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Case report

Dengue encephalopathy concurrent with secondary pulmonary tuberculosis in an elderly male with multiple comorbidities

Muhammad Abdullah [a], Mustafa Awais Choudry [a], Sheharyar Amin Sheikh [a], Faryal Shoaib [b], Manahil Jamil [c,*]

[a] Shifa College of Medicine, H-8/4, Islamabad, Pakistan
[b] Department of Internal Medicine, Shifa International Hospital, Islamabad, Pakistan
[c] Department of Physiology, Shifa College of Medicine, H-8/4, Islamabad, Pakistan

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ABSTRACT

Dengue fever (DF) and tuberculosis (TB) present significant global health challenges, often with overlapping clinical features, especially when complicated by conditions like dengue encephalopathy. We present a case study involving an 84-year-old male with a complex medical history, encompassing pulmonary tuberculosis reactivation, who subsequently developed dengue encephalitis. This underscores the complexity of managing such cases in the geriatric population. Dengue encephalitis, once considered non-neurotropic, is increasingly recognized, necessitating consideration as a potential differential diagnosis in patients with neurological symptoms, particularly in endemic regions. Our patient exhibited typical DF symptoms alongside manifestations of encephalopathy. Concurrently, secondary TB reactivation was observed, emphasizing the intricate interplay between these diseases. Additionally, lower respiratory tract infection (LRTI) further complicated the clinical picture. Timely recognition and comprehensive management are crucial, as demonstrated in our case, where prompt reporting and conservative measures led to a favorable outcome.

Introduction

Dengue virus, can be caused by any one of its four serotypes (DEN 1, 2, 3 and 4), originates from the Flaviviridae family and is transmitted through mosquito bite [1]. Infections of Dengue have risen eight-fold in the last twenty years, with approximately 390 million cases being reported annually around the globe [2]. Additionally, a concerning Dengue infection prevalence of 31.2 % has been reported in Pakistan [3]. The classical presentation of these patients includes symptoms of high fever, vomiting, joint pain and headaches [4].

Textbooks have labeled Dengue virus as not being neurotropic. However, latest literature proves an increasing number of neurological manifestations such as encephalitis are being identified in Dengue patients. Therefore, we propose in this article, that Dengue Encephalitis should be considered as a potential diagnosis when symptoms like anoxia, cerebral edema, altered sensorium and seizures are observed [5].

Similarly, Tuberculosis (TB), caused by Mycobacterium Tuberculosis, is a bacterial infectious disease currently holding the highest mortality rate, with 1.3 million deaths worldwide in 2022 [6]. In Pakistan the same year, 608,000 cases of TB were reported [7]. Fever, weight loss, persistent cough and hemoptysis are among the most common TB symptoms and this clinical presentation is notably similar to that of Dengue. The case we encountered depicted Tuberculosis as a difficult comorbidity to manage when an elderly patient has been freshly infected by Dengue virus, emphasizing the lethal nature of this combination of illnesses.

Our case reports the diagnosis and treatment of an 84-year-old man as a patient of Dengue disease which further developed into encephalitis, while also having relapsed with Tuberculosis; an extremely rare phenomenon.

Case report

An 84-year-old male presented to the emergency department with a 10-day history of productive cough, generalized weakness, and difficulty in sputum expulsion. The cough was associated with thick, yellow-colored, non-foul-smelling expectoration. He reported fever with chills

* Corresponding author.
E-mail address: manahil.jamil97@gmail.com (M. Jamil).

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without rigor over the past 5 days, exhibiting an evening rise in pattern accompanied by night sweats, relieved after taking over-the-counter antipyretics (paracetamol). He also complained of headache, retro-orbital pain, vomiting, and loss of appetite over the past 5 days, followed by altered sensorium for 3 days. There was no history of seizures. The patient was a non-smoker with no history of substance abuse. He was vaccinated against COVID-19. Past medical history revealed multiple comorbidities, including prostate carcinoma diagnosed 2 years ago and Parkinson's disease diagnosed 2 years ago. Notably, the patient had a resolved pulmonary tuberculosis 40 years ago, for which he completed the entire treatment regimen.

On clinical examination, he had a body temperature of 38.2 °C, a pulse rate of 80/min, blood pressure of 110/70 mm Hg, and a respiratory rate of 17/min with oxygen saturation of 96 %. Pallor was noted, while edema and icterus were absent. Family members reported hematuria for the past 2 days without any active bleeding sites. The Glasgow Coma Scale score was $E_4M_5V_2$, with bilateral reactive pupils and a positive Babinski sign. Coarse crepitus was auscultated in the upper and lower lobes of the right lung. The rest of the systemic examination was unremarkable. The patient was subsequently transferred to the intensive care unit for further management.

Table 1
Lab investigations.

Investigations	Results		Reference range
	Admission	**Discharge**	
WBC total	3260	5940	4000-10500 /μL
RBC	4.18	2.90	4.5-6.5 million cells/μL
Hb	12.2	8.6	13.5-18.0 g/dL
HCT	35.0	24.6	42-52 %
MCV	83.7	84.8	78-100 fL
MCH	29.2	29.7	27-31 pg
MCHC	34.9	35.0	32-36 g/dL
PLT	67000	191000	150000-400000 cells/μL
Neutrophils	63	78	54-62 %
Lymphocytes	27	9	25-33 %
Monocytes	10	12	1-4 %
Eosinophils	0	1	1-3 %
Basophils	0	0	0-0.75 %
Urine specific gravity	1.015	1.014	1.005-1.025
Blood in urine	Positive	Negative	Positive-Negative
Urine RBC	Positive	Negative	Positive-Negative
Serum sodium	136	130	136-145 mEq/L
Serum potassium	4.3	4.8	3.5-5.1 mEq/L
Serum chloride	104	98	98-107 mEq/L
Serum ionized calcium	4.3	4.3	4.6-5.3 mg/dL
Random Glucose	140	140	< 200 mg/dL
Serum creatinine	3.7	1.15	0.72-1.25 mg/dL
Serum urea	235.4	55.64	16.6-48.5 mg/dL
BUN	110	26	8-23 mg/dL
AST	106	95	0-50 U/L
ALT	52	38	0-50 U/L
ALP	67	94	40-130 U/L
Serum total bilirubin	0.23	1.77	0-1.2 mg/dL
Serum direct bilirubin	0.16	1.35	0-0.30 mg/dL
GGT	26	27	0-60 U/L
PT	23.0	14.0	9.5-11.7 s
Blood pH	7.42	7.43	7.35-7.45
Blood pCO2	29	33	32-48 mm Hg
Blood pO2	59.9	80	83-108 mm Hg
Serum bicarbonate	18	25	22-29 mmol/L
O2 Saturation	92	94	94-98 %
CRP	140	88.7	0-5.0 mg/L
Procalcitonin	0.49	0.28	0-0.10 ng/ml
Albumin	3.2	3.3	3.9-5.0 g/dL
Ammonia	584	65	27-102 μg/dL

WBC: White Blood Cells; RBC: Red Blood Cells; Hb: Hemoglobin; HCT: Hematocrit; MCV: Mean Corpuscular Volume; MCHC: Mean Corpuscular Hemoglobin Concentration; PLT: Platelets; BUN: Blood Urea Nitrogen; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; ALP: Alkaline Phosphatase; GGT: Gamma-glutamyl transferase; PT: Prothrombin time; pCO2: Partial pressure of carbon dioxide; pO2: Partial pressure of carbon dioxide; O2: Oxygen; CRP: C-reactive protein

Comprehensive investigations were conducted (Table 1). A rapid antigen test for SARS-CoV-2 yielded a negative result. Dengue serology revealed the presence of positive IgM antibodies and a positive result for Dengue NS1; however, IgG levels were noted to be weakly positive. Moreover, additional investigations, including interferon-gamma immune assays aimed at assessing immune reactivity to tuberculosis (TB), revealed the presence of Mycobacterium tuberculosis (MTB) with a measured value of 0.56 IU/ml, surpassing the defined cutoff of > 0.35 IU/ml. Furthermore, MTB DNA detected by Polymerase chain reaction (PCR) in tracheal secretions suggested tuberculosis presence, albeit at a low level, with noted susceptibility to rifampicin. Despite a 5-day incubation period, blood culture and urine culture exhibited no growth. Serological testing for hepatitis B surface antigen (HBsAg) returned a non-reactive result, with a patient S/CO score of 0.333 (below the defined cutoff of 1.0). Similarly, hepatitis C virus antibodies were also non-reactive (below the defined cutoff of 1.0). Additionally, no detection of herpes simplex virus 1 and herpes simplex virus 2 specific DNA was observed via PCR in cerebrospinal fluid (CSF). Tracheal culture reports confirmed the presence of Klebsiella pneumoniae, methicillin-resistant Staphylococcus aureus, and Actinobacterium species, indicative of a lower respiratory tract infection.

Lab investigations were performed and have been mentioned in Table 1. Normocytic, normochromic anemia alongside leukocytosis and thrombocytopenia and prolonged prothrombin time was found on complete blood count. Liver function tests were notable only for elevated levels of aspartate aminotransferase. Blood C-reactive protein levels and procalcitonin levels were raised. Moreover, serum albumin levels were decreased. Marked creatinine elevation and hyperuricemia, suggested an acute kidney injury. Moreover, initial laboratory results also suggested hyperammonemia, potentially attributable to hepatic or renal etiology. Arterial blood gas analysis indicated a compensated respiratory alkalosis and decreased oxygen saturation. CSF routine analysis did not reveal any significant abnormalities.

A 20-channel electroencephalogram (EEG) revealed findings suggestive of moderate diffuse encephalopathy, characterized by a background rhythm of 5.6 Hz theta activity of moderate amplitude and bilaterally symmetrical features (Fig. 1). Notably, no epileptiform activity was observed.

Computed tomography (CT) imaging of the brain provided limited insights, showing generalized bilateral atrophy of the parietal lobe, likely associated with age-related changes and no signs of metastasis was seen (Fig. 2). CT scan of the chest (Fig. 3) depicted soft tissue fullness at the hilum of the right lung with calcified lymph nodes. Furthermore, severe narrowing and occlusion of the right middle lobe bronchus, accompanied by corresponding distal collapse consolidation, were observed. Additionally, small subsegmental consolidation in the superior segment of the right lung, along with multiple tree-in-bud nodules, were identified.

Upon hospitalization, the patient received a diagnosis of Dengue encephalopathy with reactivation of pulmonary tuberculosis (TB) and a superimposed lower respiratory tract infection (LRTI), alongside acute kidney injury. Management commenced with intravenous (IV) normal saline with 5 % Dextrose infused at a rate of 60 ml/hr, and tablet paracetamol (antipyretic) administered once daily. For Dengue encephalopathy, the patient was initiated on tablet memantine hydrochloride (N-methyl-D-aspartate receptor antagonist) and procyclidine (central cholinergic receptor antagonist), gradually tapering off thereafter, alongside vitamin B-complex supplementation. Platelet transfusion was performed with 4 packs during the hospital stay to address the decreased platelet count. TB management involved a fixed-dose combination of ethambutol, isoniazid, rifampicin, and pyrazinamide. For the LRTI, tablet minocycline-HCL was administered twice daily, supplemented by intravenous vancomycin and meropenum. Due to elevated creatinine, urea, and ammonia levels, the patient underwent hemodialysis and was given oral lactulose. After 7 days, significant

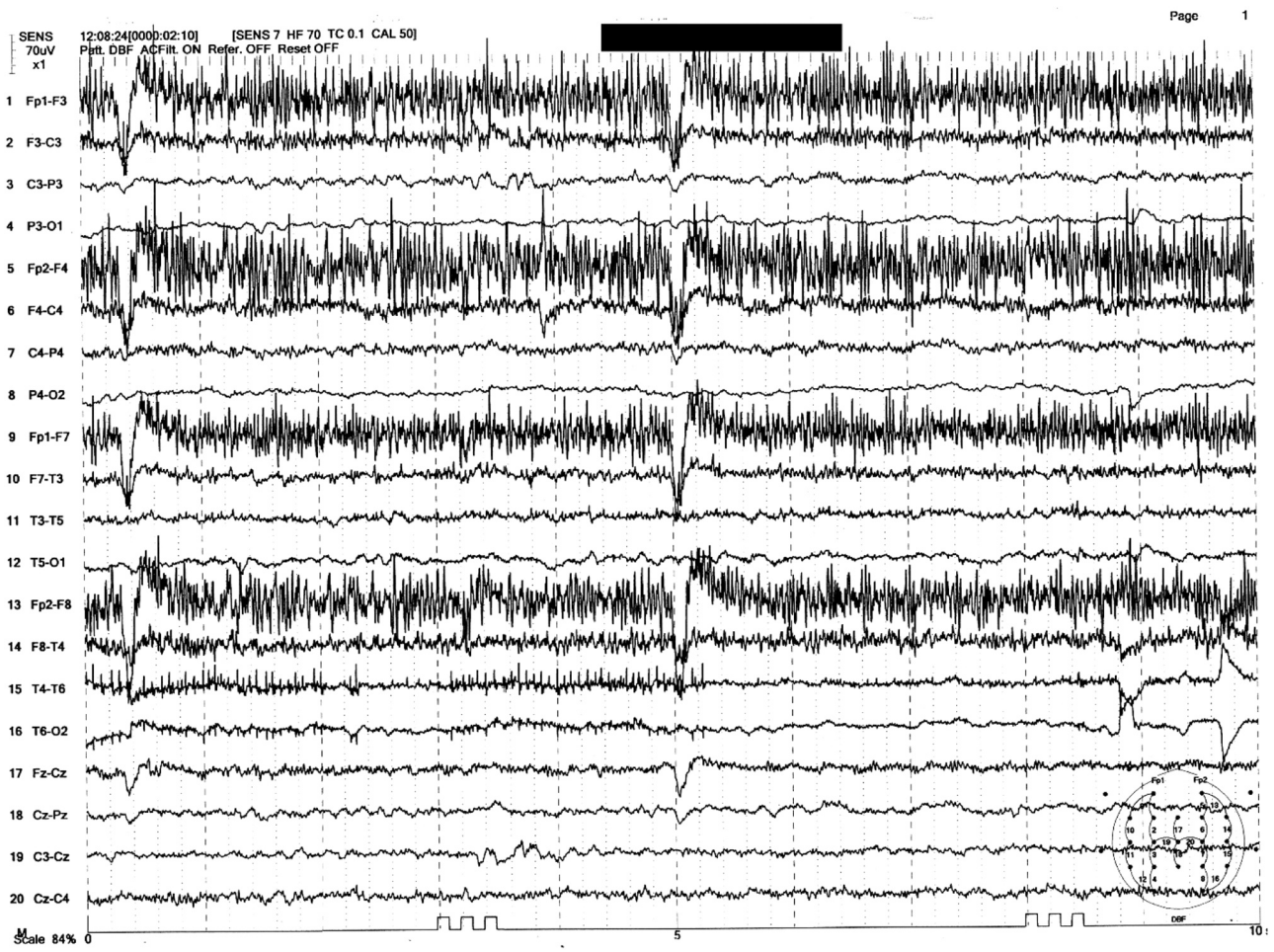

Fig. 1. A 20-channel electroencephalogram (EEG) characterized of a background rhythm of 5.6 Hz Theta Activity.

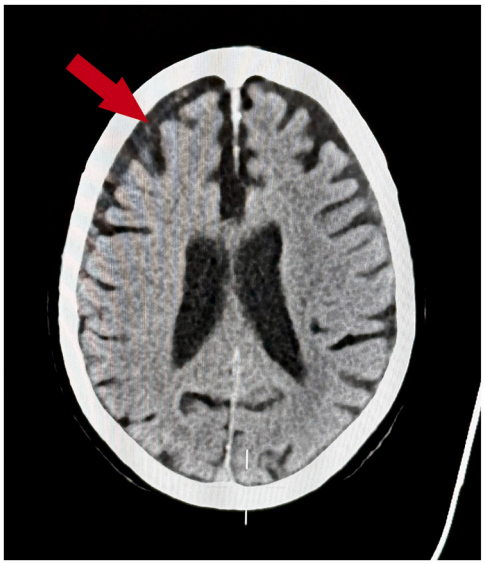

Fig. 2. Computerized tomography (CT) scan of the brain showing generalized bilateral atrophy of the parietal lobe.

improvement was noted, with subsided fever, reduced coughing episodes, decreased blood CRP levels, and normalized platelet count. The patient's Glasgow Coma Scale score improved, with reduced irritability. Consciousness and respiratory efforts had improved.

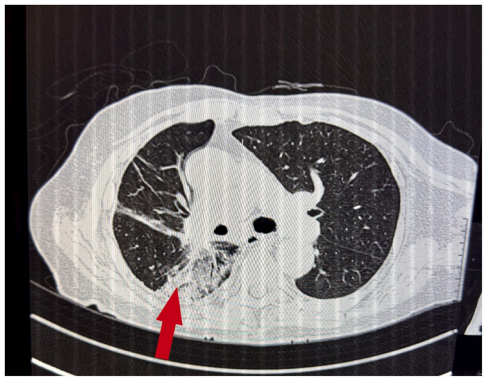

Fig. 3. Axial CT section of the thorax.

During hospitalization, the patient developed bed sores due to immobilization, managed with a local ointment containing neomycin and bacitracin. Additionally, fecal incontinence arose on the 7th day, prompting an X-ray examination of the Kidney, Ureter, and Bladder (KUB) (Fig. 4). The imaging revealed dilated air-filled large bowel loops throughout the sigmoid colon, indicating pseudo-obstruction. A digital rectal examination (DRE) confirmed stool around the perianal area with an empty rectum and no bleeding. A rectal tube was inserted for enema of polyethylene glycol.

Upon family request, the patient was discharged, with appropriate counseling provided regarding anti-TB treatment and scheduled clinic

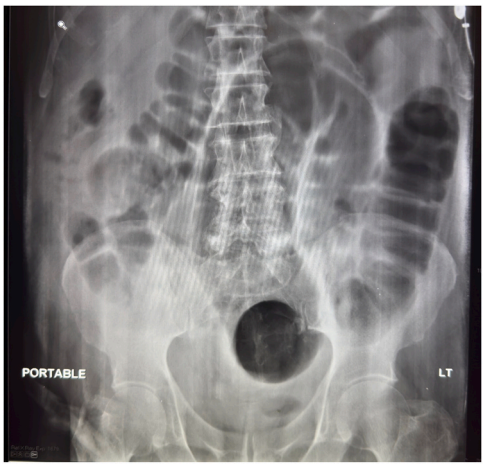

Fig. 4. XRAY abdomen frontal view.

follow-up. The family was advised to arrange home healthcare services for drugs requiring IV administration. Upon follow up, the patient had no major neurological deficit except for gait ataxia. A repeat interferon-gamma immune assays aimed at assessing immune reactivity to tuberculosis (TB), revealed very minute presence of Mycobacterium tuberculosis (MTB).

Discussion

Pathogenic mechanisms, clinical presentations, and laboratory findings overlap among Dengue Fever (DF), pulmonary Tuberculosis (TB), and Lower Respiratory Tract Infections (LRTI), as extensively documented in the literature [8]. Timely recognition and appropriate management of these infections necessitate a heightened level of clinical suspicion and comprehensive laboratory assessments. Any delay in this process may precipitate potentially life-threatening outcomes for affected individuals, emphasizing the urgency of prompt intervention [9,10]. The current case involves an elderly male with the aforementioned diseases alongside pre-existing comorbidities. This case not only presents an unusual manifestation of this combination of illnesses but also underscores the significance of managing such comorbidities in the geriatric population.

Dengue encephalitis is a rare occurrence in clinical practice. Traditionally, dengue fever has been thought of as non-neurotropic [11]. Advancing insights into the direct neurotropism of the dengue virus, where the pathogen breaches the central nervous system (CNS) through a compromised blood-brain barrier, particularly evident in cases of encephalopathy, multiorgan dysfunction, and hypoperfusion secondary to dengue fever, emphasize the importance of considering this condition as a potential differential diagnosis for neurological symptoms in areas endemic to dengue [12].

Typically, systemic and neurological symptoms manifest within a timeframe of three to seven days following the onset of dengue fever (DF). Encephalitis is characterized by symptoms such as headache, fever, altered consciousness, seizures, and focal neurological deficits, often occurring in the absence of metabolic abnormalities. Thrombocytopenia is evident in blood counts, while cerebrospinal fluid (CSF) analysis typically reveals pleocytosis with viral growth on culture. However, it's noteworthy that approximately 75 % of cases may present with normal CSF cellularity, as observed in our case as well [13]. Neuroimaging scans may or may not be helpful, as many cases fail to reveal significant findings, but MRI is preferred over CT scan [14]. Commonly affected areas of the central nervous system (CNS) may include the basal ganglia and thalamus, as seen in a case reported by Samiksha Gupta et al., where an MRI of a 37-year-old female suspected of dengue encephalopathy revealed hyperintensities in the left thalamus, occipital lobes, midbrain, and temporal lobes. Moreover, susceptibility-weighted imaging revealed thalamic bleeding [15].

Dengue fever has been associated with the development of Acute Hepatic Injury (AHI); a condition characterized by hepatic dysfunction. Suganthan N et al. reported a case of a 34-year-old male ethanol user who presented with typical dengue infection symptoms, confirmed serologically. The patient developed acute liver failure despite the absence of clinical, radiological, or laboratory evidence of plasma leakage. Initial biochemistry revealed markedly elevated ALT, AST, and prothrombin time (PT) levels of 3760 U/L, 9352 U/L, and 16.3 s, respectively [16]. There is growing evidence suggesting that hyperammonemia in AHI may contribute to the development of encephalopathy. Given the similarities between AHI and hepatic encephalopathy in cirrhosis patients, some have proposed that reducing elevated ammonia levels through enteral lactulose administration could help prevent or treat cerebral edema in AHI [17]. In our patient, treatment with enteral lactulose resulted in an improvement in Glasgow Coma Scale (GCS) score and ammonia levels. This case highlights the potential role of hyperammonemia in the pathogenesis of encephalopathy in AHI and the potential benefits of lactulose therapy in such cases. Moreover, in DF antipyretics such as acetaminophen (APAP) are given to lower the fever. However, AHI decreases APAP metabolism and this can cause hepatotoxicity with small overdoses [18] Thus upon administration of APAP, serum APAP levels should be regularly tested and dose should be adjusted accordingly.

Information concerning the correlation between secondary tuberculosis (TB) and dengue fever (DF) is limited. However, insights from existing literature suggest the potential co-occurrence of these infections, emphasizing the critical need for prompt management [8]. In our case, the patient developed secondary TB soon after being diagnosed with dengue, which may be attributed to the impaired adaptive immune response to the dengue virus production of immunosuppressive cytokines such as IL-10 [19]. This leads to inhibition of cellular antiviral responses, potentially causing reactivation of TB—a risk that is greatly increased in those with immunocompromising conditions, as observed in our patient.

Our case had an uncertainty regarding whether the tracheal culture reports, confirming the presence of Klebsiella pneumoniae, methicillin-resistant Staphylococcus aureus, and Actinobacterium species in the tracheal secretions, indicated contamination or colonization by these pathogens. However, it is crucial to differentiate between the two scenarios. Transient presence of one or more organisms suggests simple contamination, while persistent positive cultures of the same organism suggest colonization [20]. Our culture findings indicated transient presence of these pathogens despite initiation of antibiotic therapy suggesting LRTI.

Conclusion

Diseases like tuberculosis (TB), dengue fever, and lower respiratory tract infections (LRTIs) exhibit numerous similarities, posing diagnostic challenges, particularly when complicated by conditions such as dengue encephalopathy. This case highlights the simultaneous occurrence of these three diseases in an elderly male with numerous chronic comorbidities. In regions where dengue is endemic, it is imperative to consider dengue encephalitis as a potential differential diagnosis in patients presenting with a brief history of fever and altered sensorium. Thrombocytopenia, abnormal liver function tests, and abnormal EEG findings often serve as indicators of this rare manifestation of dengue fever. Physicians must consider all comorbidities, as prompt management significantly influences prognosis. In our patient, timely reporting and conservative management led to a favorable outcome.

Ethical approval

Ethical approval was taken from the Institutional Review board and

ethical committee. IRB # 112–24.

Consent

Informed written consent was obtained from the patient's guardian to publish this case report and accompanying images.

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CRediT authorship contribution statement

Manahil Jamil: Supervision, Writing – review & editing. **Muhammad Abdullah:** Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft. **Mustafa Awais Choudry:** Conceptualization, Data curation, Writing – original draft. **Sheharyar Amin Sheikh:** Data curation, Methodology, Writing – original draft, Writing – review & editing. **Faryal Shoaib:** Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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