# Elimination of oral focal infection: a new solution in chronic fatigue syndrome management?

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***ABSTRACT***

*Chronic fatigue syndrome (CFS) is an illness whose primary symptoms are debilitating fatigue and cognitive dysfunction. Substantial symptom overlaping with fibromyalgia, depression, allergic diseases, and many other illnesses, and the absence of a universally applicable diagnostic test, makes the diagnosis of CFS complex and challenging. The pathophysiology of CFS is also complex, and not clearly understood. Formerly, CFS was believed to be a variant form of depression, but due to an increasing body of evidence, CFS is now considered primarily as a biochemical derangement of the functioning of the neuroimmune and neuroendocrine systems. Recently, most treatments still primarily emphasize analgesics, anti inflammatory and psychiatric treatment which correlates to psychosomatic disorders. One of the symptoms that is poorly understood is allergy, but according to the neurogenic switching hypothesis the correlation can be explained nowadays. The role of oral focal infection as one of the possible etiology has still rarely been discussed. The goal of this article is to explain the possible pathophysiology of CFS which could be elicited by oral focal infection, especially endotoxin (lipopolysaccharide) from gram negative bacteria. This case report discusses the history of illness, previous treatments, diagnosis, case management and treatment result. Periodontal treatment of a patient with symptom mimicking CFSs undergoing periodontal treatment has a remarkable result. The conclusion is that the elimination of oral focal infection could be a new solution in CFS management.*

***Key words**: chronic fatigue syndrome, oral focal infection, neurogenic switching*

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## INTRODUCTION

The proposed criteria for the diagnosis of chronic fatigue syndrome (CFS) are the presence of persistent and disabling fatigue for at least six months, coupled with an somatic and neuropsychological symptoms that are headache, myalgias, migrating arthralgia, sore throat, forgetfulness, difficulties in concentration and thinking, cervical or axillary lymphadenopathy, low-grade fever, irritability, and sleep disturbances.[1] Other symptoms are allergies, chest pain, rapid pulse, abdominal cramps, night sweats and rash.[2] The pathophysiology and the etiology of CFS is still unclear, but the possibility of some obscure metabolic or immunologic derangement secondary to viral infection must be considered, but most of the cases lack such a history.[1]

One of the symptoms which are very disturbing in CFS is headache, that are tension headache and migraine.[3] Several headache that mimic the criteria of tension headache or migraine also accompanied by sinus pain, rhinorrhoe and nasal congestion and diagnosed as sinus headache, the problem are after consulting to an otolaryngologist (ENT specialist) it were found that they had normal sinuses.[4] However, CFS also manifest allergic symptoms that may confused with sinus headache symptoms and complicate the diagnosis.[5] The pathophysiology of this phenomenon is still in controversy, but there is a hypothesis proposed by Meggs so called neurogenic switching which can be considered as one that can satisfactory explain most of the mechanism of migraine with sinusitis-like symptoms.[4–6] Neurogenic switching explain that there is an interplay between neurogenic inflammation and immunogenic inflammation, for example the pathophysiology of allergic propagation, food allergy can elicit urticaria, rhinitis and asthma. Ingestion of foods or drugs as well as cutaneous inoculation with vespid venom can trigger systemic anaphylaxis. However, in experimental models of anaphylaxis, ablation of neuronal pathways eliminates the anaphylactic response without blocking histamine release or antibody production. This switching of the site of inflammation in allergy and chemical sensitivity may be due to the same mechanism: there are neuronal pathways from the site of stimulation through the central nervous system to other peripheral locations. This mechanism of site switching has been termed neurogenic switching.[6] The main chemical mediator involved in neurogenic switching are histamine and substance P (SP).[4,6] Other symptoms that may accompany are vestibular or cochlear disturbances and

it were caused by SP in the inner ear that stimulates expression of endothelium-leukocyte adhesion molecules from cochlea microvasculatures which decreases blood flow to cochlear sites resulting vestibular and hearing disorders.[7] Headache could be elicited by endotoxin (lipopolysaccharide) from gram negative bacteria that induced macrophages producing proinflammatory cytokines interleukin -1$\alpha$ (IL-1$\beta$), IL-6, TNF-$\alpha$[8–10] and other chemical mediators i.e. prostaglandin E2 (PGE2) and nitric oxide (NO).[8] Prostaglandin E2 mediates vasodilatation, increases vascular permeability, enhances pain perception on nociceptor to bradykinin and histamine,[8,9,11] and induce proliferation of T helper2 lymphocytes that are responsible for the development of allergy.[12] Excessive production of PGE2 and NO alter neurovascular condition which could elicit migraine.[8,9]

Nervous system also contributes to the pathophysiology of peripheral inflammation including periodontal inflammation. Inflammation that present in oral and periodontal tissue is mostly stimulated by endotoxin (LPS), LPS also stimulate nerve endings to release neuropeptides i.e SP which account for neurotransmitting and vasodilation. Release of SP could be stimulated by hot temperature, capsaicin, bradykinin and tryptase (enzyme produced in mast cell degranulation). Stress enhances the secretion of NO and other inflammatory mediators in response to LPS derived from Porphyromonas gingivalis, thus providing accelerated periodontal destruction.[13] Mast cells which have an important role in immunologic inflammation are present in oral and periodontal tissue. Degranulation of mast cells release histamine, arachidonic acid metabolites (i.e. leukotrienes, prostaglandins), enzymes (i.e. tryptase) and cytokines (i.e. IL-1, IL-6, TNF-$\alpha$).[14] It can be triggered by antigens, bacteria,[13] neuropeptides (SP and CGRP), chemokines, calcium ionophores and physical factors (i.e cold temperature, exercise, trauma).[14] Substance P has also directly effect smooth muscle and indirectly induced vasodilatation of blood vessels.[15] Periodontal inflammation give rise to SP, neurokinin A (NKA) and vasoactive intestinal peptide (VIP) in gingival crevicular fluid.[15] Periodontium act as cytokine reservoir, the pro-inflammatory cytokines TNF-$\alpha$, IL-1$\beta$, and gamma interferon as well as $PGE_2$ reach high tissue concentrations in periodontitis. The periodontium can therefore serve as a renewing reservoir for spillover of these mediators, which can enter the circulation and induce and perpetuate systemic effects.[16] Oral focal infection, has a long history of controversy, however plenty of successful results of the evidence-based therapies reported. Three mechanisms or pathways linking oral infections to systemic effects have been proposed that are 1) metastatic spread of infection from the oral cavity as a result of transient bacteremia, 2) metastatic injury from the effects of circulating oral microbial toxins (i.e LPS from gram negative bacteria), and 3) metastatic inflammation caused by immunological injury induced by oral microorganisms.[16]

In this case, symptoms of the patient that mimicking and could be related to so called chronic fatigue syndrome are gone after scaling. The problem is how to explain pathophysiologically the successful management that happens and what is the main cause of the symptoms which are related to oral focal infection.

## CASE

A male patient, 37 years, came to the clinic in the University of Airlangga Faculty of Dentistry in August 2004 complained about continuous shoulder muscle pain, headache and runny nose. Symptoms began in 2002, started with runny nose then followed by warm feeling in the ear. He had already suffered for 4 months then and had been examined and treated by a general practitioner but symptoms still exist. Gradually the symptoms were getting worse everyday, and then he suffered from headache and warm feeling in his neck. The pain spread downward to the back and headache was felt in different places all over the head, the worse pain was in the neck.

In 2004 backache went downward to the leg, the pain caused sleep disturbances, in the morning when he woke up the fatigue increased. Patient consulted to an internist, the medicaments helped for a while, but symptoms arise after the medicaments were stopped. Vertigo then arise and patient couldn't do daily work included driving and reading because everything seems to move and spinning. After consulting to a neurologist, patient was treated as vertigo patient but he still didn't feel well.

Patient already have a lot of treatment and medications, including massage. Some of the medications were anti hypertensive, analgesic, antibiotic, anti vertigo, tranquilizer, anti depressant, muscle relaxant, cerebral and peripheral vascular vasodilator and anti inflammatory. In extra-oral examination, patient looked tired in the eyes and fatigue, red and hypertrophic gingiva but only a bit of calculus were seen in intra-oral examination because the patient also has visited a dental practitioner about 2 months ago, 36 was extracted because of mobile and painful. Gingival bleed easily after probing. Periodontal pockets were found in all regios with average depth 3–5 mm except in distal 46 was 7 mm and 47 were 6 mm. In orthopantomograph revealed the existence of horizontal resorption in all regios and vertical resorption in 46 (figure 1).

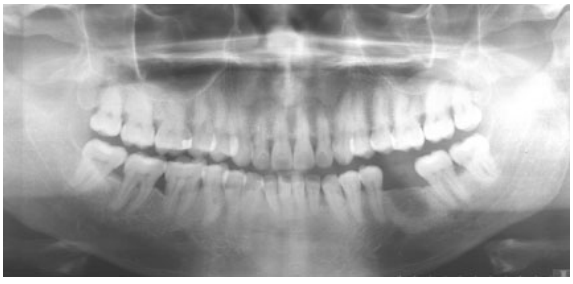

**Figure 1**. Orthopantomograph.

**CASE MANAGEMENT**

At first visit patient were asked about the medical and dental history, kinds of treatments that have already done, medications prescribed and the result of the treatments. Superficial scaling were done with piezoelectric scaler and cleaning the debris and food impaction inside the pocket with half-moon explorer on the right side then the left side of the patient, after finishing on the right side patient feel more comfortable, headache and shoulder ache gradually disappear. Then scaling were done to the left side, the result was the same. Patient was prescribed chlorhexetidine 0,1% mouth wash and thiamfenicol 500 mg, he was told to take the antibiotics 2 hours before next visit three days later. The second visit patient was asked about the treatment result and the result was remarkable because patient felt very well, headache and rhinitis stopped no sleep disturbances, backache also disappeared, patient still felt uncomfortable in the leg but was getting better. Intra oral examination revealed that the gingival was more healthy, pink colored and not easily bled. Before deep scaling was performed, patient was local anesthetize with xylocaine adrenalin, during scaling periodontal pockets were flushed intermittently with hydrogen peroxide 3%. Patient was then scheduled next visit in one week time. At the next visit pain in the legs was disappear completely and there was no complain about the recurrence of the symptoms, patient were told to check up every 6 months. On October 12nd, 2005 patient were evaluated and the symptoms did not recurrent.

**DISCUSSION**

The exact etiology and pathophysiology of chronic fatigue syndrome (CFS) is still unclear, some researchers propose the possibility of past viral infections but there are cases that the patients don't have the same medical history.[1] Some cases are accompanied with allergies such as rhinitis symptoms and sinus–headache, so the diagnosis and the treatment planning still confusing.[4,5] Drug of choice of CFS still symptomatic such as anti-inflammatory, anti depressant, corticosteroids and antibiotics.[1,5] Chronic fatigue syndrome (CFS) are also suspected as derangement of immune, neurologic and endocrine system,[2,5] so it is still a dilemma: what is the treatment of choice, should we give all kind of medication, how about drug interactions and toxicity?.

As proposed by Meggs[6] that is the neurogenic switching hypothesis, substance P (SP) produced by sensory neuron can elicit a neurogenic inflammation by degranulate mast cell thus combine neurogenic and immunologic inflammation. In this hypothesis the trigger of SP release by sensory nerves is chemical agents, LPS can also indirectly triggers SP release by inducing macrophage to produce cytokines which stimulate the sensory nerves.[15] Reflected to the fact that immunecompetent cells and SP producing nerves are also present in oral tissue so it can be predicted that resolution of oral inflammation also diminished the symptoms which related to neurologic and immunologic inflammation. The explanation as follows: at site A, chemical irritants, Ch interact with sensory nerve fibers to trigger release of substance P, Sp, and other mediators of neurogenic inflammation. At site B, antigens, Ag, are interacting with antibody on mast cells to release histamine, H, and other mediators of allergic inflammation. Histamine interacts with nerve fibers to produce signal transmission to the central nervous system. At site C these mediators acting on effector cells to produce an inflammatory response. At site D there is an inflammation that being triggered at a site distant from the stimuli. Signals from A or B are rerouted through the central nervous system to site D, where substance P, Sp, is released from the nerve endings to initiate an inflammatory response (figure 2).[6]

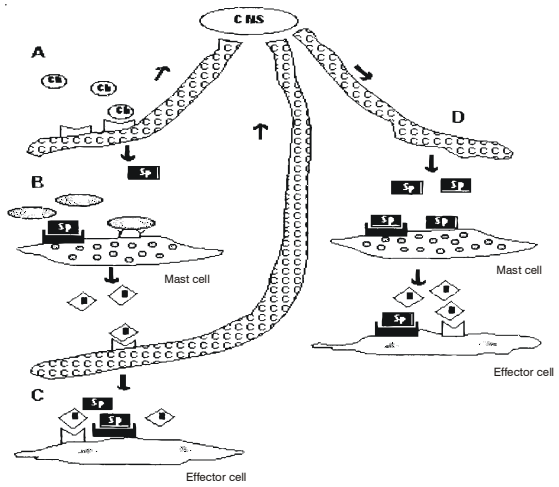


**Figure 2**. Neurogenic switching.[6]

Fibers innervating the periodontal tissues in human are immunoreactive to a number of neuropeptides, including SP, calcitonin gene-related peptide (CGRP), vasoactive intestinal peptides (VIP) and neuropeptide Y (NPY). Substance P has been located by immunohistochemistry in normal gingival tissue perivascularly and within the rete pegs. Nerve fibers originating in the subepithelial connective tissue may also penetrate the junctional epithelium, junctional epithelium is extensively innervated by SP nerve fibers.[13,15] In oral inflammation, neurogenic mechanism happened as follows, gram negative bacteria LPS stimulate macrophage to produce cytokines. Cytokines then stimulate the sensory nerves to release neuropeptides i.e SP and CGRP, SP could also interact with immune cells causing proliferation of T lymphocytes. There are several factors influencing the release of SP from sensory nerves, 1) cleavage of protease activated receptor-2 (PAR-2), 2) bradykinin binding to B2 receptors, 3) sensitization of cytokines produced by macrophages induced by LPS and 4) nitric oxide (NO) (figure 3).[15]

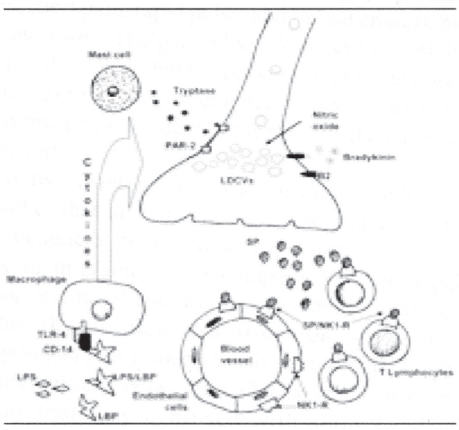


**Figure 3**. Factors influencing the release of substance P from sensory nerves.[15]

According to the past medical history, patient was prescribed anti-hypertensive, anti depressant, anti-vertigo, analgesics, muscle relaxant, cerebro-vascular vasodilator. The symptoms are relevant to chronic fatigue syndrome (CFS) criteria and still exist more than 6 months, we can conclude that this patient also suffered from CFS. In this patient, the symptoms initiates by rhinitis and warm feeling in the right side since 2002, was it the first inflammation which is the main source of the problem. Considering the patient's age, oral and periodontal health and their effect to the alveolar resorption, the poor periodontal health initiate a long time before 2002. In this case neurogenic switching hypothesis might be began with the periodontal inflammation which also a source of SP, proinflammatory cytokines and chemical mediators. Substance P then stimulates mast cell degranulation, histamine and SP then activate effector cells (i.e. lymphocytes) which also produced TNF-$\alpha$. Lymphocytic infiltrates are common to be seen in CFS patient. Tumor necrosis factor-$\alpha$ make defect in tight junction integrity of epithelial cells, when the epithelial barrier is lost, neurogenic inflammation may be triggered at much lower doses. The result is ongoing inflammation, which in turn continues the damage to the epithelial barrier, if the distant inflammation occurs in the nose then symptoms of rhinitis appear, in another part of the body can cause muscle spasm and tenderness, tension headache and migraine.[5,6] Consistent pain in shoulder, neck and head could be triggered from the proinflammatory cytokines IL-1$\beta$, IL-6 and TNF-$\alpha$ mostly produced by macrophages induced by LPS.[10] Stress which also the part of his complains also inducing the secretion of NO and production of inflammatory that enhanced the periodontal destruction[14] and in a systemic way could trigger head ache.[10] Prostaglandin E2 that is arachidonic acid metabolites from the lipooxygenase pathway lowered the pain threshold and excitability of the sensory nerves and also an immunosuppressant that will cause the patient painful and fatigue in the muscles, joint and elsewhere in the body.[9] Systemic PGE2 could also stimulate the humoral immunity (Th2) which related to allergy diseases i.e. food allergy, allergic rhinitis and asthma, IL-4 and IL-13 induced B lymphocyte into IgE specific producing plasma cells instead of IgG specific (isotype switching mechanism).[12] Vertigo also suffered by the patient, it can be the effect of neuropeptide SP that affect the expression of endothelium-leukocyte adhesion molecules from cochlear microvasculatures which decreases blood flow to cochlear sites and cause vestibular and cochlear disorders.[8]

In the conclusion, oral focal infection an inflammation that includes neurogenic and immunologic response could also play an important role in the pathophysiology of CFS. Elimination of oral focal infection is able to relief CFS symptoms, the first reason is because LPS from oral infection can stimulates both neurogenic and immunologic inflammation, and the second reason is that oral tissue has SP producing sensory nerve fibers and immunocompetent cells such as mast cells and macrophages which needed for neurogenic switching mechanism.

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