calliper.

Results: In the present study, significant differences were observed between T1, T2, T3, T4 and T5 lengths of right and left footprints (p-value<0.001). Each of the T1, T2, T3, T4 and T5 lengths of the left foot were greater than the right foot. Significant differences were observed between T2, T3, T4 and T5 lengths of right and left foot outline (P<0.001) except T1 length which was not significant (p-value>0.05). Each of the T1, T2, T3, T4 and T5 lengths of the left foot outline were greater than the right foot outline. There was a strong correlation between footprint and foot outline among Bangladeshi males (p-value<0.001).

Conclusion: All the foot lengths of left footprint and foot outline were significantly higher than the right footprint among Bangladeshi male medical students. Further studies with larger sample size are recommended to get more precise picture in order to produce a more comprehensible data that will help to determine the correlation of dimensions of footprint with foot outline of Bangladeshi medical students.

Key Words: footprint, foot outline, Bangladeshi males..

Introduction

Every part of human body is different in its own way from a similar part in another body. There is also a relationship

between each part of the body and the whole body. Footprint is the impression of the sole of the foot on an even surface which provides the size dimensions of the plantar surface of the foot actually touching a hard surface.

Footprints are of immense value in establishing personal identity of the criminals in forensic examinations. The partial or complete footprints can be found on rain covered areas, newly waxed floors, freshly cemented surfaces, moistened surfaces, in dust, mud, sand, oil, paint and can be left in blood at the crime scenes.¹ The foot dimensions derived from footprint can provide definitive information on many physical characteristics of the individual as morphology of human foot shows variations due to the combined effects of heredity, lifestyle and climatic factors.² Assessing the height of an individual from measurements of different dimensions of the foot has always been of immense interest to anatomists, anthropologists, podiatrists and industrialists involved in designing foot wears. It has been shown that the reliability of prediction of stature from foot dimensions is as high as that from long bones. Foot or shoe

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prints, if present at the scene of crime, may provide clue regarding the stature of the person which may help in establishing partial identity of the suspect. Moreover, in an aircraft accident it is the feet, which are recovered more intact than other parts of the body, as they are often shoe clad.³ As ossification of the bones of the foot occurs earlier than the long bones of the lower extremity, therefore even during adolescence, stature can be predicted more accurately from foot measurements than that from the long bones of the lower limb.⁴ This would enable forensic scientists to solve crimes in the absence of complete evidence⁵ and the anthropologist and archeologist to analyze events that occurred in remote past. Reliable anthropometric data for a target population are necessary when designing foot wears for that population, otherwise the product may not be suitable for the user.⁶

The stature was estimated from skeleton by anatomical method which was introduced by Dwight in 1894. The vertical height of a person needs an equally firm base to support it, which is provided by feet.⁷ This provides information that increase in height is associated with an increase in foot dimensions. Estimation of stature from toe lengths in a footprint are of utmost importance as they are strongly correlated with stature and thus gives a better prediction of stature than correlated with other measurements.⁸ The foot has been used to estimate stature in several studies in different tribal groups, where normograms have been derived to reconstruct stature from foot dimensions. These types of studies in different communities become essential, as several factors which include genetic and environmental, are known to affect stature and foot morphology as well as dimensions.⁹

The values of different dimensions of foot of Bangladeshi males may be helpful to the anatomists for a normative reference. For the radiologist and the podiatrists the normative values may be helpful in diagnosis of diseases in their respective fields. This knowledge of different foot dimensions and its correlation with the stature is of extreme importance for the forensic scientists to establish the identity of an individual. For proper designing of a prosthetic foot by the ergonomists and for surgical reconstruction by the plastic surgeons foot dimension data is essential.

The present study includes foot length from each toe of footprint rather than taking length and breadth only as have been done in most of the previous studies. So, the study will be applicable not only to complete footprint measurement but also to partial footprint in estimation of stature. With the above perspective, the present study was carried out to give the overview of foot dimensions of Bangladeshi males and to correlate the foot anthropometric data with stature of the same age group of Bangladeshi males.

Methods

This cross-sectional analytical study was carried out at the Department of Anatomy of Dhaka Medical College, Dhaka from July 2012 to June 2013. The study was performed on 200 male Bangladeshi medical students of age 18-25 years. Individuals with congenital anomaly of feet, any deformity of

feet, endocrine diseases like acromegaly, gigantism, those who have encountered any road traffic accident or burn injury affecting feet and tribal population were excluded from the study.

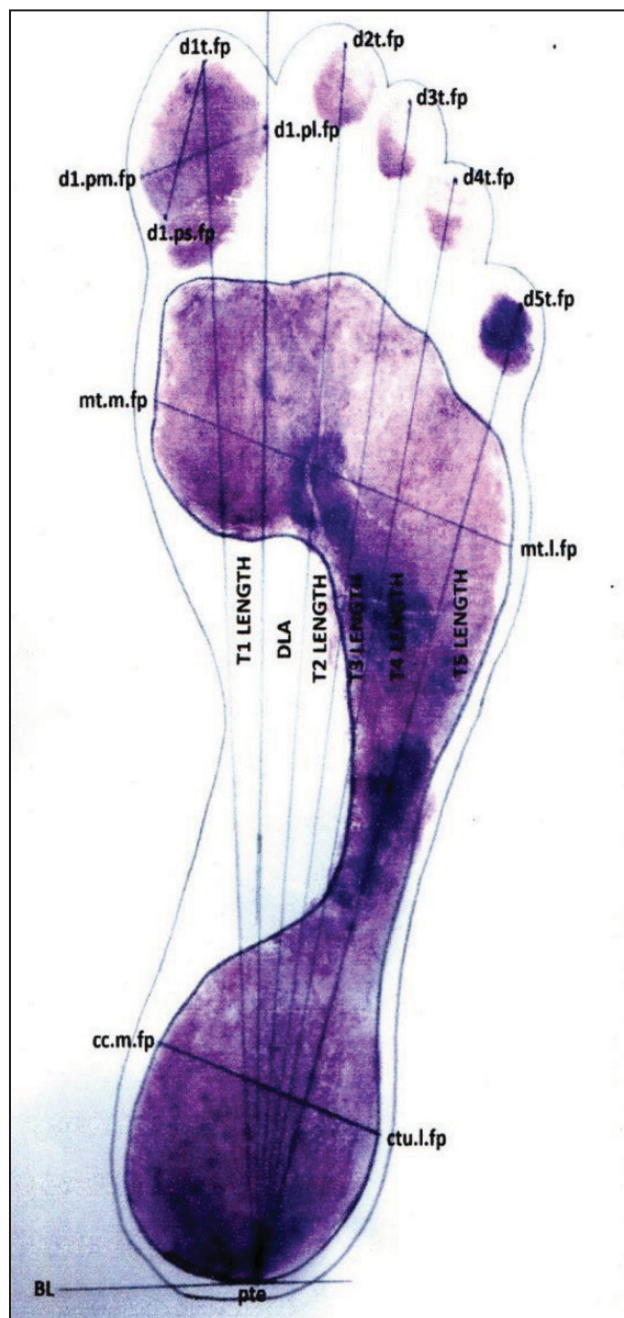


Figure-1: Footprint landmarks and measurements. mt.m.fp- anterior epiphyses of 1st metatarsal, mt.l.fp- anterior epiphyses of 5th metatarsal, cc.m.fp- medial side of heel, ctu.l.fp- lateral side of heel, d1.pm.fp to d1.pl.fp- great toe pad breadth, d1t.fp to d1.ps.fp- great toe to pad length, DLA- designated longitudinal axis, BL- base line, pterion mid-rear heel point, fp- footprint. T1, T2, T3, T4 and T5- Distance from pterion to most distal part of 1st, 2nd, 3rd, 4th and 5th toes, respectively.

The feet of the individual were washed with liquid soap before inking to remove oily or greasy substance and dirt from the foot. The feet were then wiped with a towel. Two legal size white papers were fixed on a clip board with double clips to take print of right and left feet placed on an even floor. A small amount of ink was poured into a clean and dry flat box with a wide base. The individual was asked to sit on a chair and rest his legs on a low stool with extended knee so that his feet were placed beyond the stool for proper painting of the soles. A wide paint brush was moved in the ink over flat surface of the wide based box until the ink spread thinly and homogenously in the brush.

The right and left feet were painted with ink with the help of the brush. After ensuring that toes and sole were inked properly, footprints were taken at the same time for both foot while the ink was still wet. The feet were carefully removed from the stool and the soles were placed slowly on the paper from proximal to distal end while the individual still remained seated. The individual was then asked to stand from sitting position with his feet placed on the papers on the clipboard without moving the feet. After ensuring that the feet were placed properly the individual was asked to stand erect without any support while putting equal pressure on both feet without moving their position on the papers. The foot outlines were drawn using a sharp 2B lead pencil held vertically close to the foot as much as possible.

The individual was then asked to sit. The feet were then lifted from the paper at the same time so that there was no overlapping of the already imprinted footprint. A sharp 2B lead pencil was used to mark the mid-rear heel point or pterion (pte.fp) and most distal point of each toe. Straight lines were drawn from pterion to distal points of each toe marked earlier.

Pterion is the most posteriorly projecting point on the heel when the subject stands erect. These measurements were taken from pterion (pte.fp) to the most anterior part of each toe, i.e. d1t.fp, d2t.fp, d3t.fp, d4t.fp and d5t.fp for 1st to 5th toes respectively and thus T1, T2, T3, T4, T5 lengths were measured for each toe. The vernier digital spreading caliper was placed horizontally on the landmarks and all the measurements were taken in centimeter (Fig.1). For foot outline, these measurements were taken from pterion (pte.fo) to the most anterior part of each toe, i.e. d1t.fo, d2t.fo, d3t.fo, d4t.fo and d5t.fo for 1st to 5th toes respectively and thus T1, T2, T3, T4, T5 lengths were measured for each toe. The vernier digital spreading calliper was placed horizontally on the landmarks and all the measurements were taken in centimetre (Fig.2).

For statistical analysis, SPSS version 16 was used. The relationship between the right and left footprint measurements were determined by paired t- test (Table 1) and the relationship between the right and left footprint measurements were determined by paired t- test (Table 2). Comparison between footprint and foot outline were determined by student's t-test (Table 3). The study was approved by Ethical Committee of Dhaka Medical College.

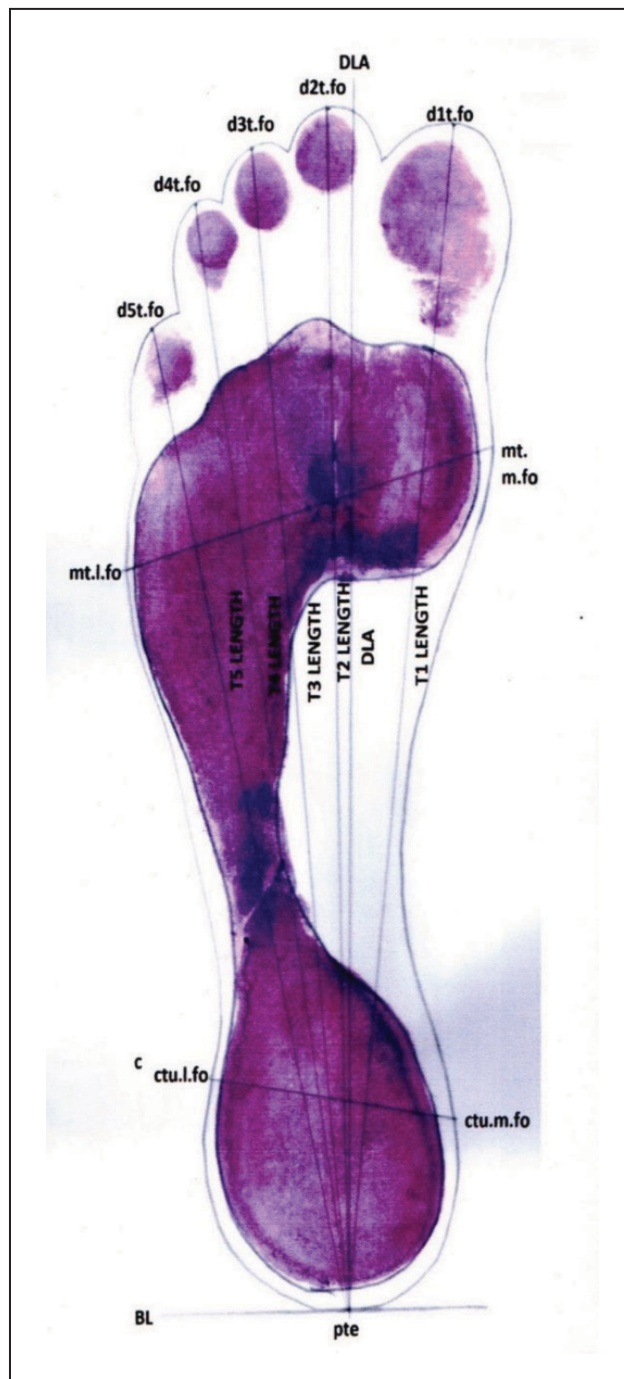


Figure-2: Foot outline landmarks and measurements. mt.m.fo- anterior epiphyses of 1st metatarsal, mt.l.fo- anterior epiphyses of 5th metatarsal, cc.m.fo- medial side of heel, ctu.l.fo- lateral side of heel, d1.p.m.fp to d1.pl.fp- great toe pad breadth, d1t.fp to d1.p.s.fp- great toe to pad length, DLA- designated longitudinal axis, BL- base line, pterion- mid-rear heel point, fo – foot outline. T1, T2, T3, T4 and T5 – Distance from pterion to most distal part of 1st, 2nd, 3rd, 4th and 5th toes, respectively.

Results

The present study was carried out on 200 male medical students (18 to 25 years of age) of different medical colleges of Dhaka city. Results and observations of this study are described below with suitable tables and graphs.

Table-1: Foot length measured in all toes in footprints both feet of the participants (n=400)

Footprint variables	Right foot (n ₁ =200)	Left foot (n ₂ =200)	p-value
T1 ¹	23.90±1.21 (20.72-27.08)	24.00±1.28 (20.72-27.58)	0.004 ^a
T2 ¹	23.68±1.29 (20.22-27.08)	23.82±1.31 (20.57-27.94)	<0.001 ^a
T3 ¹	22.83±1.26 (19.43-26.43)	22.98±1.25 (19.89-27.09)	<0.001 ^a
T4 ¹	21.69±1.23 (18.28-25.28)	21.81±1.24 (18.59-25.80)	<0.001 ^a
T5 ¹	20.09±1.12 (16.93-23.47)	20.21±1.14 (17.31-23.91)	<0.001 ^a

1-Mean±SD (Range), a-Paired t-test

Table-I shows the T1, T2, T3, T4 and T5 length of right and left footprints of the participants. All the measurements were significantly higher in left foot than the right (p-value <0.001 in T1 and <0.001 in T2, T3, T4 and T5).

Table-II: Foot length measured in all toes of in foot outlines both feet of the participants (n=400)

Foot outline variables	Right foot (n ₁ =200)	Left foot (n ₂ =200)	p-value
T1 ¹	25.00±1.24 (21.40-28.28)	25.05±1.29 (21.73-28.71)	0.011 ^a
T2 ¹	24.46±1.31 (21.14-28.14)	24.61±1.31 (21.45-28.64)	<0.001 ^a
T3 ¹	23.55±1.32 (20.48-27.83)	23.72±1.27 (20.64-27.86)	<0.001 ^a
T4 ¹	22.30±1.24 (19.08-25.78)	22.48±1.25 (19.35-26.46)	<0.001 ^a
T5 ¹	20.70±1.16 (17.45-24.14)	20.87±1.20 (17.72-24.87)	<0.001 ^a

1-Mean±SD (Range), a-Paired t-test

Table-II illustrates the T1, T2, T3, T4 and T5 length of right and left foot outlines of the participants. Left foot measurements were significantly greater in T2, T3, T4 and T5 (p-value <0.001). However, the T1-measurements were comparable between the two feet (p-value 0.11).

Table-III: Comparison between footprint and foot outline of right foot of the participants (n=200)

Foot length variables	Footprint measurement (n ₁ =200)	Foot outline measurement (n ₂ =200)	p-value
T1 ¹	23.90±1.21 (20.72-27.08)	25.00±1.24 (21.40-28.28)	<0.001 ^a
T2 ¹	23.68±1.29 (20.22-27.08)	24.46±1.31 (21.14-28.14)	<0.001 ^a
T3 ¹	22.83±1.26 (19.43-26.43)	23.55±1.32 (20.48-27.83)	<0.001 ^a
T4 ¹	21.69±1.23 (18.28-25.28)	22.30±1.24 (19.08-25.78)	<0.001 ^a
T5 ¹	20.09±1.12 (16.93-23.47)	20.70±1.16 (17.45-24.14)	<0.001 ^a

1-Mean±SD (Range), a-Paired t-test

Table-IV: Comparison between footprint and foot outline of left foot of the participants (n=200)

Foot length variables	Footprint measurement (n ₁ =200)	Foot outline measurement (n ₂ =200)	p-value
T1 ¹	24.00±1.28 (20.72-27.58)	25.05±1.29 (21.73-28.71)	<0.001 ^a
T2 ¹	23.82±1.31 (20.57-27.94)	24.61±1.31 (21.45-28.64)	<0.001 ^a
T3 ¹	22.98±1.25 (19.89-27.09)	23.72±1.27 (20.64-27.86)	<0.001 ^a
T4 ¹	21.81±1.24 (18.59-25.80)	22.48±1.25 (19.35-26.46)	<0.001 ^a
T5 ¹	20.21±1.14 (17.31-23.91)	20.87±1.20 (17.72-24.87)	<0.001 ^a

1-Mean±SD (Range), a-Paired t-test

The footprint and foot outline measurements of the right foot of all participants are compared in **Table-III** and **Table-IV**, respectively. Measurements were significantly greater in foot outline than in the footprints in both sides.

Discussion

The present work was undertaken to study foot length from footprint of 200 (two hundred) medical college students of Dhaka city and describes a statistically based analysis that illustrates the usefulness of the footprint as an indicator of correlation of stature of an individual. The footprints of the present study were collected from the Department of Anatomy of Dhaka Medical College, Dhaka and other non-government medical colleges in Dhaka city. The findings of this study were statistically analysed and revealed important information about variations in foot dimensions of Bangladeshi males.

In the present study, significant differences were observed between T1, T2, T3, T4 and T5 lengths of right and left footprints (p -value <0.001). Each of the T1, T2, T3, T4 and T5 lengths of the left foot were greater than the right foot. Kewal Krishan² reported greater T1, T2, T3, T4 and T5 lengths of the left foot than the respective lengths of the right foot. T1, T2, T3 and T4 length of the right foot except T5 length reported by Kewal Krishan² showed highly significant difference with the present study (p -value < 0.001). T5 length of the right foot was not significant with the present study (p -value >0.05). In the left foot T2, T3, T5 length were significantly higher than the present study (p -value <0.001) except T1, T4 length which again showed no significant difference with the present study (p -value >0.05).

Study by Robbins¹ showed each of the T1, T2, T3, T4 and T5 lengths of left foot was greater than the right foot. All T1, T2, T3, T4, T5 lengths of the both feet in her study were significantly lower than the findings of the present study (p -value <0.001). Dissimilarities might be due to the use of an age group with a wide range of population which included children, adolescents, adults and elderly and admixture of different races. In the present study, correlation of stature with all the dimensions of foot length were highly significant (p -value <0.001).

In the present study, significant differences were observed between T2, T3, T4 and T5 lengths of right and left foot outline (p -value <0.001). Difference between T1 length of right and left foot outline were not significant (p -value 0.110). Each of the T1, T2, T3, T4 and T5 lengths of the left foot outline were greater than the right foot outline. Kewal Krishan² reported greater T1, T2, T3, T4 and T5 lengths of the left foot than the respective lengths of the right foot. T1, T2, T3 and T4 length of the right foot except T5 length reported by Kewal Krishan² showed highly significant difference with the present study (p -value < 0.001). T5 length of the right foot was not significant with the present study (p -value >0.05). In the left foot T2, T3, T5 length were significantly higher than the present study (p -value <0.001) except T1, T4 length which again showed no significant difference with the present study (p -value >0.05).

The reason of dissimilarities might be due to racial variation as he used sample from tribal population who are mostly

engaged in the agricultural work all the time, putting more strain on their feet while working in the fields and therefore it is most natural that the foot is more used for walking or weight bearing becomes physically better developed. Another reason of dissimilarity is also supported by Rao and Kotian, cited by Kewal Krishan² as they suggested that the difference between left and right footprints in the same individual is not a coincidence but may be explained on the basis of the “dominant foot”. Most of the individuals have dominant foot, usually the left one, which always support the body to a greater extent while in standing or in walking. The shoe of this foot wears off at a faster rate than the shoe on the other foot³. The bones in the dominant foot are regularly subjected to stronger stress forces like weight bearing pressures, than the bones of the other foot. This in turn enlarges the bones of the dominant foot and therefore produces a footprint of larger dimension⁴.

Study by Robbins¹ showed each of the T1, T2, T3, T4 and T5 lengths of left foot was greater than the right foot. All T1, T2, T3, T4, T5 lengths of the both feet in her study were significantly lower than the findings of the present study (p -value <0.001). Dissimilarities might be due to the use of an age group with a wide range of population which included children, adolescents, adults and elderly and admixture of different races. In the present study, correlation of stature with all the dimensions of foot length were highly significant (p -value <0.001).

In the present study, there was a significant difference between footprint and foot outline among Bangladeshi males (p -value <0.001).

Conclusion

In the present study, distance from pternion to distal points of each toes of left footprint and left foot outline were significantly higher than the right footprint and right foot outline among Bangladeshi males. There was a significant difference between footprint and foot outline among Bangladeshi males.

Limitations

Endocrine diseases were excluded on clinical grounds only, skipping the laboratory confirmation. Inclusion of individuals of >25 years could have revealed a different result.

Only 200 adult males were included in this study. So the students of the present study do not represent all the adult male population of Bangladesh.

There was no published work on correlation of stature from the dimensions of footprint and foot outline on adult males in Bangladesh. So the result of the study could not be compared with adult Bangladeshi males.

Few numbers of publications by other researchers with similar study were available to compare with the findings of the present study.

Radiographic and computed scanner measurements of different dimensions of footprint and comparison between the radiographic and scanned findings with the manually collected findings of dimensions of footprint were not done.

Recommendations

Further studies with larger sample size are recommended to get more precise picture to produce a more comprehensible data that will help to determine the correlation of stature with dimensions of footprint and foot outline of adult males in Bangladesh.

Studies with different category of people like sportsman, industrial worker, day laborer are also recommended.

Thorough laboratory investigations are recommended to exclude acromegaly, dwarfism, gigantism and other endocrine diseases.

Radiographic and computed scanner measurements of different dimensions of footprint are recommended. Also comparison between the radiographic and scanned findings with the manually collected findings of dimensions of footprint is recommended.

Similar study on the female population and to compare between the male and female are recommended.

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Neuropsychiatric Systemic Lupus Erythematosus: From Clinical Spectrum to Diagnostic Complexity and Treatment

Rahman S¹, Wazib A², Bahar T³

Abstract

Systemic lupus erythematosus (SLE) involving multiple systems is a chronic autoinflammatory disease that can cause neuropsychiatric (NP) manifestations. The global prevalence is 11-81% varied due to different classification systems. The proposed pathogenesis is complex and combines the action of autoantibodies, complement immune complex and cytokines. Inflammation, microangiopathy and thrombosis result in neuronal damage. In 1999, the American College of Rheumatology set nomenclature criteria for 19 NPSLE syndromes. No single biomarker can diagnose NPSLE. Excluding secondary causes of NP events needs careful assessment. Anti-phospholipid antibodies should be checked in stroke cases. Till now, MRI is the most reliable neuroimaging to detect areas of defects; it might be normal in about 50% cases. The management, such as using immunosuppressants, anticoagulants, and adjunct therapy, depends on SLE disease activity and severity and the manifestation of specific NPSLE syndrome. Ongoing research on new biomarkers and more targeted, less toxic novel drugs is on the verge.

Keywords: acute confusion, cognitive dysfunction, demyelinating syndrome, neuropsychiatric, optic neuritis, psychosis, seizure, stroke, NPSLE.

Introduction

Systemic lupus erythematosus is a multi-system, chronic, autoimmune disease affecting women more than men. Previously known as lupus cerebritis or CNS lupus, neurological involvement is currently renamed 'neuropsychiatric lupus' (NPSLE) acknowledging the involvement of peripheral and autonomic nervous systems, and the psychiatric features of the condition.¹ NPSLE affects 11-81% SLE patients.^{2,3} CNS and PNS involvement occur in 93.1% and 6.1% NPSLE, respectively.⁴ NPSLE is found in 4-19% SLE patients within 2 years of diagnosis, and in 6-40% during the course of illness.⁵ The presentation may vary from mild cognitive dysfunction to severe neuropsychiatric manifestations like acute confusion, optic neuritis, myelitis, psychosis, seizure and stroke.¹ SLE-associated NP events have been associated with active SLE, concurrent non-SLE NP events excluding headache, male gender and glucocorticoid use. Asian race exhibits higher rate of resolution.⁶ NPSLE affects the health-related quality of life (HRQoL) with a higher mortality.⁷ The diagnosis is challenging due to lack of confirmatory serological markers or neuroimaging. Management of NPSLE is largely based on immunosuppressants (IS) and cognitive therapy. This

comprehensive review has covered pathogenesis, clinical presentation, diagnostic challenges and updated management.

Pathogenesis

The exact pathogenesis of NPSLE is not fully understood. Genetics, environmental factors and infection may trigger the immune cascades and production of autoantibodies. Inflammation and thrombotic events are responsible for diffuse CNS and focal CNS events, respectively. In diffuse CNS involvement, inflammation is caused by autoantibodies, complement immune complexes, and inflammatory cytokines, which disrupt the blood-brain barrier. Anti-NMDAR, anti-DNA-NR-2, anti-Smith, anti-Ro, anti-ribosomal-P, and aPL, anti-AQP4 are the responsible autoantibodies, and cytokines include IL-2, 6, 8, 10, IFN, TNF, and MMP-9.^{6,8}

Ischaemia due to microangiopathy and thrombosis is responsible for focal CNS NPSLE. Autoantibodies (anti-Smith, aPL), complement immune complex and inflammatory cytokines (IL-2, 6, 8, 10, IFN-alpha, TNF, MMP-9) are associated with these events.^{6,8}

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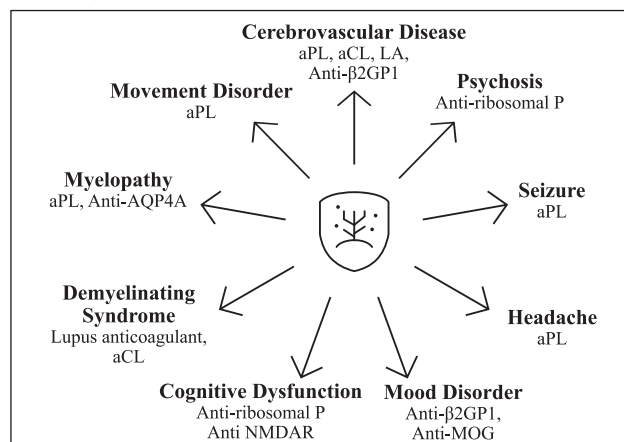


Figure-1: Biomarkers in NPSLE manifestations (aPL=anti-phospholipid ab, LA=lupus anticoagulant, aCL=anti-

cardiolipin ab, anti-β2GPI= anti beta 2 glycoprotein 1, anti-NMDAR= N-methyl-D-aspartate receptors, MOG=myelin oligodendrocyte glycoprotein, anti-AQP4A= aquaporin 4 antibody)

Figure-1 shows various biomarkers associated with NPSLE as reported by many studies.⁹⁻¹⁶ A systematic review done by Lindblom, which further assessed the utility of some potential diagnostic biomarkers are shown in **Table-I**¹⁶.

Table-I: Diagnostic biomarkers of NPSLE

Biomarkers	Type of NPSLE	Comparators	Reports
IL-6 (>74 pg/ml) ¹⁷	Diffuse	Non-NPSLE	AUROC 0.89 SEN 75%, SPE 100%
Anti-ribosomal P ¹⁸	Diffuse Unspecified	Non-NPSLE	OR 1.6-3.1
aPL	Unspecified ¹⁹	Non-NPSLE	OR 3.1
	Focal (CVD) ²⁰	Non-seizure	HR 2.2
Anti-β2GPI ^{21,22}	Focal Unsspecified	Non-seizure Non-NPSLE Non-headache	OR 2.5-11.3
Anti-Sm ^{19,23}	Focal Unspecified	Non-seizure Non-NPSLE	OR 1-3.3

CVD- Cerebrovascular disease
AUROC Area under ROC curve, SEN- sensitivity, SPE- specificity,
OR- odds ratio, , HR- hazard ratio

There are many studies reporting the association of various antibodies with different manifestations of NPSLE. However, only aPL antibodies and anti-ribosomal P are reported to have clinical utility.^{24,25}

Clinical presentation

77.2% NPSLE are attributable to SLE (primary NPSLE). The remaining 22.8% are labelled secondary NPSLE caused infections (CNS, systemic), metabolic (diabetes mellitus, dyslipidaemia, hypertension, thyroid disorders, tumour), psychiatric, and drugs (steroids, statins, CNS depressants).²⁶

Frequency of presenting symptoms of NPSLE showed wide variation across different studies. A study on Thai patients revealed seizure as the most common NP event (54.1%). Psychosis (13.3%), acute confusional state (11.2%), abnormal consciousness (6.1%), transverse myelitis

(6.1%), peripheral neuropathy (5.1%), cerebral infarct (2%) and aseptic meningitis (2%) comprised the rest. NPSLE cases had more severe mucocutaneous manifestations and less arthritis than rest.²⁶ Headache (61.81%) was the most common presenting symptoms of NPSLE in a Perivian study, that also reported major depressive disorder (30.9%), polyneuropathy (18.18%), seizures (14.54%) and cerebrovascular disorders (9.09%).²⁷ Seizure and psychosis tend to occur at an early onset of lupus (<50 years), and PNS lupus presents more at a late onset (>50 years).²⁸ The 2019 EULAR/ACR diagnostic criteria for SLE include delirium, seizure and psychosis in addition to positive ANA.²⁹

Table-II: ACR nomenclature criteria of 19 NPSLE syndromes¹

Diffuse CNS syndromes	Focal CNS syndromes	PNS syndromes
Acute confusional state/delirium	Seizure disorders	Polyneuropathy
Acute psychosis	Cerebrovascular disease	Plexopathy
Demyelinating syndrome	Myelopathy	Mononeuropathy
Aseptic meningitis	Movement disorder	Cranial neuropathy
Cognitive dysfunction		Autonomic neuropathy
Mood disorder		Myasthenia Gravis
Anxiety		Guillain -Barre syndrome
Headache		

The ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature included 19 syndromes (12 CNS and 7 PNS) to define NPSLE.¹ **(Table-II)** A revised set of 16 criteria, excluding headache, anxiety, mild depression, mild cognitive dysfunction and polyneuropathy (unconfirmed by electroneuromyography), increased the specificity of ACR NPSLE nomenclature criteria from 46% to 93%.³⁰

A single tonic-clonic seizure is common at presentation of NPSLE, and recurrence may occur within the first year of diagnosis.³¹ Cerebrovascular disease is mostly associated with aPL. So, the history in favour of associated aPL (recurrent pregnancy loss, previous thrombosis, etc.) is important.^{24,32} Demyelinating syndrome (optic neuritis and transverse myelitis) is relatively uncommon in NPSLE (0.3-2.7%) and requires exclusion of³³ Multiple sclerosis, neuromyelitis optica spectrum disorder (NMOSD).^{21,33-35} Headaches are common in SLE, most commonly migraine and tension-type headache, with in prevalence to the general population.⁴ Optic and facial neuropathy are the most common cranial neuropathies reported in NPSLE, followed by trigeminal, ocular motor and olfactory nerves in descending order.³⁶ Cerebrovascular disease, acute optic neuritis, acute confusional state, active mononeuritis multiplex, psychosis, acute myelitis, and seizure are considered as severe NPSLE.³²

Table-III: ACR recommendations for investigations for specific manifestations in NPSLE

CNS manifestations	
Diffuse CNS NPSLE	Diagnostic tests (serology and neuroimaging)
Acute confusional state/delirium	MRI and EEG (if unexplained) LP to exclude infection Investigations to exclude metabolic causes Psychiatric evaluation
Psychosis	Psychiatric evaluation
Demyelinating syndrome	LP and MRI Exclude MS Anti-AQP4A in NMOSD
Aseptic meningitis	LP and MRI Exclude infection
Mood disorders	Psychiatric evaluation
Anxiety	Psychiatric evaluation
Cognitive dysfunction	Neuropsychiatric testing
Focal CNS manifestations	
Seizure disorder	EEG (if recurrent) MRI and LP Exclude structural lesions, infection and inflammation
Cerebrovascular disease	aPL CT/MRI MRA and LP (suspected vasculitis) ECG, Echo, carotid doppler
Myelopathy	Gadolinium -enhanced MRI LP CSF analysis to exclude infection
PNS manifestations	
Polyneuropathy	NCS and EMG
Mononeuropathy	NCS and EMG
Myasthenia Gravis	CT chest to exclude thymoma, Antibody testing (AchR, Anti-Musk, LRP4
Guillain-Barre syndrome	NCS and EMG LP
AchR: acetylcholine receptor antibody, MuSK: muscle - specific kinase antibody, LRP4: low-density lipoprotein receptor-related protein 4 antibody	

Diagnosis

Diagnosing NPSLE is challenging. There are no universally accepted methods, a single biomarker, or neuroimaging that can confirm the diagnosis of NPSLE. High clinical suspicion and assessment are the cornerstone for diagnosis.³⁴ It is mostly a diagnosis of exclusion, especially in patients with known SLE. Having a strong clinical suspicion and excluding diseases with similar presentation have to be taken into account when making the diagnosis.

Immunosuppression is a common complication of SLE and its treatment, and poses a higher risk of infections. It's often imperative to rule out CNS infections with C-reactive protein, blood culture and CSF study.^{24,36}

Anti-phospholipid antibodies (aPL) should be checked if focal features (stroke, seizure).^{24,32} Stroke related to vasculitis, cardioembolic and endocarditis also needs evaluation.³³ Serological tests, especially anti-Ribosomal-P antibody is positive in cognitive dysfunction and psychosis.²¹

MRI is the most helpful neuroimaging, able to detect 75% NPSLE lesions and is indicated for both focal (thrombosis, vasculitic, along with aPL) and diffuse manifestations (unexplained acute confusion, seizure, cognitive impairment in <60 years and severe other NP symptoms).³⁷ However, 50% cases of diffuse CNS lupus may have a normal MRI. 20-50% of SLE patients without NP symptoms were found to have subcortical white matter hyperintensities.^{38,39} However, MRI is done to exclude the differential diagnoses (**Table-III**)

MRA, PET and SPECT are useful in suspected CNS vasculitis.⁴⁰ PET is highly sensitive for NPSLE detecting areas of hypometabolism, undetectable in MRI.⁴¹

Neuro-electrophysiological test are often required in NPSLE – Electroencephalogram (EEG) for recurrent seizures and unexplained acute confusional state, and nerve conduction study (NCS) and electromyogram (EMG) in PNS involvement.²⁴ CSF study is non-specific in NPSLE showing elevated high protein, WBC, IgG and IgG and low glucose, is important to rule out infections.³⁴

Psychiatric manifestations need formal assessment. Montreal Cognitive Assessment Questionnaire (MoCA), Centre for Epidemiological Studies - Depression Scale (CES-D), Hospital Anxiety and Depression Scale (HADS) and recommended for cognitive impairment, depression and anxiety, respectively.^{42,43}

Assessment of activity and severity of generalised SLE is also recommended while diagnosing NPSLE.³² An algorithm for attribution of neuropsychiatric events in SLE was developed by the Italian Society of Rheumatology in 2014, scoring comprising 4 items (total score = 0 -10) with a cut-off of ≥ 7 (sensitivity 87.9% and specificity 82.6%).⁴⁴ (**Table-IV**)

Table-IV: Categorisation and weighing of items of the algorithm of attribution NPSLE developed by the Italian Society of Rheumatology

Categories	Score
Item 1. Time of the onset of the NP event with respect to SLE clinical onset	
Before (>6 months before SLE onset)	0
Concomitant (within 6 months of SLE onset)	3
After (>6 months after SLE onset)	2
Item 2. Minor or not specific NP events^a	
Present	0
Absent	3
Item 3. Confounding factors^b or not SLE-related associations as defined by the ACR glossary	
None or not applicable	2
Present (one confounding factor)	1
Present (more than one confounding factor)	0
Item 4. Concomitant Additional (or favouring)^c factors	
None or not applicable	0
Present (one additional or favouring factor)	1
Present (more than one additional or favouring factor)	2

a- Headache, mild depression, anxiety, mild cognitive impairment, polyneuropathy without electrophysiological confirmation; b- Diabetes mellitus, dyslipidaemia, hypertension, smoking, atherosclerotic vascular disease, atrial fibrillation, valvular heart disease, atrial septal defect, hypercoagulable state, antiphospholipid syndrome; c- Cerebrovascular disease (<50 years), myelitis (response to immunosuppressives and glucocorticoids, high SLE disease activity).

Management

The management of NPSLE is multidisciplinary, involving rheumatologists, neurologists, psychiatrists, and psychologists. Exclusion of non-SLE neuropsychiatric events is crucial. The treatment of NPSLE depends on the type and severity of presentation and the severity of SLE. There are well-recognised guidelines on the management of NPSLE by the American College of Rheumatology, European Alliance for Associations of Rheumatology (EULAR) and Asian Pacific League for Associations of Rheumatology (APLAR).^{32,45}

All SLE cases are treated with hydroxychloroquine (HCQ ≤ 5 mg/kg/day) unless absolutely contraindicated.³² Discontinuation results in SLE flare.⁴⁵ HCQ may have role in easing the neural damage caused by anti-ribosomal P antibody.⁴⁶ Presence of active disease (inflammation or aPL immune-mediated) or chronic damage needs to be assessed.³²

Stroke patients should be treated by neurologists, and immunosuppressants (IS) are added only if there is active inflammation.³² aPL-ab syndrome needs treatment with a target INR of 3-4 for arterial thrombosis and 2-3 for venous thrombosis.⁴⁵

The recommended initial therapy for optic neuritis, transverse myelitis, acute confusional state, mononeuritis multiplex and psychosis in NPSLE are intravenous (IV) high dose pulse glucocorticoids (GCs) (methylprednisolone 250mg-1 gm/day for 1-3 consecutive days), and IV cyclophosphamide (CYP, 750-1000 mg/m² body surface area), GCs are tapered over time. Anti-psychotic medications are used in addition to immunosuppressives. Mycophenolate mofetil (MMF) may be chosen if CYP is contraindicated. Rituximab, plasma exchange and intravenous immunoglobulin (IVIG) are suggested for refractory disease.^{32,45}

Seizures attributed to active SLE needs antiepileptic drugs, which can be tapered after 3 months of control of SLE activity, provided cortical scars in brain are led out in MRI.²⁶ Isolated cognitive dysfunction attributable to SLE should be treated with cognitive therapy alone. No treatment is yet recommended for small fibre neuropathy.³² Aspirin is recommended for primary stroke prophylaxis in SLE with a high-risk aPL profile (triple positive, double-positive, or positive lupus anticoagulant or anticardiolipin antibody at medium to high titers).²⁵

Prognosis

Renal insufficiency and high disease activity (inflammatory lesions) are the predictors of poor prognosis.³⁸

Future research

No single biomarker to confirm the diagnosis of NPSLE has been established yet. Treatment of small fibre neuropathies

and cognitive dysfunction manifestations is a potential area of future research.^{32,47} There is ongoing research targeting mechanisms involved in neuroinflammation. BTK inhibitors (Evobrutinib, Orelabrutinib) act on B-cell survival and activation; improved cognitive function and depression-like behaviour in mice models.⁴⁸ Centrally acting angiotensin converting enzyme inhibitor (ACEi) captopril is showing promise in an ongoing clinical trial. It inhibits the conversion of angiotensin I to II, which is responsible for microglial activation.⁴⁹ Decoy antigens (blocking interaction between autoantibody and its target), dietary AhR agonist (micro-biota-gut-brain axis) and angiotensin receptor blocker are under study in mice models. Using Belimumab (possible reduction in incidence of headache) and CAR-T, which are the newer drugs used in treating lupus nephritis, is an area of further exploration.⁵⁰

Conclusion

NPSLE syndromes need careful assessment by physicians and a proper management plan for improving HRQoL and reducing mortality.

Conflict of interest

None

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N/A

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Generative AI was not used for writing the article.

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Post Tubercular Fibrosis with Mycetoma presenting with Recurrent Haemoptysis: A case report

Nuzaira Nahid¹

Abstract

We report a case of 65-year-old man who presented with recurrent episodes of haemoptysis for 3 months, which required repeated hospitalizations. He had a history of Pulmonary Tuberculosis about 35 years back, for which he completed 2 years of anti-tubercular medications. Investigations revealed extensive bronchiectasis, and presence of mycetoma in the left lung. Finally, a diagnosis of Post tubercular fibrosis with extensive bronchiectasis with mycetoma was reached. We treated the patient successfully with a prolonged course of Itraconazole, along with symptomatic management for his cough and breathlessness. The patient improved clinically and remained symptom free after 12 months of his treatment completion. This case outlines the various complications of tuberculosis that can occur, long after the primary infection, along with the occurrence of a completely new infection, and emphasizes the importance of a thorough diagnostic workup to rule out all possibilities, in similar cases.

Introduction

Hemoptysis is a common symptom of both pulmonary mycetoma and reactivated pulmonary tuberculosis (TB) infection. A fungal ball, also known as a mycetoma, can be caused by many different fungi, most commonly the *Aspergillus* species.¹ Mycetoma arises most often in immunocompetent individuals with pre-existing structural lung diseases. Worldwide prevalence is highest among those with residual lung cavities due to TB; approximately 10% of pre-existing tuberculous lung cavities will develop aspergilloma. In addition to TB, those with non-tuberculous mycobacteria, chronic obstructive pulmonary disease, and lung cancer represent high prevalence groups.²

In this case report, we present the clinical course of a 65-year-old man who presented with recurrent episodes of haemoptysis, on the background of a previous history of pulmonary Tuberculosis, leading to the discovery of a superimposed mycetoma infection in his left lung. We aim to highlight the diagnostic challenges encountered in the detection of mycetoma infection, and the importance of a thorough systemic approach in the evaluation of similar cases.

Patient Background

A 65-year-old farmer, normotensive and nondiabetic, presented with cough, shortness of breath, chest pain and recurrent episodes of hemoptysis for the last 3 months. The cough was initially dry, and then became productive, with white, odorless sputum. He also complained of right sided

chest pain, which was sharp, moderately severe, localized, appeared during the episodes of coughing, and worsened with deep breathing.

The patient noticed small amounts of blood mixed with his sputum as well. The blood was fresh at times, and at times it was clotted. He coughed up blood about 8 to 9 times in the last 3 months, and the amount of blood coughed up increased progressively (to about half a cup) during this period.

He further stated that over the last 3 months, he has been getting progressively breathless. Initially it only occurred while working in the fields, but later, he got too breathless to even carry out his daily activities, or even walk from one room to another.

On the day of admission, the patient got very breathless, and started coughing violently. Large amounts of blood (about one cup), both clotted and fresh came out with his sputum. Following this episode, he was urgently admitted to BMCH.

On questioning him further, we found out that he was diagnosed with pulmonary tuberculosis about 35 years back, following which he received 2 years of anti-Tubercular medications.

Clinical Examination

On examination, the patient was emaciated, with evidence of fat and muscle wasting. He was also severely anaemic, and mildly dehydrated, but no evidence of jaundice, cyanosis, clubbing or edema was found. Firm, non-tender, mobile lymph nodes, less than 1 cm in diameter were palpable along the anterior cervical chain, on both right and left sides. The patient was breathless at rest, with respiratory rate of 25 breaths/min, with presence of intercostal indrawing, subcostal recession and use of accessory muscles during respiration. His trachea was shifted to the right, with reduced chest movement and expansion, dull percussion note and diminished breath sounds on the right side. Coarse crepitations, altered with coughing, could be heard bilaterally.

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Laboratory evaluation

Laboratory investigations revealed Neutrophilic leukocytosis, with Haemoglobin level of 11.30 g/dl. Detailed investigations are summarized in **Table-I**.

Table-I: Laboratory investigations

Date	Lab test	Findings
17.05.2023	CBC	WBC - 12,000 Neutrophils - 85% Lymphocytes - 10% Monocytes - 3% Eosinophils - 2% Haemoglobin -11.30 g/dl Platelets - 2,00,000/L ESR - 20 mm in 1 st hour
17.05.2023	ALT	26.8 U/L
17.05.2023	S. Electrolytes	Na- 140 mmol/L K- 3.10 mmol/L Cl- 104 mmol/L HCO3- 26 mmol/L
17.05.2023	Creatinine	0.84 mg/dl

Chest imaging, including an X-ray, showed in homogenous and linear opacities in all zones of both lungs, indicating bilateral chronic inflammatory lesion, along with right sided collapse, pleural effusion, thickening and calcification (**Figure 1**).



Figure-1: Chest x-ray showing bilateral chronic inflammatory lesion, along with right sided collapse, pleural effusion, thickening and calcification.

Testing the sputum for Gram Stain, Culture and Genexpert yielded normal flora and no *Mycobacterium* was found. The patient was therefore evaluated further. An HRCT of the Chest was done, with findings suggestive of segmental atelectasis with extensive bronchiectasis in both upper lobes and suspected mycetoma on the left side. There was also compensatory pulmonary emphysema in rest of both lungs, which was possibly a sequel of pulmonary tuberculosis (**Figure-2**).

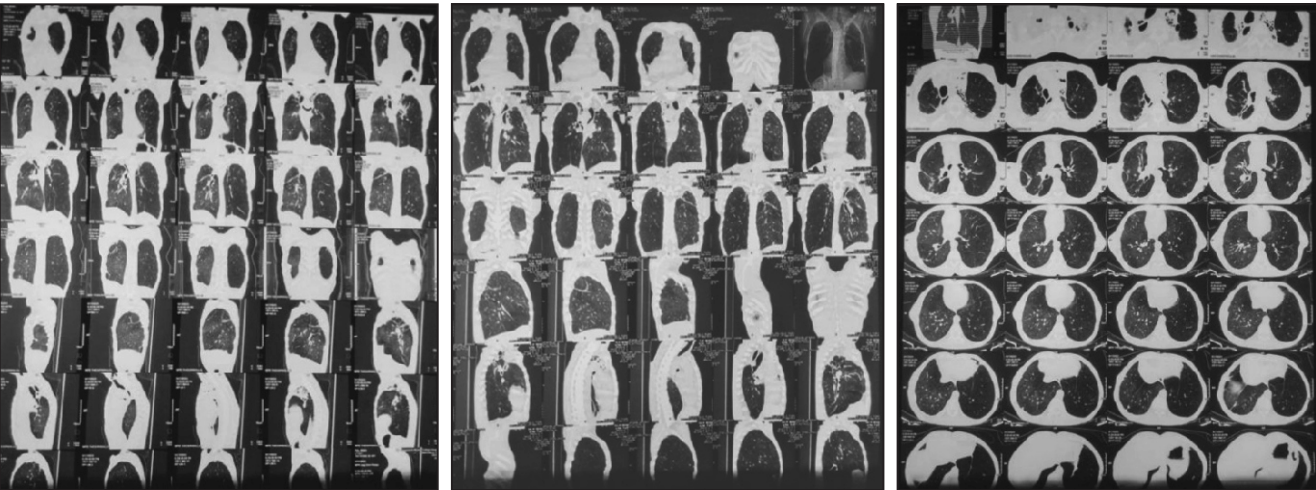


Figure-2: Contrast-enhanced CT scan of the chest showing segmental atelectasis with extensive bronchiectasis in both upper lobes, suspected mycetoma on the left side, and compensatory pulmonary emphysema in rest of both lungs.

A presumptive diagnosis of Post Tubercular Fibrosis with Bilateral bronchiectasis with left sided mycetoma was reached based on the history, clinical findings and Laboratory and imaging tests. Due to financial constraints, the patient refused to undergo any further investigations. Thus no tissue diagnosis could be achieved. Instead antifungal Itraconazole was started empirically. This caused the patient's condition to improve dramatically. His breathlessness, and haemoptysis stopped, and his coughing also decreased in severity. He was discharged in good health and advised for regular follow-up.

Discussion

Aspergilloma, also known as mycetoma or fungus ball, is the most common manifestation of pulmonary involvement by *Aspergillus* species.³ It is characterized by the formation of a mass of viable and dead fungal material, inflammatory cells, fibrin, mucus, blood, and tissue debris within preexisting cavities of the lung.³

Aspergilloma arises most often in immunocompetent individuals with pre-existing structural lung disease. Worldwide prevalence is highest among those with residual lung cavities due to TB; approximately 10% of pre-existing tuberculous lung cavities will develop aspergilloma. In addition to TB, those with non-tuberculous mycobacteria, chronic obstructive pulmonary disease, and lung cancer represent high prevalence groups.²

The clinical presentation of *Aspergillus* lung disease is determined by the interaction between the fungus and host. There are three main categories of pulmonary aspergillosis: allergic bronchopulmonary aspergillosis (ABPA), chronic pulmonary aspergillosis (CPA), and invasive pulmonary aspergillosis (IPA).⁴

The manifestations of pulmonary mycetoma are diverse, ranging from asymptomatic cases to massive and sometimes fatal haemoptysis.⁵ Most patients with aspergilloma are known to be asymptomatic, and are diagnosed incidentally during medical check-up. Even if there are symptoms, they usually are nonspecific, i.e., cough, dyspnea, and general weakness, and could be explained by the underlying lung diseases rather than the aspergilloma. However, it can also manifest itself as massive, fatal haemoptysis.⁵

Studies show that mycetoma complicates 4.9–6.3% of all treated pulmonary TB cases and 26% of cases with chest radiography cavitation. This has profound implications for

TB management programmes, and suggests that testing for CPA with *Aspergillus*-specific IgG should be routine in all patients with recurrent cough, haemoptysis or weight loss following treatment of pulmonary TB, regardless of time from completion of TB therapy. Those with raised levels should have imaging, preferably with CT of the thorax, to confirm the diagnosis. As mycetoma mimics the presentation of pulmonary TB, testing should also form part of routine investigations in any patient where empirical treatment for 'smear-negative TB' is being considered.⁶

Our case study supports this finding, with the discovery of mycetoma in the left lung of our patient. Moreover, upon initiation of anti-fungal medications, his clinical condition improved, which further confirmed the diagnosis.

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