



Review Article

Post-dengue fatigue syndrome: A comprehensive review of an emerging clinical entity

Rahul Garg¹

¹Department of Medicine, F H Medical College, Agra, Uttar Pradesh, India.

***Corresponding author:**

Rahul Garg,
Department of Medicine,
F H Medical College, Agra,
Uttar Pradesh, India.

gargrahul27@gmail.com

Received: 10 July 2024
Accepted: 11 August 2024
Epub Ahead of Print: 22 October 2024
Published:

DOI
10.25259/KMJ_27_2024

Quick Response Code:



ABSTRACT

Post-dengue fatigue syndrome (PDFS) is an emerging clinical entity characterised by persistent, debilitating fatigue and other symptoms following acute dengue infection. This review synthesises current evidence on the epidemiology, clinical features, pathophysiology and management of PDFS. Studies suggest that 20–25% of hospitalised dengue patients may develop PDFS, though population-based incidence is likely lower. Risk factors include older age, female sex and possibly host genetic factors. The hallmark symptom is profound fatigue, often accompanied by musculoskeletal pain, cognitive difficulties, sleep disturbances and mood changes. While some patients recover within weeks, others experience symptoms persisting for months or years. The pathophysiology of PDFS remains unclear but may involve persistent immune activation, hypothalamic-pituitary-adrenal axis dysfunction and autonomic nervous system disturbances. Diagnosis is based on the clinical history and exclusion of alternative causes. Management typically involves a multidisciplinary approach, including patient education, graded exercise therapy, cognitive behavioural therapy and symptomatic treatment. However, evidence for specific interventions is limited. Prognosis is variable, with some patients experiencing prolonged disability. Significant research gaps remain, including the need for standardised diagnostic criteria, biomarkers and controlled trials of potential therapies. As dengue's global burden increases, further investigation of PDFS is crucial to improve recognition and develop evidence-based treatments for this impactful sequela of dengue infection.

Keywords: Post-dengue fatigue syndrome, Dengue, Fatigue syndrome, Post-viral

INTRODUCTION

Dengue is a mosquito-borne viral infection that has become a major global public health concern, with an estimated 390 million infections occurring annually worldwide.^[1] While the acute manifestations of dengue are well characterised, there is growing recognition of persistent symptoms that can occur following the acute illness, particularly fatigue. This clinical entity, known as post-dengue fatigue syndrome (PDFS), can significantly impact the quality of life and functionality in a subset of dengue patients. This review aims to synthesise the current evidence on the epidemiology, clinical features, pathophysiology and management of PDFS.

EPIDEMIOLOGY

The reported incidence of PDFS varies across studies, likely due to differences in study design, populations and case definitions. In a prospective study of hospitalised dengue patients in Singapore, Seet *et al.* found that 24.4% of patients reported significant fatigue 2 months after acute infection.^[2] A study in Sri Lanka observed PDFS in 25% of hospitalised dengue patients.^[3]

This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-Share Alike 4.0 License, which allows others to remix, transform, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

©2024 Published by Scientific Scholar on behalf of Karnataka Medical Journal

The true population-based incidence is likely lower, as these hospital-based studies focused on more severe cases requiring admission.

PDFS appears to be less common than post-infectious fatigue syndromes associated with some other pathogens. Studies have reported post-infectious fatigue in 31–40% of patients following Epstein-Barr virus and Q fever infections.^[2] However, given the high global burden of dengue, even a relatively low incidence of PDFS could translate to a substantial number of affected individuals.

Several risk factors for developing PDFS have been identified. In the Singapore cohort, older age, female sex, presence of chills during acute illness and absence of rash were significantly associated with fatigue at 2 months.^[2] The association with female sex has been observed in other post-infectious fatigue syndromes as well.^[4] Interestingly, severity of acute dengue (i.e. dengue haemorrhagic fever vs. dengue fever) was not associated with subsequent fatigue in this study.^[2]

CLINICAL FEATURES

The hallmark symptom of PDFS is persistent, debilitating fatigue that impairs daily functioning. This fatigue is typically described as a profound lack of energy and exhaustion that is out of proportion to exertion and not alleviated by rest.^[5] Patients often report that even minor physical or mental tasks lead to disproportionate fatigue.

In addition to fatigue, a constellation of other symptoms have been reported in PDFS, including:

- *Musculoskeletal symptoms:* Muscle pain, joint pain and muscle weakness
- *Neurological symptoms:* Headache, difficulty concentrating and memory impairment
- *Sleep disturbances:* Insomnia, hypersomnia and unrefreshing sleep
- *Mood changes:* Anxiety and depression
- *Constitutional symptoms:* Low-grade fever, chills and night sweats
- *Gastrointestinal symptoms:* Nausea and loss of appetite

Umakanth *et al.* described a case series of patients with PDFS who experienced profuse sweating and hot flashes as prominent symptoms.^[6] Some patients may also experience recurrent episodes of symptoms mimicking acute dengue, such as fever and myalgias.^[7]

The severity and duration of symptoms in PDFS can vary widely. While some patients may have mild, transient fatigue lasting a few weeks, others experience severe, disabling symptoms persisting for months or even years. In a prospective cohort study in Colombia, 25% of dengue patients reported persistent symptoms at 12–30 months after infection.^[7]

PATHOPHYSIOLOGY

The exact mechanisms underlying PDFS remain unclear, but several hypotheses have been proposed based on our understanding of post-infectious fatigue syndromes and the immunopathogenesis of dengue:

1. *Persistent immune activation:* Dengue infection triggers a complex series of immune responses, including the production of pro-inflammatory cytokines and alterations in T-cell subsets. It is hypothesised that dysregulated immune activation may persist beyond the acute infection, leading to ongoing inflammation and fatigue.^[2,8]
2. *Hypothalamic-pituitary-adrenal (HPA) axis dysfunction:* Alterations in the HPA axis and cortisol levels have been implicated in chronic fatigue syndromes. Dengue infection may lead to prolonged disruption of the HPA axis.^[2]
3. *Autonomic nervous system dysfunction:* Dysregulation of the autonomic nervous system, particularly orthostatic intolerance, has been observed in other post-viral fatigue syndromes and may play a role in PDFS.^[9]
4. *Mitochondrial dysfunction:* Impaired cellular energy production due to mitochondrial dysfunction has been proposed as a mechanism for fatigue in various conditions.^[10]
5. *Persistent viral infection:* While dengue is typically an acute infection, some have hypothesised that viral persistence in certain tissues could contribute to ongoing symptoms.^[8]
6. *Host genetic factors:* Polymorphisms in immune-related genes may influence susceptibility to persistent symptoms after dengue. A study in Brazil found associations between single-nucleotide polymorphisms in certain cytokine genes and symptom persistence.^[11]

It is likely that the pathophysiology of PDFS involves a complex interplay of these and other factors, with heterogeneity between individuals. The relative importance of viral factors versus host response remains an area of ongoing investigation.

DIAGNOSIS

There are currently no established diagnostic criteria or biomarkers specific for PDFS. Diagnosis is typically based on a history of confirmed dengue infection followed by persistent, unexplained fatigue and other symptoms in the absence of alternative explanations.

A thorough clinical evaluation is essential to exclude other causes of chronic fatigue, such as anaemia, thyroid dysfunction, sleep disorders, depression and other medical conditions. Basic laboratory testing (complete blood count, metabolic panel and thyroid function tests) is often performed, but results are typically normal in PDFS.

Some researchers have used validated fatigue assessment tools, such as the fatigue questionnaire, to quantify fatigue severity.^[2] A cutoff score of 4 or higher on the dichotomised fatigue questionnaire scale has been suggested as a case definition for significant fatigue.^[2]

The *differential diagnosis* of persistent fatigue following dengue should include:

- Other post-infectious fatigue syndromes (e.g. following Epstein-Barr virus and Q fever)
- Chronic fatigue syndrome/myalgic encephalomyelitis
- Depression and other psychiatric disorders
- Fibromyalgia
- Autoimmune diseases (e.g. systemic lupus erythematosus)
- Endocrine disorders (e.g. hypothyroidism and adrenal insufficiency)
- Sleep disorders
- Nutritional deficiencies
- Medication side effects.

MANAGEMENT

There is a paucity of high-quality evidence to guide the management of PDFS, and treatment approaches are largely extrapolated from experience with other post-infectious fatigue syndromes and chronic fatigue syndrome. A multidisciplinary, patient-centred approach is generally recommended, with interventions tailored to the individual's specific symptoms and circumstances.

Key components of management may include:

1. *Patient education*: Providing information about PDFS and validating the patient's experience is an important first step.^[3]
2. *Graded exercise therapy*: A gradual, structured exercise program starting at a very low intensity and slowly progressing over time may help improve function. The principle of 'start low, go slow' is emphasised to avoid symptom exacerbation.^[3]
3. *Cognitive behavioural therapy*: This can help patients develop coping strategies and address any unhelpful thoughts or behaviours related to their symptoms.^[10]
4. *Sleep hygiene*: Addressing sleep disturbances through sleep hygiene measures and sometimes short-term use of sleep aids may be beneficial.^[10]
5. *Nutritional support*: Ensuring adequate nutrition and addressing any deficiencies is important. Some patients report benefit from dietary modifications, though evidence is limited.^[3]
6. *Symptomatic treatment*: Targeted pharmacologic interventions may be used for specific symptoms (e.g. pain management and treatment of mood symptoms).^[10]
7. *Occupational therapy*: This can help patients develop

energy conservation strategies and adapt activities to their current functional level.^[5]

While various pharmacologic agents have been studied in chronic fatigue syndrome, evidence for their efficacy is limited. Low-dose antidepressants are sometimes used, though their benefit in post-viral fatigue syndromes is unclear.^[3] There is no evidence to support the use of corticosteroids or antivirals in PDFS.^[10]

PROGNOSIS

The natural history and long-term outcomes of PDFS have not been well characterised. Available evidence suggests significant variability in symptom duration and severity between individuals. While many patients improve over time, a subset may experience prolonged disability.

In the Colombian cohort study, about 25% of dengue patients reported persistent symptoms at 12–30 months post-infection.^[7] However, this study did not specifically assess fatigue, and it is unclear what proportion of these patients met the criteria for PDFS.

Factors associated with prolonged symptoms may include older age, female sex and possibly genetic predisposition, though more research is needed to identify reliable prognostic indicators.^[2,11]

RESEARCH GAPS AND FUTURE DIRECTIONS

Despite the growing recognition of PDFS, many knowledge gaps remain. Key areas for future research include:

1. Standardised case definitions and diagnostic criteria for PDFS
2. Large-scale, population-based studies to better characterise the epidemiology and natural history
3. Identification of biomarkers to aid in diagnosis and monitoring
4. Elucidation of pathophysiologic mechanisms, including the roles of persistent inflammation, autonomic dysfunction and host genetic factors
5. Randomised controlled trials of potential therapeutic interventions
6. Investigation of potential preventive strategies during acute dengue infection.

CONCLUSION

PDFS represents an important but under-recognised sequela of dengue infection that can significantly impact patients' quality of life and functionality. While our understanding of this condition has grown in recent years, many aspects of its epidemiology, pathophysiology and optimal management remain unclear. As the global burden of dengue continues to increase, further research into PDFS is crucial to improve

recognition, develop evidence-based treatments and ultimately reduce the long-term impact of dengue infection.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

REFERENCES

- World Health Organization. Dengue- Global situation [Internet]. [cited 2024 Jan 3] Available from: (<https://www.who.int/emergencies/disease-outbreak-news/item/2023-DON498>)
- Seet RC, Quek AM, Lim EC. Post-infectious fatigue syndrome in dengue infection. *J Clin Virol.* 2007;38:1-6.
- Umakanth M. Post dengue fatigue syndrome. *Saudi J Med Pharm Sci.* 2017;3:858-61.
- Hickie I, Davenport T, Wakefield D, Vollmer-Conna U, Cameron B, Vernon SD, *et al.* Dubbo Infection Outcomes Study Group. Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. *BMJ.* 2006;333:575.
- Stormorken E, Jason LA, Kirkevold M. Fatigue in adults with post-infectious fatigue syndrome: a qualitative content analysis. *BMC Nurs.* 2015;14:64.
- Umakanth M, Narayanasami E, Suganthan N. Profuse Sweating and Hot Flashes: An Unusual Presentation of Post-Dengue Fatigue Syndrome. *Cureus.* 2020;12:e10024.
- García G, González N, Pérez AB, Sierra B, Aguirre E, Rizo D, *et al.* Long-term persistence of clinical symptoms in dengue-infected persons and its association with immunological disorders. *Int J Infect Dis.* 2011;15:e38-43.
- Mowbray JF, Yousef GE. Immunology of postviral fatigue syndrome. *Br Med Bull.* 1991;47:886-94.
- Sacco P, Hope PA, Thickbroom GW, Byrnes ML, Mastaglia FL. Corticomotor excitability and perception of effort during sustained exercise in the chronic fatigue syndrome. *Clin Neurophysiol.* 1999;110:1883-91.
- Krupp LB, Mendelson WB, Friedman R. An overview of chronic fatigue syndrome. *J Clin Psychiatry.* 1991;52:403-10.
- Dettogni RS, Tristão-Sá R, Dos Santos M, da Silva FF, Louro ID. Single nucleotide polymorphisms in immune system genes and their association with clinical symptoms persistence in dengue-infected persons. *Hum Immunol.* 2015;76:717-23.

How to cite this article: Garg R. Post-dengue fatigue syndrome: A comprehensive review of an emerging clinical entity. *Karnataka Med J.* doi: 10.25259/KMJ_27_2024