

Review Article

Post dengue fatigue syndrome

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Abstract: Post-dengue fatigue syndrome (PDFS) is not uncommon phenomenon of dengue viral infection. The PDFS has wide spectrum of musculo-skeletal and neurological features. It was observed in 25% of hospitalized patients with dengue. The exact pathogenesis is not known, but this complex interaction of immune, endocrine, musculoskeletal and neurological system act through the hypothalamic-pituitary-adrenal axis causing clinical features of fatigue in dengue. Persuade a balanced diet, and converse with patients their nutritional habits. Advice about graded exercise is essential. Anti-depressants are of minimal benefits for post viral fatigue. I performed systematic reviews of the published literature. The database, Pubmed was searched using the term of 'dengue fatigue' or 'Post dengue fatigue', or 'post viral fatigue' and 'post infectious fatigue' in any field with no data limits. After exclusion of double entries, I assessed all publications. I included articles related to fatigue due to post viral and dengue viral infection. Two articles were found related to post dengue fatigue syndrome. The rest of the information was extracted from the articles related to post viral fatigue syndrome.

Keywords: Post dengue fatigue syndrome and post viral fatigue syndrome.

INTRODUCTION

Dengue is a viral infection caused by four types of dengue viruses (DENV-1, DENV-2, DENV-3, DENV-4) belonging to the *Flaviviridae* family. The viruses are transmitted through the bite of infected *Aedes aegypti* and *Aedes albopictus* female mosquitoes that feed both indoors and outdoors during the daytime[1]. Incubation period is 2-7 days. Dengue results in a spectrum of clinical presentations, from subclinical infection to severe hemorrhagic disease. Common presentation are high fever, severe pain behind the eyeballs, in some cases a bad rash, and in most cases extreme pain in the bones and joints. This last symptom led to the virus also being known as "Breakbone Fever". The illness may progress to Dengue Hemorrhagic Fever (DHF). Symptoms include severe abdominal pain, vomiting, diarrhoea, convulsions, bruising, and uncontrolled bleeding. High fever can last from 2 to 7 days. Complications can lead to circulatory system failure and shock, and can be fatal dengue shock syndrome (DSS).The figure of dengue cases has increased over the last decade in SriLanka. According to the SriLanka epidemiology unit report that first three month of 2017, around 30,000 cases were reported, of that 41.32% were reported from western province [2].

Dengue viral fever is endemic in tropical and subtropical areas. Dengue fever is estimated by the World Health Organization (WHO) to cause about 50-

100 million infections per year Worldwide. According to the SriLanka epidemiology unit report that first three month of 2017, around 30,000 cases were reported, of that 41.32% were reported from western province [3]. Secondary dengue viral infection is more common in our clinical practice which is associated with more serious clinical outcome. Normally, natural course of the illness has three phases febrile, critical and convalescent. The febrile phase is characterized by high fever with dehydration, it last for 2-7 days. The critical phase is started with plasma leakage, it usually start 48 hours after the onset of fever and last for 48 hours [4]. Moreover, some percentage of DF patient end up with expanded dengue syndrome, where dengue fever complicated with organ involvement such as central nervous system, liver, kidney and other isolated organ involvement [1].

Most of the patient complains of frequent episode of excess sweating[5]. The post infectious fatigue has been reported not only dengue fever, also reported other infections, such as Q fever, Lyme disease and Epstein-Barr virus [6].

Post infectious fatigue syndrome (PIFS)

The fatigue is defined as a collection of symptoms, mainly from muscular and neurological origin. The muscular symptoms comprise muscle weakness with or without pain. However, weakness is

more obvious when patient do normal muscular effort. The spectrum of neurological features are recorded in the available literature such as parasthesiae in the limbs, face, diplopia , blurred vision and headache. The term Post infectious fatigue syndrome refers to severe and prolonged fatigue following infectious triggers , such as viruses [7] , bacteria , and parasites . The most frequent onset is acute. However, within days or weeks of the initiating infectious trigger, which is termed the prodromal phase, the affected patient experience a gradual decline in functional capacity. A minor group has a more gradual or insidious onset, and the decline may take many months or years[8]. Following viral infection fatigue can developed ,however degree of fatigue differ with every individuals, therefore fatigue must have resulted in a 50% decline in functional level compared with pre-viral illness and have persisted for more than six months in order to define it as PIFS.

Mechanisms of fatigue

An exact mechanism of fatigue is not known. The pathogenesis of post-dengue fatigue is likely multifactorial and could result from a combination of pathogenic effects produced by the virus and the immune response of the host to the dengue virus. But unexplained fatigue and feeling of tiredness may require some chemical or substances in our body. Following certain types of infections, toxic substances released from the body and accumulated in the brain causing fatigue. Researchers believed that lactic acid responsible for this fatigue syndrome. However it was reported recently that lactic acid is not causing fatigue rather it behaves like fatigue-preventing substance [9]. In addition to that , post febrile fatigue could be due fatigue inducing substances such as cytokines including interferon [10, 11]. However, there are cluster of cytokines are involved this fatigue syndrome, it is difficult to say which cytokines plays a central role[12].This complex immune interaction of immune, endocrine, musculoskeletal and neurological system act through the hypothalamic-pituitary-adrenal axis causing clinical features of fatigue in dengue patient [13].

Clinical features

Post infectious fatigue was observed in 25% of hospitalized patients with dengue. Interestingly, there are number of risk factors connected with development of fatigue these include older age, sex, the presence of chills and the absence of rashes[14]. Incidence of fatigue syndrome due to dengue infection is low compared with other infection especially Epstein-barr virus .In case of dengue fever, fatigue is not a late features, it could be happen even with acute dengue fever[15].Post dengue fatigue syndrome (PDFS) is not an issue of being tired or fatigue. Patient with PDF have severe fatigue that keeps them from performing their normal daily activities. They complain of body pain, poor concentration, headache, giddiness, poor sleep[16]

and sometimes excess sleep. Many people feel more tired even after long sleep. Throughout the fatigue low grade fever could be possible but most of the time patient feels feverish like feeling than recorded fever. However, they try to do some exercise or mild walk for some distance causing massive fatigue and confine them to the bed for days. In addition to that, patient also complained of muscle pain, joint pain, sore throat, headache, tender lymph node, memory loss, poor concentration, features of parkinsonism[17], anxiety, depression and low grade fever[14].Among PDFS patients,20% had DHF and 80% had DF[14].

The occurrence of significant fatigue was measured by the validated fatigue questionnaire (FQ).It consisting of eleven objects that measure fatigue-related symptoms encircling the physical and mental dimensions such as physical fatigue corresponds to the subjective feeling of being exhausted and lacking energy, whereas mental fatigue describes the subjective feeling of being mentally exhausted, incorporating items on concentration, memory and speech. The seven items on physical fatigue and the four items on mental fatigue have four response categories (0=none; 1=mild; 2=moderate; 3=severe). Thus, higher scores imply more fatigue with a maximum scale score of 33[18].

Chronic fatigue syndrome (CFS)

Chronic fatigue syndrome (CFS) also referred as myalgic encephalomyelitis (ME) and, more recently, systemic exertion intolerance disease (SEID). Although CFS/ME and SEID share the same major symptom of chronic fatigue, there is variation between the definitions of these disorders. CFS is characterized by profound, incapacitating fatigue and a combination of several other symptoms resulting in significant reduction in occupational, personal, social, and educational status for a month or longer. However, diagnosis of the chronic fatigue syndrome (CFS) can be made only after alternate medical and psychiatric causes of chronic fatiguing illness have been excluded[19].

The symptom of chronic fatigue also may occur from more than one underlying condition. The cause of chronic fatigue syndrome is unknown, although there are many theories ranging from viral infections to psychological stress. Some experts believe chronic fatigue syndrome might be triggered by a combination of factors. There's no single test to confirm a diagnosis of chronic fatigue syndrome. We could may need a variety of medical tests to rule out other health problems that have similar symptoms. Treatment for chronic fatigue syndrome focuses on symptom relief.

Causes for CFS

The cause of CFS is unknown. To discover possible triggers, researchers are studying the relationship between stress the immune system, toxins,

the central nervous systems and activation of a latent virus. Some researchers suspect a virus may cause it; however, no specific virus has been identified. Studies suggest that CFS may be caused by inflammation of the nervous system, and that this inflammation may be some immune response or process. Other factors such as age, prior illness, stress, environment, or genetics may also play a role[20].

Investigations

As patient complained of subtle neurological and muscular symptoms, it is extremely difficult task to investigate. However, set of investigations need to be rule out other possibilities of fatigue, these includes urinalysis, total protein, glucose, C-reactive protein, phosphorus, electrolyte, complete blood count with leukocyte differential, alkaline phosphatase, creatinine, blood urea nitrogen, albumin, antinuclear antibody and rheumatoid factor, globulin, calcium, alanine aminotransferase or aspartate transaminase serum level, and thyroid function tests[19].

On the other hand, evidence suggestive of some elements of brain and skeletal damages occurred during the fatigue. A study conducted in two different out breaks revealed that number of fatigue patients showed non-specific abnormalities in their electroencephalogram (EEG)[21]. Moreover, those who are complained of muscle pain, tenderness, weakness and extremely tired after exertion showed normal electromyographic (EMG) studies in most of the fatigue patients. However, biochemical evidence of muscle damage is apparent in fatigue[22]. In addition to that , increased creatinuria and myoglobin level were observed in various studies which also indicates some elements of muscle damage happened in fatigue syndrome. However, creatinine phosphokinase, lactate and ATP levels were normal[23]. Moreover couple of cases were reported that features suggestive of parkinsonism[17]. Number of study with single fibres electromyography conducted among fatigue patient interestingly significant number of patient show some sort of abnormalities called jitter without blocking the neuromuscular junction[24].

Treatment of PDFS

There are no definite guidelines for management of PDFS. However, number of studies explained the management of CFS. Educating patients about PDFS and validating their illness experience in addition to establishing a working agreement are the initial steps in the treatment. Persuade a balanced diet, and converse with patients their nutritional habits. Advice about graded exercise is essential[25]. "Start low and go slow" is the correct advice for activities and exercise. The exercises need to be followed by a rest period at a 1:3 ratio (i.e., 10 minutes of exercise: 30 minutes of rest) .Gear activities toward improving

function in areas that are of greatest importance in achieving activities of daily living and remain open minded about alternative therapies. A small study has been proven that cognitive behavioral therapy in CFS has shown improvement in function and symptom management .However, what extent it is feasible in PDFS?

Pharmacologic Treatment

Numerous studies have evaluated different treatment, including recombinant erythropoietin, psychostimulants, corticosteroids, anti-inflammatory drugs, and L-carnitine. Antidepressants are the most common medications used in this regard; selegiline had a small but significant therapeutic effect independent of its antidepressant effect. Fluoxetine has been shown to improve overall symptoms and measures of immune function in one study, however, it was failed in randomized double blind study against placebo and graded exercise. Number of studies have shown that bupropion, venlafaxine, moclobemide and duloxetine has some limited beneficial effect for CFS[26]. However, no therapeutic effects were found for natural killer cell stimulant[27], low-dose combination therapy of hydrocortisone and fludrocortisones, immunologic and antiviral substances, melatonin, or bright-light phototherapy. A study hypothesized that pharmacological property of the cannabidiol significantly reduces anxiety, has antinociceptive and anticonvulsant actions, and may be therapeutic for insomnia in post Ebola syndrome[3].

CONCLUSION

Post dengue fatigue syndrome is the late features of dengue fever. It has wide spectrum of presentation. However, musculoskeletal and central nervous system features are predominant. Though exact mechanisms of post dengue fatigue syndrome is not known, however, we believe that cluster of cytokines and host factors are involved in the pathogenesis. The involvement of age and female sex, but not dengue severity, with the development of fatigue suggests that host factors are essential in the pathogenesis of post-infectious fatigue in dengue infection. A bio-psychosocial approach in the evaluation and management is recommended. In future further studies are needed to better understand this post-infectious fatigue in dengue infection.

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