Reviews

A glance on diagnosis and treatment of profound fatigue in Multiple Sclerosis

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Multiple Sclerosis (M.S) is one of the prevalent diseases of the central nervous system which cause disability in young adults. This appears as neural signs in different parts and various times. The main defect is local deterioration or destruction of myelin tissue in the brain and spinal cord. Profound fatigue is one the most common symptoms of this disease. Because MS is prevalent in middle ages, so the presence of this symptom affects the life and activity of the patient; In these ages people have high amount of activities and this functional disorder creates many difficulties for daily works in patient. For this reason, fatigue problem in patients, always, have caught the attention of researchers.

Despite numerous studies, still the exact reason for producing fatigue have not been mentioned; But several mechanisms have been discussed, such as: autoimmune mechanism of the disease, Involvement and disorder of endocrine system , involvement of central nervous system and de-synchronization of autonom system. Among these, autoimmune mechanism is considered as a main role in producing fatigue.

Lack of proper knowledge regarding exact fatigue mechanism several problems in its treatment. Evaluation is the first step for controlling fatigue, which is done through various tests. Clear and proper evaluation can be obtained by these tests.

After evaluation, non-drug and finally drug procedures are helpful. In non-drug treatment the focus is on: sport exercises, suitable diet program, identification and improvement of the patient psychotic disorders, energy conservation methods. Finally, the use of drugs such as Amantadine, Pemoline and Modafini is recommended for fatigue treatment.

Keywords: multiple sclerosis, fatigue, diagnosis, treatment

Introduction:

Profound fatigue has different meaning for doctors and patients. Doctors consider it as excessive degradation of power of one or many muscles after activity, but patients assume psychological sensation of fatigue as physical one. So , there are several reasons for this.

If we suppose it as a somatic & psychotic sign, in patients with various diagnosis encounter with it such as: depression, rheumatoid arthritis,systemic lupus erythematosis(S.L.E) , renal insufficiency That is show itself as significant sign. On the other hand, it may be a sign in normal & healthy people which is caused after heavy works[(1)].

Fatigue is divided into two general & local types[(2)] .General fatigue remains all day and only subsides with long rest or a good night's sleep. Local fatigue, however, is caused by activity and subsides with little rest; just like blurring of vision after long period of study or tired feet after a long run. More attention is paid to general fatigue. Fatigue, perhaps, is the most common symptom of MS disease. Different studies mention 85%prevalence [(3)]. This symptom can affect the patient's life and is the main reason for the patient's disability, in a way that he/she, can not even do day-to-day activities [(1)]. On the other hand , this symptom is a big challenge for doctors , researchers and affected patients , because knowing its mechanism, evolution

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and degradation , accompanying with assimilation sensation , which is much higher than a thing that everyone normally experience in fatigue[4]. It must be considered at all times that sometimes patients explain depression as fatigue which usually is accompanied with hopelessness & despair. But, sometimes these two are accompanied with each other and aggregate their symptoms[5].

Pathophysiology of fatigue in MS:

Since the exact reason of fatigue in MS patients is not known, explanation of its pathophysiology is difficult. As a whole, fatigue may be central or peripheral. In central type, information from central nervous system (CNS) is not enough[6]. In peripheral type, the capacity of muscle for producing energy is degraded[7]. There are reports that say , in MS the fatigue is peripheral or central , but the rate of central type is much higher , in a way that , at the beginning of activity , patients have enough energy but with continuation of activity profound weakness is produced[8]).

Different mechanisms explain the appearance of fatigue in MS patients, such as: 1) Autoimmune nature of this disease , 2) Disorder in damaged neurons , 3) Change in response of endocrine system , 4) dys-synchronization of autonomous nervous system and consequently lack of energy conservation[9].

Many reasons explain that autoimmune disorder can produce severe weakness in affected patients , in a way that it is as a significant symptom in other autoimmune diseases like SLE[10] and when two autoimmune diseases arrear with each other, it can reflect as a first symptom. It have been seen that increasing of Cytokines in a track of some diseases such as MS causes fatigue & increasing of this substance during the day produces daily fatigue[11]. Also, immune system affects function of endocrine glands such as pituitary-hypothalamus axis and the way of responsiveness to stress and its effects in producing fatigue. Additionally, there is some relationships between thyroid function and fatigue[12] .On the other hand , consumption of interferon in MS patients in comparison with patients that use glatiramer acetate (with immune correction characteristic) causes more fatigue. In interferon patients, 41-76% have fatigue but in glatiramer acetate patients this is about 19%[13-16].

Central nervous system mechanism:

Different parts such as premotor cortex, limbic system, basal ganglia and brain stem are affected in fatigue of MS patients. Decrease of neural impulses in these areas can cause fatigue. Involvement of these parts, mainly because of immune disorders, are in the shape of myelin damages that secondary produce axonal destructions. In positron emission tomography (PET) test assessments , decline of frontal cortex & basal ganglia metabolism have been seen in MS patients (in comparison with normal people) [17-18].

Despite performing studies in this field, still, the specific area in brain have not determined for describing fatigue in MS patients. In some other studies , damage of neural myelin and as a result, deficit in muscles innervations have been explained as a reason of fatigue , in a way that for doing one movement or act , motor center must produce further impulses[19]& consequently consume more energy.

The other matter is the relationship between temperature & fatigue in MS patients. This condition, maybe , is not seen in other diseases. Temperature affects neural conduction.

On the other than , the relation between fatigue and depression is in favor of the presence of brain mechanism of the fatigue. Without the relation with the amount of physical activity, this relationship. Shows this fact that neural ways involve in MS have role in, both, fatigue and depression[20].

Endocrine mechanism:

In MS patients, endocrine system disorders such as thyroid disease , at least , partly participate in producing fatigue[21].

But further studies in the hypothalamus-pituitary-adrenal axis depict more things in this regard. This axis adjust body reaction to stress[22] and its role in CFS disease have known and maybe have similar effects in producing fatigue in MS patients.

Involvement of hypothalamus and pathway with dopamine, histamine and serotonin neurotransmitters can cause fatigue.

Besides, hypothalamus involvement decrease awakening and consequently increase fatigue. Since, Modafinil drug is a decrement agent of fatigue in MS patients and it does this job by the way of non-dopaminergic pathway of hypothalamus , so , this fact shows that hypothalamus indirectly participate in producing fatigue[23-24].

Involvement of autonomous neural system:

Cardiovascular disorders have been seen in some

patients with MS and fatigue. In one study, among 84 MS patients, 64% suffer from fatigue, which in 20% of them, fatigue and autonomous disorder was seen simultaneously.

Disorder in metabolic response to body activity[26]and disorder in muscular activity have been seen in MS patients with peripheral neurons and muscles involvement and also fatigue , cases of decrease in oxidative capacity[25] [27].

Factors like drug consumption, psychological disorders & sleep problems are the other reasons of fatigue in MS patients. For example the rate of sleep disorders in the society is 12% but this rate is three times higher in MS patients[28], which is caused by spasms or spasticity during sleep. Problems like neuralgia can produce sleep disorder and consequently fatigue[29].

Evaluation & diagnosis of fatigue in MS:

Proper management of fatigue in MS patients need to evaluate the client carefully. The first step is to acquire precise case history of the patient and his/her family. After that, careful general and neurological examination is necessary. Thereafter it is helpful to conduct paraclinical tests to rule out or confirm the fatigue.

All physical and psychological factors which can cause fatigue, must be considered in case history & physical examination. The items which shall be attended are: differentiation between pathologic fatigue and fatigue in healthy people that appears transiently; fatigue varies with increase of the amount of sleepiness and psychological disorder. Acute or chronic beginning of fatigue must be considered. Questions regarding the following items must be asked : fatigue intensity in day or night , general or focal fatigue , intensifying factor of fatigue such as temperature ,sport , personal&familial stress , degrading factors of fatigue , patient's work , type of daily activities , amount of stress during daily works.

In case history and examination, other diseases that may cause fatigue shall be considered such as: acute&chronic infections, Human immunodeficiency virus(HIV) , chronic kidney disease, chronic fatigue syndrome , pulmonary disease. All types of sleep disorders in patients must be assessed.

Drug consumption like Benzodiazepines , muscular relaxation agents , Antihistamines , sedatives , Interferones[30]& Mitoxantrone[31]can cause fatigue. Stimulator drugs such as caffeine, alcohol by effecting sleep, produce fatigue. This fact shall always be considered that, sometimes, patients introduce other disorders like muscular weakness as fatigue. Psychological status of the patient, his/her relationship with family and amount of stress at home must be considered. Anything in favor of depression or apathy must be considered as an important factor[32]. Depression is the most common psychological disorder that is accompanied with MS. Studies reveal that more than 50% of patients in their life are involved in significant depression[33]. This rate is higher than other neurological diseases that cause disability[34]. Psychological disorders can be seen in different types of MS, even in those people that are affected for the first time [35] . High prevalence rate of depression is attributed to the frontal lobe, around of ventricles and temporal lobe involvement[34]. On the other hand depression aggravate symptoms of disease , which is not in harmony with the amount of brain damage [36]and aggravation of symptom result in further depression. So, with incidence of depression or other psychological diseases, treatment should be done immediately. Anxiety and personal disorders are the other diseases that accompany MS.

In physical examination, vital sign, lymph nodes size, ear/nose/throat inflammation, thyroid size and cardiac&pulmonary sound must be controlled. Skin shall be assessed for presence of any damage and abdomen must be evaluated for presence of hepatosplenomegaly. Laboratory examination , helpful for diagnosis of other diseases which cause fatigue , can be performed such as : ESR, CBC, electrolyte, gloucose, BUN, creatinine, biliroubin, SGOT, SGPT, alkaline phosphatase, CPK, complete urine analysis, chest radiography, thyroid tests, HIV, diagnostic tests of tuberculosis and lymph disease[37-38]. Imaging examination include Magnetic resonance imaging(MRI) and PET can be used in diagnosis of MS and its rate of dissemination, but these tests are not included in routine tests for fatigue.

Fatigue evaluation:

One aim of fatigue evaluation is to see "how much the patient can benefit from treatment." So, before beginning of treatment relative estimation of the amount of fatigue should be done. Different approaches are used for fatigue evaluation. Among these, fatigue severity scale (FSS), fatigue assessment instrument (FAI) and fatigue impact scale(FIS) have specific importance.

In FIS 40 items are considered. 10 items are related to cognitive activities, 10 items are related to physical activities and 20 items related to psycho-physical activities. Each item has 0-4 score. So the test has 0-160 score[39].

FAS has 29 items which measures fatigue quality and quantity in all diseases that cause fatigue. Each item has 1-7 score. When the patient does not agree with the item it scores 1 and when he/she is agree with the item it scores 7[40].

FSS include 9 item in physical activities and psychological aspects and 3 items which plan as general items. Each item gets the score of 1-7. This test is valuable in evaluation of fatigue in MS patients[41].

Treatment of fatigue in M.S:

Treatment of MS patients includes two stages:1) non-drug , 2) drug.

Non-drug: At first the doctor must evaluate the patient in order to select a suitable treatment program. Unfortunately, there are few references regarding sport exercises for MS patients[42]. But, by using a daily exercise program, diet program, exercises for energy conservation and training in cases where fatigue is exaggerated by temperature , fatigue can decrease. On the other hand, doing tests to determine the mental and psychological status of patient and for different reasons can help MS patients; such as: prevention of cardiovascular disease, decrease of obesity, weight control, treatment of psychological signs[42]. Doing these, prevent muscle weakness and finally decrease fatigue. One of these exercises is cycling which have been suggested for 5 sessions, 30 minutes each, and during 3-4 weeks. For decreasing fatigue these times should be 10 weeks. Longer times have no further treatment effects[43].

The use of regular physical therapy program is another work. In one study with doing physiotherapy in one session per week and for 5 hour(for each session) and during 1 year , in comparison with control group , there have been significant treatment in fatigue patients[44]. Additionally, the use of exercises in order to increase balance, movement harmony and increase of movement amplitudes may be helpful[45]. On the other hand, condition of other organs and diseases of the patient should be considered, such as: Asthma that noted especial attention. So it is suggested that for each patient special a program is selected according to the disease severity, its type and involving parts.

Important item that should be considered is the relationship between treatment and amount of fatigue in MS patients. So, the use of different ways for reducing temperature can be helpful for the patients [46]. Unfortunately, there are few studies in this regard; but it has been observed that reducing temperature can help fatigue treatment. Effects of coolness in treatment of neural conduction is attributed to decrease in production of nitric oxide (NO) . It has been observed in one study that by this method the production of NO is declined to 41% and consequently, neural conduction is treated. Nowadays, the use of hydrotherapy is suggested for treatment of fatigue and 85 degree Fahrenheit is suggested as the best water temperature[47].

Attention to diet is a non-drug affair, which must be considered. There is no especial food diet in this regard but it has been observed that the use of solid food can help to maintain health, increase energy, treat sleep and decrease fatigue. Nutritionist can help patients in this regard. The following recommendations can help decrease fatigue: 1) control of the amount of sugar cube intake, because, its high consumption aggravates fatigue; 2) drinking enough liquids ,because , liquid insufficiency aggravates fatigue. Water drinking especially after sport exercises is recommended. But sphincter disorders , walking problems and sleep disorders limits drinking of liquids by patients. 3) caffeine consumption must be limited in patients. Smoking should be forbidden. Both of these are stimulates and may cause sleep disorders. The use of antidepressant drugs is helpful for treatment[48]. 4) diet quality should be considered. Use of a balanced food diet is recommended; included high vitamins, sufficient minerals, proper proteins and carbohydrate. Consumption of proteins with high nutritiveness such as fish, white meat maintain the size of muscles , and different types of carbohydrates such as potato and grains conserve blood glucose levels and energy. The use of foods with high amount of fiber prevent constipation. One of the reasons for fatigue is constipation. Also, there is relationship between anemia and fatigue; so, for women in menstruation period and patients who lose blood for any reason (eg. after surgery) use of ferrite complexes in food diet is recommended[49]. 5) change in food program : Eating low amount of food in several times per day is much better than eating three full meals per day. This food program conserves energy and decreases fatigue. 6) Limiting alcohol consumption must be always advised

to patients, because, alcohol decreases the activity of CNS and results in fatigue sensation. On the other hand, alcohol has interaction with other drugs that are used by these patients, like Benzodiazepines and produce severe drowsiness and lethargy in patients. 7) Regular sports is appetizing and helps to maintain a balanced weight.

Drug treatments:

If the patient does not respond to non-drug activities, use of drug is unavoidable. At first , it is important to pay attention to drugs that aggravate fatigue Drugs such as Antidepressant, analgesics, tranquilizers, sedatives, anticonvulsants , antihistamines and psychotic drugs.

If patients take this group of drugs, needed or necessitate doses must prescribed. The use of these drugs helps treatment of fatigue in day.

To date no drugs have been verified for treatment of fatigue in MS patients, but in recent two decades different drugs with various effects have been used. Among them, Amantadin, Pemoline and Modifinil have the most usage[50-51]. Also, there are drugs like Aminopyridin, Antidepressants, Transdermal caffeine/ histamine complex.

Amantadin prevents re-absorbing of dopamine in CNS and perhaps due to this dopaminergic effect, treatment the fatigue in patients. For the first time, in 1985, a patient with MS used this drug for curing influenza & the level of the patient's fatigue was reduced significantly. After that and in different studies the amount of its treatment was mentioned 62.5%[50-51].

Pemoline is the excitatory of CNS. In different studies it was seen that treatment of fatigue, high dosage of this drug must be used. Unfortunately, these doses produce side effects like: fidgety, insomnia, nausea and there is no further treatment in comparison with amantadin[52]. So, this drug is not prescribed, generally, or, at least, is not located at the front line of treatment and it is used in some patients who do not properly respond to the other drugs.

Modafinil is an excitant of CNS which is different from other CNS excitant drugs, in chemical or pharmacological point of view. Hypothalamus is this site of its effect[53-54]. In several studies its treatment rate for fatigue have been mentioned at 69%.

Antidepressants are used in MS patients. Something that necessitate its consumption is accompaniment of fatigue and depression; because if we only treat fatigue and ignore depression, in effect the treatment will have failed.

It has been observed in different studies that with treatment of depression the amount of treatment fatigue has been increased significantly[55-57].

Other drugs like 4-aminopyridine and 3,4 diaminopyridine and transdermal caffeine/histamine complex are helpful in fatigue treatment. Aminopiridines are blockers of potassium canals that prolong the nerve action potentials and treat the nerve conduction[58]. But, unfortunately, it has side effects such as convulsion and hepatitis[59] , which restrict its consumption. Another drug is Prokarin which is the composite of histamine and caffeine and used transdermally. But few studies have been done in this regard[60]. ■

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