



Stress: A Public Health Concern for Progression of Neurodegeneration and Cognitive Decline in Pakistani Population

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ABSTRACT

Purpose of the Study: The aim of the study was to relate the declining cognition, stress scores, serum cortisol, and plasma BDNF as psychophysiological markers for the effect of stress in the progression of neurodegeneration. **Methodology:** A cross-sectional examination was conducted in both the rural and urban areas of Karachi, Pakistan. Classification of stress was done on the basis of Sadaf stress scale (SSS), the neurodegenerative diagnosis was on the basis of ICD-11, mental health status with DSM-V criteria and cognitive decline through cognitive impairment test, followed by a collection of blood samples for estimation of serum cortisol and physiological measures. **Results:** Our study results shows the relationship between serum cortisol level, BDNF, cognitive decline, BMI and 7 different types of stresses reported by study population that indicated significant (correlation was significant at the 0.01 level, 2-tailed) positive correlations in case of BMI with physical stress and nutritional stress; serum cortisol with nutritional, emotional and psychosocial stress; BDNF with nutritional and emotional stress and cognitive decline with traumatic, nutritional, mental and chemical stress. **Conclusion:** Our findings further support the role of stress in the onset and outcome of neurodegeneration, as already suggested by previous studies. In turn, stress-related biological pathways, together with decreased BDNF expression, may account for the cognitive impairment. We assumed that the worse cognitive functioning was seen in those adults with the severity of stress in comparison to those with normal or milder levels that would be associated with more severe white matter hyperintensities and hippocampal volume reductions at baseline.

Keywords: Stress, Neurodegeneration, Cognitive decline, Public health, Pakistan

INTRODUCTION

Pakistan is confronting significant challenges to overall health and wellbeing with emerging insights into the root causes of these problems, Pakistan's health and well-being status are perilously in decline and the country becoming a psychological pressure vessel with an epidemic of mental disorders in Pakistan [1-4]. Stress can be considered the main reason that has become a major threat to advancing human life and can be an outcome of rapid changes and modernism in human beings, therefore this era is called the age of stress. Stress is a severe emotional reaction as a result of internal or external change while Hussien, et al., defines it a state by which the individual undergoes into extensive and mental hyperactivation and goes beyond human capacity to deal with [5,6]. Stress-related disorders are major public health issues in many industrialized and developing countries and are expected to become increasingly common in the coming decades [7,8].

Stressors yield to the aspects or stimulators that can be the cause of physical or intellectual pressure. These could be external or internal. There are very less known stressors affecting Pakistani population. These stressors may lead to a serious prevalence of clinical mental disorders [9]. In previous researches, it was hypothesized that stressors can be divided into 7 categories; physical, traumatic, nutritional, emotional, mental, psychosocial and chemical stressors. It is required to develop parameters to measure and the aware local population of Pakistan [10].

Though, the brain has certain coping mechanisms to cope with any stress such as psychological, physiological,

nutritional, etc. but if these mechanisms are altered or suppressed then the brain will suffer from massive neuronal death and dysfunctioning of the parts of the brain, but this condition depends on the severity of stress, duration of stress and neuro-restorative and neuro-protective mechanism [11,12]. Any alteration that either result in an increase or decrease in the secretion of neurotransmitter or affect the receptor of that neurotransmitter may lead to dysfunctioning of that particular area of the brain and ultimately leads to neurodegeneration [13,14]. Elevated levels of an excitatory neurotransmitter known as “glutamate” which is an amino acid, is greatly reported in cases of neurotoxicity which causes neuronal death [15]. Stress plays a major role in various pathophysiological processes associated with neurodegenerative diseases and mental disorders. Scientists have known for years that elevated cortisol levels interfere with learning and memory, lesser immune function and bone density, increase weight gain, blood pressure, cholesterol, heart disease, diabetes, etc. [5,16]. Mechanisms of stress in the brain, chronic stress and elevated cortisol levels also increase the risk for depression, mental illness, and lower life expectancy [5,17]. Biomarkers like BDNF are widely expressed in the adult mammalian brain and are known to play a crucial role in promoting proliferation, regeneration, and survival of neurons. This is predominantly significant in this context since a number of studies have shown brain volume changes at the onset of chronic stress, depression or psychosis suggesting a critical role for neuroplasticity, especially in the hippocampus and prefrontal cortex in the development of neurosis [18,19]. Furthermore, BDNF has also been involved in more complex processes in maturity, such as regulation of cognitive function that is known to be impaired in severe cases. However, the clinical and biological mechanisms behind the lower BDNF levels and the progressive brain volume changes are still under investigations [20]. Stress and the physiological systems involved in the stress response have been suggested to play a role in BDNF changes. Mild cognitive impairment can thus be regarded as a risk state for dementia, and related neurodegenerative disorders. The hippocampus acts as a brake on stress responses. Poor hippocampal function leads to an increased response to stress and consequently more damage to the brain. It was also noted that elevated stress hormone levels decreased neuro-protective-hormone. Elevated cortisol levels lead to a decrease in BDNF. Indirectly, stress reduces the effectiveness of neurochemical connection within the brain.

The aim of the present study was to extend these initial findings to a detailed reflection retro and to scrutinize whether other biological changes are associated with continuing cognitive impairments. In this study, we claim that the knowledge concerning Pakistan’s current public health stress crisis is as considerable as the germ theory [21]. The aims of the study are to identify different types of stress in relation with stressors in a selected population, to determine the relation of these stresses with cortisol levels, relate the declined stress scores, serum cortisol as psychophysiological markers for mental health in our population.

SUBJECTS AND METHODS

This cross-sectional, non-randomized, convenience sampling study was designed under declaration of Helsinki and independent ethical committee approval was also obtained from the Pakistan Medical Association Committee on ethics (Reference Number: OB/458/PMC/17). The protocol of the present study was approved by the Board of Advance Study and Research (BASR) before its commencement.

Subjects were screened at 5 different sites namely University of Karachi, Pakistan Medical Association, Institute of Behavioral Science, Koohi Goth Hospital and Atia General Hospital. Written and signed informed consent from subjects was obtained prior to inclusion. Subjects between 18 to 60 years of age, having no psychiatric and neurodegenerative disorder and only permanent residents of (urban/rural) Karachi were considered for this study. A paper-based form was designed for systematic data collection. Data collectors were designated by the investigator, fully informed the subjects about terms and conditions, objectives, constraints, duration and subjects rights. Karachi is the biggest and most overcrowded city in Pakistan with more than 24 million residents. Overall 400 participants were recruited, 392 participants completed the study, rest 8 subjects refused to participate after signing the informed consent.

In the commencement of study, basic information was collected from all subjects through a questionnaire which included questions related to their demographic, socioeconomic status, marital status, medical history, substance use/abuse followed by physiological parameters like systolic and diastolic B.P, Body mass index (BMI), perceived stress and current health status (Table 1).

Table 1 Presents an overview of the study variables for demographics including gender, age group, qualification, socioeconomic status, marital status, work status, and BMI group

| Gender | Frequency | Percent (%) |
|-----------------------|-----------|-------------|
| Female | 263 | 67.1% |
| Male | 129 | 32.9% |
| Age Groups (Years) | | |
| 19-28 | 157 | 40.1% |
| 29-38 | 148 | 37.8% |
| 39-48 | 48 | 12.2% |
| 49-58 | 39 | 9.9% |
| Qualification | | |
| Uneducated | 9 | 2.3% |
| Primary | 29 | 7.4% |
| Matric | 65 | 16.6% |
| Inter | 116 | 29.6% |
| Graduate | 141 | 36.0% |
| Post Graduate | 32 | 8.2% |
| Socio-Economic Status | | |
| Lower | 2 | 0.5% |
| Lower middle | 222 | 56.6% |
| upper middle | 144 | 36.7% |
| Upper | 24 | 6.1% |
| Marital Status | | |
| Unmarried | 110 | 28.1% |
| Married | 282 | 71.9% |
| Work Status | | |
| Non-working | 115 | 29.3% |
| Working | 277 | 70.7% |
| BMI Group | | |
| Under Weight | 7 | 1.8% |
| Normal | 126 | 32.1% |
| Over Weight | 132 | 33.7% |
| Obese | 127 | 32.4% |

The presence of any psychophysiological factors was evaluated by Sadaf stress scale. The Sadaf stress scale (SSS) is the psychological instrument for measuring stress [22]. The most basic objective of using this tool was its specificity so far tested in Pakistani population. The tool comprised of 95 items that differentiate physical, psychosocial, mental, nutritional, traumatic, emotional and chemical stress. SSS assess major signs and symptoms and act as a forecaster of somatic health than major life events (Table 2).

Table 2 Showing the mean values with minimum and maximum scores for physical, psychological and biochemical variables

| Variables | Mean | Std. Deviation | Std. Error |
|---------------------|-----------|----------------|------------|
| AGE | 32.49000 | 9.73000 | 0.49000 |
| BMI | 27.07000 | 4.96000 | 0.25000 |
| SBP | 122.34000 | 19.21000 | 0.97000 |
| DBP | 80.01000 | 13.98000 | 0.70000 |
| PR | 93.10000 | 11.57000 | 0.58000 |
| Physical Stress | 19.76020 | 7.68888 | 0.38835 |
| Traumatic Stress | 13.33930 | 4.04004 | 0.20405 |
| Nutritional Stress | 23.30870 | 7.54690 | 0.38118 |
| Emotional Stress | 24.33420 | 7.64313 | 0.38604 |
| Psychosocial Stress | 42.96430 | 11.75382 | 0.59366 |
| Mental Stress | 26.59180 | 7.15354 | 0.36131 |
| Chemical Stress | 16.04590 | 4.95173 | 0.2501 |

| | | | |
|-------------------|---------|---------|---------|
| Cognitive Decline | 6.71680 | 1.52521 | 0.07703 |
| Serum Cortisol | 19.7596 | 3.66660 | 0.18519 |
| BDNF | 23.0863 | 3.86563 | 0.19524 |

Cognitive decline was screened through cognitive impairment test 6CIT, serum cortisol concentrations were determined by chemiluminescent microparticle immunoassay (CMIA) and analysis of BDNF concentration in the serum was performed with human BDNF ELISA kit. Double entry of data was done by 3rd party data punch operator on Epidata v.3.1. Statistical analysis was done using statistical package for social science (SPSS version 22.0).

RESULTS

Figure 1 represents the frequency of the population presented with a different severity level of cognitive decline. According to the results, 64.8% were found normal while 34.7% of the subjects showed mild cognitive impairment and significant cognitive impairment showed by 0.5% populace.

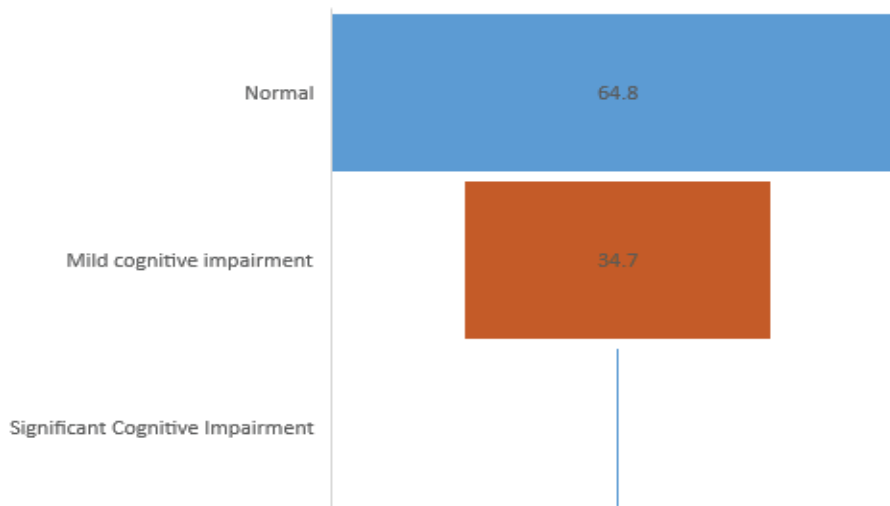


Figure 1 Frequency of cognitive impairment among the study population

Table 3 shows the relationship between serum cortisol level, BDNF, cognitive decline and 7 different types of stresses reported by study population that indicated significant positive correlations in case of BMI with physical stress and nutritional stress; serum cortisol with nutritional, emotional and psychosocial stress; BDNF with nutritional and emotional stress and cognitive decline with traumatic, nutritional, mental and chemical stress.

Table 3 Showing the correlations and p-values for 7 sorts of stresses, physiological and biochemical variables

| Variables | Serum Cortisol | BDNF | Cognitive Decline |
|---------------------|----------------|---------|-------------------|
| Physical Stress | 0.083 | 0.218 | 0.062 |
| Traumatic Stress | 0.077 | 0.079 | 0.003** |
| Nutritional Stress | 0.006** | 0.008** | 0.001** |
| Emotional Stress | 0.000** | 0.000** | 0.025 |
| Psychosocial Stress | 0.005** | 0.139 | 0.031 |
| Mental Stress | 0.048 | 0.025 | 0.005** |
| Chemical Stress | 0.08 | 0.068 | 0.005** |

**Correlation is significant at the 0.01 level (2-tailed)

Figure 2 shows the relationship between BDNF and serum cortisol that shows a positive correlation. According to the results, there is a significant relationship between BDNF and serum cortisol with p=0.000 reported that correlation is significant at the 0.01 level (2-tailed).

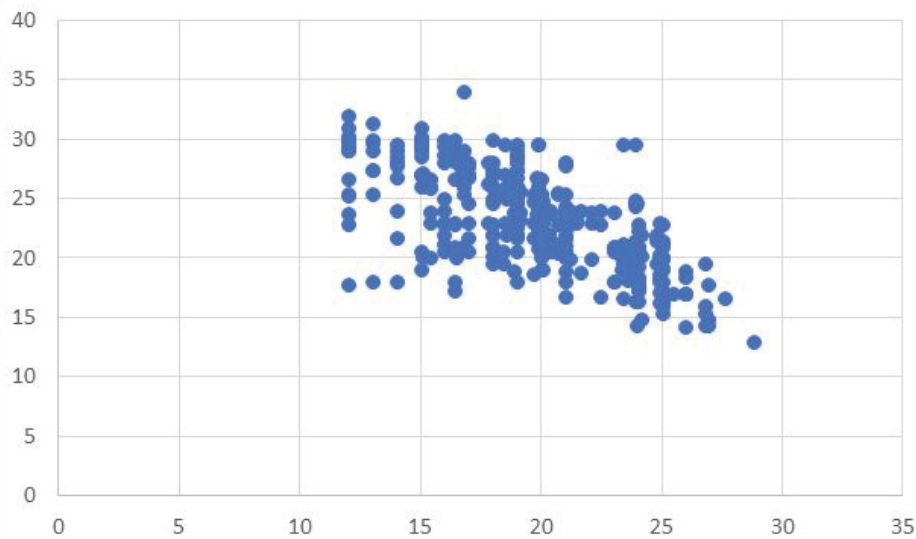


Figure 2 Correlation of serum cortisol ug/dl and BDNF in the study population

DISCUSSION

Study results demonstrate that stress can be positive to an individual in enabling them to perform better but on the other hand, it makes the individual more vulnerable for the consequences in the long run as the sensitivities to stressful situations can also be exhilarating. However, there was a clear difference in associations among 7 different types of stresses and psychophysiological biomarkers [9,23,24]. As our study show, a significant number of stress affected population developed mild cognitive impairment and few have developed significant cognitive impairment (Figure 1). Cognitive deficits are usually known to be associated with persistent stress, unhappiness, irritability, exaggerated emotional aspects that cause for an earlier onset of cognitive decline or dementia. Association between stress and subsequent cognitive decline was not only due to the somatic component but was also associated with a higher risk of neurodegeneration that is indicated by relative measures for serum cortisol and BDNF (Figure 2). This result is in affirmation with the observation that people who are more severely symptomatic often suffer from cognitive impairment, which may be severe for future progression of neurodegenerative disease or may accounted as pseudo-dementia if remains temporary and resolves on management of stress some studies have inveterate that chronic stress causes cognitive decline by consequent secretion of glucocorticoids that have damaging effects and lead to hippocampal atrophy [18]. There is a significant relation found among stress scores, intensity of declining cognition along with significant elevation in serum cortisol levels and a crackdown in serum BDNF that supports new studies about stress making changes in the brain raising the sensitivity to stress that can be detected as severity and more consistent findings on chronic stress (Figure 2 and Table 3). While psychophysiological factors countersigning susceptibility of individuals or target population that seems increasingly high with adverse life events play a significant causal role in the development of neuropsychological pathologies, because of the many mechanisms including release of large quantities of excitatory amino acids, such as aspartate and glutamate, in different brain areas, an effect occurring rapidly after the onset of stress, the damaging effect of calcium, alteration in energy metabolism, the altered level of various hormones, degranulation of mast cells in meningeal blood vessels, local vasodilatation, increased permeability of the blood-brain barrier; could be triggered by CRH bursts as well as glucocorticoids triggered ROS, cytokines and pathophysiological pathways. It is assumed that these positive correlations could be caused by stress-induced, excessive sympathetic or parasympathetic system outflow, frequent acute stress-induced attacks that can be attributed to increased secretion and effects of the major stress mediators in the context of a vulnerable circumstantial [18,25].

It is still to be made clear, that deviations in the set point for variables such as blood pressure are relatable to cumulative stressors or not, at least in healthy young individuals. Nevertheless, by emphasizing the role that chronic stressors may play in multiple disease outcomes. Other sets of findings reveal that the nutritional stress which is a direct indication of malnutrition and undernutrition of vital vitamins, minerals, and other essential molecules demonstrated the significant

impact of nutrition on serum cortisol, cognitive functions and BDNF referring to brain health that explains how dietary nutrients and non-nutrient may affect cognitive and behavioral performances. The main hypothesis supported with studies that point to the role of the chronic deprivation of vital molecules like the state of anemia, low oxygenation of the aerobic cortical tissue can lead to compromised compensatory processes due to the neurodegenerative or vascular pathology underlying cognitive decline [26]. Conditions like anemia subjected to decreased erythropoietin levels, in turn, may increase the risk of neurodegeneration. It has been found, that nutritional discrepancy induces systemic inflammation that exacerbates immune response in the CNS and priming pattern triggered by activated microglia, that makes the microglia susceptible to a secondary inflammatory stimulus [27], these activated microglia has the capacity to synthesize a wide range of pro-inflammatory and anti-inflammatory cytokines and molecular mediators, which contribute to the progression of neurodegenerative disease following the exposure to cytokines and lipopolysaccharide that are sufficient to trigger microglia activation and sickness behavior [28-31]. Deficiencies of magnesium, zinc, vitamin B and C and essential fatty acids sensitize the body's response to stress and may worsen conditions like depression and anxiety. These deficiencies upset the balance of chemicals (neurotransmitters) on the brain, leading to an increase in the stress response. Further, the adrenal gland requires these nutrients to cope with excessive stress [32]. There is a significant relationship found among stress scores, the intensity of declining cognition along with significant elevation in serum cortisol levels and a crackdown in serum BDNF that supports new studies about stress making changes in the brain raising the sensitivity to stress that can be detected as severity and more consistent findings on chronic stress. Exposures to stress-inducing events are more accessible to one's consciousness than the biological degenerations that eventuate in physical health ailments and chronic health conditions [4,33]. Thus, we assume that when individuals are chronically confronted with stressful conditions in daily life they will engage in unhealthy behaviors (e.g., smoking, alcohol use and abuse, drug use, and overeating, especially of comfort foods) that further exaggerate stress symptoms. However, these same behaviors silently contribute to physical health morbidities and early mortality. Thus, we theorize that engaging in unhealthy behaviors alleviates the symptoms of stress and the possible biological cascade to mental disorders while simultaneously combining with the effects of poor living conditions to contribute to the development of physical health ailments and chronic physical health disorders later in life. We assume that these unhealthy behaviors may either block the neurologic cascade or mask the psychophysiological experiences of poor mental health by acting on HPA axis and related biological systems.

CONCLUSION

Our findings support the role of stress in the onset and outcome of neurodegeneration, as already suggested by previous studies. In turn, stress-related biological pathways, together with decreased BDNF expression, may account for the cognitive impairment. We believe that these biological pathways should be considered for the development of future therapeutic strategies in this condition. We do not yet know about the association between stress and health, but we believe that these findings specifically for Karachi populace will add scientific and improved health conclusions. We have recognized associations between stressors and risk of developing psychiatric illnesses but most prominently neurodegeneration that was evident in positive correlations of endocrine-immune interactions like BDNF and serum cortisol appear to arbitrate the influence and related psychopathology. It is also concluded how psychosocial, emotional, nutritional and chemical stressors influence psychophysiological interactions. Interestingly, this is also the first clinical study suggesting that the effects of psychosocial stressors on BDNF expression are mediated by increased levels of serum cortisol. From a clinical point of view, our findings further support the role of stress in the onset and outcome of neurodegeneration, as already suggested by previous studies. In turn, stress-related biological pathways, together with decreased BDNF expression, may account for the cognitive impairment.

Recommendations

We believe that these biological pathways should be considered for the development of future therapeutic strategies in this condition. Though we do not yet know much about the association between stress and health, we believe that these findings specifically for a selected set of the populace will add scientific findings being made in the area of cognitive-emotional psychology, neuroscience and public health that will undoubtedly lead to improved health conclusions.

DECLARATIONS

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Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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