INTRODUCTION

Stroke is the second – ranked cause of mortality in the world and a major cause of disability ***(Donnan et al., 2008)*** and the fifth leading cause of death in the United States ***(Mozzafarian et al., 2015).*** Whether ischemic or hemorrhagic, stroke can induce physical disabilities ***(Wolfe et al., 2000)***, cognitive, psychological, and behavioral impairments ***(Kneebone and Lincoln, 2012).***

Post-stroke depression is of particular interest ***(Dafr et al., 2008)*** and for several decades, fatigue was considered to be a symptom of post-stroke depression. However, the fact that depression- free patients frequently complain of fatigue has prompted the examination of "post-stroke fatigue" (PSF) as a specific syndrome ***(Ingles et al., 1999)***.

At present, there is no consensual, clear definition of PSF and this is partly because of the syndrome's complexity. PSF is generally defined in subjective terms as an overall state of " a feeling of early exhaustion, weariness, and aversion to effort that develops during physical or mental activity and is usually not relieved by rest " ***(Staub and Bogousslavsky, 2001)***.

This type of fatigue has been studied with qualitative approaches such as patient interviews ***(Eilertsen et al., 2013)*** and patient questionnaires like the Fatigue Severity Scale (FSS)

(Krupp et al., 1989) and Fatigue Assessment Scale (FAS) ***(Schwartz et al., 1993)***.

The prevalence of PSF varies between 23% and 75% and this wide variation is related to differences in used scales, methodology in each study ***(Choi-Kwon and Kim, 2011).***

PSF has a negative impact on stroke survivors' rehabilitation, neurological recovery quality of life and work capacity ***(Andresen et al., 2012; Duncan et al., 2012).*** More seriously, PSF increases the risk of suicide ***(Tang et al., 2011),*** and all-cause mortality ***(Naess et al., 2012)*** and considered by many patients as one of the most troublesome symptoms to deal with ***(Staub and Bogousslavsky, 2001).***

Previous studies showed that potential predisposing factors for PSF could be older age, female gender, neurological deficits, medical complications, use of medications, sleep disturbances, pre-stroke fatigue, depression, cognitive ability decline and lesion location ***(Choi-kwon and Kim, 2011).*** Also several studies found significant association between PSF and depressive symptoms and a trend toward an association between PSF and anxiety ***(Wu et al., 2014)***, association between PSF and lesion location like caudate infarction ***(Tang et al., 2013)***, basilar artery infarction ***(Naess et al., 2005),*** corona radiate or internal capsule infarction ***(Changjuan et al., 2016)*** and lesions in the posterior circulation territory ***(Staub and Bogousslavsky, 2001).***

Biological factors have been also involved in PSF and provide promising field of study in order to find pharmacological treatments, like serum level of C-reactive protein, higher levels of glucose, IL-1 beta and IL-9 were associated with greater fatigue ***(McKechnie et al., 2010)***.

Studies also found an association between stroke severity at admission and fatigue after stroke ***(Jaracz et al., 2007; Radman et al., 2012).***

PSF has been linked to a number of comorbidities like heart diseases ***(Wang et al., 2014),*** diabetes mellitus ***(Naess et al., 2005),*** hypertension ***(Harbison et al., 2009)*** and dyslipidemia ***(Tang et al., 2013)***.

PSF is heavily linked with poor health-related quality of life (HRQL) among stroke survivors even with complete recovery of functional disability and other stroke symptoms ***(Vincent-Onabajo and Adamu, 2014)***.

It is therefore necessary to identify possible risk for PSF in order to develop effective preventive and therapeutic measures to improve the patients' quality of life following stroke.

AIM OF THE WORK

Evaluation of post-stroke fatigue as an important factor affecting the quality of life in stroke patients through assessment of its frequency and possible predictors in a sample of Egyptian patients with ischemic stroke.

FATIGUE IN DIFFERENT NEUROLOGICAL CONDITIONS

Introduction

Fatigue is a common symptom experienced by everyone at some time during life. It is possibly considered the most common symptom to be found throughout medical conditions ***(Chaudhuri and Behan, 2004)***.

Fatigue is definitely common and debilitating symptom in many chronic neurological conditions with heavy impact on person's daily life. people with severe fatigue have poor quality of life, with limited occupational performance and high rate of unemployment. So it's of great importance for health care professionals to study and understand fatigue, its causes, types and its effect on person's quality of life especially those with chronic neurological conditions ***(Amato et al., 2001)***.

There are many researches on fatigue in different medical conditions; however sever studies on different neurological conditions reported both similarities and differences regarding prevalence, causes, types and impact life quality.

In chronic conditions fatigue can be defined as "an overwhelming sustained sense of exhaustions and decreased capacity for physical and mental work at usual level" ***(NANDA, 2001 -2002).***

Fatigue in multiple sclerosis (MS)

Fatigue is one of the most common prominent and disabling symptoms of MS, causing restriction of patients' societal participation and performance of daily activities and subsequently affect the quality of life. It has reported that, at least 75% of patients with MS suffer from fatigue ***(Braley and Chervin, 2010)***.

Fatigue related to MS can be subdivided into primary and secondary fatigue; Primary fatigue related to specific pathophysiological mechanisms which are the direct consequences of the disease process of MS, like demyelination and axonal loss, while secondary fatigue may be related to symptoms or disease burden accumulation including depression, sleep disorders and side effects of MS therapies. However, it is difficult to differentiate between primary and secondary fatigue as both could be present simultaneously in a patient at the same time and may impact each other. Depression is a common example due to the major effect of primary fatigue on patients' quality of life and the depression itself can then lead to further worsen fatigue ***(Kos et al., 2008).***

Specialized radiological testing has suggested a link between the level of fatigue and functional and structural changes of cerebral grey matter, especially in the frontal cortex and basal ganglia ***(Derache et al., 2013)***. Fatigue in MS can be

exacerbated by heat and may improve with cooling ***(Charvet et al., 2014)***.

Fatigue in stroke patients

PSF is frequently reported and the prevalence of PSF varies between 23% and 75% which will be detailed later in chapter two of the review ***(Choi-Kwon and Kim, 2011)***.

Fatigue in patients with Post-Polio Syndrome (PPS)

Fatigue is also reported in 59% - 89% of patients suffering PPS, which is considered the major and most disabling symptom in chronic disease ***(Schanke et al., 2002)***.

The cause of fatigue in PPS still unclear and is likely to be multifactorial, the possible causes may be related to increasing weakness and muscular fatigability, chronic pain, respiratory dysfunction, sleep disorders, fibromyalgia, muscle abnormalities, reduced dopamine secretion, high levels of pro-inflammatory mediators and injury to the brainstem reticular activating system occurring during acute polio-myelitis encephalitis ***(Gonzalez et al., 2002; Trojan and Cashman, 2005).***

Fatigue in Parkinson's disease (PD) patients

Patients with PD also reported fatigue at considerable rates. A prevalence study by Friedman & Friedman using the modified version of FSS revealed that 67% of 58 patients with PD rated their fatigue as being different that experienced before the onset of the disease and more than 50% of participants reported that fatigue constituted to be one of the three most disabling symptoms of the disease ***(Friedman and Friedman, 2001)***.

In another prevalence study of 245 patients suffering from PD; 43% of the participants revealed fatigue; however the fatigue scale used for the study regarding its reliability and validity was not discussed ***(Karalsen et al., 1991)***.

Fatigue in PD is independent of motor severity and has been recognized as a key for non motor symptoms (NMS) in PD and could be present at diagnosis and also can lead to late disease complication and become a major problem for both patients and relatives ***(Alves et al., 2004)***. The Parkinson's disease non motor group **(PDNMG)** including fatigue, apathy, depression and excessive daytime sleepiness, had led pivotal studies targeting validation of non motor questionnaire and also non motor symptoms scale (NMSS) for PD, Fatigue is a key component of domain 2 of that scale ***(Chaudhuri et al., 2005)***.

Types of fatigue

1- According to its origin

It can be classified as a primary symptom or as a secondary symptom in a chronic disease. Primary fatigue may result from centrally mediated processes characterized by the disease itself, such as demyelination and axonal loss in the central nervous system or immune reactions. Secondary fatigue due to medical drugs or disease – related manifestations.

Fatigue and depression also interact each other. Depression resulting from primary fatigue may lead to decrease in the activity level and performance, this lowering of activity may in turn increase secondary fatigability due to deconditioning ***(Kos et al., 2008)***.

2- According to its anatomical cause

It can be classified into central and peripheral fatigue.

Peripheral fatigue can be defined as a sense of exhaustion caused by repeated use of muscles, also it can be due to disorders in muscles and neuromuscular junction and frequently observed in many neurological disorders such as Myasthenia gravis and Guillain-Barre syndrome ***(Merkies et al., 1991)***, in addition to immunological disorders such as Rheumatoid arthritis ***(Swain et al., 2000)***.

This objective reduction in motor power is measured by testing the decline rate in peak force generated during maximum voluntary muscle contraction. Peripheral fatigue is a distinctive topographic pattern of myopathic weakness while central or cortical fatigue is characterized by constant feeling of exhaustion, and those with central fatigue have difficulty with initiating and maintaining any voluntary physical or even mental activity ***(Chaudhuri and Behan, 2000)***. This subjective sense of fatigue is essentially perceived at the level of central nervous system ***(Chaudhuri and Behan, 2004).***

3- According to length of time with symptom

Fatigue can be classified into acute fatigue or chronic fatigue. Acute fatigue can be defined as fatigue that exists for 6 weeks or less and chronic fatigue that present more than 50% of time for more than 6 weeks ***(Bethoux et al., 2006)***.

4- According to its dimensions

It can be classified into physical and mental fatigue. physical fatigue may occur after minimal physical effort and in neurological conditions and worsens as the day progresses.

Mental fatigue usually reported in MS patients specifically in the cognitive domains of memory, attention, learning and information processing ***(Krupp and Pollina, 1996)***. Word-Finding difficulty and anomia are examples of

task-specific mental fatigue which is seen in patients with PPS ***(Bruno et al., 2000)***.

Physical fatigue is reported after physical exertion and mental fatigue is reported after mental effort. Apathy is a characteristic symptom of patients with PD ***(Isella et al., 2002).***

Although there are differences in the dimensions of fatigue according to the diagnosis, the overall pattern of fatigue is similar in different neurological conditions.

In this review we will focus on post stroke fatigue, prevalence, mechanism, associated risk factors, treatments and its impact on the patients' quality of life.

POST – STROKE FATIGUE

Stroke is the second – ranked cause of mortality in the world and major cause of disability ***(Donnan et al., 2008)*** and the fifth cause of of death in United States ***(Mozzafrarian et al., 2015).*** Whether ischemic or hemorrhagic, Stroke can induce physical disabilities ***(Wolfe et al., 2000)***, cognitive, psychological and behavioral impairments ***(Kneebone and Lincoln, 2012).***

Post-stroke depression is of particular interest ***(Dafer et al., 2008)*** and fatigue was considered to be one of symptoms of depression for several decades. However, depression-free patients frequently complain of fatigue has encouraged the examination of PSF as a specific syndrome ***(Ingles et al., 1991).***

At present, there is no accurate and clear definition of PSF and this explained partly because of the syndrome's complexity. PSF can be defined generally in subjective terms as an overall state of: " a feeling of early exhaustion, weariness and aversion to effort that develops during physical or mental activity and not relieved by rest" ***(Staub and Bogousslavsky, 2001).***

Several studies reported that PSF prevalence values range from 16% ***(Hubacher et al., 2012)*** Up to 74% ***(Van de port et al., 2007)*** of stroke patients and this wide variation is

related to differences in scales used for assessment of PSF, methodology and time-point follow up.

Besides being frequent, 23% and 59.5% of stroke patients reported PSF to be one of their worst symptoms ***(Naess et al., 2012)***. Although PSF is thought to less specific and less severe than that present in patients with MS, it seems to have nearly similar functional impacts on psychological functioning, professional, social and familial activities ***(Eramigna et al., 2007)***. Furthermore, PSF has negative impact on subjective feelings of recovery during rehabilitation ***(Winward et al., 2009).***

PSF is considered to be a major cause of invisible handicap because of lack of awareness of this condition among relatives, work colleagues and medical staff.

Studies have shown that stroke patients have little information about PSF and do not understand why they feel fatigued ***(Choi-kwon et al., 2005).***

Fatigue may lead to misunderstanding of the patient's behavior by the family and friends, also excessive demands may be over the patient's abilities and performance capacity, thus may lead to maintain anxiety or depression and consequently may lead to withdrawal from certain activities and social life ***(Flinn and Stube, 2010).***

PSF is thought to be a syndrome results from complex interactions between biological, psycho-social, behavioral

factors and the severity of post-stroke disability was positively correlated with PSF which had significant contribution to disability over and above functional recovery and depression ***(Alok et al., 2016).*** Therefore it is important to understand deeply PSF and identify its risk factors and develop novel treatments in order to improve patients' quality of life.

Factors associated with PSF

- ***Sociodemographic Factors***

Several studies had tested the association between gender and PSF, many studies had showed a predominance of PSF in females ***(Lynch et al., 2007; Naess et al., 2012; Tang et al., 2013)***, and one study showed a predominance of physical fatigue in males ***(Falconer et al., 2010)***. Similarily a number of studies had showed a positive association between PSF and age ***(Glader et al., 2002; Chestnut et al., 2010; Radman et al., 2012).*** Educational level also, was examined in a number of studies and had showed no association with PSF ***(Miller et al., 2013; Naess and Nyland, 2013; Tang et al., 2013; Pihlaja et al., 2014)***.

Studies had showed no association between PSF and ethnicity ***(Bult et al., 2013; Miller et al., 2013)***, but another one study had linked ethnicity to PSF ***(Feigin et al., 2012)***.

The impact of social factors on PSF had been tested in a few studies but the results still have to be confirmed. However, only one study revealed this association between PSF and

marital status ***(Glader et al., 2002)***, Author of this study found that PSF might be frequent in patients who are living alone. Also PSF is more associated with lack of social support as reported in two studies ***(Michael et al., 2006; Suh and Choi-Kwon, 2010)***, but others had showed no association ***(Wang et al., 2006).*** However, this last study had revealed higher incidence of PSF in patients who had disturbances in familial relationships, those who had a lower family income and those who are living in rural areas.

PSF was not associated with family income in one study ***(Suh and Choi-Kwon, 2010)***.

Also several studies found association between PSF and greater disability and dependency ***(Naess et al., 2012; Radman et al., 2012; Pihlaja et al., 2014)***. However, this association thought to be mediated by depression ***(Badaru et al., 2013)***, and was not found in other studies ***(Parks et al., 2012; Becker et al., 2015)***.

PSF also was linked to less return to work, particularly a return to full-time work either soon or long time after the stroke as revealed in a number of studies ***(Radman et al., 2012; Pihlaja et al., 2014)***, but this was not linked in another study ***(Lerdal et al., 2011)***.

Finally, only few reported associations between socio-demographic factors and PSF. However, there is a trend