Original Research

The prevalence and correlates of post-infectious fatigue following dengue infection among adults admitted to two selected hospitals in Colombo District, Sri Lanka

Nadeeka Perera[1*], Ananda Wijewickrama [2], Dulshika Waas[3], Shamini Prathapan[4]

[1]National Institute of Health Sciences, Kalutara, Sri Lanka; [2]National Institute for Infectious Diseases, Sri Lanka; [3]Department of Psychiatry, Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Lanka; [4]Department of Community Medicine, Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Lanka

*Correspondence: nadeekayasanth@gmail.com https://orcid.org/0000-0003-2725-3086

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Abstract

Introduction: Dengue illness, an acute viral infection, is endemic in Sri Lanka causing a substantial public health challenge today in all dimensions of health. Post-infectious fatigue (PIF) after dengue infection had been reported in several studies as well as in textbooks of medicine.

Objectives: To describe the prevalence and correlates of PIF at one-month follow-up among adults confirmed with dengue infection admitted to selected healthcare institutions in Colombo District, Sri Lanka

Methods: A longitudinal study was conducted among 480 patients from July 2018 to January 2019. Participants were recruited on discharge from the hospital. We adopted systematic sampling method and followed them up one month after day 1 of the fever. Prevalence was assessed by the culturally adapted and validated Sinhala version of the Chalder Fatigue Questionnaire. Correlates were assessed by a pre-tested interviewer-administered questionnaire. A binomial multiple logistic regression analysis was carried out via the SPSS-21 version.

Results: The response rate was 84.58 (406/480). The majority were between 18-35 years (69.2%) and male (60.15%). The prevalence of PIF at one month was 35% (95% CI: 30.3, 39.8). After controlling for confounders, age ≥35 years (adjusted OR (AOR)=4.05; 95% CI: 2.04, 8.04), not being married (AOR=2.7; 95% CI: 1.38, 5.28), having experience of stress full life events (AOR=1.98; 95%CI: 1.16, 3.36), not receiving an adequate quantity of sleep (AOR=2.51; 95% CI: 1.00, 6.31), poor quality of sleep (AOR=15.34; 95% CI: 3.25, 72.49), headache post-discharge (AOR=2.69; 95% CI: 1.6, 4.53), presence of myalgia post-discharge (AOR=3.63; 95% CI: 2.16, 6.11), haemoglobin <11 g/dl at acute stage (AOR=2.01; 95% CI: 1.02, 3.98) and having a platelet count ≤30,000/mm^3 (AOR=2.38; 95% CI: 1.42, 3.99) showed significant associations with having PIF.

Conclusions & Recommendations: Post-infectious fatigue was present among approximately one in three patients after one month following a dengue infection. The modifiable correlates suggest the indications for screening and prevention which is more applicable to clinicians.

Keywords: *post-viral fatigue, persistent fatigue, dengue fever, post-dengue complications*

Introduction

Today, dengue is existing in every World Health Organization (WHO) region and is endemic in 125 countries (1). Around 2.5 billion people are living in dengue endemic countries, where more than half of them are concentrated in the countries in South-East Asia (2). In Sri Lanka, all four serotypes of dengue virus (DENV) are currently present, while DENV 2 and DENV 3 are the prevalent serotypes (3-4).

Though the acute stage symptoms of dengue illness are well studied, less attention has been paid to the convalescence period. Persistent symptoms, even after recovering from acute febrile illness have been reported in the literature and textbooks of medicine (5-7). Halsey et al. (2014) investigated 17 clinical symptoms within 10-60 days of the onset of dengue fever. At least one symptom was present in 9.3% of the cases who were aged 5-17 years (5). A prospective study from Brazil reports that some symptoms persist beyond two weeks (54%), while 6.2% had symptoms for more than six months (6).

"Fatigue" is a subjective term and various scales have been developed and validated to measure this construct. It is not just the normal experience of tiredness or sleepiness. It can be expressed as a feeling of extreme and persistent tiredness or weakness (8). The Chalder Fatigue Questionnaire (CFQ), Fatigue Impact Scale and Piper Fatigue Scale have been used to assess fatigue after infection (9). Of these, CFQ has been developed to measure the severity of fatigue and validated in a general practice setting by comparing the fatigue section in the revised Clinical Interview Schedule (CIS-R). With a cut-off score of ¾, the sensitivity and specificity were 75.5% and 74.5%, respectively. It is a short easy to administer tool with satisfactory validity and reliability. The internal consistency was good with a Cronbach's alpha of 0.88 (10). The CFQ was locally adapted and validated by the author with confirmatory factor analysis, which confirmed the two-factor model in the original study. Reliability was satisfactory with an internal consistency for the overall scale with a Cronbach's alpha coefficient of 0.85 and a correlation coefficient of >0.7 (11).

There is evidence for developing a fatigue syndrome after Epstein-Barr infection, Q fever and viral meningitis. A systematic review by Hulme et al. (2017) describes the risk factors for persistent fatigue after acute infections and used a standardized measure to assess PIF (12-13). Kularathna et al. (2005) reports findings from a survey among 35 clinicians in Sri Lanka, in which the majority (77%) had observed PIF following dengue infection (14). A study in Singapore among 127 patients with dengue infection at two months of follow-up showed that 24.4% (n=31) had PIF (15). Umakanth (2018) describes findings from a descriptive prospective study among 52 dengue-positive patients who attended Teaching Hospital, Batticaloa, Sri Lanka. They reassessed the patients after one month, conducting a telephone interview. The study tool was the Fatigue Questionnaire and 17.3% (n=9) had features suggestive of post dengue fatigue syndrome (16). Another study examining the prevalence and aetiology of fatigue in Sri Lanka and its overlap with depressive episodes. They reported an overall abnormal fatigue prevalence of 25.3% (95% CI: 23.9, 26.7) and a prolonged fatigue prevalence of 1.1% (95% CI: 0.7, 1.4) (17).

There were limited studies available on the correlates of PIF following a dengue infection. Seet et al. (2007) have described the correlates of PIF two months after acute infection and after multivariate analysis, increased age, being a female, not developing rashes and the appearance of chills were described as significant findings at $p<0.05$ level (15). Therefore, this study was designed to assess the prevalence and correlates of PIF following dengue infection among adults who received institutional care in Colombo District, Sri Lanka.

Methods

A longitudinal study was developed in assessing the

prevalence of PIF (18). However, risk factors for the above outcomes could not be assessed, therefore correlates associated with PIF were assessed with an analytical component within the same study (19). This study was developed as part of a study assessing PIF and psychological morbidity following dengue infection.

In Colombo District, six health care institutions provide inward patient care for adult dengue patients, where patient care is directed by a consultant physician. Considering the annual patient turnover, the National Institute of Infectious Diseases (NIID) and Base Hospital, Homagama were selected as the study setting. The follow-up interviews were conducted at the clinic setting in the respective hospitals/patient residences or the Medical Officer of Health Office, Homagama. The study was carried out from July 2018 to January 2019.

Clinical diagnosis by a consultant physician as dengue fever or dengue haemorrhagic fever was the main criterion in defining the study population. The presence of NS I antigen or dengue-specific IgM in their serum provided supportive evidence. Dengue illness classification was considered based on the WHO, Regional Office for Southeast Asia Guideline published in 2011 since this classification was followed in Sri Lanka in dengue patient diagnosis (2, 4). The minimum sample size accounted for 480 (20) with a 20% loss to follow-up and recruited every patient with a skip interval of one.

The first interview was conducted on the day of discharge from the hospital (Interview I). Day one of fever was considered as the first day of infection in deciding the time frame. The study participants were re-assessed with a follow-up visit (interview II) in the hospital clinic at a period of four weeks post-infection.

Post-infectious fatigue following dengue infection was operationalized as "a subjective feeling of tiredness, lack of energy and exhaustion lasting for at least one-month duration following dengue infection". This was conducted via a Modified Delphi process and based on available literature (12, 15, 21). PIF was assessed using the Sinhala version of the CFQ (11). The CFQ consists of 11 items and each item was scored on a four-point Likert scale ranging from zero to three (10). Those having a CFQ score ≥4 were considered as having PIF.

The selected correlates were assessed via an interviewer-administered questionnaire and a data extraction sheet. These variables were basic socio-demographic and socio-economic factors, personal and lifestyle-related correlates, dengue illness-related factors, inward treatment and investigations. Quantity and quality of sleep was enquired since sleep was described as a potential confounder to fatigue. The quality of sleep was assessed using the Sinhala version of Epsworth Sleepiness Scale which is a tool validated for Sri Lanka (22). In addition, the questionnaire on correlates was further validated (face, content, and consensual validity) and pre-tested (23). The data collectors were trained uniformly, and they were provided with an interviewer guide. Before data collection, administrative clearance was obtained from the relevant parties.

Data analysis

Data were analysed using the Statistical Package for the Social Sciences (SPSS) version 21. The prevalence of PIF was estimated with 95% CI (number of participants who became positive for the disease out of the total number of participants). The prevalence odds ratio (OR) was used to evaluate the odds of having PIF with the presence or absence of each correlate (23). The Chi-squared test and 95% CI of prevalence ORs were used to assess the statistical significance. A binary logistic regression analysis was carried out to identify the correlates of PIF when controlled for the effect of confounding. Adjusted OR (AOR) and 95% CI were calculated in the model.

Results

Only 406 completed interview II at the follow-up, giving a response rate of 84.6%. There were 14 (2.9%) patients who had given wrong contact numbers and 60 (12.5%) of them did not answer the given contact number even after three calls within three weeks and did not come for the scheduled clinic. Therefore, 15.4% were lost to follow-up (n=74). Furthermore, the full blood count at one month was traced from 321 participants, giving a response rate of 66.9%. When the participants were compared with those who were loss to follow up, there was no difference between the two groups ($p>0.05$).

In the sample, the mean age was 30.8 (SD=11.5) years, while the median age was 27 (IQR: 21.8-39.0) years (Table 1). Most of the study participants stated that they had slept well every day or at least on four days in the preceding week when assessed at the follow-up interview (Table 2). During the acute stage, 79.8% had white blood cell (WBC) less than 4000, and at follow-up, only 0.6% had a WBC count <4000/ mm^3. During the hospital stay, 14.3% had a haemoglobin level <11 g/dl, whereas at follow-up, only 4% had a lower haemoglobin level. During the hospital stay, 35.5% had a platelet count of <30 000/ mm^3 and at follow-up, none had a platelet count <30 000/ mm^3.

The total PIF scores showed a positively skewed distribution with standardized skewness of 5.8 and standardized kurtosis of 2.4 showing significance at 5% level. Also, the Kolmogorov-Smirnov test and Shapiro-Wilk's test were both significant at $p<0.001$ level. The Wilcoxon Signed-rank Test performed to compare the median PIF scores at interview I and interview II showed significance at $p<0.001$ level. On discharge from the hospital, fatigue-associated symptoms were present among 81.5% (95% CI: 77.4, 85.2) of the study population, and at one month from day one of fever, 35% (95% CI: 30.3, 39.8) had PIF.

Table 3 summarizes the unadjusted ORs calculated for the correlates of PIF. Table 4 further summarizes the results of the final model retained after binary logistic regression upon controlling for the confounders. Out of 16 factors included in the regression analysis, nine factors were retained in the final model. In the model, the probability fixed for entry was 0.05 and removal was at 0.1. The omnibus tests of model coefficients revealed a final model with a model Chi-squared of 141.71, which was statistically significant at $p<0.001$ level. The Hosmer-Lameshow test supported the fit of the final model ($\chi^2=2.81$; df=8; $p=0.945$).

Discussion

At the stage of discharge from the hospital, PIF-associated symptoms were present among 81.5% (n=331) and PIF at follow-up was 35% (n=142). It is well known that acute stage of dengue illness, symptoms of fatigue are common. At one month, nearly one in three study participants were having symptoms of fatigue. Further, the longitudinal prospective study design would minimize recall bias enhancing the internal validity of the study.

A few studies reported the prevalence of PIF at different time intervals following a dengue infection. In comparing the results of those with the current study, certain differences in the study setting, eligibility criteria, sample size, study instrument, assessment of cut-off values and length of follow-up should be clearly and critically evaluated.

The study by Umakanth (2018) reported a PIF prevalence of 17.3% (n=9) at one month following dengue infection (16). This finding is less compared to the prevalence in the current study. It could be due to the smaller sample size and assessment via telephone interview, whereas a recently published study conducted in the National Hospital of Sri Lanka reports a prevalence of post-dengue fatigue at two months as 32.3%, yet they have explored only limited correlates (24). The prevalence in the study by Seet et al. (2007) is 10% lower than in the current

study, yet it is justifiable, considering the duration of follow-up (15).

Table 1: Basic characteristics of the study population (N=406)

Characteristic	No.	%
Age (in years)		
18-25	168	41.4
26-35	113	27.8
36-45	68	16.7
46-60	57	14.0
Sex		
Male	244	60.1
Female	162	39.9
Ethnicity		
Sinhala	376	92.6
Tamil	7	1.7
Moor	21	5.2
Burger	2	0.5
Current marital status		
Married	203	50.0
Single	194	47.8
Divorced/ widowed	9	2.2
Highest educational level		
Never attended school	6	1.5
Grade 1-5	4	1.0
Passed Grade 8	35	8.7
G.C.E. O/L[1] passed	143	35.2
G.C.E. A/L[2] passed	112	27.6
Diploma/ Vocational training	44	10.8
Degree/ Postgraduate	62	15.3
Total monthly income		
Less than Rs. 25,000 (< 132.5 USD[3])	37	9.1
Rs. 25,000 – 50,0000 (132.5-265 USD)	153	37.7
Rs. 50,001 – 75,000 (265-397.5 USD)	79	19.5
Rs. 75,001 – 100,000 (397.5-530 USD)	56	13.8
More than Rs. 100,001 (> 530 USD)	81	20.0
Social support		
Higher	177	43.6
Lower	229	56.4

[1] General Certificate of Education – Ordinary Level

[2] General Certificate of Education – Advanced Level

[3]US Dollars

Table 2: Personal, lifestyle and disease-related characteristics (N=406)

Characteristic	No.	%
Chronic disease		
Presence	77	19.0
Absence	330	81.0
History of dengue infection		
Yes	61	15.0
No	345	85.0
Smoking status		
Never smoker	347	85.5
Former smoker	27	6.7
Current smoker	32	7.9
Alcohol consumption		
Lifetime abstainer	310	76.4
Former drinker	28	6.9
Current drinker	68	16.7
Experience of a stressful life event		
Yes	139	34.2
No	267	65.8
Quantity of sleep		
Adequate	373	91.9
Not adequate	33	8.1
Quality of sleep		
Good	384	94.6
Average	6	1.5
Poor	16	3.9
Dengue diagnosis		
Dengue fever	257	63.3
Dengue haemorrhagic fever	149	36.7

In Colombo Twin Study, the participants were selected as having abnormal fatigue if at least three out of 11 symptoms were present when screened by the CFQ. Prolonged fatigue was assessed with four or more symptoms of fatigue lasting at least 50% of the time for a period of six months. Among the twin population, the abnormal fatigue was almost 10% lower than in the current study, yet they have used a relatively healthy population, a smaller cut-off value in assessing abnormal fatigue, and not considering a time duration as opposed to the current study.

The final logistic regression model describing the correlates for PIF, explained 29.5% (Cox and Snell R^2) to 40.6% (Nagelkerke R^2) of the variance in PIF. This could be because potential correlates, such as self-efficacy, personality traits, serological and immunological parameters, the strain of the dengue virus and genetic factors were not included in the current study (17, 25).

Considering the socio-demographic factors, in the current study, elderly people were not included since they tend to have more fatigue due to aging (26). Despite excluding the much older people, those who were ≥35 years were experiencing more PIF than

those who were younger than them, which is similar to the findings from Singapore (15). Seet et al. (2007) revealed that after regression analysis, females were having almost nine times higher likelihood of having PIF at two-month follow-up. Yet, being a female was not retained in the final model because of confounding. "Being not in marriage" emerged as a factor causing fatigue. This may be because those who are married will have more support from the family and they might have to return to their usual lifestyle early due to their commitments, leading them to less fatigue.

Personal and lifestyle-related factors showed significant associations with having PIF. Those who had experienced at least one life event within the last year were 1.98 times more likely to have PIF as opposed to their counterparts. Jason et al. (2014) have assessed the relationship between the experience of stressful life events and chronic fatigue among a group of infectious mononucleosis patients and a control group. Those who had experienced stressful life events were 1.83 times more likely to have chronic fatigue syndrome ($p<0.05$) (27).

Table 3: Summary of the list of correlates included in the multivariate analysis (N=406)

Correlate	Unadjusted OR	95% CI	p value
Age ≥35 years	2.78	1.81, 4.27	<0.001
Female sex	1.82	1.2, 2.75	0.005
Not being in marriage	0.71	0.47, 1.06	0.096
Education attainment up to G.C.E O/L[1]	1.45	0.99, 2.25	0.054
Lesser social support	1.49	0.98, 2.26	0.06
Having a significant past medical history	2.25	1.36, 3.73	0.001
Experience of stressful life events	2.17	1.42, 3.32	<0.001
Not having an adequate quantity of sleep	4.21	1.98, 8.98	<0.001
Poor quality of sleep	21.48	4.9, 93.34	<0.001
Headache post discharge	4.14	2.68, 6.38	<0.001
Myalgia post discharge	5.5	3.52, 8.58	<0.001
Arthralgia post discharge	3.63	2.35, 5.59	<0.001
Fever post discharge	3.35	1.43, 7.86	0.004
Having dengue haemorrhagic fever	1.58	1.04, 2.4	0.03
Haemoglobin <11 g/dl at acute stage	2.08	1.19, 3.65	0.01
Platelet count ≤ 30,000 at acute stage	1.8	1.18, 2.75	0.006

[1] General Certificate of Education Ordinary Level

Those who were not getting adequate sleep were 2.5 times more likely to have PIF. Further, the group having poor quality of sleep was 15 times more likely to have PIF than their counterparts. The association between sleep and fatigue among dengue patients was first explored in the current study and this could be considered a modifiable correlate with lifestyle modifications and improved awareness among patients. Generally, sleep apnoea and narcolepsy are discussed as a cause of chronic fatigue (21).

Those who were experiencing headache or myalgia after discharge were having a higher likelihood to develop PIF. Both these associations were statistically significant, and these symptoms could have been managed with simple interventions. Yet, Seet et al. (2007) assessed the relationship between having headache or myalgia at the acute stage with PIF and did not show a statistically significant association (15).

Concerning the laboratory investigation-related factors, having a haemoglobin level <11 g/dl and the lowest platelet count ≤30 000/mm^3 at the acute stage of the illness were significant predictors of having PIF. The unadjusted OR and AOR for both these factors were almost similar with narrow CIs indicating the satisfactory quality of data. No studies have previously reported significant associations between PIF and laboratory investigation parameters (p>0.05). It is noted that these investigation findings are related to the severity of dengue illness. At the same time, anaemia is a known cause of fatigue-associated symptoms such as tiredness and lack of energy (7).

The findings of the study are important especially in the Sri Lankan context; patients doing a job get only two weeks of medical leave from the day of hospitalization, people who study and are self-employed need to initiate their routine work and it may affect the families financially as well. Therefore, these persistent symptoms could affect the quality of their life and at the same time could be managed easily upon early identification and management.

Table 4: Correlates of post-infectious fatigue following dengue infection after multivariate analysis (N=406)

Factor	B	SE(B)	Wald	df	p value	Adjusted OR	95% CI
Age ≥35 years	1.39	0.35	15.99	1	<0.001	4.05	2.04, 8.04
Currently not married	0.99	0.34	8.41	1	0.004	2.7	1.38, 5.28
Experience of life events	0.68	0.27	6.34	1	0.01	1.98	1.16, 3.36
Not adequate quantity of sleep	0.92	0.47	3.84	1	0.05	2.51	1.00, 6.31
Poor quality of sleep	2.7	0.79	11.87	1	0.001	15.34	3.25, 72.49
Headache post discharge	0.99	0.27	13.94	1	<0.001	2.69	1.6, 4.53
Myalgia post discharge	1.29	0.27	23.53	1	<0.001	3.63	2.16, 6.11
Haemoglobin <11 g/dl in acute stage	0.69	0.35	4.05	1	0.04	2.01	1.02, 3.98
Platelet ≤ 30,000 in acute stage	0.87	0.26	10.87	1	0.001	2.38	1.42, 3.99

Several limitations need to be considered in interpreting the results. The Sinhala version of the CFQ was not evaluated for criterion validity, due to the absence of a locally validated gold standard measure. Since PIF was a screening tool, the study design was limited to a descriptive longitudinal study with an analytical component, assessing correlates. Therefore, the causal inferences cannot be decided from this study as temporal relationships could not be established. Genetic, serological, and immunological factors were not assessed as correlates. Therefore, the final logistic regression model explained 40.6% of the variance of PIF following dengue infection. In the current study, the absence of a comparative group limits comparison and interpreting the findings with other patients with fever or with the general population. Further, even with a comparative group, there is the limitation of mixing of patients with asymptomatic dengue and other diseases that can cause fatigue. Yet, the current study was designed to explore the magnitude of this clinical entity following a scientific process in the local setting.

Conclusions & Recommendations

The prevalence of post-infectious fatigue following a Dengue infection, at one-month follow-up, was high. Considering the significant correlates of having post-infectious fatigue; age ≥35 years, being not in marriage, and having experience of stressful life events emerged as non-modifiable correlates. Not receiving an adequate amount of sleep, poor quality

of sleep, headache post-discharge, and presence of myalgia post-discharge could aid in patient management since management options are available for these conditions as these could be modified. The investigation findings at the acute stage, of having a haemoglobin level <11 g/dl and the lowest platelet count ≤30,000 /mm^3 could be identified as significant predictors of having PIF before the patients are discharged from the healthcare institutions and they could be counselled on prevention of PIF.

Public Health Implications

- This study discusses the burden of post-infectious fatigue at month following a Dengue infection, which is high. Currently, patients who are being discharged from hospitals after infection with Dengue, are not routinely followed at the hospital clinic. The patients as well as clinicians may be unaware of the long-term symptoms of PIF. It is important to improve awareness among both these groups on modifiable correlates.

Author Declarations

Competing interests: None

Ethics approval and consent to participate: Informed written consent was obtained from the participants, at the recruitment stage. Ethical clearance was obtained from the Ethics Review Committee, Faculty of Medicine, University of Kelaniya (P/78/02/2018). Care was taken to ensure the confidentiality of the data. Patients screened positive for any disease condition or having post-infectious symptoms were referred to the Consultant Physician/Consultant Psychiatrist or the respective medical clinic.

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Author contributions: All four authors contributed to the design of the study. NP coordinated data collection, data analysis, and drafting of the first version of the manuscript. SP, DW and AW were involved in the interpretation of data and read and approve the final version of the manuscript.

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